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A Case-Only Genome-wide Association Study of Gender- and Age-specific Risk Markers for Childhood Leukemia

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FLORIDA INTERNATIONAL UNIVERSITY

Miami, Florida

A CASE-ONLY GENOME-WIDE ASSOCIATION STUDY OF GENDER- AND
AGE-SPECIFIC RISK MARKERS FOR CHILDHOOD LEUKEMIA

A dissertation submitted in partial fulfillment of

the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

PUBLIC HEALTH

by

Sandeep Kumar Singh

2015

To: Interim Dean Mark Williams
Robert Stempel College of Public Health & Social Work

This dissertation, written by Sandeep Kumar Singh, and entitled A Case-only Genome-Wide Association Study of Gender- and Age- Specific Risk Markers for Childhood Leukemia, having been approved in respect to style and intellectual content, is referred to you for judgment.

We have read this dissertation and recommend that it be approved.

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Date of Defense: March 26, 2015

The dissertation of Sandeep Kumar Singh is approved.

Interim Dean Mark Williams
Robert Stempel College of Public Health & Social Work

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University Graduate School

Florida International University, 2015

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DEDICATION

I dedicate this dissertation to my entire family, especially to the three beautiful ladies of my life: my wife Anusha, my daughter Aanya, and my late grandmother Pannavati Singh. My parents never left my side and are very special. Without support and encouragement of my late grandfather, Bhagwati Prasad Singh, this dissertation was not possible.

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ABSTRACT OF THE DISSERTATION

A CASE-ONLY GENOME-WIDE ASSOCIATION STUDY OF GENDER- AND AGE-SPECIFIC RISK MARKERS FOR CHILDHOOD LEUKEMIA

by

Sandeep Kumar Singh

Florida International University, 2015

Miami, Florida

Professor Stanislaw F. Wnuk, Co-Major Professor

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Males and age group 1 to 5 years show a much higher risk for childhood acute lymphoblastic leukemia (ALL). We performed a case-only genome-wide association study (GWAS), using the Illumina Infinium HumanCoreExome Chip, to unmask gender- and age-specific risk variants in 240 non-Hispanic white children with ALL recruited at Texas Children's Cancer Center, Houston, Texas. Besides statistically most significant results, we also considered results that yielded the highest effect sizes. Existing experimental data and bioinformatic predictions were used to complement results, and to examine the biological significance of statistical results.

Our study identified novel risk variants for childhood ALL. The SNP, rs4813720 (*RASSF2*), showed the statistically most significant gender-specific associations ($P < 2 \times 10^{-6}$). Likewise, rs10505918 (*SOX5*) yielded the lowest P value ($P < 1 \times 10^{-5}$) for age-specific associations, and also showed the statistically most significant association with age-at-onset ($P < 1 \times 10^{-4}$). Two SNPs, rs12722042 and 12722039, from the *HLA-DQA1* region yielded the highest effect sizes (odds ratio (OR) = 15.7; $P = 0.002$) for gender-

specific results, and the SNP, rs17109582 (OR = 12.5; P = 0.006), showed the highest effect size for age-specific results. Sex chromosome variants did not appear to be involved in gender-specific associations.

The *HLA-DQA1* SNPs belong to DQA1*01:07 and confirmed previously reported male-specific association with DQA1*01:07. Twenty one of the SNPs identified as risk markers for gender- or age-specific associations were located in the transcription factor binding sites and 56 SNPs were non-synonymous variants, likely to alter protein function. Although bioinformatic analysis did not implicate a particular mechanism for gender- and age-specific associations, *RASSF2* has an estrogen receptor-alpha binding site in its promoter. The unknown mechanisms may be due to lack of interest in gender- and age-specificity in associations. These results provide a foundation for further studies to examine the gender- and age-differential in childhood ALL risk. Following replication and mechanistic studies, risk factors for one gender or age group may have a potential to be used as biomarkers for targeted intervention for prevention and maybe also for treatment.

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ABBREVIATIONS AND ACRONYMS

ALL	Acute lymphoblastic leukemia
AD	Alzheimer disease
BCM	Baylor College of Medicine
CI	Confidence interval
COSMIC	Catalogue of Somatic Mutations in Cancers
CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
CTD	Comparative Toxicogenomics Database
CD	Crohn disease
DNA	Deoxyribonucleic acid
eQTL	Expression quantitative trait locus
FDA	Food and Drug Administration
F-SNP	Functional Single Nucleotide Polymorphism
GWAS	Genome-wide association study
GC	Genomic control
HR	Hazard ratio
HWE	Hardy-Weinberg equilibrium
HCC	Hepatocellular carcinoma
HLA	Human leukocyte antigens
HIHG	Hussman Institute for Human Genomics
IARC	International Agency for Research on Cancer

IBS	Identity by state
IOM	Institute of Medicine
IRB	Institutional Review Board
IRR	Incidence rate ratio
LCL	Lymphoblastoid cell line
MAF	Minor allele frequency
NCI	National Cancer Institute
NIH	National Institute Health
NHGRI	National Human Genome Research Institute
OR	Odds ratio
PASS	Power analysis and sample size
PAH	Poly aromatic hydrocarbon
QC	Quality control
RA	Rheumatoid arthritis
RNA	Ribonucleic acid
SNP	Single nucleotide polymorphism
SD	Standard deviation
SEER	Surveillance Epidemiology and End Result
T1D	Type 1 diabetes
TXCCC	Texas Children's Cancer Center

1. INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a cancer of white blood cells¹. ALL is the most common form of childhood cancer in most parts of the world, except in Africa². Although ALL is relatively rare, its incidence rate has significantly increased (0.8% per year) since 1975 in the United States³⁻⁵. The reasons for the increasing incidence rate are still unknown. Change in environmental factors may be responsible for some increase². Unfortunately, childhood cancers are not public health priorities in most part of the world despite being a major cause of childhood death²⁻⁴. Unlike adult cancers, preventable risk factors for childhood cancers are mostly unknown³. Incomplete knowledge of childhood ALL etiology, unknown environmental risk factors, and known but understudied gender, age, and race/ethnicity differences signify the need for more research. For more than 95% of cases, childhood ALL etiology is still unknown¹⁻⁴, which makes formulating policies to reduce childhood ALL incidence impossible. Therefore, focused research to unmask the causes of childhood ALL is crucial.

1.1. Descriptive epidemiology of childhood acute lymphoblastic leukemia

Cancers are one of the major causes of death among children in the United States of America²⁻⁴. Leukemia alone represents one-third of all childhood cancers of which 80% are ALL, with an annual incidence rate of 38 cases per 10⁶ children per year under age 14, or 31 cases per 10⁶ children per year under age 19 in the United States²⁻⁵. Although treatment is now more successful, there is an increase in annual incidence rate by 0.6 % per year from 2006 to 2010 in children aged 14 years and younger²⁻⁴. This trend has been consistent since 1975 (Figure 1).

Figure 1. Childhood acute lymphoblastic leukemia incidence rates from 1975 to 2010

Age-adjusted Surveillance, Epidemiology, and End Results cancer-incidence rates, in childhood ALL, age 0-14 years. Incidence rates are per 1,000,000 per year and are age-adjusted to the United States standard population. X-axis represents years and Y-axis represents incidence rate per 1,000,000 per year.

Source: National Cancer Institute, Surveillance, Epidemiology, and End Results⁵

Furthermore, survivors of childhood ALL still suffer from late effects like relapse, social and behavioral issues, and secondary malignancies⁶⁻¹⁶. Thus, prevention is of paramount importance.

1.2. Gender difference in childhood acute lymphoblastic leukemia

Gender difference in cancers, whether it is childhood¹⁷⁻²³ or adult^{4, 24-26}, specifically in hematological cancers²⁷, is well known. Descriptive epidemiology consistently shows male predominance in childhood ALL (Figure 2)^{2-4, 19, 21, 22, 26-30}. Males experience around 20% higher incidence and worse prognosis than females in all ethnicities^{2-4, 28}. Moreover, the 5-year and 30-year survival rates are worse in male children with ALL, even after adjusting for age-at-diagnosis, race, year of diagnosis, and

cell type³¹. Furthermore, relapse and secondary malignancies have been consistently reported more frequently in males³¹. Males are subject to more intense treatment protocols in childhood ALL as a result of having more severe disease²³.

Figure 2. Gender differences in the incidence rate of childhood acute lymphoblastic leukemia
Age-adjusted Surveillance, Epidemiology, and End Results cancer-incidence rates, 2006-2010, in childhood ALL, age 0-14 years. Incidence rates are per 1,000,000 per year and are age-adjusted to the United States standard population. Males show higher incidence rates. X-axis represents incidence rate per 1,000,000 per year and Y-axis represents both genders and overall incidence rates.

Source: National Cancer Institute, Surveillance, Epidemiology, and End Results⁵

1.3. Age peak in childhood acute lymphoblastic leukemia

Childhood ALL risk is highest among age group 1-5 years^{2,3,5} (Figure 3) with an annual incidence rate of 72 cases per 10⁶ children per year. Precursor B-cell leukemia is the most common type of childhood ALL in the age group 1-5 years. In contrast, infants < 1 year of age suffer from a morphologically different type of leukemia that is more aggressive and shows a less favorable outcome¹.

Figure 3. Age-specific incidence rates in childhood acute lymphoblastic leukemia by single year of age-at-diagnosis

Age-adjusted Surveillance, Epidemiology, and End Results cancer-incidence rates, 2006-2010, in childhood ALL, age 0-14 years. Incidence rates are per 1,000,000 per year and are age-adjusted to the United States standard population. Y-axis represents incidence rate per 1,000,000 per year and X-axis represents age in years.

Source: National Cancer Institute, Surveillance, Epidemiology, and End Results⁵

1.4. Ethnic differences in childhood acute lymphoblastic leukemia

ALL risk is higher in Hispanics and Non-Hispanic White children than in any other ethnicity^{30, 32}. African-Americans have the lowest risk although the mortality rate is higher in African American and Hispanic children^{3, 33-35}.

1.5. Risk factors contributing to childhood acute lymphoblastic leukemia

Although the pathogenic events behind the development of childhood ALL risk are still ambiguous, several congenital syndromes, such as Down syndrome, show significant associations with childhood ALL risk^{1, 36}. The only known environmental risk factor is ionizing radiation¹. Descriptive epidemiology consistently showed male gender (M:F = 1.2), age peak (1-5 years), White race (White: African American = 2.0) and to a

Table 1. Risk factors (known, suggestive or with limited evidence) associated with childhood acute lymphoblastic

Known	Suggestive	Limited evidence
Gender (M:F = 1.2)	Maternal fetal loss	Paternal smoking before conception
Congenital disorders, ataxia-telangiectasia, neurofibromatosis, Fanconi anemia and Nijmegen breakage syndrome	Mother older than 35 years at pregnancy	Parental occupational exposure Hydrocarbon Paint Motor vehicle exhaust
White: African American = 2.0		60-Hz magnetic fields > 0.4 uT
Age peak (1-5 y)		Postnatal chloramphenicol use
Down syndrome		Family history
Ionizing radiation (diagnostic, <i>in utero</i> therapeutic, postnatal)		Decreased risk associated with breastfeeding
Birth weight > 4000 g		
Higher socioeconomic status		

M:F indicates male-to-female ratio of incidence

Source: Linet MS *et al.* Interpreting epidemiological research: lessons from studies of childhood cancer. *Pediatrics* 2003; 112:218-232 ²².

degree, birth weight (> 4000 g) as risk factors for childhood ALL²². Several other epidemiological studies have found environmental exposure such as parental occupation^{37, 38}, smoking, tobacco & alcohol use^{38, 39}, maternal reproductive history⁴⁰, maternal diet⁴¹, exposure to pesticides or solvents^{42, 43}, and exposure to residential power-frequency magnetic fields⁴⁴ to be associated with childhood ALL risk with inconsistent results²². Most of these exposures are either maternal, during pregnancy, or early childhood. Studies suggest that the incidence of ALL is higher in developed countries than developing and under developed countries⁴⁵. A list of risk factors that are known, suggestive or with limited evidence is provided in Table 1.

The types of cancers that most frequently develop in children are different from the most common adult cancers^{3, 4}. For example, although leukemia, lymphoma, and brain/other nervous system cancers account for more than half of all childhood cancers, they account for less than 10% of cancer cases in adults. In addition, etiologic differences and genomic variations within the same cancer type suggest that the childhood and adult cancers may be discrete diseases⁴⁶. Because more than 95% of causal risk factors, including environmental risk factors, for childhood ALL are still unknown^{1, 36}, the current focus is on unraveling genetic risk markers³⁶ to develop a predictive model and learn more about disease causation for preventive and therapeutic purposes.

1.6. Statement of the problem and public health significance

Among all childhood cancers, ALL alone accounts for more than 30% of cases in children up to 19 years of age, with approximately 3000 to 3500 cases diagnosed annually in the U.S.²⁻⁴. Over the past few decades there has been tremendous progress in

early diagnosis and treatment of childhood cancers in the U.S.^{6, 19} yet childhood cancers are still the leading cause of disease-related mortality^{3, 4} Childhood leukemia is the most costly pediatric cancer to treat and average annual hospitalization cost is around \$385.8 million⁴⁷. The survival rate of childhood ALL has improved with new treatments, and current 5 year survival rate is around 90%⁵. According to Surveillance, Epidemiology, and End, Result (SEER) data (Figure 4), as of 2010, there were around 379,112 childhood and adolescent cancer survivors (diagnosed at age 0-19 years) and around 60,489 of them were ALL survivors^{2, 3}.

Figure 4. United States childhood cancer survivors

Number of people previously diagnosed with cancer as children in the United States and alive January 1, 2010. Y-axis represents complete prevalence count by age-at-prevalence and X-axis represents age group in years.

Source: National Cancer Institute, Surveillance, Epidemiology, and End Results⁵

As of January 1st 2010, more than 70% of childhood cancer survivors are 20 years of age and older and the majority of them are childhood ALL survivors. It has been estimated that, approximately 1 out of every 530 young adults between the ages of 20 years and 39 years is a childhood cancer survivor^{2, 3}. Childhood ALL survivors will soon be a significant proportion of young adults in the U.S., this suggests an immediate step towards prevention to reduce the increasing burden on public health is necessary.

Family burden, in the form of grief and financial burden starts at the time of diagnosis, when parents learn that their child has cancer and will go through necessary harm in order to survive⁷. It is important to recognize that “children are not little adults”. Their bodies are still developing during illness and treatment. Therefore, cancer treatment affects them unequally over their life compared with adults. Although survival statistics have improved dramatically, the literature suggests that preventable suffering is a part of a childhood survivors’ life⁸. It significantly affects the quality of life of these children and their families. The extreme cost of survival for some treatable cancers is one of gross mental impairment. Even after treatment, these children suffer from poor motor functioning and compromised social well-being for decades of life⁷.

For cancers, which show higher survival probabilities, such as childhood ALL, a significant proportion of survivors will have chronic and life altering side effects as a result of treatment^{7, 8}. Childhood cancer survivors continue to have social and behavioral difficulties⁹. Two-thirds of childhood ALL survivors also experience one or more permanent side effects of treatment such as heart dysfunction, neurocognitive impairment, osteonecrosis, osteoporosis, reproductive issues, severe growth retardation, permanent hearing loss, obesity or second malignant neoplasm^{6, 8, 10-16}.

Every year, more than 200,000 children under the age of 15 years are diagnosed with cancer all over the world⁸. Low-income countries represent four-fifths of all childhood cancers, and in the absence of best therapies and/or a very high cost, the mortality rate is significantly high (> 80%) in comparison with that of developed countries (< 20%)^{21, 48}. Therefore, an urgent action toward prevention is highly recommended by the International Society of Pediatric Oncology to reduce the mortality, life-long burden of survivors, burden on the health care system and society¹⁷.

A few genome-wide association studies (GWAS) have been completed in childhood ALL⁴⁹⁻⁵⁴. These studies yielded somewhat consistent associations, but with small effect sizes. Thus, the explained proportion of genetic susceptibility is very low. A recent re-analysis, however, showed that by considering all genotyped single nucleotide polymorphisms (SNPs) simultaneously, 24% of the total variation in precursor B-cell ALL risk is accounted by common genetic variation⁵⁵. This result provides support for the involvement of many more SNPs than already identified in susceptibility to precursor B-cell ALL. The reasons for failure to obtain individual significant results are much debated⁵⁶. One of the reasons that is most relevant to the current work is the possibility of associations masked by effect modification (interactions with other genes or environmental factors, gender or age)⁵⁷.

1.7. Consideration of study design

We used a case-only design to see associations differing by gender and age groups. This study design is more efficient than other traditional epidemiological studies at detecting such effect modifications, which were the main focus of this study⁵⁸.

Recruitment of cases in a rare disease like childhood ALL is a challenge⁵⁹, and hence, preferring a statistically powerful research design is more practical.

The case-only design is a transformation of the conventional case-control design to detect statistical interactions. An assumption of the case-only design, requires genotype and gender/age to be independent in the population i.e., genotype frequencies should not differ between genders or age groups in a healthy population. When this assumption is met, it is easy why a case-only study can be used instead of a case-control study⁵⁹.

Table 2. Odds ratio calculation for association of disease with gender, by genotype

Gender	Risk genotype positive		Risk genotype negative	
	Cases	Controls	Cases	Controls
Male	a	b	e	f
Female	c	d	g	h
Odds ratio	ad/bc		eh/fg	

Table 3. Odds ratio calculation for association of disease with gender and genotype, in cases and controls separately

Gender	Cases		Controls	
	Risk genotype positive	Risk genotype negative	Risk genotype positive	Risk genotype negative
Male	a	e	b	f
Female	c	g	d	h
Odds ratio	ag/ce		bh/df	

In a traditional case-control study, interaction will be measured by their ratio $adfg/bceh$ (Table 2), which is basically the ratio of two odds ratios (ORs) (ad/bc and

eh/fg). Now, the same data is rearranged in Table 3. Again, interaction will be measured by the ratio $agdf/cebh$, which is the ratio of two ORs (ag/ce and bh/df) and equivalent to the OR derived in Table 2. According to the main assumption, genotype and gender/age should not be correlated⁶⁰. In case of a rare disease, such as childhood ALL, disease-free controls would be representative of the normal population and second OR bh/df should be one, meaning genotype frequencies between two genders and age groups will be similar. This is the simplest rationale to explain the case-only design. It suggests that under the required assumption of test of independence, it is possible to estimate interactions from the cases-only design⁶⁰.

In this scenario, we can estimate a statistical interaction from the association between genotypes and gender or age in the case-only study design, under the assumption that exposures and genotypes are independent^{60, 61}. There is no reason to believe that healthy males and female controls⁶², and healthy controls in two age groups (1-5 years and 6-10 years) have different genotype frequencies. The preference of the case-only design over the case-control is also due to its greater precision in estimating interaction (i.e., smaller standard errors)⁶⁰ and smaller variance based on four cells of individuals (Table 4) instead of eight cells of individuals in the case-control design (Table 2)⁶³.

Table 4. Odds ratio for association of disease with gender and genotype, in case-only studies

Gender	Cases	
	Risk genotype positive	Risk genotype negative
Male	a	e
Female	c	g
Odds ratio	ag/ce	

This study design is only good to calculate OR for interactions^{61, 64}. It cannot calculate OR for the main effects of genotype (OR_g) or gender/age (OR_e) individually. Our main interest is in gender- and age-specific risk markers, and we were not interested in the main effects.

The statistical power of the case-control design and the case-only design was compared in a study by hypothetical (200 cases and 400 controls vs 200 cases) and empirical data (four case-control studies)⁶⁵. Although results showed similar ORs for interaction in both study designs, the case-only design had a much narrower 95% confidence interval. Similarly, the four case-control studies also showed no substantial difference in OR for interaction, but confidence intervals were narrower in the case-only analysis. It suggests that the case-only study design has greater statistical power for detecting gender-genotype or age-genotype interactions with smaller sample size in comparison to a case-control study design⁶⁵.

Table 5. Odds ratio for association of disease with age and genotype, in case-only studies

Age	Cases	
	Risk genotype positive	Risk genotype negative
Age (1 to 5 years)	a	e
Age (6 to 10 years)	c	g
Odds ratio	ag/ce	

A case-only study was also used to examine the age-specific associations with childhood ALL. In this scenario, we used the same approach as it has been explained earlier for gender (Table 5). Again, in the case of effect modification by age, the case-

only approach provides more statistical power than traditional case-control design when the case group is split into two age groups.

1.8. Structure of the dissertation

This dissertation is written in a traditional style which contains eight chapters including this chapter. Following this chapter, Chapter 2 comprehensively reviews literature relating to gender- and age-specific associations in general, including childhood ALL. The purpose of the literature review is to provide insight that genetic architecture can significantly contribute to gender- and age-specific risk associations in childhood ALL. Chapter 3 explains hypothesis and specific aims of the study.

Chapter 4 provides an overview of the methods used for the gender- and age-specific associations in childhood ALL. It mainly addresses: rationale for quality controls (QCs) to assess the sample, genotyping method, and generated results, statistical analyses used to identify gender- and age-specific associations. Bioinformatic and empirical analyses were also performed for all identified markers to assess their functionality as explained in Chapter 4.

All gender- and age-specific association results and bioinformatic analyses of identified markers are provided in Chapter 5. Relevant tables with interaction ORs and interaction P values are provided at the end of Chapter 5. Chapter 6 provides a detailed discussion of identified genetic markers or genes and their possible relevance to gender- or age-specific associations. Limitations and strengths of the present study are provided in Chapter 7. Conclusion is explained in Chapter 8.

All tables and figures are provided in the relevant section of the chapters or in the appendix. All references are provided at the end of the dissertation.

1.9. Significance of the dissertation

This dissertation mainly focused on gender- and age-specific risk markers. This was the first GWAS of childhood ALL specifically addressing these issues. Gender difference is an underappreciated and understudied research area in cancer research²⁶. Findings from this dissertation may inform future studies of childhood ALL as well as other diseases, which show significant gender and age differences.

In majority of developing and underdeveloped countries, childhood cancers are not considered a major public health issue because of the high numbers of deaths from infectious diseases⁶⁶. Most importantly these countries also represent a higher percentage of younger population. Recent studies suggest that childhood cancers are among top five leading cause of death in children in developing and underdeveloped countries². Even countries like U.S. invest little on childhood cancer prevention⁶⁷. Childhood cancers, gender and age difference in cancers are major public health issues and medical concern. Therefore, this research and the results from this project addressed a major public health issue aiming to elucidate currently unknown risk factors for childhood ALL.

1.9.1. Better understanding of gender- and age-disparities in childhood acute lymphoblastic leukemia

Although descriptive epidemiological data have shown a significant role of gender and age specificity in childhood ALL, to date there have been few examples of gender- and age-specific associations. Our main interest was, therefore, the detection of

association differing in directions between males and females (risk vs protection), means risk association for one gender and protective association for another. Interaction with gender implies statistically significant differences in male- and female-specific ORs which is basically a difference in magnitude (for example, an OR = 1.5 in females and 3.5 in males and $P_{\text{interaction}} < 0.05$). This type of quantitative interaction in the overall analysis would yield an OR that is approximately the average of the two gender-specific ORs. We were interested in qualitative interactions that would be missed in the overall analysis (like in previous GWASs)^{50-53, 68}. A qualitative interaction is a result of two ORs differs in their directions (risk vs protection) rather than being in the same direction (differ in magnitude). Cross-over effect (association differing in direction) usually results in an OR close to the unity (OR = 1.0) with no statistical significance in the overall analysis. Such SNPs are typically dismissed for any further consideration. Gender-specific associations, differing in direction, are difficult to identify, even in secondary analysis, unless all of the raw data are re-analyzed. Associations differing in direction are simple examples of an effect modification where a polymorphism shows a risk association in one gender and a protective association in the other. Our main objective was to unravel associations differing in direction that would have remained undetected in the overall analysis.

A list of previously identified childhood ALL risk markers in GWAS are reported in the appendix Table 1. Our long-term aspirations are to learn more about the gender and age disparity and exploit this information to implement preventive and therapeutic measures. Because males are more prone to develop ALL and more likely to have unfavorable clinical outcome, it may appear that only males will benefit from the results.

This is not our thinking, and we believe that any information on disease pathogenesis will have multiple beneficiaries including other people with other childhood and adult cancers that show differential distribution between genders and among age groups.

1.9.2. Guidance for new strategies for studying other complex diseases

The case-only design circumvents several limitations of the traditional case-control design in interaction analysis. Successful application of this approach may be conducive, not only for childhood ALL, but also for research on other rare, gender-and age-specific disorders. It is well known that the time course and cost of recruiting subjects is hard for a prospective cohort study in case of rare diseases. Therefore, this project could provide guidance for new strategies to investigate an unidentified component of genetic susceptibility and effect modification in more common complex diseases.

2. REVIEW OF LITERATURE

Descriptive epidemiological data have consistently provided evidence for gender and age differences in distribution of nearly all cancers^{18, 24, 69}. Males generally show higher susceptibility, mortality and worst survival in most cancers. Studies that exploited gender differential for etiological clues identified several gender-specific risk markers^{68, 70-74}. Similarly, studies that used age differential for clues also unmasked risk markers for early or late-onset of diseases⁷⁵⁻⁷⁸. Prior to the present study, there was no GWAS in childhood ALL that has used a gender- and age-specific approach to identify markers for childhood ALL susceptibility. Furthermore, a time-to-event analysis approach was used to unravel risk markers that might be associated with early-onset of childhood ALL risk.

2.1. Genome-wide association studies

The National Institute of Health (NIH) defines GWAS as a study of common genetic variations across the entire genome designed to identify genetic associations with observable traits^{79, 80}. A GWAS uses high-throughput genotyping technology. It examines thousands of polymorphisms to relate them to a clinical condition or measurable traits⁸⁰. It is a hypothesis-free approach to scan markers across the whole genome. There are millions of genetic variants in the human genome. A traditional case-control study design is the most common approach in GWASs. GWASs also use stringent QC protocols to reduce the error in the study⁸¹. These QC protocols assess the sample, genotyping methods and generate results for potential causes of systematic error⁸². All QCs measured in this case-only GWAS are explained in Chapter 4.

The human genome contains around 19,881 genes^{83, 84}. These genes are discrete segments of deoxyribonucleic acid (DNA) that convey information to protein via ribonucleic acid (RNA). Genetic variation refers to DNA sequence polymorphism⁸³. An allele is one of the several forms of a DNA segment (e.g. a gene or locus).

There are many forms and levels of genetic variations⁸³. The most common genetic variation that has been examined in this study is called a SNP. For example, the same nucleotide position may be occupied by a guanine (G) in one individual and a cytosine (C) in another. An allele, which occurs less frequent in a population is called a minor allele. In the example given below, C is the minor allele, and polymorphism will be represented as G>C polymorphism.

Subject 1:	ACT G ACTCAT
Subject 2:	ACT C ACTCAT

In this instance, the two nucleotides represent two different alleles. These SNPs occur in every 100 to 300 nucleotides on average in human genome. It has been estimated that number of SNPs in the human genome is up to 40 million. The most common variation of a SNP has two alleles. There are three possible genotypes from a SNP with two alleles. Genotype is the genetic constitution of an organism specifying the particular alleles at a defined locus in the genome. It is basically two alleles inherited at a specific locus. Human genome contains 22 pairs of autosomal chromosomes and a pair of sex chromosomes. Males have one X and one Y chromosome, and females have one pair of X chromosomes. So, the genotype is the combination of two alleles, one from each chromosome. For example, the three genotypes in a population are:

Subject 1 = GG (wild-type), both chromosomes have G allele and G allele is commonly present in the population

ACTGACTCAT
ACTGACTCAT

Subject 2 = GC (heterozygote), one chromosome has G allele and another chromosome has C allele.

ACTGACTCAT
ACTCACTCAT

Subject 3 = CC (homozygous variant), both chromosomes have C alleles, and C allele is less frequently present in the population.

ACTCACTCAT
ACTCACTCAT

The wild-type genotype is the referent group in a statistical analysis. The other two genotypes may be included in the analysis as they are (gene dosage analysis) or may be pooled depending on the genetic model. Genetic models are explained in Chapter 4. Most genetic associations are mediated by gene expression changes due to genetic variation and their effect may be opposite in males and female^{83, 85, 86}.

2.2. Gender disparity in cancer incidence

Gender is an important risk factor in disease pathogenesis^{24, 32, 68, 87, 88}. Studies clearly suggest biological, physiological and behavioral differences between males and females, including differences in the incidence, progression, mortality and survival of many diseases^{24, 26, 32, 86}. Males have a higher life time probability of developing cancer than females (43.9% vs 38.0%)⁴. The National Cancer Institute (NCI) SEER database shows that males consistently have a higher incidence (males: 542.3 vs females 418.8 per

100,000) and mortality rates (males: 215.3 vs females: 149.7 per 100,000)^{4, 24}. Incidence rates were age-standardized to the 2000 US standard population and are for all cancers for 2006-2010. Males also show worse survival than females. Cook et al²⁴ in a recent study used SEER data to calculate gender-specific incidence rates and male-to-female incidence rate-ratios (IRR) for specific cancer sites for the period 1975 to 2004. Only five cancers (breast, gall bladder, thyroid, peritoneum/omentum/mesentery, and anus/anal canal/anorectum) were significantly higher in females when compared with males⁴. The leading cancers also show a higher male-to-female (M:F) ratio: lung and bronchus: 1.45; colorectal cancers: 1.32; urinary bladder: 4.05; non-Hodgkin lymphoma (NHL): 1.43⁴. Males consistently show higher cancer risk in 32 of 35 cancer sites, excluding sex-specific cancers, across geographical regions²⁵.

Likewise, for all childhood cancers, males show a higher incidence rate than females (178.0 vs 160.1 per 1,000,000)³. Incidence rates were age-standardized to the 2000 US standard population and are for all cancers for 2006-2010. These observations suggest the importance of analyzing results by gender, and how it may provide a fundamental understanding of human physiology, pathology and pharmacology that will ultimately benefit both genders⁸⁸. Cancer epidemiology has been more concerned with disease etiology than disease heterogeneity and failed to examine gender as a major risk factor²⁴. Adjusting the results for gender does not explain gender difference in susceptibility of a disease, it rules out confounding by gender²⁶. Stratified analysis by gender is one approach to unravel a gender-specific association, which can be confirmed by a statistical interaction analysis. Thus, gender-specific approach may provide important etiological clues in disease pathogenesis, progression, and treatment. Examples

include liver, colon and thyroid cancer. Higher interleukin-6 (IL6) levels may be one reason for higher incidence of hepatocellular carcinoma (HCC) in males^{89, 90}. A study on endogenous hormones suggests the protective role of estrogen in women through suppressing *IL6* mediated inflammation of the liver. On the contrary, testosterone can increase liver cell proliferation in men. Likewise, males again show higher incidence rate than females to develop colon cancer⁴. Estrogen plays a protective role in women for the development of colon cancer, and estrogen replacement therapy further reduces the incidence of colorectal cancer in postmenopausal women^{91, 92}. The androgen receptor expression in thyroid follicular cells may be responsible for higher incidence of thyroid follicular cancer in females^{93, 94}. These physiological differences elucidate the importance of gender difference in cancer. Thus, it would be difficult to predict a disease risk with the same accuracy in both genders, if results are not analyzed by gender⁶⁸.

2.3. Gender disparity in other diseases

Gender differences are also common in other diseases. Like cancers, susceptibility to infections is greater in males from birth^{95, 96}. For example, incidence of septicemia, meningitis and tuberculosis is higher in males from infancy to childhood. Moreover, males have a poorer immune response than females to several bacterial and viral infections^{87, 97-101}. Gender differences in infections are similar to cancer. Immune surveillance mechanisms are similar against cancers and infections. This suggests that the difference in immune system activity between males and females may play a significant role in gender differences. As in cancers, only few infections show higher morbidity and mortality rates in females, such as pertussis and mycoplasma pneumonia^{102, 103}. Nearly all

human diseases show gender-specific differences in prevalence, age of onset and/or severity. *In utero* loss is also more prominent with the male fetus¹⁰⁴. In comparison to males, average life span of females is longer¹⁰⁵, and not only they are healthier, but the survival rates from infectious diseases, sepsis, trauma or injury are also higher^{106, 107}.

The immunological disadvantage of being males in comparison to females is well known^{96, 108}. Lower production of antibodies has been noted in males in comparison to females. In general, females have a better innate and adaptive immune system¹⁰⁹. These also contribute to higher incidence of autoimmune and inflammatory diseases in females. For example, autoimmune thyroid diseases (Hashimoto thyroiditis and Graves' disease), systemic lupus erythrmatosus, Sjogren syndrome, multiple sclerosis, primary biliary cirrohsis and celiac disease are more common in females¹¹⁰.

The X chromosome contains the largest number of immune-related genes in the whole human genome⁹⁶. The difference in X chromosome numbers results in immunological differences in males and females despite the presence of dosage compensation mechanisms in females^{96, 111}. X-linked primary immunodeficiencies are typical examples of gender difference and the disadvantage of being male⁹⁶. Mutations or polymorphisms of an X chromosome-linked gene phenotypically expressed in males, who then show functional impairment of the respective proteins leading to diseases such as primary immunodeficiencies^{96, 111}.

Environmental and occupational exposures are commonly believed to play a significant role in gender differences in diseases. The male excess in cancers may be due to some environmental factors, including smoking, diet and life style, but environmental variations alone cannot explain gender difference in cancer risk²⁶. Thus, genetic factors

may shed some light on male excess in cancers. The examples given above suggest that physiological differences, immune system, X chromosome number, environmental risk factors and genetics may affect the disease susceptibility with gender specificity. Most of the endogenous causes of gender differences in disease are still unknown. In comparison to most of these endogenous causes, such as sex hormones and immune functions, the genetic contribution to gender difference, until recently, is an understudied research area. A stratified result by gender would produce more meaningful results, if one gender has a higher risk.

To understand the biology of sex and gender difference, the Institute of Medicine (IOM) formed a committee in November 1999¹¹². The committee issued three common messages:

- 1- Sex matters.
- 2- The study of sex difference is evolving into a mature science.
- 3- Barriers to the advancement of knowledge about sex differences in health and illness exist and must be eliminated.

It is important to understand that gender differences in health and disease need scientific inquiry in all aspects of biomedical, health-related and epidemiological research. The committee made several recommendations including¹¹²:

- 1- Promote research on sex at the cellular level. Determine how genetic sex differences influence other level of biological information, including susceptibility to disease, and develop systems that can identify and distinguish between the effects of genes and the effects of hormones.

- 2- Study sex differences from womb to tomb. Inclusion of sex as a variable in basic research design.
- 3- Investigate natural variations. Examine genetic variability, disorders of sex differentiation, reproductive status, and environmental influences to better understand human health.
- 4- Monitor sex differences and similarities for all human diseases that affect both sexes.

Therefore, further studies designed to look for possible gender differences in all clinical and epidemiological research has been encouraged.

2.4. Genetic basis of gender disparity

The role of sex hormones, oxidative stress, chromosomal telomere length, iron level, and immune function are thought to be the reasons for gender differential in human diseases¹¹³. Genetic contribution to gender differences, however, has rarely been explored. Although the role of X chromosome is mainly hypothesized for gender-specific gene expressions, autosomal chromosomes show gender-specific gene expression patterns^{86, 96, 114}. It has been assumed that autosomal genome is similar between males and females. However, studies suggest that genetic variations within autosomal genomes affect anatomical, behavioral and physiological traits differently in males and females^{86, 114-117}. Thus, potential of a polymorphism to show a gender-specific association does not depend on its genomic location²⁶.

Recent evidence suggests that the regulatory genome is sexually dimorphic¹¹⁸ i.e., there is a phenotypic difference between the two genders. Most phenotypic sexual

dimorphisms, including gender-specific effects on diseases, are a result of gender-specific differences in gene expression regulation. Sexually dimorphic gene expression at messenger RNA level has been observed in a wide range of organisms, including primates, rodents, fish, worms and flies^{114, 118-121}. A mouse study on gender-specific gene expression identified thousands of gender-biased genes in autosomes¹¹⁹. Thus, mammalian genomes are enriched with gender-biased genes that show gender-specific expression. These animal models also suggest that genotype gender-interactions are prevalent and that genetic contribution to disease etiology will be masked if gender-specific analysis is overlooked.

There are, however, very few examples of documented genetic basis behind a gender differential in humans, presumably due to lack of analysis by gender. Studies that have used gender-specific approaches have so far successfully unmasked a number of gender-specific risk markers in childhood ALL (Table 6)¹²²⁻¹³¹ and in other diseases¹³²⁻¹³⁸. For example, two *ARID5B* (AT rich interactive domain 5B (MRF-1 like)) polymorphisms (rs10994982 and rs10740055), previously identified as a risk marker in childhood ALL in GWAS^{51, 52} (Table 6), yielded significant gender-specific associations ($P_{\text{interaction}} = 0.01$ and $P_{\text{interaction}} = 0.03$, respectively)¹³⁹ (Table 7). These SNPs were significantly associated with risk only in males (OR = 3.79 and OR = 4.35, respectively; ORs for females were: 1.03 and 1.37). Other *ARID5B* polymorphisms did not show any statistically significant interactions, but males had a higher risk (Table 7). However, one major limitation of this study is selection of controls, as controls are mainly adults (median age 30.1 years vs 4.2 years in cases) and recruited at locations different from childhood ALL cases. Thus, gender-specific results might be affected by selection bias,

Table 6. SNPs associated with gender-specificity in childhood acute lymphoblastic leukemia risk

SNP	Overall (OR; 95% CI)	Males (OR; 95%CI)	Females (OR; 95%CI)	P_{int}	References
<i>HLA-DRB9</i> rs2395185	2.49 (1.43-4.34)	6.07 (2.85-12.9)	0.62 (0.21-1.86)	0.001	125
<i>HLA-DRA</i> rs7192	1.05 (0.68-1.63)	0.66 (0.37-1.20)	1.84 (0.92-3.68)	0.03	130
<i>TNXB</i> rs3130342	1.35 (0.85-2.15)	0.85 (0.44-1.65)	2.22 (1.15-4.29)	0.04	130
<i>SKIV2L</i> rs419788	1.25 (0.80-1.94)	0.82 (0.45-1.50)	2.11 (1.07-4.15)	0.04	130
<i>SLC11A2</i> rs224589	0.89 (0.55-1.43)	1.44 (0.78-2.67)	0.43 (0.19-0.98)	0.02	Unpublished (Dorak et al)
<i>NRAMP2</i> rs422982	0.74 (0.53-1.04)	1.15 (0.73-1.82)	0.44 (0.26-0.74)	0.007	Unpublished (Dorak et al)
<i>HFE</i> rs807212	0.77 (0.35-1.70)	0.28 (0.06-1.21)	1.69 (0.63-4.56)	0.05	128
<i>HLA-DRA</i> rs313588	1.39 (0.95-2.04)	0.95 (0.54-1.66)	2.05 (1.21-3.49)	0.05	130
<i>ARID5B</i> rs10994982	2.29 (1.42-3.69)	3.79 (1.94-7.45)	1.03 (0.45-2.39)	0.01 [†]	139
<i>ARID5B</i> rs10740055	2.76 (1.68-4.53)	4.35 (2.16-8.84)	1.37 (0.58-3.23)	0.03 [†]	139

SNP = single nucleotide polymorphism; OR = odds ratio; CI = confidence interval; P_{int} = P value for interaction

[†]P values denotes the Mantel-Haenszel χ^2 test of homogeneity for risk differences between males and females

Table 7. SNPs associated with childhood acute lymphoblastic leukemia risk in previous genome-wide association studies with gender- and age-specificity

				Gender-specific			Age-specific		
SNP	Gene	OR (95% CI)	P value	Male	Female	P value (interaction)	P value	Ref GWAS	Other Ref**
rs10821936	ARID5B	1.91 (1.60-2.20)	1.4×10^{-15}					51	
		1.86 (1.71-2.03)	5.90×10^{-46}				0.02^{††}	53	
		3.11 (1.90-5.10)	4.8×10^{-6}	3.92 (1.98-7.84)	2.05 (0.85-4.95)	0.21 [†]			139
rs10994982	ARID5B	1.61 (1.30-1.90)	5.70×10^{-9}					51	
		2.29 (1.42-3.69)	6.6×10^{-4}	3.79 (1.94-7.45)	1.03 (0.45-2.39)	0.01[†]			139
rs7073837	ARID5B	1.58 (1.35-1.89)	4.66×10^{-16}					52	
		2.37 (1.45-3.85)	4.8×10^{-4}	3.15 (1.60-6.25)	1.52 (0.65-3.35)	0.15			139
		1.64 (1.40-1.92)	1.0×10^{-9}					49	
rs10740055	ARID5B	1.53 (1.41-1.64)	5.35×10^{-14}					52	
		2.76 (1.68-4.53)	5×10^{-5}	4.35 (2.16-8.84)	1.37 (0.58-3.23)	0.03[†]			139
		1.75 (1.49-2.06)	1.8×10^{-11}					49	
rs7089424	ARID5B	1.65 (1.54-1.76)	6.69×10^{-19}					52	
		1.83 (1.55-2.15)	6.13×10^{-13}					49	
		3.11 (1.89-5.12)	6.11×10^{-6}	4.11 (2.04-8.35)	1.92 (0.81-4.58)	0.15 [†]			139
rs4132601	IKZF1	1.69 (1.58-1.81)	1.20×10^{-19}					52	
		1.59 (1.34-1.89)	1.2×10^{-7}					49	
							0.04^{†††}		140

**Candidate gene studies, Ref = reference; [†]P values denotes the Mantel-Haenszel χ^2 test of homogeneity for risk differences between males and females; ^{††}Comparison between age group before 10 y and older than 10 y ; ^{†††} Recessive model (TT+GT vs GG) yielded significant association (3.83 year vs 5.58 year)

as these controls may have different environmental exposures than childhood ALL cases. Re-analysis of GWAS datasets revealed 12 polymorphisms in: coronary artery diseases (CAD; rs7865618), Crohn disease (CD; rs3792106 and 6431654), rheumatoid arthritis (RA; rs3134926, rs4947244 and rs3132666) and type1 diabetes (T1D; rs2763979, rs4148873, rs3131622, rs480092, rs3134926 and rs12660883) that show gender-specific associations with increased disease risk in only one gender⁶⁸. A study on rs3792106 and CD successfully replicated gender-specific association (OR heterogeneity P value 0.04; OR for females = 1.48, $P = 6.9 \times 10^{-13}$; OR for male = 1.22, $P = 0.01$)¹⁴¹. These examples emphasize the importance of gender-specific analysis.

Gender differences play a critical role in drug efficacy and safety profile, and are well recognized in drug pharmacokinetics and pharmacodynamics¹⁴². Women are at far greater risk than men of developing unfavorable outcome to some drugs^{88, 142-144}. Many drugs for cardiovascular disorders show significant gender differences in their pharmacokinetics profiling¹⁴². For example, *CYP* (cytochrome P450) genes show significant gender-specific activity differences. *CYP1A2*, *CYP2E1* and *CYP2D6* genes, all have higher activity in males, but *CYP3A4* has higher activity in females. These results suggest that gender plays a significant role on *CYP* genes expression levels¹⁴².

Another example of a gender-specific association is glucocorticoid treatment. Expression of specific genes is altered in response to glucocorticoid treatment, but in opposite directions in males and females¹⁴⁵. It has been suggested that anti-inflammatory actions of glucocorticoid are more effective in males. These studies suggest that physiological phenomenon, such as sex hormones and immune system, that differs

between males and females provide the basis for gender-specific genetic associations with disease susceptibility^{86, 88}.

The translation of gender-specific gene expression differences at the protein level is imperative²⁶. Studies that compared the proteome of males and females like transcriptomic studies, also identified prominent gender differences¹¹⁷. Likewise, a study unmasked remarkable gender differences in serum metabolite concentrations. A total of 102 out of 131 metabolites were statistically different between males and females ($P < 3.8 \times 10^{-4}$; Bonferroni correction threshold) and were correlated with genetic variants in metabolism-related genes¹⁴⁶. It suggests sexual dimorphism is also present at the metabolomic and proteomic level. To date, no systematic survey has addressed gender-specific associations in cancer²⁶. Thus, gender-specific analysis may help to identify some of the missing heritability in GWAS^{56, 68}. Sexual dimorphism in gene expression may result in such associations (Figure 5), which has been recognized as a common occurrence^{26, 86, 147, 148}.

It has been suggested that "one potential source of genetic variation that may contribute to missing heritability is the associations which differ in magnitude and/or direction between males and females"⁵⁷.

Figure 5. Genetic variants may be either protective or risk markers for childhood ALL depending on the presence or absence of environmental risk factors

Note: Most genetic associations are mediated by gene expression changes due to genetic variation and their effect may be different in males and females.

Figure 6. Difference in the direction of a gender-specific association for childhood ALL
 Note: Males show a risk association and females show a protective association after stratified analysis by gender. Net effect (odds ratio) is close to one and statistically nonsignificant. OR = odds ratio

Figure 7. Difference in the magnitude of a gender-specific association for childhood ALL
 Note: Males show a risk association and females do not show any association after stratified analysis by gender. Net effect (odds ratio) shows an average of two odds ratio. OR = odds ratio

In gene expression or genetic association studies, two kinds of gender differences are possible²⁶: associations differing in direction (Figure 6) or differing in magnitude (Figure 7). The main interest of the present study was to identify the associations that differ in direction between males and females. This type of association is called “sexually antagonistic interaction”, “cross-over effect” or “qualitative interaction”. The examples stated below may arise from known differences in human physiologic functions and gene expression levels between males and females²⁶.

Several examples of associations differing in direction between males and females in genetic associations have been reported⁸⁶. The most remarkable one differing in direction concerns the genetic regulation of genetic recombination rates in the human genome¹⁴⁹. A GWAS designed to examine the genetic basis of recombination rate differences has shown an association differing in direction between males and females in *RNF212* (ring finger protein 212) SNPs¹⁴⁹. Two *RNF212* SNPs (rs3796619 and rs1670533) are associated with higher recombination rate in males. The same two SNPs were associated with low recombination rate in females. These associations were replicated successfully in an independent sample in the same study¹⁴⁹. It was suggested that if the frequency of the risk markers changes, the average recombination rate will increase for one gender and decrease for the other, but the gender-averaged recombination rate of the population can stay relatively constant. The presence of similar robust and replicated associations in *IFNG* (interferon gamma) polymorphism (rs2069727) in asthma further confirms the existence of associations differing in direction in two genders. The *IFNG* association in asthma is particularly intriguing in that the association is with the heterozygous genotype, but in opposite directions in males and

females, heterozygote advantage in females and heterozygote disadvantage in males ($P_{\text{int}} = 0.008$)⁷⁰. Most importantly, this SNP did not show a significant main effect in overall analysis. The same SNP also yielded gender-specific association in childhood ALL risk¹³⁰.

Since most genetic associations are due to the correlation of associated SNPs with gene expression levels, it is of interest to know whether associations differing in directions may be due to sexually dimorphic gene expression²⁶. A recent comprehensive survey of HapMap population samples for correlation between SNPs and gene expression levels by gender revealed that 12% to 15% of autosomal SNPs function in a gender-biased manner¹¹⁸. It was concluded that such signals are likely to be diluted when both genders are analyzed simultaneously. This study highlighted the importance of considering each gender separately in genomic studies to uncover new disease and trait variants. In another study, the effect of serotonin-related gene polymorphisms on the central nervous serotonergic function has showed associations differing in direction between two genders: 5HTTLPR (rs479554, *SL6A4*; solute carrier family 6) short/short genotype is associated with higher 5-hydroxyindoleacetic acid (5-HIAA) levels in women but with lower levels in men¹⁵⁰. A gender-genotype interaction was found ($P_{\text{interaction}} = 0.04$). However, the sample size was small ($n = 165$). A GWAS meta-analysis identified gender differential in associations with sex hormone-binding globulin levels. The loci 4q13.2-*UGT2B15* (rs293428, $P_{\text{interaction}} = 0.003$), 17p13.1-*SHBG* (rs12150660, $P_{\text{interaction}} = 0.02$) and Xq22.3-*TDGF3* (rs1573036, $P_{\text{interaction}} = 0.02$) were stronger in men whereas 8q21.12-*ZBTB10* (rs440837, $P_{\text{interaction}} = 0.02$) was stronger in women. This study underscored the gender-differentiated effects in complex trait variance¹⁵¹. Thus, in

addition to physiological differences in males and females, there are also differences in the correlations between genetic variants and gene expression levels that suggest feasibility of gender-specific associations we investigated in the present study.

There are also examples of gender-specific associations that are only evident in one gender (male-specific or female-specific). A GWAS on schizophrenia identified a female-specific association with *RELN* (reelin) gene polymorphism (rs7341475; $P_{\text{interaction}} = 1.8 \times 10^{-4}$)⁷². This polymorphism was further analyzed in four additional populations in the same study, and showed a female-specific association (OR = 1.58, $P = 8.8 \times 10^{-7}$) with a significant gender-genotype interaction ($P_{\text{interaction}} = 1.6 \times 10^{-5}$). Similarly, *LYPLAL1* polymorphism (rs2605100) in waist-hip ratio¹⁵² also shows a female-specific association. These examples provide the proof of principle that heterogeneity in genetic associations between two genders exist⁵⁷. Thus, it is evident that gender could be considered as an environmental variable in a gene and environment interaction analysis.

In this study, we addressed the gender differences, by treating gender as an environmental factor, to obtain clues about the etiology of childhood ALL pathogenesis. Although the NIH, the Food and Drug Administration (FDA), and the IOM have highly recommended the use of gender-specific analysis, to date gender-specificity remains underappreciated^{112, 153}. We expected that the proposed study may shed light on the influence of genetic factors in gender related differences in disease pathophysiology. In the absence of known environmental risk factors, genetic markers have the potential to provide etiological clues, and gender-specific analysis is a powerful approach in a disease which shows gender effect⁶⁸.

2.5. Age-specific associations

Like gender, age also plays a significant role in childhood cancer risk²².

Epidemiological data consistently show a unique age distribution for childhood ALL.

Childhood ALL incidence shows highest peak between 1 and 5 years of age, with 72

cases per 1,000,000 per year in the U.S. In contrast, overall incidence rate of childhood

ALL is around 23 cases per 1,000,000 per year under age 14, excluding the age group of

1 to 5 years. Overall incidence rate of childhood ALL risk in different age groups are

shown in Table 8. Tumors of the nervous system also show a higher incidence rate in

children 0 to 4 years⁵.

Table 8. Descriptive epidemiology of childhood acute lymphoblastic leukemia by age-at-diagnosis

Age at diagnosis (y)	Incidence rate*	Number of cases (n)	% of cases
<1	20.0	119	2.87
1-5	72.2	2091	50.41
6-10	30.6	868	20.93
11-14	21.3	514	12.39
15-19	17.8	556	13.40

*Rate per 1,000,000 per year.

Source: National Cancer Institute, Surveillance, Epidemiology, and End Results⁵

There is significant heterogeneity in the age-of-disease-onset of childhood ALL

(Table 8). Around 50% of childhood ALL occurs between 1 and 5 years. This

heterogeneity in age groups suggests that certain factors (genetics or environmental) may

influence the severity and early-onset of ALL risk¹⁵⁴. To understand the relationship

between age and childhood ALL risk, direct assessment of the age variation at the

population level is important¹⁵⁵. Just like gender-specific associations may be missed in

the overall analysis, age-specific ones should also be unmasked by stratification. An

association with a small effect size in the overall analysis may become stronger in a certain age group. Statistical interaction analysis is one way to identify age-specific associations or effect modification by age.

2.6. Genetic basis of age-specific associations

Cancer in genetically predisposed people occurs at an early age^{36, 156}. Rare hereditary cancer syndromes, such as Li-Fraumeni syndrome, accelerate the development of several adult cancers^{134, 157}. Just like the effect of the *TP53* (tumor protein 53) mutation in Li-Fraumeni syndrome on age-of-onset, genetic polymorphisms may also accelerate or delay the development of childhood ALL. Any age-specific association, which we aim to find would have been missed in previous studies and would contribute to disease biology in childhood ALL risk. One of the main purposes of GWAS is to find genetic variants that may provide some clues about disease biology related to disease phenotype⁶⁸. Thus, a variant showing a larger effect size for one age group may explain a greater proportion of the population attributable risk estimates, which could improve early detection, treatment and prevention^{158, 159}.

Several studies have provided empirical evidence for early- or late- onset of diseases, along with severity and their associations with genetic markers. One of the classic examples is late-onset Alzheimer disease (AD) and its association with apolipoprotein E (*APOE*) allele^{75, 76}. With increasing number of *APOE* type 4 alleles, mean age-at-onset decreases from 84 to 68 years⁷⁵. *APOE* codes for the major carrier protein in the brain¹⁶⁰, and is an important regulator of lipids¹⁶¹. It is hypothesized that the presence of *APOE* type 4 alleles leads to excess amyloid formation in brain¹⁶². A few

studies in multiple sclerosis also yielded an association with *APOE* type 4 alleles and disease severity^{160, 163, 164}. A study on African American females has yielded an earlier age-of-onset of multiple sclerosis (MS) in people with the *APOE* risk genotype¹⁶⁴. However, a few of these studies suffer from low statistical power, as the sample size was low^{163, 165}.

The SNP309 (rs2279744) variant allele, present in the *MDM2* (mouse double minute 2) oncogene (cancer causing), is more common in early-onset (AA = 85.2 months vs AB + BB = 70.5 months) childhood ALL in a multiethnic sample ($P = 0.04$)¹⁵⁴. Likewise, the same association with age-at-onset ($P = 0.002$) is successfully replicated in another childhood ALL samples with gender-specificity in a non-Hispanic white population¹²⁶. Results showed a trend toward an earlier age at diagnosis in females (AA = 59 months vs AB = 44 months vs BB = 32 months) (133). Studies found that *MDM2* expression level is regulated by estrogen signaling in the presence of rs2279744 variant allele^{134, 166, 167}. It has been suggested that rs2279744 variant allele may play a significant role through negatively regulating *TP53*. *TP53* encoded molecules play an important role in genome surveillance (133). *MDM2* is a known key negative regulator of *TP53* protein, and dysregulation of *MDM2* may significantly impact the *TP53* functions, and increase tumorigenesis, including leukemia, via apoptotic pathway. Likewise, recent studies have revealed that variant allele of *MDM2* rs2279744 can also accelerate tumorigenesis and increase the risk of several cancers, through estrogen-signaling pathway, exclusively in females¹⁶⁷. Estrogen levels in children are negligible, which suggests *in utero* exposure of estrogen in childhood ALL risk (133).

A study on colorectal cancer, in two independent groups, showed that women who carry the variant allele of rs2279744 have a nine year earlier (at 61 years vs 70 years) onset than women who carried the wild-type genotype ($P = 0.001$)¹⁶⁸. Results were not statistically significant for men. The authors suggest that estrogen influences variant allele to accelerate colorectal tumor formation in women at a younger age. Likewise, *MDM4* polymorphism (rs1563828) had shown an association with an early age-of-onset of estrogen-receptor negative breast cancer in two independent cohorts¹⁶⁹. Women who possess homozygous variant (TT) develop estrogen-receptor negative breast cancer at an earlier age than homozygous wild-type (CC) and heterozygote (CT) (first cohort: $P = 0.018$ & second cohort: $P = 0.006$). In both cohorts, age-at-diagnosis is accelerated by 5 years (43.8 years vs 48.8 years) and 3.8 years (37.2 years vs 41.0 years), respectively.

An human leukocyte antigen (HLA) study on chronic myeloid leukemia (CML) found the age-related effects of HLA-DRB3 and HLA-DRB4 homozygosity¹⁷⁰. The presence of DRB4 homozygous genotype was associated with risk ($OR = 3.36$; $P = 0.01$) and homozygosity for DRB3 was protective ($OR = 0.51$; $P = 0.007$). DRB4 homozygosity rate was high and DRB3 homozygosity rate was low in patients with early-onset CML. The age-related changes in their frequencies shown a significant separation ($P = 0.02$) in three age groups (18-32 years, 33-42 years and 43-60 years). The presence of similar associations of *PTPN2* (protein tyrosine phosphatase, non-receptor 2) polymorphisms (rs2542151) in T1D⁷⁸ and hemochromatosis *HFE* (hemochromatosis) gene variants in colorectal carcinoma¹⁷¹ further confirms the genetic effect on age-at-onset of cancers. It is only natural that future association studies should pay attention to these clues.

A recent study on *IKZF1* (IKORAS family zinc finger one) polymorphisms, previously identified as risk markers in childhood ALL⁵², yielded a significant association between rs4132601 with age at diagnosis ($P = 0.04$)¹⁴⁰. The mean age-at-onset decreases from 5.58 to 3.83 years (TT + TG = 5.58 vs GG = 3.83) with the possession of two G alleles. The most recent childhood ALL GWAS⁵³ compared the variant allele frequency of rs10821936 between cases that diagnosed ALL before 10 years of age to those that diagnosed at an older age (> 10 y). Results showed an association with non-Hispanic whites ($P = 0.02$) and Hispanics ($P = 0.007$). This study also yielded a trend for decreasing ORs with increasing age (less than 5 y, 5 to 10 y and more than 10 y) for the same polymorphism: 2.0 (1.9-2.2), 1.8 (1.6-2.02) and 1.5 (1.3-1.7), respectively. Therefore, there are also examples of what we aim to show, namely, age-specific genetic associations in childhood ALL.

Although there are many reports of association with gender and age in cancer susceptibility, they are no more than statistical correlations with yet unknown biological significance and most have not been replicated. These studies need to be confirmed in a much larger population to rule out chance findings. A few of these studies also suffer from multiple comparisons. Most of these associations are identified in a case-control study design, specifically gender-specific associations. A few studies have used convenient samples as a control group, which suggest selection bias. Thus, it is important that controls should be representative of the general population. Future studies should consider the case-only design to avoid problems related to selection bias and insufficient statistical power⁶⁰. Strong effects play an important role in public health interventions or risk profiling^{158, 159}. We proposed to identify the strongest associations that interact with

gender and/or age which would have yielded no main effects in the overall analysis in a case-control study. In the present study, we used gender and age as effect modifiers.

Although multiple GWAS have been published in childhood ALL⁴⁹⁻⁵⁴, results are consistent but the magnitude of effect is small as in most GWAS. These studies only used an overall analysis approach. Prior to the present study, no GWAS in childhood ALL has used gender- or age-specific analysis. The presence of gender- and age-specific associations underlines the need to conduct a dedicated study on gender- and age-specific analysis to identify the previously missed associations in GWAS and candidate gene studies. The aim of this study was to fill these gaps in knowledge by performing a comprehensive GWAS of genetic susceptibility in childhood ALL to uncover otherwise masked gender- and age-specific associations.

3. PROJECT AIMS AND HYPOTHESIS

Despite multiple published GWAS in childhood ALL, identified genetic susceptibility represents a small fraction, and leaves a large proportion to be defined. We exploited an underutilized design to unravel strong genetic risk markers.

We hypothesized that age and gender differences in childhood ALL risk have a genetic basis, and the effect modification by gender and age can be exploited to unmask yet unknown genetic risk markers.

To assess the validity of this hypothesis, the proposed study had two specific aims:

Specific Aim 1: To examine gender-specific associations that differs in their directions in males and females to gain insight into the pathophysiology of gender differences and childhood ALL pathogenesis.

Specific Aim 2: To examine the relationships of genetic risk markers with age-of-onset of ALL to gain insight into the pathophysiology of age peak in childhood ALL.

The main purpose of this dissertation was to identify gender- and age-specific associations. In case of gender-specific associations we are more interested in the associations which differ in direction (explained in Chapter 2). No study has explored gender-specific associations in childhood ALL GWASs, but all of them only considered the overall group. Likewise, age-specific associations may have been missed in the analyses of the overall sample. For age-specific associations, the peak age (1-5 years) group was compared with the rest of the cases (6-10 years). A time-to-event analysis was also performed for the whole case group. These differences in childhood ALL should be able to provide some clues on disease pathogenesis. The amalgamation of gender- and

age-specific genome-based knowledge related to disease susceptibility into public health may contribute to disease prevention, health promotion and risk reduction¹⁷².

Bioinformatic analyses were also performed to examine the functionality of the markers that have shown associations. Likewise, empirical data screening was performed to check whether these markers regulate expression of any genes or interfere with the genome biology in any way. The aim of this effort was to identify causal risk factors and gain insight into mechanism of their associations with age-at-onset or gender differential of childhood ALL.

4. MATERIALS AND METHODS

This study was based on two specific aims to identify gender- and age-specific associations with childhood ALL risk. Genome-wide microarray chips were used for all genotyping. Logistic regression, using Plink software, was used to identify gender- and age-specific associations. A time-to-event analysis was performed for the whole group to explore association with age-at-onset.

4.1. Ethics statement

Institutional review board (IRB) approval was granted by Florida International University, Office of Research Integrity (**IRB-13-0546**). A copy of IRB from Baylor College of Medicine (BCM) was also submitted to Office of Research Integrity, Florida International University. All samples received from the primary study site were de-identified, and no one at the FIU site could identify any subject.

4.2. Research design

The traditional case-control approach is commonly used in genetic association studies for rare diseases such as childhood ALL. In spite of numerous advantages over other classical epidemiological study designs, case-control study design has several limitations, particularly recruitment of an appropriate control group. The case-only design (explained in Chapter 1) is more efficient than other traditional epidemiological studies at detecting statistical interactions, which was the main focus of this project⁵⁸. Recruitment of cases in a rare disease like childhood ALL is a challenge⁵⁹ and hence, preferring a statistically powerful research design was more practical and is used in the present study. A flow chart explaining whole method section is delineated in Figure 8.

Figure 8. A flowchart explaining method section

4.3. Recruitment of study subjects

A case-control study design was used to recruit the childhood ALL samples in the parent study¹³¹. In the present study, only cases were used for GWAS to assess the gender- and age-specific analysis. The cases were incident cases of childhood ALL consecutively recruited in Texas Children's Cancer Center (TXCCC), BCM, Pediatric Hematology/Oncology Clinic, Houston, Texas from 2007 to 2012. All newly diagnosed childhood (age 1-18 years) ALL cases and their parents were approached for informed consent and the participation rate was 95%. At the time of enrollment, no case had any other disease. The proposed study used 240 cases for case-only analysis. All of these cases were non-Hispanic whites aged 1 to 10 years. Demographic characteristics of childhood ALL cases collected through questionnaires and are explained in result section (Chapter 5).

4.3.1. Inclusion criteria

- 1- All incident cases diagnosed with acute lymphoblastic leukemia confirmed by immunophenotyping
- 2- Age 1-18 y in the parent study, but only subjects age 1 to 10 years of age were included in this study nested within the parent study
- 3- All samples were recruited from TXCCC, BCM, Pediatric Hematology/Oncology Clinic, Houston, Texas

4.3.2. Exclusion criteria

- 1- The exclusion criteria was refusal to participate or diagnosed with any other disease

4.4. Statistical power calculation for statistical interaction when gender-specific associations differ in direction (qualitative interaction)

Figure 9. Statistical power calculation for the detection of interactions using the case-only design
X-axis is odds ratio, Y-axis is statistical power. Each curve is for a different risk genotype frequency (in the dominant model, the risk genotypes are AB + BB where A is the common and B is the variant allele). N= 240

We performed statistical power calculation using power analysis and sample size (PASS) software for the case-only design for various risk genotype frequencies and ORs (Figure 9 & Table 9). For 240 cases, assuming equal number of males and females, to achieve 80% statistical power for risk genotype frequency of 30%, minimum OR should be 2.2; and for risk genotype frequency of 10% , OR should be at least 2.8 for the association to reach statistical significance. Risk genotype frequency 0.10 corresponds to 0.05 variant allele frequency in the dominant risk model (AA vs AB + BB).

Table 9. Statistical power calculations for the detection of interactions when associations differ in direction

Power	Sample size N1 males	Sample size N2 females	Genotype frequency in male cases	Genotype frequency in female cases	OR for interaction	Alpha (α)
0.8147	120	120	0.24	0.10	2.8	0.05
0.8686	120	120	0.25	0.10	3.0	0.05
0.7865	120	120	0.30	0.15	2.4	0.05
0.8596	120	120	0.31	0.15	2.6	0.05
0.7673	120	120	0.35	0.20	2.2	0.05
0.8543	120	120	0.38	0.20	2.4	0.05
0.8139	120	120	0.42	0.25	2.2	0.05
0.8407	120	120	0.49	0.30	2.2	0.05

OR = odds ratio

4.5. Statistical power calculation for statistical interaction when gender-specific associations differ in magnitude (quantitative interaction)

We also performed a statistical power calculation for various genotype risk frequencies and effect size for 240 samples (Table 10). However, to achieve 80% statistical power for risk genotype frequency of 10% and minimum OR should be 1.59, and sample size should be 686 in each arm; and for risk genotype frequency 30% and OR 1.55, sample size should be 356 in each arm. Thus, with a sample size of a total of 240 subjects, we did not have sufficient statistical power to detect quantitative interactions, which we did not aim to detect.

Table 10. Statistical power calculations for association differing in magnitude

Power	Sample size N1 male	Sample size N2 female	Genotype frequency in male cases	Genotype frequency in female cases	OR for interaction	Alpha (α)
0.22	120	120	0.15	0.10	1.59	0.05
0.58	120	120	0.20	0.10	2.25	0.05
0.29	120	120	0.22	0.15	1.60	0.05
0.49	120	120	0.25	0.15	1.89	0.05
0.43	120	120	0.30	0.20	1.71	0.05
0.35	120	120	0.35	0.20	2.15	0.05
0.39	120	120	0.35	0.25	1.62	0.05
0.37	120	120	0.40	0.30	1.55	0.05

OR = odds ratio

4.6. Statistical power calculation for time-to-event analysis

We used STATA v13 for statistical power analysis to compare two survival rates (wild-type vs allele positivity). Here we used the dominant genetic risk model (AA as referent vs AB + BB as risk genotypes) for statistical power calculation. We calculated statistical power for a range of genotype frequencies. Table 11 represents statistical power for time-to-event analysis for a sample size of 240 based on a range of risk genotype frequencies. The study had 80% statistical power for the statistical significance threshold of 0.05, for hazard ratios (HR) ranging between 1.43 and 1.90 for a range of risk genotype frequencies.

Table 11. Statistical power calculation for time-to-event analysis

Power	Alpha (α)	Risk genotype frequency	Hazard Ratio
0.80	0.05	0.05	1.90
0.80	0.05	0.10	1.65
0.80	0.05	0.15	1.55
0.80	0.05	0.20	1.50
0.80	0.05	0.25	1.47
0.80	0.05	0.30	1.45
0.80	0.05	0.35	1.44
0.80	0.05	0.40	1.43

4.7. DNA extraction

Genomic DNA was extracted from blood samples using the Qiagen Blood Mini Kit (Qiagen, Valencia, California) according to manufacturer's protocol at TXCCC, BCM. Only DNA samples with study IDs without any personal identifiers were received from TXCCC, BCM, Pediatric Hematology/Oncology Clinic, Houston, Texas. Established childhood ALL risk associations identified in GWAS^{51, 52} have been replicated to validate the parent case-control study sample using TaqMan allelic discrimination assays at FIU¹³¹.

4.8. DNA quantification

DNA samples were quantified via the ND-8000 spectrophotometer and DNA quality was evaluated via gel electrophoresis on a 0.8% agarose gel at the Hussman Institute for Human Genomics (HIHG), University of Miami. The concentration for all qualified samples was normalized to 50ng/ul and samples were arrayed in Matrix 0.5ml 2D barcoded tubes in racks of 96.

4.9. Genotyping methods

Genotypings for 240 childhood ALL cases were achieved by Illumina Infinium HumanCoreExome Chip (Illumina, San Diego, CA, USA). Genotyping was performed at the HHG, University of Miami on the Illumina iScan array scanner system.

Samples that passed the above exclusion criteria (DNA quantification) were genotyped using Illumina Infinium HumanCoreExome Chip, that interrogates approximately 500,000 markers. The samples were processed according to Illumina Procedures for processing of the Infinium HD assay. In brief, on day one of the procedure 200ng of DNA were denatured and neutralized in preparation for isothermal amplification in an overnight step. On day two, the amplified products were fragmented, precipitated and re-suspended in hybridization buffer. It was then applied to the Infinium HumanCoreExome Chip and the chips were incubated overnight in the Illumina hybridization oven. During this incubation the DNA sample was allowed to anneal to locus-specific 50mers which were covalently attached to beads assembled into micro-wells on the ExomeChips substrate. On day 3, unhybridized DNA was washed away. Then during a single-base extension of the oligos on the ExomeChips, using the captured DNA as a template, fluorescent labels were incorporated on the ExomeChips and the genotypes were determined. The ExomeChips were then scanned on the Illumina iScan.

The above protocol was automated using the Tecan EVO-1 to further enhance the efficiency and consistency of the assay. Samples were processed in batches of 96. In order to ensure reproducibility of results one quality control DNA sample (CEPH DNA) was repeated in each 96 well plate. Genotype concordance was checked for replicate samples following each genotyping run. Data were extracted by the Illumina ® Genome

Studio software from data files created by the Illumina iscan. No additional pre-Plink QC steps was performed on either the SNPs or the samples.

All post Plink QC steps and association analysis of the genotype data were conducted with the dedicated GWAS analysis software Plink¹⁷³. Plink (<http://pngu.mgh.harvard.edu/~purcell/plink>) is a free toolset for whole genome association analysis. Most analyses were performed on a Linux-based computer.

4.10. Quality control

Genotyping errors have the potential to introduce bias in a genetic association study. QCs are required to remove subjects and genetic markers that do not yield satisfactory results as they may generate false-positive results. 240 samples were genotyped at the UM. All standard GWAS QC steps^{82, 173-177} were applied before the analysis. A flowchart of all performed QC steps is given in Figure 10. Results of all QC steps are provided in Chapter 5.

4.10.1. Per-individual quality control

Per-individual QC step screens genotypes to identify subjects that may introduce bias if not removed. Poorly genotyped (low call rate) individuals will increase error in the study and may significantly affect the results. All steps performed in this study are explained below.

Figure 10. A flow chart of quality control steps used before the gender- and age-specific analysis

4.10.1.1. Identification of individuals with discordant gender information

This was the first step of QC, performed to identify subjects that have inconclusive/contradictory gender information^{82, 173}, as it can lead to spurious associations. In a case-control study, samples that show the wrong gender information are suggested to be excluded from further QC and statistical analysis. Subjects were appropriately recoded or removed, if information was inconclusive, for further analyses.

4.10.1.2. Identification of individuals with excessive missing rate or outlying heterozygosity rates

This QC step was used to identify and exclude individuals with too much missing genotype data and outlying heterozygosity rate. Genotype accuracy and genotype call rate can be significantly affected by variations in DNA quality⁸². A high genotype failure rate and heterozygosity rate suggest poor DNA sample quality. A high heterozygosity rate also suggests DNA contamination. We examined the distribution of missing genotypes in entire data set, and set a threshold of 1%. It means that individuals with more than 1% missing genotypes would be removed from further QC steps.

4.10.1.3. Identification of duplicated or related individuals

In a population based study, it is important that all samples should be unrelated. Presence of duplicate, first- or second-degree relatives will introduce bias in the study as their genotypes will be overrepresented. This step was used to identify all related and duplicate individuals for removal. A metric (identity by state, IBS) for each pair of individuals was calculated to identify duplicate samples. IBS is defined as, at a locus, two

individuals who have an identical nucleotide sequence or the same allele. An IBS score 1 suggests relatedness between two samples.

4.10.2. Per-marker quality control

Like low quality individual samples, low quality markers can also threaten internal validity of the results. Exclusion of these markers is necessary to avoid spurious associations. The QCs used for marker exclusions are explained below.

4.10.2.1. Identification of SNPs with an excessive missing genotyping rate

Like individuals with a high rate of poor genotypes, we also removed the markers that had high genotyping failure rate. It is important to remove only poorly characterized markers because every removed marker is a potentially missed disease variant⁸². We used a 99% threshold to remove markers after carefully scrutinizing the data set. It means to include only those SNPs for further analysis which have at least 99% genotyping call rate. Acceptable genotyping call rates in GWAS are 1 to 5%.

4.10.2.2. Removal of markers with a very low minor allele frequency

In this step of QC, we excluded polymorphisms that had a low minor allele frequency (MAF). These SNPs are mostly non-informative as they show little variation in the sample set being analyzed. Even power to detect an association will also be low. We used a stringent threshold for MAF. SNPs with $MAF \leq 0.03$ in the data set were removed.

4.10.2.3. Identification of SNPs with significantly different missing genotype rates between comparison groups

Substantial differences in genotyping rates between males and females may confound the result if the difference is caused by DNA sample quality. To reduce confounding, the exclusion of markers with substantially different genotyping rates between these groups is crucial. Likewise, for age-specific association, we also checked differential missing rates between two age groups (1-5 years and 6-10 years). All markers that showed significant difference between two groups were removed from further QC, and gender-and age-specific analyses. We used a threshold of < 0.05 after scrutinizing the data set.

4.10.2.4. Identification of SNPs showing a significant deviation from Hardy-Weinberg equilibrium

Hardy-Weinberg equilibrium (HWE) refers to genotype frequencies being close to their expected frequencies estimated from allele frequencies. Goodness-of-fit test is used to test the agreement between observed and expected frequencies. In a case-control study, markers which significantly deviate from HWE in controls are usually excluded from analysis since this finding is an indication of genotyping error. Since this is a case-only study, HWE test has not been used as a QC step to detect genotyping error before the analysis, but markers that have shown associations, were retrospectively assessed for their conformity to HWE in the whole group of subjects and in males and females, or in age groups separately for gross violations that would indicate genotyping errors rather than valid associations.

4.11. Genomic control

The genomic control (GC) is a method to control for population stratification in a genetic association study to reduce type I error^{176, 178, 179}. Population stratification may confound results, if not adjusted. A population in a genetic association study may arise from two distinct sub-populations which may differ in their genetic ancestry. The presence of systematic differences in allele frequencies between these two sub-populations may confound the result. There are thousands of neutral loci, known as genomic controls used to correct for population stratification in GWASs. The GC first estimates an inflation factor (λ), then adjust all of the test statistics downward by λ . Inflation factor $\lambda > 1$ indicates population substructure and/or genotyping error. Plink was used to adjust results for genomic control. In this study, only non-Hispanic whites were used for gender- and age-specific associations. We still adjusted results for GC to avoid any confounding by population stratification.

4.12. Permutation test

Permutation testing, also known as randomization testing, is a type of statistical significance test that is not influenced by multiple comparisons¹⁸⁰. Rearrangement of the phenotype status, such as case-control status, of each sample is the first step of this test. The second step is to compute association analysis after each rearrangement of the case-control status. This whole procedure is performed by predefined number of times, 10,000 times in the present study. Test statistics is calculated for actual data set, and each permuted data set for predefined number of times. The procedure keeps the P value after each permutation. At the end, it compares the distribution of permuted P values with the

P value yielded by the original data set. This comparison estimates the proportion of chance findings if the study was repeated predefined number of times under the null hypothesis. These results are free from multiple comparison issues, as each permutation on each SNP assesses the role of chance, and can be performed on thousand of SNPs independently. In this study, for gender-specific association analysis, the rearrangement of phenotype status involved males and females. Likewise, for age-specific analysis, the shuffle was performed between age group 1-5 years (coded as one) and 6-10 years (coded as two).

4.13. Data analysis

All data analyses were performed using Plink and Stata v13 (StataCorp, College Station, TX). For the comparison of continuous variables, results were expressed as means and standard deviations (SD) and student t-test (for means) was performed. Dichotomous or categorical variables were summarized as a table with counts and percentages for comparison, and Pearson's chi-squared and fisher exact test were performed.

Unconditional logistic regression was used to calculate OR and 95% CI for gender- and age-specific analyses. The main interest was detecting the genotype frequency differences between males and females cases. We used logistic regression after coding males and females as "2" and "1" as if they were cases and controls, respectively. Similarly, in age-specific analysis, we compared different genotype frequencies between two age groups (1-5 years vs 6-10 years). Logistic regression was also used for age-specific analysis after coding age group 1-5 years as "2" and 6-10 years as "1".

Definition of variables for gender-specific and age-specific are summarized in respective tables (Tables 12 and 13). We used GC to adjust for population heterogeneity^{178, 179}, however, all of these samples were non-Hispanic whites.

Table 12. Summary of variables for gender-specific association

Variables	Classification	Measurement
Outcome variable		
Gender	Dichotomous	2 (male) or 1 (Female)
Explanatory variable		
Genotype	Categorical	AA, AB, BB
Confounding variable		
Age	Continuous	years

Table 13. Summary of variables for age-specific association

Variables	Classification	Measurement
Outcome variable		
Age	Dichotomous	2 (1 to 5 y) or 1 (6 to 10 y)
Explanatory variable		
Genotype	Categorical	AA, AB, BB
Confounding variable		
Gender	Categorical	1 (Females) or 2 (Male)

4.14. Genetic models for different association tests

There are several genetic models (Figure 11) used in the analysis of a genetic association study¹⁸¹. These genetic models have similarities to the models used in

Figure 11. Common genetic risk models use in a genetic association study

Here, A and B are two alleles of a SNP. AA is a wild-type, AB is a heterozygote and BB is a variant genotype.

Adapted from: Lewis CM, Knight J. Introduction to genetic association studies. *Cold Spring Harb Protoc* 2012; **2012**(3): 297-306

environmental epidemiological studies. An additive genetic model was used gender- and age-specific association analyses. X-chromosome analysis was based on multiplicative genetic model. Time-to-event analysis genetic models were based on Kaplan-Meier plot. The counts for three genotypes of a SNP can be analyzed by a 2 x 3 contingency table. For a SNP with allele A and B, genotypes will be AA (wild-type), AB (heterozygote) and BB (variant).

4.14.1. Additive model

The most common genetic model used in the analysis of an association study is known as an additive model (Figure 11). This model is tested by Cochran-Armitage trend test which assesses gene-dosage effect. This model assumes that having two copies of minor allele (BB) will have double the effect of having a single copy of minor allele (AB). This genetic model is very similar to a basic epidemiological model (no smoking vs 5 cigarettes/day vs 10 cigarettes/day). This test has one degree of freedom. These data can be analyzed by logistic regression in which the genotypes are represented as 0 (AA), 1 (AB) and 2 (BB).

4.14.2. Dominant model

This model (Figure 11) suggests that even a single copy of the variant allele has an effect on phenotype. We categorized individuals into two groups (AA vs AB + BB) based on whether they have at least one minor allele B (either AB or BB) or no copies of minor allele (AA). It is a 2x2 table test with one degree of freedom. This model is also very similar to basic epidemiological model, for example presence or absence of exposure.

4.14.3. Recessive model

In the recessive genetic risk model, two copies of variant allele (BB) is associated with risk (Figure 11). In other words, heterozygosity (AB) is not associated with risk. Here, we categorized individuals in two groups (AA + AB vs BB). It is tested in a 2x2 table test with 1 degree of freedom.

4.14.4. Multiplicative model

In case of X-chromosome analysis, genotype-based models are not practical for statistical analysis. Females have two copies of X chromosomes and males have one copy of X chromosome. The most appropriate test is allelic association test. In allelic association test (Figure 11) the unit of test is the allele (A and B) rather than individual, as each individual contributes two alleles for autosomal chromosomes. Allele counts for X-chromosome are obtained in a different way for X chromosome polymorphisms, and are given below.

In case of X chromosome analysis

Females have a pair of X chromosome means two copies of alleles (AA or AB or BB).

AA = two A alleles

AB = one A and one B allele

BB = two B alleles

Males have one X chromosome, means one copy of allele (A or B).

A = 1 allele

B = 1 allele

4.15. Time-to-event analysis

Time-to-event analysis (survival analysis) was performed on each SNP that has shown an association in gender- and age-specific analysis. The top 100 results based on the P value and the effect size were used for time-to-event analysis. Kaplan-Meier plots were used to generate the survival curves between two or three groups, cases possessing different genotypes (wild-type vs heterozygote vs homozygous variant). It also provided clues for appropriate genetic model (additive, dominant or recessive) to test the statistical significance between three or two curves (depending on the genetic risk model).

Log-rank test was used to test the statistical difference between survival times (time to having leukemia) between two (dominant or recessive model) or three (additive model) groups. Cox-proportion hazard model were used to calculate the HR^{182, 183}.

Definition of variables for survival analysis is summarized in Table 14.

Table 14. Summary of variables for survival analysis

Variables	Classification	Measurement
Outcome variable		
Time-to-event	Continuous	years
Explanatory variable		
Genotype	Categorical	AA, AB, BB
Confounding variable		
Gender	Categorical	1 (Female) or 2 (Male)

All statistical tests were two-tailed and threshold for statistical significance was 0.05. We performed a permutation test for gender- and age-specific associations which is not influenced by multiple comparisons.

4.16. Bioinformatic and empirical screening of data for functional annotation of associated markers

To assess the functionality of identified gender- and age-specific associated SNPs, several bioinformatic tools were used. The main purpose was to examine whether identified variants are causative or proxy markers. RegulomeDB¹⁸⁴ (<http://regulomedb.org/>) and Functional Single Nucleotide Polymorphism (F-SNP)¹⁸⁵ (<http://compbio.cs.queensu.ca/F-SNP/>) were the two main databases used for this purpose. RegulomeDB predicts a score for a variant from 1 to 7. A score of 1 signifies the highest functionality of the variant, and 7 the least functional variant. To assess functionality, RegulomeDB uses high throughput, computational predictions and other sources such as experimental results. F-SNP database generates a score between 0 and 1. A score of 1 suggests a high functional score and 0 suggests least functional score. This database incorporates information obtained from 16 other bioinformatic tools and the functional effects of SNPs. These databases identify and focus on SNPs with potential harmful effect on human health.

Two SNPs, close to each other, on the same chromosome may be statistically correlated. These highly correlated SNPs will not provide any additional information for statistical analysis. It means that SNP1 and SNP2 will give the same information, such as effect size (OR) and P value. These highly correlated SNPs, included in the GWAS chip,

were identified through Plink analysis, to avoid redundancy. All top SNPs that show correlations are reported in the appendix.

Most of the time, genetic association studies yield associations with nearby correlated SNPs, known as indirect associations. The second step of correlation analysis was to identify primary causal SNP, which was not included in the GWAS chip. We generated a list of SNPs, using HaploReg (<http://www.broadinstitute.org/mammals/haploreg/haploreg.php>), for all gender- and age-specific risk variants, which were correlated. Bioinformatic and empirical analyses were performed to identify potentially causal SNPs.

We also used empirical analysis using SNP and Copy Number Annotation (SCAN) database¹⁸⁶ (<http://www.scandb.org/newinterface/index.html>). For each SNP, SCAN database provides information from experimental data on gene expression regulation. Gene expression is a quantitative trait and an important intermediate phenotype that link the genetic polymorphisms and phenotype (here, ALL). Any genetic variant that regulates gene expression levels of mRNA and protein is known as an expression quantitative trait locus (eQTL). The correlations between SNPs and gene expressions ultimately modify disease susceptibility. Thus, eQTL analysis was used to evaluate whether the identified gender- and age-specific variants influence expression levels of genes. We searched SCAN database and only explored the eQTL effects of identified variants in lymphoblastoid cell lines (LCLs) in the Caucasian population. The P value was $\leq 1 \times 10^{-5}$.

Phenotype-Genotype Integrator (PheGenI) database (<http://www.ncbi.nlm.nih.gov/gap/phegeni>) was used to increase chances of findings of

susceptible candidate genes¹⁸⁷. The PheGenI, merges National Human Genome Research Institute (NHGRI) GWAS catalog data with several other databases housed at the National Center for Biotechnology Information. SNPnexus database (<http://www.snp-nexus.org/>) was used to retrieve additional information, such as genomic mapping (using dbSNP), gene/protein consequences, effect on protein function, regulatory elements, and phenotype and disease association¹⁸⁸.

Gene enrichment analysis, also known as pathway-based analysis, is a powerful approach to identify disease causal genes from genomic, proteomic and bioinformatics dataset. It looks an identified gene list, here gender- and age-specific genes, and finds out whether any group of genes belonging to the same pathway are overrepresented in the list. We used the Gene Ontology Consortium (<http://geneontology.org/>) for gene enrichment analysis¹⁸⁹. Bonferroni correction was used for multiple comparisons. The Comparative Toxicogenomics Database (CTD) was used to identify chemical-gene-disease relationships¹⁹⁰. The CTD also provides insight into chemical-gene, gene-disease and chemical-disease interactions. It nearly contains 15 million toxicogenomic relationships.

5. RESULTS

The project, which investigated gender- and age-specific genetic associations with childhood ALL risk using a GWAS design has yielded positive results as presented in this chapter.

5.1. Quality control results

The main aim of QC was to minimize potential bias and error by excluding samples and markers, which failed at QC steps. These excluded samples were also compared with samples analyzed in this study to check whether their exclusion introduced any bias. All steps of QC, explained in Chapter 4, and their results, are explained below. Four samples were excluded after agarose gel DNA quantification based on lower DNA concentration.

5.1.1. Results from discordant gender information

The first step of QC was used to check the self-reported gender information of each individual using genetic data. Plink uses X chromosome data to determine gender empirically. This calculation is based on the difference between X chromosome numbers in males (one X chromosome) and females (a pair of X chromosomes)⁸². Males cannot be heterozygous (AB) for any marker. Genotype-calling algorithm for this QC step counts heterozygote as a missing genotype. A female marked as a male in the data set will show a large amount of missing data. This step of QC gives a score between 0 and 1. In an ideal situation, we expect homozygosity rate one for males and < 0.2 for a female subject. However, a score of ≤ 0.2 suggests a female, and a score of ≥ 0.8 suggests a male. Scores

between 0.2 and 0.8 suggest ambiguity in gender information. In the case of discrepancy between self-reported sex and genetically determined sex, the genetically determined sex was used in the analysis. Seven males (≥ 0.8) and six females (≤ 0.2) were re-coded on re-examination of their gender in the original dataset. Four samples scored between 0.2 and 0.8, and were removed from further QC steps due to ambiguous gender information which could not be verified. However, most of these gender discordant samples also failed further QC steps suggesting that the ambiguity was due to poor DNA sample quality. Inclusion of individuals, with discordant gender information, could have yielded spurious associations, and could have hampered the first aim of the study. The idea with gender QC is not just to get the genders right, but also to rule out any sample handling/labeling problems.

5.1.2. Results from individuals genotype and heterozygosity rates

The aim of this QC step was to identify individuals who had low genotype call (genotyping) rates and higher heterozygosity rates. Low genotype call rates and higher heterozygosity rates are indicative of poor DNA quality. Aberrant genotype calling would increase errors in the study, and those samples should be excluded. We excluded twenty samples that had the genotype failure rate $\geq 1\%$ and /or the heterozygosity rate outside of ± 3 standard deviations from the mean. A graph showing how the heterozygosity rate and genotype call rate correlate is presented in the appendix (Figure 1). These excluded samples were further analyzed to check if there is any substantial difference between them and the rest of the samples (explained in 5.2).

5.1.3. Results from duplicates and related samples

This step of QC was used to identify duplicates and samples from closely related individuals to avoid overrepresentation of their genotypes which would introduce bias in the study. Plink calculates a metric for each pair of individuals and generates a score between 0 and 1. A score of one suggests the presence of a duplicate sample in the data set. A total of five samples were excluded from further analysis as they scored more than 98% (> 0.98) with another sample. All other samples had very low scores (< 0.14). Among these five samples, one DNA sample was repeated in each 96 well plate (total three), and one sample was used a duplicate. Our results yielded one more sample as a duplicate.

5.1.4. Results from genotyping efficiency

This step of QC was used to examine the markers genotyping efficiency. Marker genotype efficiency (genotyping rate per marker) indicates marker quality. This QC step was used to identify and exclude poorly genotyped markers. These markers are likely to increase false associations, if not excluded. We used a $\geq 99\%$ threshold to remove markers after carefully scrutinizing the data set. This suggests that markers with 1% or more missing data were excluded. A total of 4,710 out of 538,449 markers failed this QC step, and were removed from further analysis.

5.1.5. Results from minor allele frequency filter

Removal of markers based on a low allele frequency rate was the next step of the QC. Although this step is a part of QC, it does not mean that quality of markers was low. These SNPs are mostly non-informative as they show little variation in the sample set

being analyzed. The statistical power to detect an association will also be low. The main aim of this step was not to hamper the quality of the subsequent analysis. A stringent threshold (≤ 0.03) was used to filter rare alleles. A total of 259,565 markers had minor allele frequency ≤ 0.03 and were excluded from further analysis.

5.1.6. Results from genotyping rates between two groups

The next step of QC was to identify markers that show significant differences in genotyping rates between two groups (males vs females and age groups 1-5 y vs 6-10 y). To minimize confounding, markers that showed significant difference in their genotyping rates between two groups were excluded from further analysis. We used a threshold of > 0.05 after critically scrutinizing the data set. A total of 569 SNPs had significantly different (> 0.05) genotyping rates between two genders and were removed. Likewise, 217 SNPs showed a significant difference between the two age groups and were excluded from analysis.

5.1.7. Results from Hardy-Weinberg equilibrium

In this study, HWE was used retrospectively to assess their conformity in the whole group of subjects in gender- and age-specific analyses. A significant deviation from HWE in healthy controls suggests genotyping error, and must be excluded from analysis. After critically examining the data set we used a threshold of $P < 10^{-3}$. None of the top one hundred polymorphisms in gender- and age-specific associations showed a significant deviation from HWE in gender- and age-specific analyses.

Genotype call rates were greater than 99.9% for all childhood ALL cases after all QC steps were implemented for gender- and age-specific association analyses. This

translates into < 0.01 missing data points. Figure 12 explains a brief summary of all QC steps and results. Differences between samples that were excluded from final analysis and samples that were retained are reported in the next section.

Figure 12. Quality control steps, and samples and markers exclusion

5.2. Characteristics of childhood ALL study subjects

All of these samples identified themselves as non-Hispanic white. The final sample included 117 males (55.5%) and 94 females (45.5%) (Table 17). This study was restricted to age group 1-10 years. There was no statistically significant difference ($P = 0.10$) between two genders in their age distribution (Table 18). The mean ages in males (4.44 years) and females (4.70 years) were not different ($P = 0.45$). For age-specific analysis, 143 samples (67.8%) were age 1-5 years and 68 samples (32.2%) were age 6-10 years. Male-to-female ratios were not different ($P = 0.42$) between the two age groups. Individuals excluded after QC were compared with individuals retained for final analysis to check any substantial difference between the two groups. A total of 37 individuals were excluded from final analysis, including individuals who were excluded before genotyping. There were no significant differences between the mean ages ($P = 0.67$; samples excluded: 4.35 years vs samples included: 4.56 years) or male-to-female ratios between the two groups ($P = 0.45$). Thus, there appeared to be no substantial difference between the subgroup of excluded samples and the rest of the sample to implicate any selection bias.

Table 15. Characteristics of childhood ALL cases

Gender	
Male	117 (55.5%)
Female	94 (45.5%)
Age (year)	
Mean (SD)	4.56 (2.46)
Median (IQR)	4 (3-6)
Age (year)	
1	17 (8.10%)
2	28 (13.30%)
3	45 (21.30%)
4	29 (13.70%)
5	24 (11.40%)
6	17 (8.10%)
7	17 (8.10%)
8	15 (7.10%)
9	13 (6.20%)
10	6 (2.80%)
Age groups	
1-5 year	143 (67.8%)
6-10 year	68 (32.2%)
Ethnicity	Non-Hispanic white

SD: standard deviation, IQR: Inter quartile range, ALL: acute lymphoblastic leukemia

Table 16. Characteristics of male and female childhood acute lymphoblastic leukemia cases

Age/Gender	Male	Female	P value
1	13 (11.1%)	4 (4.3%)	
2	12 (10.3%)	16 (17.0%)	
3	31 (26.5%)	14 (14.9%)	
4	15 (12.8%)	14 (14.9%)	
5	11 (9.4%)	13 (13.8%)	
6	6 (5.1%)	11 (11.7%)	
7	10 (8.5%)	7 (7.4%)	
8	6 (5.1%)	9 (9.6%)	
9	9 (7.7%)	4 (4.3%)	
10	4 (3.4%)	2 (2.1%)	
	117 (100%)	94 (100%)	0.10
Age (year)			
Mean (SD)	4.44 (2.56)	4.70 (2.33)	0.45
Median (IQR)	4 (3-6)	4 (3-6)	0.31

SD: standard deviation, IQR: Inter quartile range

5.3. Results of gender- and age-specific associations

As routinely done in GWAS, the additive genetic risk model was used for gender- and age-specific analyses using logistic regression. In addition, permutation testing (10,000 permutations; $P \leq 0.05$ for statistical significance) was performed for top one hundred results, using Plink, to eliminate false-positives due to chance. These results are, therefore, free from multiple comparison issues as the permutation test assesses the role of chance on each SNP. Thus, no other statistical approach was used to correct these

results for multiple comparisons. Permutation P values alongside the logistic regression results are reported in all tables.

5.3.1. Results of gender-specific associations

Figure 13. Q-Q plot for gender-specific association analysis for childhood ALL risk

The x-axis represents expected P value on logarithmic scale (genomic control), and the y-axis represents observed P value on logarithmic scale (GC); A: Q-Q plot is unadjusted for GC. B: Q-Q plot is adjusted for genomic control.

The additive genetic risk model was used for analysis of genotype distribution differences between male and female cases for each SNP, and results were adjusted for potential population stratification using the genomic control (GC) method. A quantile-quantile (Q-Q) plot (Figure 13) was used to explore systematic errors, and to generate a visual representation of observed P values of GWAS results against expected P values. The genomic inflation factor for gender-specific analysis was one. A score of one indicates no confounding by population stratification. Manhattan plot was generated using the results for the additive model (Figure 14).

Figure 14. Manhattan plot for gender-specific association analysis for childhood acute lymphoblastic leukemia risk

The x-axis represents position on each chromosome and the y-axis shows the P value on logarithm scale from the additive genetic model.

The Manhattan plot visualizes the distribution of association results across the genome and with their statistical significance. Here, the X-axis represents SNPs position on each chromosome and the Y-axis shows P values on a log scale.

When results were ranked by their *P* values, the smallest *P* value was 1.9×10^{-6} (*RASSF2*, rs4813720, $OR_{interaction} = 0.29$) (Table 17). Appendix Table 2 shows results for the top one hundred gender-specific associations based on the lowest P value. Altogether 18 SNPs showed associations with a *P* value of $< 1 \times 10^{-4}$ (Figure 15). Of the top 100 ranking associations, the maximum number of gender-specific associations was found on chromosome 17 (n=15). Several genomic loci, such as 17q12 (*ACACA*) and 2p22.1, yielded multiple associations. However, some of these associations (rs7583193 and rs17027254; rs1899286, rs6732320 and rs11687208; rs8081866, rs2542653, rs2542660 and rs12948120) were due to correlated SNPs (Appendix Table 3).

Table 17. SNPs showed gender-specific associations in childhood ALL risk at the significance level $< 1 \times 10^{-4}$

					Minor allele frequency				
SNP	Gene/region	Chr [†]	Minor allele	Feature	Males	Females	OR _{allele} (95% CI)*	P value**	P value (permutation) ^{††}
rs4813720	RASSF2	20	A	5upstream	0.23	0.47	0.29 (0.17 - 0.48)	1.90×10^{-06}	1.0×10^{-4}
rs231237	HSPB6	19	A	5upstream	0.42	0.21	3.00 (1.86 - 4.85)	7.15×10^{-06}	1.0×10^{-4}
rs7323018	13q14.1	13	G	intergenic	0.17	0.36	0.31 (0.18 - 0.52)	8.40×10^{-06}	1.0×10^{-4}
rs17027254	2p22	2	T	intergenic	0.19	0.39	0.37 (0.23 - 0.58)	1.86×10^{-05}	1.0×10^{-4}
rs7912381	10q26.3	10	G	intergenic	0.39	0.21	2.78 (1.71 - 4.51)	3.68×10^{-05}	1.0×10^{-4}
rs11687208	2p22	2	C	intergenic	0.21	0.40	0.40 (0.26 - 0.62)	4.81×10^{-05}	1.0×10^{-4}
rs798292	MAGI2	7	G	intronic	0.16	0.35	0.38 (0.24 - 0.61)	4.88×10^{-05}	1.5×10^{-4}
rs13107783	4p15.3	4	C	intergenic	0.32	0.52	0.40 (0.26 - 0.62)	5.16×10^{-05}	2.0×10^{-4}
rs4470624	4p15.3	4	T	intergenic	0.32	0.52	0.40 (0.25 - 0.62)	5.16×10^{-05}	2.0×10^{-4}
rs1849374	12p11.2	12	A	intergenic	0.44	0.25	2.48 (1.58 - 3.88)	7.35×10^{-05}	2.0×10^{-4}
rs12948120	ACACA	17	C	intronic	0.29	0.49	0.44 (0.29 - 0.66)	7.46×10^{-05}	3.0×10^{-4}
rs6904762	6q23	6	G	intergenic	0.27	0.46	0.41 (0.26 - 0.64)	1.00×10^{-05}	1.0×10^{-4}
rs506389	8q22.3	8	A	intergenic	0.28	0.11	2.99 (1.74 - 5.15)	7.98×10^{-05}	2.0×10^{-4}
rs6732320	2p22	2	T	intergenic	0.2	0.38	0.41 (0.26 - 0.64)	8.08×10^{-05}	3.0×10^{-4}
rs8081866	ACACA	17	T	intronic	0.28	0.48	0.45 (0.30 - 0.67)	8.64×10^{-05}	3.0×10^{-4}
rs349714	3p25	3	G	intergenic	0.44	0.26	2.43 (1.56 - 3.80)	8.76×10^{-05}	2.0×10^{-4}
rs7583193	2p22	2	G	intergenic	0.19	0.38	0.41 (0.26 - 0.64)	9.09×10^{-05}	1.0×10^{-4}

*OR_{interaction} per allele (OR_{allele}) for the additive model; **P value adjusted for genomic control; [†]Chr = Chromosome, SNP = single nucleotide polymorphism; ^{††}P value permutation = point wise P value from maxT permutation analysis after 10,000 permutation

Figure 15. Genome view of single nucleotide polymorphisms or associated genes in gender-specific associations based on P values

Figure 16. Genome view of single nucleotide polymorphisms or associated genes in gender-specific associations based on effect size

When we ranked the results by their effect size, the largest effect size (OR) was 15.7 (*HLA-DQA1*; rs12722042) (Table 18). Strength of the association was remarkably high ($OR_{\text{interaction}} \geq 10.0$) for nine SNPs. The top two associations were from the *HLA-DQA1* gene with SNPs (rs12722042 and 12722039), which were correlated. Chromosome 2 and chromosome 6 yielded the maximum number of associations, 15 and 13, respectively (Figure 16). There were sets of SNPs from these regions that were correlated with one another (Appendix Table 4). *ADAM28*, at chromosome 8, showed the maximum number of associations (rs11992342, rs7829965, rs36041430), however, correlated. Around 50% of identified variants were from intergenic regions (regions between genes). Appendix Table 5 shows results for the top one hundred gender-specific associations based on the highest effect size.

Table 18. SNPs showed gender-specific associations in childhood ALL risk with the highest effect sizes (OR > 10; P value < 0.05)

					Minor allele frequency				
SNP	Gene/region	Chr [†]	Minor allele	Feature	Males	Females	OR _{allele} (95% CI)*	P value**	P value (permutation) ^{††}
rs12722042	<i>HLA-DQA1</i>	6	G	coding	0.07	0.005	15.68 (2.03 - 121.2)	0.008	0.001
rs12722039	<i>HLA-DQA1</i>	6	A	coding	0.07	0.005	14.87 (1.94 - 114.0)	0.009	0.002
rs11992342	<i>ADAM28</i>	8	T	intron	0.07	0.005	14.73 (1.92 - 113.9)	0.01	0.001
rs80040922	<i>UMODL1</i>	21	A	coding	0.06	0.005	13.68 (1.77 - 105.6)	0.01	0.004
rs61753605	LOC100996481	6	C	coding	0.06	0.005	13.38 (1.73 - 103.3)	0.01	0.004
rs35665085	<i>CECR5</i>	22	A	coding	0.06	0.005	12.64 (1.63 - 98.00)	0.02	0.006
rs143021649	<i>CNTN3</i>	3	T	coding	0.06	0.005	11.62 (1.49 - 90.58)	0.02	0.009
rs6795524	<i>PROS1</i>	3	G	intron	0.05	0.005	10.63 (1.36 - 83.31)	0.02	0.006
rs10003468	4q28.1	4	C	intergenic	0.05	0.005	10.63 (1.36 - 83.31)	0.02	0.005

*OR_{interaction} per allele (OR_{allele}) for the additive model; **P value adjusted for genomic control; [†]Chr = Chromosome; SNP = single nucleotide polymorphism; ^{††}P value permutation = point wise P value from maxT permutation analysis after 10,000 permutation

Top ranking results based on the effect size showed associations with more missense (resulting in amino acid changes) variations than the results based on the P values (29 vs 2) (Appendix Table 6 and Table7). Thus, OR-based top ranking results were enriched for missense and/or highly functional SNPs. These missense SNP associations with high effect sizes and obvious functional effects on protein structure suggest that most of these variants may be causative rather than indirect associations. We performed bioinformatic analyses to examine functionality of all gender-specific markers. The aim was to check whether these markers were direct or indirect associations with childhood ALL risk. Two main databases (RegulomeDB and F-SNP, explained in Chapter 4) were used to obtain functional score of markers. Bioinformatic analyses of these SNPs yielded high levels of functionality by at least one algorithm for 13 SNPs based on the P value, and for 25 SNPs based on the effect size (Appendix Table 6 and Table7). Two SNPs, rs8106959 and rs739924, scored 1f for results based on the P value. The SNP rs739924 also scored one for F-SNP. Likewise, one SNP (rs6929434) scored 1b and four SNPs (rs12722042, rs3847262, rs11751765 and rs130069) scored ≥ 0.75 by F-SNP database. We also performed bioinformatic analysis of SNPs which were not included in the GWAS chip but were highly correlated with gender-specific markers (Appendix Table 6 and Table7). Results are only provided if a correlated SNP showed a much higher score, by bioinformatic analysis, than associated SNP. Several associated SNPs showed correlation with multiple functional variants. The SNP rs9913430 scored 1a, as the most credible

functional variants for results based on the P value. Moreover, two SNPs scored 1d (rs9314355 and rs7224979) and two SNPs (rs10413852 and rs1275051) scored 1f for results based on the P values. For results based on the effect size one SNP (rs12349952) scored 1f. We also performed empirical data screening to complement bioinformatics assessment (Appendix Table 8). When we screened existing experimental data, using SCAN, only eleven SNPs (results based on the P value) and one SNP (results based on the effect size) showed substantial effects on regulation of several genes in the non-Hispanic population.

The SNPnexus database provided information from the GWAS catalogue and the Catalogue of Somatic Mutations in Cancer (COSMIC). A total of five SNPs (rs552976, rs563694, rs560887, rs12940887 and rs9305777) previously showed associations with other diseases and traits (Appendix Table 9). Interestingly three SNPs (rs552976, rs563694 and rs560887) were located in the same gene (*G6PC2*). All of these three associated SNPs were associated with glucose-related traits. The SNP rs12940887 showed an association with blood pressure level and rs9305777 was associated with platelet aggregation. The COSMIC database showed three SNPs (rs61753605, rs35693261 and rs4645656), which may cause functional changes that are advantageous for cancer occurrence and/or progression. The SNP rs61753605 showed associations with two cancer sites (breast cancer and prostate cancer). However, the SNP, rs35693261, may increase the risk of intestinal cancer and rs4645656 may increase the chance of stomach cancer. These are somatic mutations. Somatic mutations in cancer cells may be drivers (causing or helping progression of cancer) or passengers (just the results of random events). All somatic mutations were associations from the highest effect sizes from

gender-specific associations. A total of seven SNPs were located in the transcription factor binding sites. The transcription factor binding sites are mostly located within the promoter region of genes, and may initiate gene function. Thus, SNPs located in these regions may have more regulatory functional effects.

The CTD was used to examine associated genes for their interactions with environmental exposures, such as carcinogens. A list of gender-specific genes accompanied by their interacting chemicals and appropriate references can be found in the appendix (Table 10 & Table 11). Nearly all genes have shown substantial potential with chemical interactions in humans and animal models. The most common environmental interactions were with vehicle emissions (benzene, 2,6-dinitrotoluene, ozone), drugs (acetaminophen), tobacco smoke (benzo(a)pyrene, benzo(a)pyrene diol epoxide, nicotine), poly aromatic hydrocarbons (PAH) (benzo(a)pyrene), food cooked on the barbecue (benzo(a)pyrene, benzo(a)pyrene diol epoxide), pesticides (fonofos, parathion, terbufos, methoxychlor, chlorpyrifos), polychlorinated biphenyls, bisphenol A, formaldehyde and hormones (estrogen, progesterone and testosterone). Most of these environmental chemicals are ubiquitous and classified as class 1 (benzene, benzo(a)pyrene, benzo(a)pyrene diol epoxide tetrachlorodibenzodioxin, aflatoxin B1, formaldehyde, asbestos, arsenic, nicotine and estradiol) and class 2 (progesterone, polychlorinated biphenyls, ethanol) carcinogens by International Agency for Research on Cancer (IARC)¹⁹¹. Some of these chemicals also act as teratogens, such as alcohol, tobacco smoke, lead, mercury, benzene, benzo(a)pyrene, estradiol, progesterone, arsenic, pesticides and formaldehyde, and may affect disease susceptibility *in utero*. There are few examples of gene-environment interaction and childhood ALL risk. Most of these

environmental exposures have not yet been properly evaluated in childhood ALL risk. Several studies have found that exposure to these environmental pollutants, such as pesticides, benzene, tobacco smoke, formaldehyde and polychlorinated biphenyls, specifically during pregnancy, can increase risk of hematopoietic cancers including childhood ALL¹⁹²⁻¹⁹⁶, however, these results are not robust and confirmed ones. Gene-environment interaction with gender-specificity may unravel some environmental risk factors and increased childhood ALL risk. Studies have also unraveled gender-specificity in chemical exposures and metabolisms¹⁹⁷⁻²⁰⁰.

5.3.2. Results of age-specific associations

As in gender-specific associations, the additive genetic model was used to compare genotype distributions between two age groups, and results were adjusted for population stratification using the genomic control method. A Q-Q plot (Figure 17) was used to explore systematic errors in the age-specific associations. The adjusted results again yielded a genomic inflation factor one for age-specific association. Again, inflation factor one ruling out confounding by cryptic population stratification.

Figure 17. Q-Q plot for age-specific association analysis for childhood ALL risk

The x-axis represents expected P value on logarithm scale (genomic control), and the y-axis represents observed P value on logarithm scale (GC); A: Q-Q plot unadjusted for GC and observed before QC B: Q-Q plot adjusted for genomic control and observed after QC.

A total of ten SNPs showed statistically highly significant age-specific associations (P value $\leq 1 \times 10^{-4}$), and the lowest P value was 9.84×10^{-6} (*SOX5*; rs10505918) (Table 19). Among the top one hundred associations (Appendix Table 12), chromosome 14 yielded the maximum number of results (Figure 18), some SNPs being in correlation with one another (Appendix Table 13). All three polymorphisms (rs8021355, rs7144565 and rs2274068) at *RALGAP1* (chromosome 11) were perfectly correlated. Several other genomic loci, such as 2p24.3, 5q14.2, 16q22.2 and 21q21.3, also showed multiple associations, but few variants (rs377621 and rs16979806; rs6739633 and rs1521244) at these loci were correlated.

When results were ranked by their effect size, the largest effect size was 12.5 (*DIO1*, rs17109582) (Table 20 and Appendix Table 14). A total of 4 SNPs have shown high effect sizes ($OR_{\text{interaction}} > 10$, all with $P < 0.05$). The maximum number of age-specific association (12 associations) was observed at chromosome 2 and chromosome 6 (Figure 19). Some of these associations were correlated (Appendix Table 15).

Table 19. SNPs showed age-specific associations in childhood ALL risk at the significance level $< 1 \times 10^{-4}$

					Minor allele frequency				
SNP	Gene/region	Chr [†]	Minor allele	Feature	1-5 y	6-10 y	OR _{allele} (95% CI)*	P value**	P value (permutation) ^{††}
rs10505918	<i>SOX5</i>	12	A	intron	0.42	0.19	3.15 (1.90 - 5.24)	9.84×10^{-06}	1×10^{-4}
rs11997355	8q21.11	8	T	intergenic	0.05	0.19	0.22 (0.11 - 0.44)	2.74×10^{-05}	1×10^{-4}
rs2388773	16q12.2	16	C	intergenic	0.14	0.35	0.35 (0.21 - 0.57)	3.78×10^{-05}	1×10^{-4}
rs665159	<i>CHRM3</i>	1	T	intron	0.55	0.33	2.46 (1.58 - 3.84)	7.42×10^{-05}	2×10^{-4}
rs3954950	9p24.2	9	T	intergenic	0.24	0.43	0.38 (0.24 - 0.62)	7.77×10^{-05}	1×10^{-4}
rs7818844	8p12	8	T	intergenic	0.40	0.60	0.38 (0.23 - 0.61)	7.86×10^{-05}	1×10^{-4}
rs6972158	<i>NPSR1</i>	7	G	intron	0.34	0.14	3.03 (1.74 - 5.25)	8.30×10^{-05}	1×10^{-4}
rs7320982	8p12	13	C	intergenic	0.19	0.38	0.39 (0.24 - 0.62)	8.33×10^{-05}	1×10^{-4}
rs7583258	2q22.3	2	G	intergenic	0.09	0.24	0.29 (0.16 - 0.54)	8.79×10^{-05}	2×10^{-4}
rs1882591	16q12.2	16	G	intergenic	0.22	0.42	0.42 (0.27 - 0.64)	9.60×10^{-05}	2×10^{-4}

*OR_{interaction} per allele (OR_{allele}) for the additive model; **P value adjusted for genomic control; [†]Chr = Chromosome, SNP = single nucleotide polymorphism; ^{††}P value permutation = point wise P value from maxT permutation analysis after 10,000 permutation

Figure 18. Genome view of single nucleotide polymorphisms or associated genes in age-specific associations based on P values

Figure 19. Genome view of single nucleotide polymorphisms or associated genes in age-specific associations based on effect size

Table 20. SNPs showed age-specific associations in childhood ALL risk with the highest effect sizes (OR > 9; P value < 0.05)

					Minor allele frequency				
SNP	Gene/region	Chr [†]	Minor allele	Feature	1-5 y	6-10 y	ORallele (95% CI)*	P value**	P value (permutation) ^{††}
rs17109582	<i>DIO1</i>	1	C	intron	0.09	0.007	12.46 (1.67 - 93.01)	0.01	0.006
rs7304215	<i>TMEM132D</i>	12	G	intron	0.07	0.007	11.25 (1.47 - 85.90)	0.02	0.01
rs10999147	<i>AIFM2</i>	10	G	coding	0.07	0.007	10.89 (1.43 - 83.02)	0.02	0.01
rs7330286	13q33.2	13	T	intergenic	0.07	0.007	10.01 (1.33 - 75.63)	0.03	0.01
rs41309927	<i>SEC23B</i>	20	A	coding	0.07	0.007	9.70 (1.28 - 73.39)	0.03	0.02
rs36086854	<i>CFAP99</i>	4	A	coding	0.06	0.007	9.42 (1.23 - 72.26)	0.03	0.02
rs17409162	<i>ANO10</i>	3	A	coding	0.06	0.007	9.24 (1.20 - 71.06)	0.03	0.02
rs13129052	4p16.3	4	G	intron	0.06	0.007	9.24 (1.20 - 71.06)	0.03	0.02

*OR_{interaction} per allele (OR_{allele}) for the additive model; **P value adjusted for genomic control; [†]Chr = Chromosome, SNP = single nucleotide polymorphism; ^{††}P value permutation = point wise P value from maxT permutation analysis after 10,000 permutation

The Manhattan plot (Figure 20) was generated to visualize the data. Like gender-specific associations, this study yielded several risk markers which may increase the risk of ALL in a specific age group.

Figure 20. Manhattan plot for age-specific association analysis for childhood acute lymphoblastic leukemia risk

The x-axis represents position on each chromosome and the y-axis shows the P value on logarithm scale from the additive genetic model

Like gender-specific associations, results based on the effect size again showed associations with more missense (resulting in amino acid change) variations than results based on the P value (24 vs 6), including correlated variants (Appendix Table 16 and Table 17). One SNP, rs75411676, results based on effect size, also showed a nonsense variation. Nonsense variation is the most severe change, as it prematurely stops protein formation. RegulomeDB and F-SNP (explained in Chapter 4) were assessed the functionality of all age-specific markers. All six missense variations, results based on P value, showed benign/tolerable effect in resulting protein formation. Four SNPs

(rs2101919, rs237318, rs6883 and rs6972158) were located in transcription factor binding sites, and may affect gene regulation, as they have more chance of regulatory effect (Appendix Table 16 and Table 17). A total of 24 SNPs (RegulomeDB $\leq 3a$ and F-SNP ≥ 0.2), results based on the P value, yielded much higher functional score by at least one algorithm. Two SNPs (rs139886 and rs9897794), scored “1f” (RegulomeDB), were suggested most credible functional variants. Nine SNPs scored a much higher functional score (≥ 0.5) for F-SNP. Results suggest these associated SNPs may be the main causal SNPs rather than proxy associations. Correlated SNPs with age-specific association markers, when complemented with RegulomeDB, yielded 34 highly functional variants. One SNP (rs4821717) scored “1b”. Moreover, one SNP (rs9897794) scored “1d”, and another seven SNPs scored “1f”. Several age-specific risk markers also yielded multiple functional variants, including missense variations. These correlated functional variants might be the main causal SNPs for which these age-specific risk markers may be proxies. Eleven SNPs (results based on the P values) had potential eQTL effects (explained in chapter4) on thirteen genes (Appendix Table 18). Six highly functional correlated SNPs (results based on the P values) showed eQTL effects on 3 unique genes.

Ten SNPs were located in TFBSs (Appendix Table 16 and Table 17), and may influence disease risk by change in binding site. Results based on effect size showed 28 SNPs with higher functional score by at least one algorithm. It again suggests that these SNPs might be causal variants rather than indirect associations. The SNP rs3204798 showed a much higher functional score (0.91) by F-SNP. Functional analysis of correlated SNPs also showed 36 unique risk variants with much higher functional scores or missense variations. One SNP (rs12632793) scored “1d” and two SNPs (rs16909527

and rs373690) scored “1f”. The eQTL analysis yielded 3 SNPs with potential effect on 14 genes (Appendix Table 18). Additional bioinformatic analysis of correlated SNPs suggested that several of these associated risk markers might be proxy for highly functional correlated SNPs. Results based on effect size were enriched with more missense variations with deleterious effect, and also showed more functional variants. Overall, our bioinformatic analyses yielded highly functional variants with potential regulation effect.

As for the gender-specific associations, the SNPnexus provided valuable information from the GWAS catalogue and the COSMIC database. A total of six SNPs were previously associated with some types of traits or diseases (Appendix Table 9), including chronic lymphocytic leukemia (CLL) (rs7169431) and nasopharyngeal carcinoma (rs28421666). The COSMIC database yielded three SNPs, rs34099167, rs762562 and rs1800141, which may increase the risk of stomach cancer, pancreas cancer and large intestinal cancer, respectively.

Like gender-specific associations, the Comparative Toxicogenomics Database (CTD) was also used to examine associated genes for their interaction with environmental pollutants (Appendix: Table 19 & 20). A detailed list with appropriate references can be found in the appendix. Most of the identified genes or nearest genes physically located at two sides of SNPs, in case of intergenic variants, have shown potential effect of several chemicals, such as poly aromatic hydrocarbons (benzo(a)pyrene), tobacco smoke (benzo(a)pyrene, benzo(a)pyrene diol epoxide, nicotine), pesticides (insecticides, fungicides, herbicides), vehicle emissions, occupational exposures (formaldehyde), polychlorinated biphenyls, bisphenol A, and

hormones (estrogen, progesterone and testosterone). However, several of these chemicals have previously showed association with childhood ALL, but evidence is limited.

We also predicted the deleterious effect of missense variations, including statistically correlated SNPs, associated with gender- and age-specificity using SNPnexus database (Appendix Table 21 and Table 22). A total of eighteen SNPs from gender-specific associations and seven SNPs from age-specific associations yielded deleterious effects. All of these deleterious missense variations were associated with results based on the highest effect sizes.

5.3.3. Time-to-event analysis

Figure 21. A flow chart explaining marker selection for time-to-event analysis

Table 21. Time-to-event analysis of identified gender- and age-specific childhood ALL risk markers at the significance level $< 1 \times 10^{-4}$

		Overall		Male		Female	
SNP	Log rank P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
rs10505918 ^{(D)*}	$< 1 \times 10^{-4}$	1.69 (1.27 - 2.24)	$< 1 \times 10^{-3}$	1.55 (1.06 - 2.25)	0.02	1.93 (1.25 - 2.96)	3×10^{-3}
rs2949827 ^{(D)*}	$< 1 \times 10^{-4}$	0.54 (0.38 - 0.77)	1×10^{-3}	0.72 (0.46 - 1.12)	0.15	0.39 (0.23 - 0.66)	$< 1 \times 10^{-3}$
rs2212824 ^{(D)*}	$< 1 \times 10^{-4}$	1.76 (1.30 - 2.38)	$< 1 \times 10^{-3}$	1.76 (1.20 - 2.59)	4×10^{-3}	1.76 (1.09 - 2.83)	0.02
rs1209145 ^{(D)*}	$< 1 \times 10^{-4}$	1.80 (1.31 - 2.48)	$< 1 \times 10^{-3}$	1.62 (1.05 - 2.51)	0.03	2.05 (1.28 - 3.27)	3×10^{-3}
rs1209145 ^{(D)*}	$< 1 \times 10^{-4}$	1.76 (1.28 - 2.41)	$< 1 \times 10^{-3}$	1.62 (1.05 - 2.51)	0.03	2.05 (1.28 - 3.27)	3×10^{-3}
rs738027 ^{(D)*}	$< 1 \times 10^{-4}$	1.62 (1.22 - 2.15)	1×10^{-3}	1.62 (1.10 - 2.38)	0.01	1.62 (1.06 - 2.47)	0.03
rs2101919 ^{(D)*}	$< 1 \times 10^{-4}$	0.61 (0.46 - 0.80)	1×10^{-3}	0.64 (0.44 - 0.94)	0.02	0.56 (0.37 - 0.86)	8×10^{-3}
rs9809647 ^{(D)*}	$< 1 \times 10^{-4}$	0.60 (0.45 - 0.78)	1×10^{-3}	0.57 (0.39 - 0.84)	4×10^{-3}	0.64 (0.42 - 0.98)	0.04
rs10133677 ^{(D)*}	$< 1 \times 10^{-4}$	1.78 (1.28 - 2.46)	1×10^{-3}	1.65 (1.05 - 2.61)	0.03	1.92 (1.21 - 3.06)	6×10^{-3}
rs10999147 ^{(D)**}	$< 1 \times 10^{-4}$	2.55 (1.59 - 4.08)	$< 1 \times 10^{-3}$	2.01 (1.09 - 3.71)	0.03	3.90 (1.85 - 8.22)	$< 1 \times 10^{-3}$

(D): Dominant genetic model; *Age P; **Age OR; HR = hazard ratio; CI = confidence interval

Time-to-event analysis was performed on the top one hundred SNPs for gender- and age-specific associations (Figure 21). The log rank test was used for different genetic models (additive, dominant and recessive), to compare the differences between time to having leukemia between two (dominant or recessive genetic model) or three genotypes (additive genetic model). SNPs, which showed statistically significant associations ($P \leq 0.05$) with age-at-onset, are listed in Appendix Table 23. KM plots, only for the SNPs with the lowest P values (by log rank), are illustrated in the result section. The Cox proportion hazard modeling was also performed for all statistically significant associations (log rank P value ≤ 0.05) with age-at-onset to calculate effect size (hazard ratio).

Figure 22. Genome view of single nucleotide polymorphisms or associated genes with age-at-onset

A total of 196 SNPs, based on the log rank test, yielded statistically significant associations ($P \leq 0.05$) with age-at-onset (Table 21 and Figure 22). The maximum number of associations ($n = 13$) with age-at-onset were observed on chromosomes 1, 8, 12 and 14. Among the top one hundred markers based on effect size for age-specific association results, 91 markers showed associations with age-at-onset. Gender-specific association (effect size results) yielded the lowest number of associations ($n = 11$) with age-at-onset. Most of these associations best fitted in the dominant genetic model. Few of these SNPs were also correlated. A total of ten SNPs yielded P values $< 1 \times 10^{-4}$ with age-at-onset (Table 23).

Figure 23. Kaplan-Meier plot estimates for age-at-diagnosis in childhood ALL with rs10505918 genotypes

AA = wild-type; AB = heterozygote; BB = homozygote variant. Note: X-axis represents age-of-onset in years, and Y-axis represents survival function. Plot compares genotypes and age-of-onset. Dominant genetic model.

The *SOX5* rs10505918, which was the top hit for age-specific results (Table 23), also yielded the most statistically significant association with age-at-onset (Figure 23).

Childhood ALL cases who possessed heterozygote (AB) and homozygote variants (BB)

developed ALL on average 2 year earlier than participants who were AA genotype (wild-type) for rs10505918 (median age, 3 years vs 5 years). The HR was 1.69 that suggests 1.69 times increased risk of early-onset ALL for children possessing heterozygote (AB) and homozygote (BB) genotype.

Figure 24. Kaplan-Meier plot estimates for age-at-diagnosis in childhood ALL with rs2949827 genotypes

AA = wild-type; AB = heterozygote; BB = homozygote variant. Note: X-axis represents age-of-onset in years, and Y-axis represents survival function. Plot compares genotypes and age-of-onset. Dominant genetic model

Likewise, SNP rs2949827 also showed a low P value ($< 1 \times 10^{-4}$), however, HR was in opposite direction (HR = 0.54) (Figure 24). The HR 0.54 suggests nearly two times increased risk for early-onset of childhood ALL for children possessing wild-type genotype (AA). Children homozygote for wild-type (AA) developed ALL on average 2 years earlier than children who were heterozygote (AB) and variant genotype (BB) (median age 4 years vs 6 years). Several of these associations were only statistically significant ($P \leq 0.05$) in one gender. Two associations (rs17170286 and rs1800141) with

age-at-onset were gender-specific ($P_{\text{interaction}} \leq 0.05$). Both associations were in the same direction but differed in magnitude. For example, overall HR for rs17170286 was 1.60 ($P = 0.03$), however, when results were stratified by gender, males showed a much higher increased risk 2.36 ($P = 0.003$). HR for female was 1.12 ($P = 0.72$).

5.3.4. Gene enrichment analysis

Gene enrichment analysis was performed to examine the pathways associated with male or the age group 1-5 year. The main purpose was to assign biological meanings to some group of genes. Our results did not yield any statistically significant association with any pathways.

5.3.5. Previously identified gender- and age-specific associations

We also analyzed previously identified gender-specific associations in childhood ALL. To avoid any discrepancy from previous associations, we performed same genetic models for association analysis. Our results did not replicate all previous gender-specific associations (Appendix Table 24). Two SNPs, rs419788 and rs224589, showed the lowest P value, 0.06 and 0.08, respectively. Like gender-specific associations, previously identified age-specific childhood ALL SNPs did not show the same association in the present study (not reported). Most of the previous associations were either with age-at-onset or different age groups.

Previous studies did not counteract the problem of multiple comparisons. Even, few studies used adults and convenient samples as a control group. Environmental factors play a major role in disease association, and different geographical regions (USA vs UK) can also increase the chance of replication failure, as few of these studies were done at

the United Kingdom. Many non-cancer gender-specific associations were also analyzed, and two of the previously identified associations, rs3131622 (type 1 diabetes) and rs10195252 (waist-height ratio) were statistically significant (P value < 0.05).

6. DISCUSSION

To our knowledge, this is the first GWAS, which used a gender- and age-specific approach to unravel childhood ALL risk variants. We reported the statistically most significant top one hundred results. Permutation testing was performed to eliminate chance findings (explained in Chapter 4). These results are free from multiple comparison issues, as each permutation on each SNP assesses the role of chance. The rs4813720 (*RASSF2*), rs231237 (*HSPB6*) and rs7323018 (13q14.1) SNPs showed the most statistically significant gender-specific associations. Likewise, the SNP rs10505918 (*SOX5*) showed the lowest P value for age-specific associations, and also yielded the most statistically significant association with age-at-onset.

Unlike previous GWASs, as a second approach, we also analyzed results based on the effect size, as effect size helps to explore clinically meaningful results, which may not have reached statistical significance due to insufficient power^{201, 202}. Again, we applied permutation testing for the highest ranking results (top 100 associations), based on the effect size, to eliminate chance findings. Two *HLA-DQA1* missense SNPs (rs12722042 and rs12722039) showed the highest effect sizes for gender-specific associations. Several other SNPs, such as rs11992342 (*ADAM28*) and rs80040922 (*UMODL1*) also yielded the highest effect sizes for gender-specific associations. The SNPs rs17109582 (*DIO*), rs7304215 (*TMEM132D*), rs10999147 (*AIFM2*) and rs7330286 (13q33.2) yielded the highest effect sizes for age-specific associations.

Among 400 gender- or age-specific variants, only 14 variants were previously observed associations with other diseases/traits, including CLL (rs7169431)²⁰³ and nasopharyngeal carcinoma (rs28421666)²⁰⁴. The CLL association (rs7169431) was a risk

association (OR = 1.36, $P = 4.74 \times 10^{-7}$) in a previous GWAS. This SNP is located at chromosome 15, between the *NEDD4* and *RFX7* genes. Our results provide further evidence for genetic susceptibility of this SNP in childhood ALL with an increased risk to the age-group 1-5 years. Bioinformatic analysis did not suggest any functional mechanism for increased risk in this age group. Experimental studies are needed to understand the mechanism of this SNP on the age effect.

In this study, we also unmasked several associations located within the HLA region at rs28421666, located between the *HLA-DRB1* and *HLA-DQA1* loci, rs3130161, located between *HLA-DPBI* and *COL11A2*, and two missense SNPs (rs12722042 and rs12722039) located in the *HLA-DQA1* gene. Among all of these previous associations, the rs28421666 SNP has shown a protective association with nasopharyngeal carcinoma²⁰⁴. Another SNP, rs3130161, has yielded an association with type 1 diabetes (T1D)²⁰⁵. Both of these results were linked with age-specific associations in childhood ALL risk. These results suggest a role for HLA in childhood ALL risk with age specificity. The HLA region is the most polymorphic region in the human genome, which plays an important role in the regulation of the immune system. Although the role of HLA in ALL etiology is not known, several previous studies suggest the role of HLA in childhood ALL risk with gender differential^{123-125, 206-208}. Most of the previously identified HLA associations in childhood ALL are in the HLA class II region. All HLA associated SNPs are also located in the same region. All of these associations yielded significant associations only for males (rs12722042 and rs12722039) or the age group 1-5 years (rs28421666 and rs3130161), when we ranked results based on the highest effect sizes for gender- and age-specific associations. The rs3130161 SNP is statistically

correlated with a much higher functional SNP, rs3129203. It suggests the statistically correlated SNP might be the main causal SNP, which can affect the gene regulation through transcription factor binding site. Extensive bioinformatic screening of these SNPs, excluding rs3129203, did not implicate a mechanism behind gender- and age-specificity in childhood ALL risk, except for rs3130161. Further functional studies are warranted to understand the mechanism of these SNPs in sub groups (male gender and age group 1-5 year) of children with ALL.

Among previously identified associations, several of these variants were associated with autoimmune disorders, such as T1D (rs3130161 and rs4948088)^{205, 209} MS (rs2116078)²¹⁰, psoriatic arthritis (rs12188300)²¹¹ and Crohn disease (CD) (rs798292)²¹². The MS association (rs2116078) was with age-at-onset (mean age = 34 y)²¹⁰. Our results also yielded an age-specific association (rs2116078) in childhood ALL risk with an increased risk to age-group 1-5 years. Previous epidemiological studies have shown an increased risk of hematological malignancies with autoimmune disorders²¹³⁻²¹⁸. This observation has been commonly noted in MS and risk of leukemia/lymphoma in adults²¹³. Epidemiological studies have also shown four times increased risk of ALL in children of women with MS²¹⁴. Thus, the MS risk variant rs2116078 might be commonly shared between MS and childhood ALL in age-specific manner, as previously also observed¹³⁰.

The *MAGI2* (membrane associated guanylate kinase, WW and PDZ domain containing 2) rs798292 has been previously associated (OR = 1.30, P = 1.01 – 1.69) with CD in the Caucasian population²¹². A previous GWAS on childhood ALL relapse also suggests the role of the *MAGI2* (rs1496766) gene in childhood ALL risk²¹⁹. The two

polymorphisms (rs798292 and rs1496766) were also not statistically correlated, which suggests independent associations. Bioinformatic analyses of gene expression profiles of B-cell precursor childhood ALL also suggests that the *MAGI2* gene may increase the risk of childhood ALL²²⁰. Alternatively, *MAGI2* inhibits cell migration and proliferation through *PTEN* (phosphatase and tensin homolog), a tumour suppressor gene. *PTEN* is a key regulator in apoptosis, and defects in apoptosis can increase leukemia risk^{221, 222}. Moreover, a study on adult B-ALL patients has shown decreased *PTEN* activity²²³. Empirical analysis also suggested regulatory effect of rs798292 on three genes (*MYST2*, *ATAD2B* and *EIF1AX*). It means that the SNP, rs798292, is a putative regulation site and it has allele-specific effects on gene expression. Thus, rs798292 may play a significant role in childhood ALL risk through regulatory effects or through *PTEN* interaction.

A cohort of 24,052 patients of T1D in Sweden showed a co-morbidity between early-onset leukemia and T1D (standardized incidence ratio = 8.30; P = 4.91-13.14)²¹⁸. The two polymorphisms (rs3130161 and rs4948088) previously identified as risk variants for T1D^{205, 209} also yielded age-specific associations in childhood ALL. The SNP, rs3130161, showed an association with the age-group 1-5 years and the rs4948088 SNP yielded an association with the age-group 6-10 years. Autoimmune diseases are the most common group that have shown associations with our results presumably due to them being more common in one sex. This epidemiological evidence suggests biological plausibility between few autoimmune disorders and hematological malignancies, including childhood ALL with gender-specificity²¹³⁻²¹⁸. Interestingly, autoimmune disorders are the most common group that have shown associations with our results due to them being more common in one gender¹¹⁰.

Childhood ALL shows a consistent association with recurrent miscarriages, specifically in males²²⁴. The *PRLR* (prolactin receptor) polymorphism rs37389 is involved in recurrent miscarriages²²⁵. The role of the *PRLR* gene is not established in leukemogenesis, but a higher expression of this gene in cancer etiology cannot be neglected²²⁶. Several other previous associations are with HBA1c level (rs552976) and fasting glucose level (rs563694). One SNP, rs560887, yielded multiple associations with glycemic traits.

In this study, we have also observed a statistically significant difference for the frequency of the *ERCC1* (excision repair cross-complementation group 1) rs762562 polymorphism between two age groups. The functional role of *ERCC1* is not clear in leukemia. Similar results, however, with different polymorphisms (rs3212986 and rs11615), have previously shown associations with childhood ALL risk in a Chinese population²²⁷. Moreover, the rs3212986 SNP has yielded a much higher risk (OR = 1.87; P = 0.04) in the age group < 8 years compare to age group > 8 years (OR = 1.44; P = 0.24). Both SNPs (rs3212986 and rs11615), in the previous study, have shown an increased risk in males (OR = 1.94; P = 0.02 and OR = 2.36; P = 0.04, respectively) in comparison to females (OR = 1.19; P = 0.57 and OR = 0.46; P = 0.05). Furthermore, rs11615 also yielded a gender-specific association in the present study (P = 0.03), with an increased risk in males. Thus, results suggest that *ERCC1* gene may be a potential target to examine gender- and age-specificity in childhood ALL risk. The SNP rs762562 is located in an overlapping region of *ERCC1* and *CD3EAP*. The rs762562 SNP shows a missense variation in the *CD3EAP* gene, which suggests an obvious change in protein

function. The SNP rs762562 also showed a somatic mutation by bioinformatic analysis (explained later). Thus, it increases the validity of our results.

The SNP, rs9282777, is present in the coding region of the *LMO2* (LIM only protein 2) gene and yielded a much higher risk in males. The *LMO2* gene plays a crucial role in hematopoietic stem cell development, angiogenesis and embryogenesis^{228, 229}. Higher expression of the *LMO2* gene during immature stages of lymphocyte formation has been observed²³⁰. The *LMO2* gene is considered as a cancer causing gene, and it increases the risk of T-cell ALL^{228, 231-233}. Studies also report the higher expression of the *LMO2* gene in B-cell ALL and other lymphomas^{229, 234}. Our result suggests that rs928277 may play a significant role in B-cell etiology. Bioinformatic screening did not suggest any mechanism in childhood ALL risk with male susceptibility. More functional study is needed to understand the mechanism of rs9282777 in gender differential in leukemia risk.

The rs10505918 SNP showed the most statistically significant age-specific association. This SNP is located in the *SOX5* (SRY (sex determining region Y)-box 5) gene, which is involved in the regulation of embryonic development, however, its role in childhood ALL etiology is not clear. Studies suggest that the *SOX5* gene expresses in B-cells and has a functional role in late B-cell development and B-cell differentiation²³⁵. This gene is also highly expressed in B-cell lymphomas²³⁶. The SNP rs10505918 also yielded the most statistically significant association with age-at-onset ($P < 10^{-4}$). Interestingly, the *SOX5* gene, however, a different polymorphism (rs7294845), also showed a gender-specific association based on the P value in this study. This evidence altogether suggests a role of *SOX5* in childhood ALL risk with gender- and age-specificity.

The SNP rs11992342 yielded a higher effect size for gender-specific associations. This SNP is located in the *ADAM28* gene. Recent evidence suggests that *ADAM28* is expressed on the surface of human lymphocytes²³⁷. The role of *ADAM28* in leukemogenesis is not established, but our results suggest that *ADAM28* polymorphism (rs11992342) was associated with the gender differential in childhood ALL risk with the highest effect sizes. A total of three *ADAM28* SNPs (rs11992342, rs7829965 and rs36041430) showed gender-specific associations, however, all three SNPs were statistically correlated. The rs7829965 is a missense variation, and also yielded a higher score for gene expression regulation, which suggests regulatory effects on binding site.

The *ACACA* (acetyl-CoA carboxylase alpha) gene is located at chromosome 7, which yielded multiple gender-specific associations (rs12948120, rs8081866, rs2542660, rs2542653, rs725038) with an increased risk in females. *ACACA* plays an important role in fatty acid synthesis and is regulated by the thyroid hormone²³⁸. *BRCA1* affects fatty acid synthesis through its interaction with *ACACA*, and this interaction may exert a tumor suppressor function²³⁹⁻²⁴¹. *ACACA* has also shown associations with breast cancer risk²⁴². Childhood leukemia patients have been found to carry *MLL* fusion to *ACACA*²⁴³. A statistically correlated SNP, rs9330250, yielded a higher functional score, which suggests gene regulatory function the SNP rs9330250. The SNP rs9330250 was annotated as a credible functional variant and may play a mechanistic role in pathogenesis of childhood ALL. Thus, *ACACA* seems to have an additional biological feature, and it may increase the risk of leukemogenesis²⁴⁴.

The *N4BP2* (NEDD4 binding protein 2) gene yielded two missense variations (rs61748746 and rs61748749). The encoded protein by this gene binds to B-cell

CLL/lymphoma 3 (BCL-3) protein²⁴⁵. The *BCL3* translocation with *IGH* is found in some patients with childhood ALL²⁴⁶, and subsequent overexpression of *BCL3*²⁴⁷ in childhood ALL. The gender-specific association we found in this study might be the results of obvious change in protein function and its effect on *BCL3* expression. However, more functional studies need to prove this hypothesis, as bioinformatic analysis did not unravel any functional mechanism for male-specific childhood ALL.

A recent study has shown fusion of *HIP1* to *PDGFRB* in chronic myelomonocytic leukemia²⁴⁸. Furthermore, *HIP1* is localized in 7q11.3 region, and the possibility of 7q deletions is associated with some acute non-lymphocytic leukemia cases²⁴⁹. However, its role in lymphoblastic leukemia is not yet established, but our result (rs6962352) suggests an additional role of *HIP1* in the pathogenesis of leukemia. Down syndrome is a known risk factor for childhood ALL. The *KIF21A* gene shows much higher expression in Down syndrome patients in leukocytes^{250, 251}. Unfortunately, unavailability of cytogenetic data is a limitation of this study to reach any conclusion. Additional functional studies need to confirm the role of rs11172024 (*KIF21A*) in childhood ALL etiology.

The rs6151599 SNP yielded an age-specific association result based on the effect size. This SNP is located in a common region shared between the *MSH3* (mutS homolog 3) and *DHFR* (dihydrofolate reductase) gene. Bioinformatic analysis yielded a statistically correlated SNP (rs11749051) with a higher functional score located in the *DHFR* gene. It suggests that the rs11749051 SNP may be the main causal SNP. Studies suggest the low *DHFR* expression may be an important prognostic factor in childhood ALL^{252, 253}.

In this functional analysis of gender- and age-specific risk variants, our results yielded nine highly functional SNPs (six for gender-specific associations and three for age-specific associations). Among these SNPs, one SNP (rs6929434) scored 1b and four other SNPs (rs8106959, rs739924, rs139886 and rs9897794) scored 1f. Likewise, rs739924 and rs130069 scored 1 for F-SNP analysis, and rs11751765 and rs3204798 scored 0.9. These SNPs are highly functional and likely to be the causal SNPs. However, in the results we reported all SNPs which showed RegulomeDB score $\leq 3a$.

In a genetic association study, functional variants are most likely to be located at nearby genes around associated risk markers²⁵⁴. These functional variants are mostly in strong correlation with associated variants and may be the main causal SNPs. Correlation analysis was complemented with functional analysis to identify the causal SNPs. Some gender- and age-specific associated risk variants also yielded several statistically correlated functional variants. A total of 20 statistically correlated risk variants yielded a much higher functional score ($\leq 1f$). rs9913430 (correlated with rs739924) scored 1a, and rs139852 (correlated with rs4821717) scored 1b. These highly functional correlated SNPs might be the main causal SNPs for which associated results may be proxies.

RegulomeDB is a database that explains SNPs with known or predicted functions¹⁸⁴. Lower scores suggest evidence for a variant to be located in a functional region. It has strong power to separate truly functional variants and provide putative regulation site. A score $\leq 1f$ suggests that functional variants are likely to affect the binding site and/or be linked to the expression of a gene target.

Genetic variants play a major role in disease susceptibility by altering gene expressions. The eQTL analysis is a well recognized method in evaluating the effect of

SNPs in mRNA or protein levels (explained in Chapter 4). eQTL refers explicitly to the genomic locus, which influences the variable mRNA or protein level. We found 15 gender- and age-specific associations with eQTL SNPs. Among all highly functional statistically correlated SNPs, nine SNPs showed significant eQTL expressions in LCLs. These 24 eQTL SNPs yielded 52 eQTL target genes (n = 22 gender-specific results; n = 30 age-specific results). Multiple eQTL SNPs identified several common eQTL target genes, such as *SPATA20*, *FGD6*, *LMF1*, *ZNF420*, *MRPL14* and *SLC13A2*, which suggest these genes may contribute to the risk of childhood ALL. The eQTL database was explored to find whether these SNPs are putative regulations sites and can affect gene expressions. For example, the eQTL SNP rs9493135 (gender-specific results based on effect size) located in the 6q23.2 region, regulates several eQTL genes, including *PTPN11*. This gene is a member of the protein tyrosine phosphatase family and is highly expressed in hematopoietic cells²⁵⁵. This gene plays a very important role in Ras and Jak-Stat pathways. Both pathways are significantly associated with leukemogenesis^{221, 255}.

A total of 21 SNPs (seven gender-specific results and 14 age-specific results) were located in transcription factor binding sites. These binding sites are mostly concentrated within the promoter regions of genes. A promoter is a region of a gene that initiates gene function. These 21 SNPs may therefore have greater functional effects on gene expression. Genetic variants can also alter protein structure and modify disease risk. Fifty-five of gender- and age-specific associations were with missense (31 gender-specific results and 24 age-specific results) SNPs. However, most of these missense SNPs (n = 48) were in the top 100 list based on the effect sizes. These missense variations substitute amino acids, which alter the final protein function. Our result also yielded a

nonsense variation (rs75411676). Nonsense variation is the most severe change, as it prematurely stops the protein formation. These missense or nonsense variations have deleterious effect and can increase the risk of childhood ALL. However, we performed bioinformatic analysis to identify the significance of these variations. PolyPhen and SIFT predicted the damaging effect of 25 missense variations. It suggests that amino acid substitutions will have deleterious effect in protein function. We also explored functional similarity of identified genes for gender- and age-specific associations, by using stringent criteria. We only used eQTL target genes, missense and nonsense variations (only for damaging effect) associated genes, and only if a SNP showed a very high functional score. However, our results did not show any statistically significant pathway associations. Overall, bioinformatic and empirical analyses of gender- and age-specific results, including correlation analysis, yielded several functional variants. These functional variants may be associated with gender and age differential in childhood ALL risk and should be pursued in future studies.

Although gene enrichment analysis did not yield any statistically significant pathway, some genes are associated with several pathways associated with leukemia. As mentioned, most of these gender- and age-specific associated childhood ALL SNPs are novel risk variants, as expected. The role of these SNPs is still not clear in childhood ALL etiology, however, some of these associated genes play a major role in several leukemia associated pathways. For example, Notch1 signaling plays an important role in childhood leukemia²⁵⁶. Recent studies have shown the role of *MAML1* (mastermind-like1) in the regulation of Notch oncogenic activities in leukemic cells²⁵⁷⁻²⁵⁹. The *MAML1* rs41285557 showed a male-specific association in this study.

The *RASSF2* (Ras association (RalGDS/AF-6) domain family member 2) SNP, rs4813720, yielded the lowest P value for gender-specific associations. *RASSF2* is a novel tumor suppressor gene and a member of the Ras family that regulates a wide range of biological process, including Ras signalling and apoptosis²⁵⁹⁻²⁶¹. Studies suggest that genes affecting the Ras pathway is the most common occurrence in human cancer, including childhood ALL^{262, 263}. Likewise, several other genes, *RAB28* (rs10003958), *ADAMTS12* (rs7700370) and *RSU1* (rs4748309) may play a significant role on leukemogenesis through the Ras pathway²⁶⁴. The role of gender- and age-specific associated risk variants in the Ras pathway may be important to increase the risk of leukemia.

The *HSPB6* (rs231237) gene encodes a heat shock protein and is constitutively expressed in various tissues²⁶⁵. A study on hepatocellular carcinoma showed its interaction with P13K, which ultimately results in suppression of the AKT pathway. P13K/AKT pathways also play an important role in childhood leukemogenesis, specifically T-cell ALL^{221, 222}. Likewise, the *CYFIP2* (rs1030270), *OSGIN1* (rs62640905), *ZNF420* (rs4254428 and rs6510588), *AIFM2* (rs10999147) and *RASSF3* (rs11175471) genes show TP53 dependent apoptosis and may increase childhood ALL susceptibility²⁶⁶⁻²⁷¹. Studies suggest that leukemia may be more sensitive to change in TP53 dependent apoptosis¹²⁶. The present findings suggest that the associated variants may alter the pathway mediated by TP53 and increase leukemia risk. Some of these SNPs were missense variations or yielded a much higher functional prediction score.

These pathways may play a significant role in childhood ALL etiology with gender- and age-specificity. However, these results should be interpreted cautiously, as

none of the age- or gender-specific SNPs or associated genes are directly associated with leukemogenesis. How these SNPs affect on gender- and age-specificity in childhood ALL risk is still not clear. Some studies suggest that genetic variants in the TP53 pathway could interact with gender to affect cancers^{134, 272}.

Previous GWASs have missed these gender- and age-specific variants as they did not stratify their results by gender and age. Association differing in direction, usually results in an OR close to the unity (OR = 1.0) with no statistical significance in the overall analysis. These SNPs were dismissed by previous studies for further considerations. Stratified analysis reduces statistical power. However, it is not true in the case of gender- and age-specific associations. In gender- or age-specificity, an overall analysis approach does not have sufficient statistical power to detect the association. If there is a gender- or age-specificity, stratified analysis will yield much higher effect size for a particular group, such as males or the age-group 1-5 years. The statistical power will be greater in this case than combined analysis. Other problems with previous studies were adjusting the results for gender and declaring there is no gender-specific association. Statistical adjustment only rules out confounding by gender, which is not equivalent to gender-specificity²⁶. Thus, our approach unraveled novel risk variants, which are associated with a particular gender or age group in childhood ALL risk.

SNPnexus database used COSMIC database to identify SNPs associated with somatic mutations. Somatic mutation is only present in somatic cells. It means that they are not present in all body cells or germ cells. Unlike germline mutations, these mutations are acquired. Somatic mutations either randomly occur or generate by environmental chemicals. Our results yielded several SNPs associated with several cancers through

somatic mutations. It has been suggested that somatic mutations in cancer cells may be drivers (causing progression of cancer) or passengers (just the results of random mutations). A total of six SNPs, rs61753605 (*PRIM2B*), rs35693261 (*MTG2*), rs180041 (*LRP1/MIR1228*), rs4645656 (*ZNF782*), rs34099167 (*NEK1*) and rs762562 (*ERCC1/CD3EAP*), detected as somatic mutations by COSMIC database. It suggests that these SNPs may cause functional changes that are advantageous for cancer occurrence and/or progression. These somatic mutations were associated with prostate, breast, large intestine, stomach and pancreatic cancers. The *LRP1* gene promotes cancer cell invasion by supporting ERK and inhibiting and JNK signaling pathway²⁷³. ERK signaling pathway is associated with leukemogenesis. Studies suggest that mutation in the *NEK1* gene may lead to chromosomal instability, and thus increase the risk of cancer. The *ERCC1* gene has previously showed an increase risk of childhood ALL with male- and age-specificity²²⁷.

In this study, we found a number of associations with gender- and age-specificity. Bioinformatic and empirical analyses suggested that several of associated SNPs may play a functional role in gender and age differential in childhood ALL risk, through change in protein function (missense variations), regulatory effects on gene expression (eQTL) or through alterations of transcription factor binding sites. Although gene enrichment analysis did not yield any pathway to explore gender- and age-specificity, several genomic locations of associated risk variants are associated with leukemogenesis.

In the past few years, GWASs have yielded hundreds of associations for around hundred traits and diseases. However, the effect sizes are modest ($OR < 1.5$)^{274, 275}. The median OR for binary traits is 1.28 (interquartile range (IQR) 1.17 to 1.55). Most of the

previous GWASs used genome-wide significance ($P < 10^{-8}$) level to show an association. Our results did not reach this significance level for gender- and age-specific associations. In comparison to previous GWASs, our gender- and age-specific analyses, which are based on statistical significance, yielded a much higher median OR (2.44; IQR = 2.22 - 2.78). Interpretation of an OR, in a case-only analysis, is important, as a statistically significant association with $OR > 1$ only suggests a positive interaction (risk to males or age group 1-5 y). A higher effect size, however, suggests a higher risk to a particular gender or age group. An $OR < 1$ in the present study suggests risk to females or to the age group 6-10 years. Even, an inverse relationship has been observed between sample sizes and effect sizes. Studies with larger sample sizes mostly yielded lower effect size associations. Of course, larger sample sizes provide more statistical power to detect even a minute effect size such as $OR = 1.1$, but the clinical or public health utility of these associations is questionable.

Most of the previously identified variants, in general, around 88%, were located in non-coding regions (43% in intergenic region and 45% in intron). In the present study, around 94% of associations were in non coding regions (57% intergenic regions and 38% in intron). In comparison to 9% nonsynonymous variations (missense or nonsense) in previous GWASs, our results only showed 3% of nonsynonymous variations. In case of SNPs location at 3' or 5' untranslated region, results were similar (2%). Although we used a different GWAS chip, enriched with coding SNPs, gender- and age-specific results, based on SNPs location, differ from the previous GWASs. Results based on the highest effect sizes for gender- and age-specific associations yielded more meaningful SNP locations. Around 67% of identified associations were located in non-coding region

of genes (39% in intergenic region and 28% in intron). A total of 25% SNPs were missense variations, and 5% of SNPs were located in the 3' or 5' untranslated region. Results based on the effect sizes yielded more meaningful results in comparison to results based on the lowest P values, such as more SNPs in coding region and missense variations.

Genetic variants usually modify disease susceptibility in the presence of environmental exposures²⁷⁶. Genetic factors play a predominant role in diseases due to rare and highly penetrant mutations. However, common genetic polymorphisms modify disease susceptibility in the presence of environmental exposure. Unfortunately, in the case of childhood ALL, the only known environmental risk factor is ionizing radiations. In this study, the CTD was used to explore the gender- and age-specific associated genes and their interactions with environmental chemicals²⁷⁷. The most common environmental pollutants interacting with the target genes of the SNPs that have shown in the present study were PAH, vehicle emissions, cigarette smoke, pesticides, drugs such as acetaminophen, alcohol and formaldehyde. A detailed list of gene-chemical interactions and appropriate references are provided in the appendix (Table 10, 11, 19 and 20). These environmental chemicals are ubiquitous and show associations with an increased risk for childhood ALL^{192-196, 278}. Most of these chemicals are classified as class 1 and class 2 carcinogens¹⁹¹ or teratogens. Studies suggest that age plays an important role in the susceptibility to environmental toxicants²⁷⁹. Because of differential exposure, children are more susceptible to a number of different environmental pollutants, including PAH, air pollution, cigarette smoke and pesticides. Children consume more foods and water per pound of body weight when compared to adults. They breathe air at a faster rate than

adults. Thus, children are more vulnerable to environmental toxicants. There is also evidence of prenatal exposures and childhood ALL risk, such parental occupational exposure, pesticide exposure, tobacco smoke and air pollutants²⁸⁰.

Like age-specificity, studies also suggest gender-specificity in chemical exposures¹⁹⁷⁻²⁰⁰. Benzene and ethanol toxicity is much higher in males, regardless of whether exposures occur *in utero* or adulthood^{197, 198}. These results suggest the importance of gender-difference in benzene induced toxicity. Likewise, females have an increased risk for acute pesticide-related illness. Exposures during pregnancy may increase the susceptibility of childhood ALL. Thus, age and gender differences in the toxicity of environmental chemicals may play a significant role in ALL biology. However, interaction between environmental pollutants and gender- and age-specific risk markers are not yet known.

Rarity of childhood ALL makes it difficult to study the cause of the disease. Most epidemiological studies of childhood ALL and environmental exposures are case-control studies. Case-control studies mostly rely on parents' recall for environmental exposure. Parents of childhood cancers may recall their memories more thoroughly than healthy controls. Thus, recall bias may inflate the results and introduce systematic error. That is one of the potential reasons for the limited evidence for the involvement of environmental exposures in the development of childhood ALL.

There are very few examples of gender- and age-specific associations in disease risk. A recent genome-wide meta-analysis of asthma reported gender-specific candidate risk markers in *IRF1* (rs2549003) and *RAP1GAP2* (rs9895098) with regulatory effects in gene regulation as eQTL²⁸¹. Asthma prevalence also shows intriguing gender-specific

architecture that differs by age. Males are more susceptible during early childhood and females develop asthma during puberty. That study also confirmed the advantage of gender-specific approach in a genetic association study to understand disease etiology.

Likewise, another study in 5,254 participants (2,833 females and 2,421 males) from Framingham Heart Study has shown 14 eQTL SNPs (13 autosomal and one X chromosome) with gender-genotype interactions and ten eQTL SNPs with age-genotype interactions after multiple comparisons²⁸². These eQTL SNPs are associated with several complex traits/diseases. Overall they found 5,866 genes differently expressed between males and females. Interestingly, they have also shown different gender-specific models, such as associations differing in direction and associations differing in magnitude, in gender-genotype interactions, which we also aimed in this study. For example, the *C5orf35* rs686798, association with plasma triglyceride levels, has shown opposite effects on the expression of the *IL6ST* gene, increased expressions in females ($P = 0.0006$) and decreased expressions in males ($P = 0.05$). Another SNP, rs8047080, associated with high-density lipoprotein, has shown higher expression only in males (7.03×10^{-5}). Thus, these recent studies support the rationale of this dissertation.

These examples are very recent examples of a gender- and age-specific approach, which we had also proposed in this study. Age related eQTL SNPs have also confirmed the effects of genetic variants on gene expression throughout the age span. We examined these associations in our study, however, none of these showed any age- or gender-specific associations in childhood ALL risk. These gender- and age-specific variants might only be associated with particular diseases/traits.

Most of the previous gender-specific associations in childhood ALL are within the HLA region. Our results further confirm the role of HLA in childhood ALL risk with male-specificity. Early-onset of childhood ALL and HLA associations are new findings and may shed some light on childhood ALL risk. Van Der Meulen et al, recently, have demonstrated the loss-of-function mutation in the X-linked *UTX* (*KDM6A*) gene in childhood T-ALL²⁸³. This *UTX* mutation was exclusively present in males, which suggest the role of X chromosomes in ALL etiology. Our results did not show any gender-specific or age-specific associations with X chromosome in the top one hundred associations.

Our results did not replicate the same gender-specific associations for previously identified childhood ALL risk markers, even after applying the same genetic models as used in previous childhood ALL studies. The closest association was the *SKIV2L* rs419788 ($P_{\text{interaction}} = 0.06$). Some of these studies may have suffered from multiple comparison issues. Due to rarity of childhood ALL, case-control study design was used to identify gender-specific associations. Thus, controls should be representative of the general population. One study used adults as a control group¹²⁵, and another study used convenience samples as controls¹³⁹ to identify gender-specific associations. Thus, gender-specific associations might be affected by selection bias, as controls may have different environmental exposures than childhood ALL. Genetic variants modify disease susceptibility in the presence of environmental risk factors, so geographical differences may also apply in some replication failure, as few of these gender-specific associations were studied in the United Kingdom^{125, 128, 130}.

Even after clear heterogeneity in age differences (age peak 1-5 y) in childhood ALL, there is not much effort to unravel genetic risk markers in this age group. More than 50% of childhood ALL cases belong to the age group 1-5 years. Only four SNPs (rs3212986, rs2279744, rs4132601 and rs10821936) have shown age-specificity in childhood ALL risk^{51, 52, 126, 227}, and two of them are known childhood ALL risk markers (rs4132601 and rs10821936)^{51, 52}. The SNP rs10821936 was compared between age group 1-10 years and 11-18 years. Another association (rs4132601) was with age-at-onset in childhood ALL risk¹⁴⁰. rs2279744 and rs10821936 also failed to replicate previous age-specific associations.

7. STRENGTHS AND LIMITATIONS

Due to the rarity of childhood ALL, the sample size of the present study was small. Twenty nine samples were excluded after strict QC steps, further reducing statistical power. Another limitation was external validity of these results, as all of these samples were Non-Hispanic whites. Thus, these results cannot be generalized in any other ethnic population. Our study was also restricted to age group 1-10 years, which also lessened the statistical power. Self-reported gender, age and ethnicity data may be of concern, as misclassification biases. Population-based studies mostly rely on self-reported data, and residual confounding is possible. In terms of gender, we verified discordant gender information by the usage of sex-chromosome genotyping results and excluded the samples in case of ambiguity in gender information. Thus, it resulted as a strength of this study. Self-reported ethnicity may be reliable²⁸⁴. To avoid false positive associations due to population stratification, we adjusted our results using genomic controls, which is also a strength of the present study. In the case of age, we depended on self-reported data. Lack of cytogenetic data is another limitation of this study. Chromosomal aberrations, such as chromosomal trisomies (such as Down syndrome) or chromosomal translocations (fusion of two genes from different chromosomes) are associated with childhood ALL risk. Still these chromosomal aberrations represent only a fraction of cases, leaving a large proportion with undefined etiology.

We followed strict safeguards to control genotyping errors. We used a GWAS chip developed by Illumina, the industry leader. Our genotyping call rate was 99.9%. A limitation of this study was that we were not able to assess the associations between genetic risk markers and childhood ALL risk in males and the age group 1-5 years.

However, our interest in this study differed from the traditional approach, and we were more interested in identifying gender- and age-specific associations. We used gender and age as effect modifiers to identify gender- and age-specific associations. The case-only design is based on the independence of exposure and genotype, which means there should not be any difference in allele frequencies in two groups. Departures from this independence may affect the results. In the case of gender and age, it seems impossible to have different allele frequencies between males and females and between two age groups (1-5 years vs 6-10 years) in a healthy population. A genome-wide meta-analysis across 51 studies including overall 114,863 samples (61,094 women and 53,769) of European ancestry did not find any allele frequency difference at common loci between men and women⁶². However, another study in four different GWAS datasets ($n < 165$), identified allele frequency differences between healthy males and females in European samples²⁸⁵. However, none of the confounding SNPs in the second study²⁸⁵ showed statistical significant associations in gender-specific analysis in the present study. Such an association would be invalid due to the violation of the major assumption of case-only approach.

Issues related with case-control design do not necessarily apply to a case-only design. All of these cases were incident cases of childhood ALL and have a well-defined phenotype, with molecular ALL sub-types. However, we did not have complete data to examine associations in childhood ALL sub-types. One more strength of the present study is the validation of previously known leukemia risk markers in the parent case-control group. Thus, it increases the validity of our results.

8. CONCLUSION

This research was conducted to explore the effect modification by gender and age of the risk for childhood ALL. A case-only study was used to examine the gender- and age-specific associations. The parent study was a case-control study, and replication of GWAS childhood ALL risk markers validated our parent data set and increased the credibility of our study. Our study identified novel risk variants for childhood ALL. These risk variants are gender- and age-specific, which means they are associated with a particular gender (males or females) or age groups (1-5 years or 6-10 years). A total of fourteen risk markers were previously yielded associations with other diseases, such as autoimmune disorders, CLL (rs7169431) and nasopharyngeal carcinoma (rs28421666).

The aim to unmask hidden gender- and age-specific risk variants was based on clear heterogeneity between two genders and age groups. There are, however, very few examples of gender- and age-specific associations in the risk of childhood ALL, but a dedicated GWAS was needed to unravel these hidden risk variants. Our results were based on two approaches: a conventional statistical analysis based on the most statistically significant associations and the results based on the highest effect sizes. The SNPs, rs4813720, rs231237 and rs7323018, yielded the statistically most significant gender-specific associations. Likewise, rs10505918 yielded the lowest P value for age-specific associations, and also yielded the most statistically significant association with age-at-onset. Two SNPs, rs12722042 and rs12722039, from the HLA-DQA1 region yielded the highest effect sizes for gender-specific results, and the SNP, rs17109582 and rs7304215, yielded the highest effect sizes for age-specific results.

The statistical gender- or age-specific associations were complemented with bioinformatics and empirical analyses for causality assessment, and yielded some functional variants among the set of SNPs. A total of 29 SNPs showed a very high functional score for gender- and age-specific results, which suggests they may be very important for regulatory effects. Our results also identified a total of 56 nonsynonymous variations (55 missense and one nonsense) for gender- and age-specific associations; however, most of these nonsynonymous variations were associated with the results based on the effect size. These nonsynonymous variations clearly suggest an obvious change in protein function. Likewise, 21 SNPs were located in TFBS and may affect the regulatory function.

Gene enrichment analysis did not yield any specific pathways for childhood ALL risk in gender and age-specific manner. We still explored the functions of associated genes. Several of these genes are associated with RAS, PTEN, JAK/STAT and P13/AKT signaling pathways^{221, 255}. These pathways play a significant role in leukemogenesis. Overall our results yielded novel gender- and age- specific risk variants in this study. Further studies are warranted to replicate the gender- and age-specific associations and to examine mechanisms of those that are confirmed.

Markers, which showed associations differing in directions, will be very useful once confirmed risk to males and protection to females. It is important to know that because any future intervention to protect males may do harm to females if this difference is not recognized. Thus, there is potential for targeted intervention (and maybe treatment approaches) of one gender while the same intervention would not be useful to the other. These results, once confirmed, may also help to devise more personalized treatment for

males. Just now, they get the same treatment but at a higher dose (with more side effects and late effects etc).

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APPENDIX

Appendix Table 1: Genetic risk markers for childhood acute lymphoblastic leukemia in previous genome-wide association studies

SNP	Gene	Gene function	OR (95% CI)	P value	Ref
rs10821936	<i>ARID5B</i>	differentiation of B lymphocyte progenitor	1.91 (1.60-2.20)	1.4×10^{-15}	51
			1.86 (1.71-2.03)	5.90×10^{-46}	53
rs10994982	<i>ARID5B</i>	differentiation of B lymphocyte progenitor	1.61 (1.30-1.90)	5.70×10^{-9}	51
rs7073837	<i>ARID5B</i>	differentiation of B lymphocyte progenitor	1.58 (1.35-1.89)	4.66×10^{-16}	52
			1.64 (1.40-1.92)	1.0×10^{-9}	49
rs10740055	<i>ARID5B</i>	differentiation of B lymphocyte progenitor	1.53 (1.41-1.64)	5.35×10^{-14}	52
			1.75 (1.49-2.06)	1.8×10^{-11}	49
rs7089424	<i>ARID5B</i>	differentiation of B lymphocyte progenitor	1.65 (1.54-1.76)	6.69×10^{-19}	52
			1.83 (1.55-2.15)	6.13×10^{-13}	49
rs11978267	<i>IKZF1</i>	regulator of lymphocyte differentiation	1.69 (1.40-1.90)	8.8×10^{-11}	51
rs4132601	<i>IKZF1</i>	regulator of lymphocyte differentiation	1.69 (1.58-1.81)	1.20×10^{-19}	52
			1.59 (1.34-1.89)	1.2×10^{-7}	49
rs6964969	<i>IKZF1</i>	regulator of lymphocyte differentiation	1.59 (1.45-1.74)	1.59×10^{-29}	53
rs2239633	<i>CEBPE</i>	functional maturation of granulocyte progenitor cells	1.34 (1.22-1.45)	2.88×10^{-7}	52
rs4982731	<i>CEBPE</i>	functional maturation of granulocyte progenitor cells	1.36 (1.24-1.48)	8.97×10^{-12}	53
rs2089222	<i>KRT85</i>	hair and nail formation	2.26 (1.60-3.00)	8.40×10^{-8}	51
rs11155133	6q24	NA	3.62 (2.10-6.00)	3.0×10^{-7}	51
rs2191566	<i>ZNF230</i>	NA	1.52 (1.20-1.70)	3.5×10^{-7}	51
rs6509133	<i>ZNF230</i>	NA	1.48 (1.20-1.70)	1.4×10^{-6}	51
rs7554607	<i>RXR2</i>	calcium channel	1.49 (1.20-1.70)	1.6×10^{-6}	51
rs12621643	<i>KCNE4</i>	voltage-gated potassium channel activity	1.48 (1.20-1.70)	2.8×10^{-6}	51
rs10873876	<i>ST6GALNAC3</i>	NA	1.55 (1.20-1.80)	4×10^{-6}	51
rs9290663	<i>KCNMB2</i>	voltage-gated potassium channel activity	1.58 (1.20-1.90)	6×10^{-6}	51
rs6428370	1q31	NA	1.43 (1.20-1.60)	7×10^{-6}	51
rs1881797	<i>OR2C3</i>	G protein coupled receptor activity	1.52 (1.20-1.80)	7×10^{-6}	51

Appendix Table 1 continued....

SNP	Gene	Gene function	OR (95% CI)	P value	Ref
rs10849033	<i>C12orf5</i>	TP53-induced glycolysis and apoptosis	2.55 (1.60-3.80)	9×10^{-6}	51
rs1879352	18p11.32	NA	1.53 (1.20-1.80)	9×10^{-6}	51
rs563507	<i>PARD3</i>	protein phosphatase binding	2.00 (1.40-2.70)	9×10^{-6}	51
rs3779084	<i>DDC</i>	amino acid binding and protein domain specific binding	1.44 (1.32-1.56)	8.81×10^{-9}	52
rs880028	<i>DDC</i>	amino acid binding and protein domain specific binding	1.43 (1.30-1.56)	1.26×10^{-7}	52
rs7809758	<i>DDC</i>	amino acid binding and protein domain specific binding	1.44 (1.32-1.54)	2.41×10^{-10}	52
rs2242041	<i>DDC</i>	amino acid binding and protein domain specific binding	1.72 (1.30-2.10)	9.9×10^{-7}	51
rs2167364	<i>DDC</i>	amino acid binding and protein domain specific binding	1.46 (1.20-1.70)	2.8×10^{-6}	51
rs930372	<i>ANKRD44</i>	recognition of phosphoprotein substrate	2.37 (1.65-3.41)	3.1×10^{-6}	49
rs1945213	<i>OR8U8</i>	G protein coupled receptor activity	1.30 (1.19-1.43)	3×10^{-8}	54
rs17505102	<i>TP63</i>	sequence specific DNA binding transcriptional activator or repressor	1.47 (1.28-1.67)	2×10^{-8}	54
rs7156960	<i>GPATCH2L</i>	NA	1.22 (1.12-1.33)	3×10^{-6}	54
rs7738636	6q14	NA	1.27 (1.15-1.41)	6×10^{-6}	54
rs282708	4q13.1	NA	1.23 (1.12-1.35)	8×10^{-6}	54
rs4748793	<i>COMMD3</i>	may down-regulate activation of NF-kappa-B	1.40 (1.26-1.57)	8.40×10^{-9}	53
rs3776932	<i>MAN2A1</i>	biosynthesis of complex N-glycans	0.23 (0.10-0.50)	0.0006	50
rs6140264	<i>HAO1</i>	has 2-hydroxyacid oxidase activity	4.33 (1.8-10.20)	0.0008	50
rs12105972	<i>GCFC2</i>	factor that represses transcription, bind to GC-rich sequences	0.30 (0.10-0.60)	0.0015	50
rs17837497	<i>TBXAS1</i>	electron carrier activity and heme binding	2.34 (1.65-3.31)	1.89×10^{-6}	219
rs1496766	<i>MAGI2</i>	enhances the ability of <i>PTEN</i> to suppress AKT1 activation	2.84 (1.81-4.44)	5.45×10^{-6}	219

Appendix Table 1 continued....

SNP	Gene	Gene function	OR (95% CI)	P value	Ref
rs17079534	<i>MYRIP</i>	melanosome transport	4.07 (2.04-6.87)	1.65×10^{-7}	²¹⁹
rs10170236	<i>LOC642340</i>	NA	1.45 (1.24-1.69)	3.92×10^{-6}	²¹⁹
rs7578361	2q23	NA	1.40 (1.21-1.63)	8.40×10^{-6}	²¹⁹
rs7142143	<i>PYGL</i>	pyridoxal phosphate binding and protein homodimerization activity	3.61 (2.34-5.57)	6.72×10^{-9}	²¹⁹
rs6683977	<i>PDE4B</i>	ion channel binding	1.41 (1.22-1.64)	5.13×10^{-6}	²¹⁹
rs546784	<i>PDE4B</i>	ion channel binding	1.40 (1.20-1.62)	1.17×10^{-5}	²¹⁹

SNP = single nucleotide polymorphism; OR = odds ratio; CI = confidence interval; Ref = reference

Appendix Table 2: Top one hundred SNPs associated with childhood ALL risk with gender-specificity, results based on the lowest P values

					Minor allele frequency				
SNP	Gene/region	Chr [†]	Minor allele	Feature	Males	Females	OR _{allele} (95% CI)*	P value**	P value (permutation) ^{††}
rs4813720	<i>RASSF2</i>	20	A	5upstream	0.23	0.47	0.29 (0.17 - 0.48)	1.90 x 10 ⁻⁰⁶	1.0 x 10 ⁻⁴
rs231237	<i>HSPB6</i>	19	A	5upstream	0.42	0.21	3.00 (1.86 - 4.85)	7.15 x 10 ⁻⁰⁶	1.0 x 10 ⁻⁴
rs7323018	13q14.1	13	G	intergenic	0.17	0.36	0.31 (0.18 - 0.52)	8.40 x 10 ⁻⁰⁶	1.0 x 10 ⁻⁴
rs17027254	2p22	2	T	intergenic	0.19	0.39	0.37 (0.23 - 0.58)	1.86 x 10 ⁻⁰⁵	1.0 x 10 ⁻⁴
rs7912381	10q26.3	10	G	intergenic	0.39	0.21	2.78 (1.71 - 4.51)	3.68 x 10 ⁻⁰⁵	1.0 x 10 ⁻⁴
rs11687208	2p22	2	C	intergenic	0.21	0.4	0.40 (0.26 - 0.62)	4.81 x 10 ⁻⁰⁵	1.0 x 10 ⁻⁴
rs798292	<i>MAGI2</i>	7	G	intronic	0.16	0.35	0.38 (0.24 - 0.61)	4.88 x 10 ⁻⁰⁵	1.5 x 10 ⁻⁴
rs13107783	4p15.3	4	C	intergenic	0.32	0.52	0.40 (0.26 - 0.62)	5.16 x 10 ⁻⁰⁵	2.0 x 10 ⁻⁴
rs4470624	4p15.3	4	T	intergenic	0.32	0.52	0.40 (0.25 - 0.62)	5.16 x 10 ⁻⁰⁵	2.0 x 10 ⁻⁴
rs1849374	12p11.2	12	A	intergenic	0.44	0.25	2.48 (1.58 - 3.88)	7.35 x 10 ⁻⁰⁵	2.0 x 10 ⁻⁴
rs12948120	<i>ACACA</i>	17	C	intronic	0.29	0.49	0.44 (0.29 - 0.66)	7.46 x 10 ⁻⁰⁵	3.0 x 10 ⁻⁴
rs6904762	6q23	6	G	intergenic	0.27	0.46	0.41 (0.26 - 0.64)	1.00 x 10 ⁻⁰⁵	1.0 x 10 ⁻⁴
rs506389	8q22.3	8	A	intergenic	0.28	0.11	2.99 (1.74 - 5.15)	7.98 x 10 ⁻⁰⁵	2.0 x 10 ⁻⁴
rs6732320	2p22	2	T	intergenic	0.2	0.38	0.41 (0.26 - 0.64)	8.08 x 10 ⁻⁰⁵	3.0 x 10 ⁻⁴
rs8081866	<i>ACACA</i>	17	T	intronic	0.28	0.48	0.45 (0.30 - 0.67)	8.64 x 10 ⁻⁰⁵	3.0 x 10 ⁻⁴
rs349714	3p25	3	G	intergenic	0.44	0.26	2.43 (1.56 - 3.80)	8.76 x 10 ⁻⁰⁵	2.0 x 10 ⁻⁴
rs7583193	2p22	2	G	intergenic	0.19	0.38	0.41 (0.26 - 0.64)	9.09 x 10 ⁻⁰⁵	1.0 x 10 ⁻⁴
rs206457	18p11.2	18	A	intergenic	0.59	0.38	2.24 (1.49 - 3.35)	9.32 x 10 ⁻⁰⁴	1.0 x 10 ⁻⁴
rs7723568	5p15.3	5	A	intergenic	0.35	0.18	2.66 (1.62 - 4.36)	1.10 x 10 ⁻⁰⁴	2.0 x 10 ⁻⁴
rs2542660	<i>ACACA</i>	17	C	intronic	0.26	0.46	0.45 (0.30 - 0.68)	1.16 x 10 ⁻⁰⁴	3.0 x 10 ⁻⁴

Appendix Table 2 continued....

					Minor allele frequency				
SNP	Gene/region	Chr [†]	Minor allele	Feature	Males	Females	OR _{allele} (95% CI)*	P value**	P value (permutation) ^{††}
rs1899286	2p22	2	A	intergenic	0.21	0.39	0.42 (0.27 - 0.66)	1.19 x 10 ⁻⁰⁴	2.0 x 10 ⁻⁴
rs9563035	13q14	13	G	intergenic	0.5	0.31	2.30 (1.50 - 3.52)	1.24 x 10 ⁻⁰⁴	1.0 x 10 ⁻⁴
rs2542653	ACACA	17	C	intronic	0.26	0.46	0.46 (0.31 - 0.68)	1.32 x 10 ⁻⁰⁴	2.0 x 10 ⁻⁴
rs6490437	13q12	13	G	intergenic	0.41	0.6	0.44 (0.29 - 0.67)	1.34 x 10 ⁻⁰⁴	2.0 x 10 ⁻⁴
rs4794031	17q21	17	C	intergenic	0.43	0.24	2.32 (1.50 - 3.58)	1.42 x 10 ⁻⁰⁴	3.0 x 10 ⁻⁴
rs2544371	2q31	2	G	intergenic	0.37	0.57	0.45 (0.30 - 0.68)	1.52 x 10 ⁻⁰⁴	1.0 x 10 ⁻⁴
rs1372166	2p22	2	C	intergenic	0.13	0.28	0.36 (0.21 - 0.61)	1.83 x 10 ⁻⁰⁴	2.0 x 10 ⁻⁴
rs7294845	SOX5	12	T	intronic	0.20	0.37	0.41 (0.26 - 0.65)	1.59 x 10 ⁻⁰⁴	1.0 x 10 ⁻⁴
rs12219278	10q26	10	T	intergenic	0.29	0.14	2.74 (1.62 - 4.64)	1.79 x 10 ⁻⁰⁴	2.0 x 10 ⁻⁴
rs4942264	13q13	13	T	intergenic	0.12	0.26	0.36 (0.21 - 0.62)	2.04 x 10 ⁻⁰⁴	2.5 x 10 ⁻⁴
rs11708505	3p13	3	A	intergenic	0.41	0.6	0.47 (0.31 - 0.70)	2.11 x 10 ⁻⁰⁴	2.0 x 10 ⁻⁴
rs6540610	HHAT	1	A	intronic	0.18	0.39	0.39 (0.24 - 0.65)	2.18 x 10 ⁻⁰⁴	4.0 x 10 ⁻⁴
rs2764928	1p32	1	A	intergenic	0.12	0.26	0.36 (0.21 - 0.62)	2.43 x 10 ⁻⁰⁴	2.0 x 10 ⁻⁴
rs1550017	4q32	4	A	intergenic	0.17	0.05	4.23 (1.96 - 9.14)	2.45 x 10 ⁻⁰⁴	1.0 x 10 ⁻⁴
rs12054636	4q32	4	A	intergenic	0.17	0.05	4.23 (1.96 - 9.14)	2.45 x 10 ⁻⁰⁴	1.0 x 10 ⁻⁴
rs2764933	1p32	1	A	intergenic	0.32	0.51	0.45 (0.30 - 0.69)	2.48 x 10 ⁻⁰⁴	2.0 x 10 ⁻⁴
rs468771	GRIK1	21	T	intronic	0.33	0.17	2.48 (1.52 - 4.02)	2.54 x 10 ⁻⁰⁴	3.0 x 10 ⁻⁴
rs864674	5p13	5	C	intergenic	0.55	0.38	2.27 (1.46 - 3.53)	2.65 x 10 ⁻⁰⁴	1.0 x 10 ⁻⁴
rs8106959	KMT2B	19	G	intronic	0.25	0.11	2.87 (1.63 - 5.07)	2.66 x 10 ⁻⁰⁴	3.0 x 10 ⁻⁴
rs9561489	GPC6	13	A	intronic	0.40	0.57	0.45 (0.29 - 0.70)	2.86 x 10 ⁻⁰⁴	4.0 x 10 ⁻⁴
rs4934956	10p11.2	10	T	intergenic	0.56	0.38	2.20 (1.44 - 3.37)	2.91 x 10 ⁻⁰⁴	3.0 x 10 ⁻⁴

Appendix Table 2 continued....

					Minor allele frequency				
SNP	Gene/region	Chr [†]	Minor allele	Feature	Males	Females	OR _{allele} (95% CI)*	P value**	P value (permutation) ^{††}
rs9897342	17q11.1	17	A	intergenic	0.43	0.26	2.21 (1.44 - 3.40)	3.03 x 10 ⁻⁰⁴	5.0 x 10 ⁻⁴
rs756134	1p13	1	A	intergenic	0.53	0.35	2.10 (1.40 - 3.15)	3.11 x 10 ⁻⁰⁴	4.0 x 10 ⁻⁴
rs4926465	<i>KIF28P</i>	1	G	5upstream	0.49	0.44	0.43 (0.27 - 0.68)	3.14 x 10 ⁻⁰⁴	3.0 x 10 ⁻⁴
rs552976	<i>ABCB11</i>	2	T	intronic	0.17	0.53	0.40 (0.24 - 0.66)	3.15 x 10 ⁻⁰⁴	1.0 x 10 ⁻⁴
rs563694	2q31	2	G	intergenic	0.16	0.54	0.38 (0.23 - 0.65)	3.20 x 10 ⁻⁰⁴	3.0 x 10 ⁻⁴
rs1529186	3q13.1	3	A	intergenic	0.14	0.29	0.40 (0.24 - 0.66)	3.47 x 10 ⁻⁰⁴	2.0 x 10 ⁻⁴
rs11049786	12p11.2	12	G	intergenic	0.44	0.27	2.24 (1.44 - 3.50)	3.50 x 10 ⁻⁰⁴	4.0 x 10 ⁻⁴
rs9510793	<i>TNFRSF19</i>	13	C	intronic	0.35	0.20	2.40 (1.49 - 3.88)	3.51 x 10 ⁻⁰⁴	3.0 x 10 ⁻⁴
rs61748746	<i>N4BP2</i>	4	A	coding	0.02	0.10	0.10 (0.02 - 0.36)	3.64 x 10 ⁻⁰⁴	1.5 x 10 ⁻⁴
rs2874641	<i>SHISA6</i>	17	G	intronic	0.19	0.35	0.43 (0.27 - 0.69)	3.64 x 10 ⁻⁰⁴	2.0 x 10 ⁻⁴
rs560887	<i>G6PC2</i>	2	A	intronic	0.14	0.59	0.37 (0.21 - 0.64)	3.72 x 10 ⁻⁰⁴	4.5 x 10 ⁻⁴
rs7025331	9p24	9	C	intergenic	0.40	0.57	0.46 (0.30 - 0.71)	3.72 x 10 ⁻⁰⁴	4.5 x 10 ⁻⁴
rs7917910	10q26	10	A	intronic	0.24	0.33	0.43 (0.27 - 0.69)	3.74 x 10 ⁻⁰⁴	6.0 x 10 ⁻⁴
rs349707	3p25	3	G	intergenic	0.43	0.57	0.51 (0.35 - 0.74)	3.76 x 10 ⁻⁰⁴	2.0 x 10 ⁻⁴
rs61748749	<i>N4BP2</i>	4	G	coding	0.16	0.10	0.10 (0.03 - 0.36)	3.93 x 10 ⁻⁰⁴	1.5 x 10 ⁻⁴
rs9873177	<i>PDIA5</i>	3	C	intronic	0.06	0.18	0.30 (0.16 - 0.59)	4.03 x 10 ⁻⁰⁴	2.0 x 10 ⁻⁴
rs739924	<i>SPATA20</i>	17	C	intronic	0.25	0.43	0.45 (0.29 - 0.70)	4.04 x 10 ⁻⁰⁴	4.0 x 10 ⁻⁴
rs12505859	4q35	4	G	intergenic	0.39	0.30	2.07 (1.38 - 3.11)	4.10 x 10 ⁻⁰⁴	4.0 x 10 ⁻⁴
rs7322477	<i>LINC00284</i>	13	C	intronic	0.14	0.27	0.39 (0.23 - 0.66)	4.15 x 10 ⁻⁰⁴	6.0 x 10 ⁻⁴
rs1978759	<i>MGMT</i>	10	A	intronic	0.36	0.36	0.44 (0.27 - 0.69)	4.17 x 10 ⁻⁰⁴	6.0 x 10 ⁻⁴
rs725038	<i>ACACA</i>	17	C	intronic	0.32	0.55	0.51 (0.35 - 0.74)	4.18 x 10 ⁻⁰⁴	5.0 x 10 ⁻⁴

Appendix Table 2 continued....

					Minor allele frequency				
SNP	Gene/region	Chr [†]	Minor allele	Feature	Males	Females	OR _{allele} (95% CI)*	P value**	P value (permutation) ^{††}
rs729867	<i>CSRNP3</i>	2	T	intronic	0.18	0.09	2.92 (1.61 - 5.31)	4.33 x 10 ⁻⁰⁴	3.0 x 10 ⁻⁴
rs4875742	<i>CSMD1</i>	8	C	intronic	0.30	0.23	0.36 (0.20 - 0.64)	4.63 x 10 ⁻⁰⁴	2.0 x 10 ⁻⁴
rs1720326	11q24	11	G	intergenic	0.49	0.25	2.18 (1.41 - 3.39)	5.06 x 10 ⁻⁰⁴	2.0 x 10 ⁻⁴
rs1713676	11q23	11	T	intergenic	0.43	0.39	2.21 (1.41 - 3.45)	5.10 x 10 ⁻⁰⁴	6.0 x 10 ⁻⁴
rs3857193	<i>SORCS2</i>	4	C	intronic	0.25	0.36	0.46 (0.29 - 0.71)	5.18 x 10 ⁻⁰⁴	8.0 x 10 ⁻⁴
rs6987111	<i>CCDC25</i>	8	A	intronic	0.15	0.05	3.91 (1.81 - 8.46)	5.21 x 10 ⁻⁰⁴	4.0 x 10 ⁻⁴
rs4801931	<i>ZNF611</i>	19	C	intronic	0.28	0.54	0.49 (0.32 - 0.73)	5.24 x 10 ⁻⁰⁴	6.0 x 10 ⁻⁴
rs12940887	<i>ZNF652</i>	17	T	intronic	0.30	0.19	2.27 (1.43 - 3.61)	5.28 x 10 ⁻⁰⁴	2.0 x 10 ⁻⁴
rs7225787	<i>ZNF652</i>	17	C	intronic	0.34	0.27	2.09 (1.38 - 3.16)	5.28 x 10 ⁻⁰⁴	3.0 x 10 ⁻⁴
rs11079867	17q21	17	C	intergenic	0.44	0.28	2.07 (1.37 - 3.12)	5.32 x 10 ⁻⁰⁴	7.0 x 10 ⁻⁴
rs4680582	<i>SMC4</i>	3	A	intronic	0.16	0.06	3.33 (1.69 - 6.58)	5.33 x 10 ⁻⁰⁴	5.0 x 10 ⁻⁴
rs1429143	6p12	6	G	intergenic	0.37	0.34	0.43 (0.27 - 0.69)	5.39 x 10 ⁻⁰⁴	3.0 x 10 ⁻⁴
rs10506041	12p11.2	12	A	intergenic	0.46	0.38	2.16 (1.40 - 3.34)	5.47 x 10 ⁻⁰⁴	4.0 x 10 ⁻⁴
rs1915337	3q13.1	3	A	intergenic	0.10	0.24	0.39 (0.22 - 0.66)	5.50 x 10 ⁻⁰⁴	7.0 x 10 ⁻⁴
rs6962352	<i>HIP1</i>	7	G	intronic	0.21	0.45	0.49 (0.33 - 0.74)	5.52 x 10 ⁻⁰⁴	5.0 x 10 ⁻⁴
rs634413	<i>LINC00544</i>	13	A	intronic	0.30	0.59	0.50 (0.34 - 0.74)	5.56 x 10 ⁻⁰⁴	4.0 x 10 ⁻⁴
rs4074605	<i>SYNRG</i>	17	C	intronic	0.21	0.1	2.84 (1.57 - 5.14)	5.66 x 10 ⁻⁰⁴	5.0 x 10 ⁻⁴
rs7407281	18p21	18	A	intergenic	0.23	0.1	2.69 (1.53 - 4.74)	6.04 x 10 ⁻⁰⁴	7.0 x 10 ⁻⁴
rs10778311	<i>TXNRD1</i>	12	G	intronic	0.26	0.24	2.09 (1.37 - 3.20)	6.06 x 10 ⁻⁰⁴	4.0 x 10 ⁻⁴
rs7492685	14q21	14	C	intergenic	0.16	0.11	0.10 (0.03 - 0.39)	6.08 x 10 ⁻⁰⁴	3.0 x 10 ⁻⁴
rs4246284	15q26	15	C	intergenic	0.16	0.26	0.40 (0.24 - 0.67)	6.12 x 10 ⁻⁰⁴	2.0 x 10 ⁻⁴

Appendix Table 2 continued....

					Minor allele frequency				
SNP	Gene/region	Chr [†]	Minor allele	Feature	Males	Females	OR _{allele} (95% CI)*	P value**	P value (permutation) ^{††}
rs10128580	<i>ZBTB16</i>	11	G	intronic	0.21	0.09	3.04 (1.61 - 5.74)	6.13 x 10 ⁻⁰⁴	7.0 x 10 ⁻⁴
rs7243843	<i>DLGAPI</i>	18	T	intronic	0.28	0.55	0.51 (0.34 - 0.75)	6.20 x 10 ⁻⁰⁴	8.0 x 10 ⁻⁴
rs1602491	4q34	4	G	intergenic	0.36	0.21	2.24 (1.41 - 3.55)	6.23 x 10 ⁻⁰⁴	7.0 x 10 ⁻⁴
rs17439813	12p11.2	12	C	intergenic	0.44	0.27	2.17 (1.39 - 3.37)	6.23 x 10 ⁻⁰⁴	7.0 x 10 ⁻⁴
rs9373051	<i>EYA4</i>	6	T	intronic	0.25	0.07	3.18 (1.64 - 6.16)	6.26 x 10 ⁻⁰⁴	6.0 x 10 ⁻⁴
rs309026	12p11.2	12	T	intergenic	0.46	0.29	2.07 (1.36 - 3.15)	6.30 x 10 ⁻⁴	1.0 x 10 ⁻⁴
rs11011225	10p11.2	10	T	intergenic	0.07	0.18	0.32 (0.17 - 0.62)	6.62 x 10 ⁻⁴	2.0 x 10 ⁻⁴
rs12904345	15q26.2	15	C	intergenic	0.02	0.24	0.39 (0.23 - 0.67)	6.64 x 10 ⁻⁴	3.0 x 10 ⁻⁴
rs7700370	<i>ADAMTS12</i>	5	C	intronic	0.37	0.21	2.18 (1.39 - 3.40)	6.69 x 10 ⁻⁴	4.0 x 10 ⁻⁴
rs910850	<i>DOK5</i>	20	G	intronic	0.42	0.26	2.08 (1.36 - 3.16)	6.73 x 10 ⁻⁴	4.0 x 10 ⁻⁴
rs12822012	12q13.1	12	C	intergenic	0.09	0.20	0.34 (0.18 - 0.63)	6.81 x 10 ⁻⁴	9.0 x 10 ⁻⁴
rs7237664	18q11.2	18	T	intergenic	0.25	0.54	0.51 (0.34 - 0.75)	6.86 x 10 ⁻⁴	4.0 x 10 ⁻⁴
rs1821567	<i>C8orf34</i>	8	C	intronic	0.31	0.29	2.13 (1.38 - 3.31)	7.07 x 10 ⁻⁴	5.0 x 10 ⁻⁴
rs1477656	5q21	5	T	intergenic	0.23	0.10	2.75 (1.53 - 4.95)	7.09 x 10 ⁻⁴	3.0 x 10 ⁻⁴
rs7163190	15q14	15	G	intergenic	0.20	0.36	0.47 (0.30 - 0.72)	7.12 x 10 ⁻⁴	7.0 x 10 ⁻⁴
rs11648233	<i>HSD17B2</i>	16	C	intronic	0.26	0.44	0.49 (0.32 - 0.74)	7.15 x 10 ⁻⁴	5.0 x 10 ⁻⁴

*OR_{interaction} per allele (OR_{allele}) for the additive model; **P value adjusted for genomic control; ^{††}P value permutation = point wise P value from maxT permutation analysis after 10,000 permutation

[†]Chr = Chromosome, SNP = single nucleotide polymorphism

Appendix Table 3: List of single nucleotide polymorphisms that showed gender-specific associations based on the P value and were statistically correlated

Chr A	SNP 1	Chr B	SNP 2
2	rs7583193	2	rs17027254
2	rs6732320	2	rs1899286
2	rs6732320	2	rs11687208
2	rs1899286	2	rs11687208
2	rs563694	2	rs552976
2	rs17027254	2	rs6732320
2	rs7583193	2	rs6732320
2	rs7583193	2	rs1899286
2	rs17027254	2	rs11687208
2	rs17027254	2	rs1899286
2	rs560887	2	rs563694
2	rs7583193	2	rs11687208
4	rs13107783	4	rs4470624
4	rs61748746	4	rs61748749
4	rs1550017	4	rs12054636
12	rs17439813	12	rs11049786
12	rs17439813	12	rs1849374
12	rs11049786	12	rs1849374
13	rs4942264	13	rs7322477
13	rs634413	13	rs6490437
15	rs4246284	15	rs12904345
17	rs8081866	17	rs2542653
17	rs8081866	17	rs2542660
17	rs8081866	17	rs12948120
17	rs2542653	17	rs2542660
17	rs2542653	17	rs12948120
17	rs2542660	17	rs12948120
17	rs4794031	17	rs7225787
17	rs11079867	17	rs7225787
17	rs4794031	17	rs11079867
17	rs12940887	17	rs7225787
17	rs725038	17	rs2542653

Appendix Table 3 continued....

Chr A	SNP 1	Chr B	SNP 2
17	rs725038	17	rs2542660
17	rs4794031	17	rs12940887

Chr = chromosome; SNP = single nucleotide polymorphism

Note: Chromosome A and Chromosome B are same chromosome. SNP1 and SNP2 are statistically correlated SNPs

Appendix Table 4: List of single nucleotide polymorphisms that showed gender-specific associations based on effect size and were statistically correlated

Chr A	SNP 1	Chr B	SNP 2
2	rs1049894	2	rs11904365
4	rs10003958	4	rs9993832
6	rs130069	6	rs6929434
6	rs12722039	6	rs12722042
6	rs17080410	6	rs61742396
7	rs4496864	7	rs35912436
7	rs4496864	7	rs2160271
7	rs35912436	7	rs2160271
8	rs34265667	8	rs34664882
8	rs11992342	8	rs36041430
8	rs36041430	8	rs7829965
8	rs11992342	8	rs7829965
9	rs3847262	9	rs2890707
9	rs4645656	9	rs7848710
9	rs4645656	9	rs7037100
9	rs4645656	9	rs6477733
9	rs7848710	9	rs7037100
9	rs7848710	9	rs6477733
9	rs7037100	9	rs6477733
19	rs16973890	19	rs117923468
19	rs16973890	19	rs182319278
19	rs117923468	19	rs182319278

Chr = chromosome; SNP = single nucleotide polymorphism

Note: Chromosome A and Chromosome B are same chromosome.
SNP1 and SNP2 and statistically correlated SNPs

Appendix Table 5: Top one hundred SNPs associated with childhood ALL risk with gender-specificity, results based on the highest effect sizes ($P < 0.05$)

					Minor allele frequency				
SNP	Gene/region	Chr	Minor allele	Feature	Males	Females	OR _{allele} (95% CI)*	P value**	P value (permutation) ^{††}
rs12722042	<i>HLA-DQA1</i>	6	G	coding	0.07	0.005	15.68 (2.03 - 121.2)	0.008	0.001
rs12722039	<i>HLA-DQA1</i>	6	A	coding	0.07	0.005	14.87 (1.94 - 114.0)	0.009	0.002
rs11992342	<i>ADAM28</i>	8	T	intron	0.07	0.005	14.73 (1.92 - 113.9)	0.01	0.001
rs80040922	<i>UMODL1</i>	21	A	coding	0.06	0.005	13.68 (1.77 - 105.6)	0.01	0.004
rs61753605	LOC100996481	6	C	coding	0.06	0.005	13.38 (1.73 - 103.3)	0.01	0.004
rs35665085	<i>CECR5</i>	22	A	coding	0.06	0.005	12.64 (1.63 - 98.00)	0.02	0.006
rs143021649	<i>CNTN3</i>	3	T	coding	0.06	0.005	11.62 (1.49 - 90.58)	0.02	0.009
rs6795524	<i>PROS1</i>	3	G	intron	0.05	0.005	10.63 (1.36 - 83.31)	0.02	0.006
rs10003468	4q28.1	4	C	intergenic	0.05	0.005	10.63 (1.36 - 83.31)	0.02	0.005
rs10131142	14q11.2	14	A	intergenic	0.07	0.01	7.82 (1.76 - 34.78)	0.007	0.002
rs3732042	<i>CNRIP1</i>	2	A	3utr	0.08	0.01	7.50 (1.71 - 32.96)	0.008	0.002
rs34022679	<i>GRK4</i>	4	C	coding	0.07	0.01	6.98 (1.58 - 30.76)	0.01	0.003
rs7829965	<i>ADAM28</i>	8	A	coding	0.06	0.01	6.77 (1.51 - 30.38)	0.01	0.007
rs7097067	10q22.1	10	T	intergenic	0.06	0.01	6.77 (1.51 - 30.38)	0.01	0.01
rs35912436	7p21.3	7	C	intergenic	0.08	0.01	6.69 (1.54 - 29.00)	0.01	0.003
rs2160271	7p21.3	7	C	intergenic	0.08	0.01	6.69 (1.54 - 29.00)	0.01	0.003
rs17588454	13q12.3	13	G	intergenic	0.07	0.01	6.47 (1.46 - 28.61)	0.01	0.006
rs368390	<i>C18orf42</i>	18	T	intron	0.09	0.02	6.25 (1.80 - 21.76)	0.004	0.001
rs17080410	<i>PLEKHG1</i>	6	C	coding	0.06	0.01	6.25 (1.38 - 28.25)	0.02	0.01

Appendix Table 5 continued....

					Minor allele frequency				
SNP	Gene/region	Chr	Minor allele	Feature	Males	Females	OR _{allele} (95% CI)*	P value**	P value (permutation) ^{††}
rs61742396	<i>PLEKHG1</i>	6	A	coding	0.06	0.01	6.25 (1.38 - 28.25)	0.02	0.01
rs35672330	<i>EXO5</i>	1	C	coding	0.06	0.01	5.98 (1.35 - 26.50)	0.02	0.01
rs1503292	<i>TLL1</i>	4	C	intron	0.06	0.01	5.97 (1.35 - 26.47)	0.02	0.01
rs1978526	2q24.3	2	G	intergenic	0.06	0.01	5.91 (1.33 - 26.19)	0.02	0.01
rs6887604	5q12.3	5	T	intergenic	0.06	0.01	5.75 (1.26 - 26.16)	0.02	0.01
rs10063286	5q35.2	5	G	intergenic	0.06	0.01	5.75 (1.26 - 26.16)	0.02	0.01
rs16879126	<i>NT5C3A</i>	7	C	intron	0.06	0.01	5.75 (1.26 - 26.16)	0.02	0.009
rs34265667	<i>ANK1</i>	8	A	coding	0.06	0.01	5.75 (1.26 - 26.16)	0.02	0.009
rs34664882	<i>ANK1</i>	8	A	coding	0.06	0.01	5.75 (1.26 - 26.16)	0.02	0.009
rs61731389	<i>PCDH15</i>	10	C	coding	0.06	0.01	5.75 (1.26 - 26.16)	0.02	0.01
rs4764332	12p13.2	12	T	intergenic	0.06	0.01	5.75 (1.26 - 26.16)	0.02	0.01
rs4496864	7p21.3	7	T	intergenic	0.07	0.01	5.72 (1.32 - 24.80)	0.02	0.01
rs6936494	6q15	6	T	intergenic	0.11	0.02	5.67 (1.91 - 16.83)	0.002	7.5 x 10 ⁻⁴
rs3847262	<i>TPD52L3</i>	9	T	coding	0.06	0.01	5.49 (1.24 - 24.43)	0.03	0.009
rs2890707	<i>TPD52L3</i>	9	A	3utr	0.06	0.01	5.49 (1.24 - 24.43)	0.03	0.009
rs7626907	3p24.3	3	A	intergenic	0.10	0.02	5.37 (1.81 - 15.99)	0.003	0.001
rs2229528	<i>ACAA1</i>	3	G	coding	0.05	0.01	5.26 (1.15 - 24.11)	0.03	0.02
rs9842465	<i>SCHIP1</i>	3	T	intron	0.05	0.01	5.26 (1.15 - 24.11)	0.03	0.01
rs6796558	3q28	3	A	intergenic	0.05	0.01	5.26 (1.15 - 24.11)	0.03	0.02
rs55882716	<i>MAST4</i>	5	T	coding	0.05	0.01	5.26 (1.15 - 24.11)	0.03	0.01
rs1030270	<i>CYFIP2</i>	5	A	intron	0.05	0.01	5.26 (1.15 - 24.11)	0.03	0.01

Appendix Table 5 continued....

SNP	Gene/region	Chr	Minor allele	Feature	Minor allele frequency		OR _{allele} (95% CI)*	P value**	P value (permutation) ^{††}
					Males	Females			
rs205944	<i>SLC35F1</i>	6	A	intron	0.05	0.01	5.26 (1.15 - 24.11)	0.03	0.02
rs381783	<i>IL20RA</i>	6	T	intron	0.05	0.01	5.26 (1.15 - 24.11)	0.03	0.01
rs11980237	<i>KDELR2</i>	7	A	intron	0.05	0.01	5.26 (1.15 - 24.11)	0.03	0.01
rs720872	7p21.2	7	C	intergenic	0.05	0.01	5.26 (1.15 - 24.11)	0.03	0.01
rs147596194	<i>RGS3</i>	9	T	intron	0.05	0.01	5.26 (1.15 - 24.11)	0.03	0.01
rs61745456	<i>MAMDC4</i>	9	T	coding	0.05	0.01	5.26 (1.15 - 24.11)	0.03	0.01
rs117923468	<i>WDR87</i>	19	A	coding	0.05	0.01	5.26 (1.15 - 24.11)	0.03	0.01
rs182319278	<i>WDR87</i>	19	C	coding	0.05	0.01	5.26 (1.15 - 24.11)	0.03	0.01
rs9305777	21q21.1	21	T	intergenic	0.05	0.01	5.26 (1.15 - 24.11)	0.03	0.02
rs8129749	21q21.2	21	T	intergenic	0.05	0.01	5.26 (1.15 - 24.11)	0.03	0.01
rs985456	21q21.3	21	C	intergenic	0.05	0.01	5.26 (1.15 - 24.11)	0.03	0.01
rs16863233	<i>LPP</i>	3	C	intron	0.07	0.02	5.16 (1.46 - 18.18)	0.01	0.008
rs7037100	<i>ZNF782</i>	9	C	intron	0.07	0.02	5.16 (1.46 - 18.18)	0.01	0.008
rs7630157	<i>EGFEM1P</i>	3	C	intron	0.06	0.01	5.07 (1.14 - 22.62)	0.03	0.01
rs62640905	<i>OSGIN1</i>	16	C	coding	0.06	0.01	5.02 (1.13 - 22.40)	0.03	0.01
rs16973890	<i>ZNF571/ZNF540</i>	19	C	intron	0.06	0.01	5.02 (1.13 - 22.40)	0.03	0.01
rs35693261	<i>MTG2</i>	20	T	coding	0.06	0.01	5.02 (1.13 - 22.40)	0.03	0.01
rs7539097	<i>TNR</i>	1	G	intron	0.08	0.02	5.00 (1.44 - 17.32)	0.01	0.005
rs9493135	6q23.2	6	A	intergenic	0.08	0.01	4.94 (1.43 - 17.14)	0.01	0.005
rs6722598	<i>MFF</i>	2	A	5upstream	0.09	0.02	4.92 (1.63 - 14.89)	0.005	0.002
rs1049894	<i>PSME4</i>	2	T	coding	0.07	0.02	4.81 (1.36 - 17.03)	0.02	0.01

Appendix Table 5 continued....

SNP	Gene/region	Chr	Minor allele	Feature	Minor allele frequency		OR _{allele} (95% CI)*	P value**	P value (permutation) ^{††}
					Males	Females			
rs11904365	2p16.2	2	C	intergenic	0.07	0.02	4.81 (1.36 - 17.03)	0.02	0.009
rs10003958	<i>RAB28</i>	4	C	intron	0.07	0.02	4.81 (1.36 - 17.03)	0.02	0.01
rs9993832	<i>RAB28</i>	4	T	intron	0.07	0.02	4.81 (1.36 - 17.03)	0.02	0.01
rs36041430	<i>ADAM28</i>	8	A	coding	0.07	0.02	4.81 (1.36 - 17.03)	0.02	0.01
rs78888579	<i>CROCC</i>	1	A	coding	0.05	0.01	4.77 (1.03 - 22.10)	0.05	0.01
rs10218650	1q31.3	1	T	intergenic	0.05	0.01	4.77 (1.03 - 22.10)	0.05	0.04
rs13405142	2p22.1	2	T	intergenic	0.05	0.01	4.77 (1.03 - 22.10)	0.05	0.03
rs10194197	2p12	2	T	intergenic	0.05	0.01	4.77 (1.03 - 22.10)	0.05	0.04
rs61741435	<i>CCDC173</i>	2	T	coding	0.05	0.01	4.77 (1.03 - 22.10)	0.05	0.02
rs4856270	<i>CADM2</i>	3	T	intron	0.05	0.01	4.77 (1.03 - 22.10)	0.05	0.02
rs2165084	4q31.3	4	G	intergenic	0.05	0.01	4.77 (1.03 - 22.10)	0.05	0.02
rs7703414	5p13.1	5	A	intergenic	0.05	0.01	4.77 (1.03 - 22.10)	0.05	0.03
rs11751765	<i>TRERF1</i>	6	T	coding	0.05	0.01	4.77 (1.03 - 22.10)	0.05	0.04
rs7797334	7p21.2	7	C	intergenic	0.05	0.01	4.77 (1.03 - 22.10)	0.05	0.02
rs4278110	7p12.2	7	A	intergenic	0.05	0.02	4.77 (1.03 - 22.10)	0.05	0.03
rs11987106	<i>COLEC10</i>	8	A	intron	0.05	0.01	4.77 (1.03 - 22.10)	0.05	0.03
rs61735202	<i>CCIN</i>	9	A	coding	0.05	0.01	4.77 (1.03 - 22.10)	0.05	0.04
rs943811	10q26.2	10	A	intergenic	0.05	0.01	4.77 (1.03 - 22.10)	0.05	0.03
rs10430621	10q26.3	10	C	intergenic	0.05	0.01	4.77 (1.03 - 22.10)	0.05	0.04
rs11182332	<i>TMEM117</i>	12	A	intron	0.05	0.01	4.77 (1.03 - 22.10)	0.05	0.04
rs2293624	<i>C12orf73</i>	12	A	coding	0.05	0.01	4.77 (1.03 - 22.10)	0.05	0.04

Appendix Table 5 continued....

SNP	Gene/region	Chr	Minor allele	Feature	Minor allele frequency		OR _{allele} (95% CI)*	P value**	P value (permutation) ^{††}
					Males	Females			
rs4770684	<i>PARP4</i>	13	A	coding	0.05	0.01	4.77 (1.03 - 22.10)	0.05	0.03
rs7182827	<i>UBE3A</i>	15	C	intron	0.05	0.01	4.77 (1.03 - 22.10)	0.05	0.04
rs12621721	<i>MAP3K19</i>	2	A	intron	0.05	0.01	4.72 (1.02 - 21.86)	0.05	0.03
rs7275217	21q22.1	21	G	intergenic	0.05	0.01	4.72 (1.02 - 21.86)	0.05	0.03
rs41299607	<i>RGS1</i>	1	A	coding	0.05	0.01	4.56 (1.02 - 20.41)	0.05	0.03
rs9282777	<i>LMO2</i>	11	A	coding	0.05	0.01	4.56 (1.02 - 20.41)	0.05	0.02
rs10520291	2p12	2	A	intergenic	0.08	0.02	4.52 (1.33 - 15.39)	0.02	0.009
rs12037891	<i>PDE4B</i>	1	A	intron	0.06	0.02	4.46 (1.25 - 15.91)	0.02	0.02
rs73022563	<i>PLEKHG4B</i>	5	T	coding	0.06	0.02	4.46 (1.25 - 15.91)	0.02	0.02
rs130069	<i>CCHCR1</i>	6	T	coding	0.06	0.02	4.46 (1.25 - 15.91)	0.02	0.02
rs6929434	<i>TCF19</i>	6	A	5upstream	0.06	0.02	4.46 (1.25 - 15.91)	0.02	0.02
rs10975823	<i>KDM4C</i>	9	C	intron	0.06	0.02	4.46 (1.25 - 15.91)	0.02	0.02
rs4645656	<i>ZNF782</i>	9	T	coding	0.06	0.02	4.46 (1.25 - 15.91)	0.02	0.02
rs7848710	<i>ZNF782</i>	9	T	intron	0.06	0.02	4.46 (1.25 - 15.91)	0.02	0.02
rs6477733	<i>ZNF782</i>	9	G	intron	0.06	0.02	4.46 (1.25 - 15.91)	0.02	0.02
rs17000817	21q21.2	21	C	intergenic	0.08	0.02	4.45 (1.46 - 13.59)	0.009	0.004
rs2633820	<i>SUMF1</i>	3	A	intron	0.08	0.02	4.39 (1.32 - 14.63)	0.02	0.007
rs9469223	6p24	6	G	intergenic	0.08	0.02	4.39 (1.32 - 14.63)	0.02	0.007

*OR_{interaction} per allele (OR_{allele}) for the additive model; **P value adjusted for genomic control; ^{††}P value permutation = point wise P value from maxT permutation analysis after 10,000 permutation

Chr = Chromosome, SNP = single nucleotide polymorphism

Appendix Table 6: Bioinformatic analysis of genetic risk markers for the top one hundred gender-specific associations, results based on the lowest P values

SNP	Chr	RegulomeDB score [†]	F-SNP ^{**}	Gene	Correlated SNP	RegulomeDB score [†]	Gene (correlated SNPs)
rs4813720	20	NS	0.18	<i>RASSF2</i>	rs3215695	2b	<i>RASSF2</i>
rs231237	19	2b	0.12	<i>HSPB6</i>	.	.	.
rs7323018	13	5	NS	<i>LACC1-SMIM2</i>	.	.	.
rs17027254	2	6	NS	<i>HNRNPA1P57-LDHAL3</i>	.	.	.
rs7912381	2	NS	0.1	<i>TCERG1L-PPP2R2D</i>	.	.	.
rs11687208	2	NS	0.1	<i>HNRNPA1P57-LDHAL3</i>	rs1899286	3a	<i>HNRNPA1P57-LDHAL3</i>
rs798292	7	6	NS	<i>MAGI2</i>	.	.	.
rs13107783	4	6	0.1	<i>RPL21P46-SLIT2</i>	rs1905844	2b	<i>RPL21P46-SLIT2</i>
rs4470624	6	6	0.1	<i>RPL21P46-SLIT2</i>	rs1905844	2b	<i>RPL21P46-SLIT2</i>
rs1849374	12	6	NS	<i>CCDC91- FAR2</i>	.	.	.
rs12948120	17	6	0.21	<i>ACACA</i>	rs9330250	2b	<i>ACACA</i>
rs6904762	6	5	NS	<i>TMEM244-L3MBTL3</i>	.	.	.
rs506389	8	NS	NS	<i>ZNF706-DUXAP2</i>	.	.	.
rs6732320	2	6	NS	<i>HNRNPA1P57-LDHAL3</i>	rs1899286	3a	<i>HNRNPA1P57-LDHAL3</i>
rs8081866	17	4	0.21	<i>ACACA</i>	rs9330250	2b	<i>ACACA</i>
rs349714	3	5	0.1	<i>SLC6A1-HRH1</i>	rs13317174	2b	<i>SLC6A1-HRH1</i>
rs7583193	2	NS	NS	<i>HNRNPA1P57-LDHAL3</i>	.	.	.
rs206457	18	6	NS	<i>VAPA-APCDD1</i>	.	.	.
rs7723568	5	5	NS	<i>IRX1-LOC101929153</i>	.	.	.
rs2542660	17	5	0.18	<i>ACACA</i>	rs9330250	2b	<i>ACACA</i>
rs37389	5	NS	0.27	<i>PRLR</i>	.	.	.

Appendix Table 6 continued....

SNP	Chr	RegulomeDB score [†]	F-SNP**	Gene	Correlated SNP	RegulomeDB score [†]	Gene (correlated SNPs)
rs1899286	2	3a	0.1	<i>HNRNPA1P57-LDHAL3</i>	.	.	.
rs9563035	13	NS	NS	<i>LINC00371-FAM124A</i>	.	.	.
rs2542653	17	NS	0	<i>ACACA</i>	rs4299194	2b	<i>ACACA</i>
rs2542653	17	NS	0	<i>ACACA</i>	rs9330250	2b	<i>ACACA</i>
rs6490437	13	6	NS	<i>LINC00544-LINC00384</i>	rs7334559	2b	<i>LINC00544-LINC00384</i>
rs4794031	17	5	0.5	<i>PHOSPHO1-ZNF652</i>	.	.	.
rs2544371	2	6	NS	<i>LRP2-BBS5</i>	.	.	.
rs1372166	2	NS	0.1	<i>HNRNPA1P57-LDHAL3</i>	.	.	.
rs7294845	12	5	NS	<i>SOX5</i>	rs11047322	3a	<i>SOX5</i>
rs7294845	12	5	NS	<i>SOX5</i>	rs11047322	3a	<i>SOX5</i>
rs12219278	10	5	NS	<i>TCERG1L-BNIP3</i>	.	.	.
rs4942264	13	NS	NS	<i>DGKZP1-LINC00284</i>	rs4418956	2b	<i>LINC00284</i>
rs11708505	3	5	0.1	<i>RYBP-SHQ1</i>	rs11708482	2b	<i>RYBP-SHQ1</i>
rs6540610	1	NS	0.1	<i>HHAT</i>	.	.	.
rs2764928	1	NS	0.1	<i>LINC01135-PHBP3</i>	rs7555848	3a	<i>LINC01135-PHBP3</i>
rs1550017	4	6	NS	<i>GRIA2-LOC340017</i>	rs7694905	3a	<i>GRIA2-LOC340017</i>
rs12054636	4	NS	NS	<i>GRIA2-LOC340017</i>	rs7694905	3a	<i>GRIA2-LOC340017</i>
rs2764933	1	5	NS	<i>LINC01135-PHBP3</i>	.	.	.
rs468771	21	NS	NS	<i>GRIK1</i>	.	.	.
rs864674	5	5	0.1	<i>SUB1-NPR3</i>	.	.	.
rs8106959	19	1f	NS	<i>KMT2B</i>	rs10413852	1f	<i>UPK1A</i>
rs8106959	19	1f	NS	<i>KMT2B</i>	rs12461333	1f	<i>UPK1A-ZBTB32</i>

Appendix Table 6 continued....

SNP	Chr	RegulomeDB score [†]	F-SNP**	Gene	Correlated SNP	RegulomeDB score [†]	Gene (correlated SNPs)
rs8106959	19	1f	NS	<i>KMT2B</i>	rs12461285	1f	<i>UPK1A-ZBTB32</i>
rs8106959	19	1f	NS	<i>KMT2B</i>	rs3848662	1f	<i>KMT2B</i>
rs9561489	13	NS	NS	<i>GPC6</i>	rs9556347	3a	<i>GPC6</i>
rs4934956	10	5	NS	<i>CICP9-ABCDIP2</i>	.	.	.
rs9897342	17	2b	0.5	<i>MYO18A-TWF1P1</i>	rs7225149	2a	<i>MYO18A</i>
rs756134	1	4	NS	<i>ALX3-UBL4B</i>	.	.	.
rs4926465	1	6	NS	<i>KIF28P</i>	rs7520180	3a	<i>KIF28P</i>
rs552976	2	3a	0.27	<i>ABCB11</i>	.	.	.
rs563694	2	NS	0.1	<i>G6PC2-ABCB11</i>	rs566879	3a	<i>ABCB11</i>
rs1529186	3	4	0.1	<i>LOC100422385- LOC440973</i>	rs62281690	3a	<i>LOC100422385- LOC440973</i>
rs11049786	12	6	NS	<i>CCDC91-FAR2</i>	.	.	.
rs9510793	13	6	NS	<i>TNFRSF19</i>	.	.	.
rs61748746*	4	6	NS	<i>N4BP2</i>	.	.	.
rs2874641	17	5	NS	<i>SHISA6</i>	.	.	.
rs560887	2	NS	NS	<i>G6PC2</i>	.	.	.
rs7025331	9	4	NS	<i>SMARCA2- LOC102723835</i>	.	.	.
rs7917910	10	NS	NS	<i>C10orf90-DOCK1</i>	.	.	.
rs349707	3	6	NS	<i>SLC6A1-HRH1</i>	.	.	.
rs61748749*	4	2b	NS	<i>N4BP2</i>	.	.	.
rs9873177	3	5	0.1	<i>PDIA5</i>	.	.	.
rs739924	17	1f	1	<i>SPATA20</i>	rs9913430	1a	<i>SPATA20</i>
rs12505859	4	NS	0.5	<i>ICE2P1-LINC01060</i>	.	.	.

Appendix Table 6 continued....

SNP	Chr	RegulomeDB score [†]	F-SNP ^{**}	Gene	Correlated SNP	RegulomeDB score [†]	Gene (correlated SNPs)
rs7322477	13	NS	0	<i>LINC00284</i>	rs4418956	2b	<i>LINC00284</i>
rs1978759	10	4	NS	<i>MGMT</i>	rs1978756	2b	<i>MGMT</i>
rs725038	17	6	0.21	<i>ACACA</i>	.	.	.
rs729867	2	6	0.1	<i>CSRNP3</i>	.	.	.
rs4875742	8	6	NS	<i>CSMD1</i>	.	.	.
rs1720326	11	4	NS	<i>SCN3B-ZNF202</i>	rs1275051	1f	<i>SCN3B-ZNF202</i>
rs1713676	11	5	NS	<i>LOC390251-USP28</i>	rs11214739	3a	<i>USP28</i>
rs3857193	4	3a	NS	<i>SORCS2</i>	.	.	.
rs6987111	8	6	NS	<i>CCDC25</i>	rs9314355	1d	<i>LOC100130612- SCARA5</i>
rs6987111	8	6	NS	<i>CCDC25</i>	rs17057911	1f	<i>PBK</i>
rs6987111	8	6	NS	<i>CCDC25</i>	rs17057863	1f	<i>ESCO2</i>
rs4801931	19	5	NS	<i>ZNF611</i>	.	.	.
rs12940887	17	NS	NS	<i>ZNF652</i>	rs16948048	3a	<i>ZNF652</i>
rs7225787	17	NS	NS	<i>ZNF652</i>	.	.	.
rs11079867	17	NS	NS	<i>FLJ40194-ZNF652</i>	rs2011767	2a	<i>FLJ40194-ZNF652</i>
rs4680582	3	6	0.1	<i>SMC4</i>	rs73155903	2b	<i>TRIM59</i>
rs1429143	6	NS	NS	<i>ELOVL5-NANOGP3</i>	.	.	.
rs10506041	12	NS	NS	<i>LOC101928705-FAR2</i>	.	.	.
rs1915337	3	NS	NS	<i>LOC100422385- LOC440973</i>	.	.	.
rs6962352	7	5	0.18	<i>HIP1</i>	.	.	.
rs634413	13	5	NS	<i>LINC00544</i>	rs4769779	3a	<i>LINC00544</i>
rs4074605	17	4	NS	<i>SYNRG</i>	rs7224979	1d	<i>SYNRG</i>

Appendix Table 6 continued....

SNP	Chr	RegulomeDB score [†]	F-SNP ^{**}	Gene	Correlated SNP	RegulomeDB score [†]	Gene (correlated SNPs)
rs4074605	17	4	NS	<i>SYNRG</i>	rs3110626	1f	<i>SYNRG</i>
rs4074605	17	4	NS	<i>SYNRG</i>	rs6607279	1f	<i>SYNRG</i>
rs4074605	17	4	NS	<i>SYNRG</i>	rs8080313	1f	<i>SYNRG</i>
rs7407281	18	NS	NS	<i>LOC100128022- NFE2L3P1</i>	.	.	.
rs10778311	12	5	NS	<i>TXNRD1</i>	rs7138523	3a	<i>TXNRD1</i>
rs10778311	12	5	NS	<i>TXNRD1</i>	rs4329742	3a	<i>TXNRD1</i>
rs10778311	12	5	NS	<i>TXNRD1</i>	rs4569072	3a	<i>TXNRD1</i>
rs7492685	14	6	NS	<i>RPL18P1-ATP5GP2</i>	.	.	.
rs4246284	15	6	NS	<i>RPL31P55- FAM149B1P1</i>	rs12898262	3a	<i>RPL31P55- FAM149B1P1</i>
rs10128580	11	5	0	<i>ZBTB16</i>	.	.	.
rs7243843	18	5	0.55	<i>DLGAP1</i>	rs7228679	2b	<i>DLGAP1</i>
rs1602491	4	5	0.1	<i>ADAM29- LOC100129957</i>	.	.	.
rs17439813	12	NS	NS	<i>LOC101928705- FAR2</i>	.	.	.
rs9373051	6	6	NS	<i>EYA4</i>	.	.	.
rs309026	12	5	NS	<i>LOC101928705- FAR2</i>	.	.	.
rs11011225	10	5	NS	<i>TMEM161BP1- TACC1P1</i>	.	.	.
rs12904345	15	NS	NS	<i>RPL31P55- FAM149B1P1</i>	rs12898262	3a	<i>RPL31P55- FAM149B1P1</i>
rs7700370	5	6	0.1	<i>ADAMTS12</i>	.	.	.
rs910850	20	5	NS	<i>DOK5</i>	.	.	.
rs12822012	12	NS	NS	<i>RPL13AP21- SLC38A1</i>	.	.	.
rs7237664	18	5	NS	<i>CDH2-ARIH2P</i>	.	.	.

Appendix Table 6 continued....

SNP	Chr	RegulomeDB score [†]	F-SNP ^{**}	Gene	Correlated SNP	RegulomeDB score [†]	Gene (correlated SNPs)
rs1821567	8	NS	NS	<i>C8orf34</i>	.	.	.
rs1477656	5	6	0.24	<i>LOC285706-EEF1A1P20</i>	.	.	.
rs7163190	15	NS	NS	<i>GOLGA8B-GJD2</i>	.	.	.
rs11648233	16	6	0.5	<i>HSD17B2</i>	.	.	.

Note: Some associated SNPs showed multiple statistically correlated functional variants

Chr = Chromosome; NS = No score; SNP = single nucleotide polymorphism; *Missense; ^{††}SNPs change or create a binding site for transcription factors

[†]RegulomDb predicts score from 1 to 7. A score of one suggests SNPs have higher functionality and may play an important role in gene regulation A score of 7 predicts least functionality

^{**}F-SNP predicts score from 0 to 1. A score of one suggest higher functionality and a score zero suggests no functional role of a SNP

Appendix Table 7: Bioinformatic analysis of genetic risk markers for the top one hundred gender-specific associations with childhood ALL with the highest effect sizes ($P < 0.05$)

SNP	Chr	Feature	RegulomeDB Score [†]	F-SNP**	Gene/region	Correlated SNP	RegulomeDB score [†]	Gene (Correlated SNPs)
rs12722042*	6	coding	4	0.75	<i>HLA-DQA1</i>	rs28619112	3a	<i>HLA-DQA1</i>
rs12722039*	6	coding	4	0.41	<i>HLA-DQA1</i>	rs28619112	3a	<i>HLA-DQA1</i>
rs11992342	8	intron	6	0.5	<i>ADAM28</i>	.	.	.
rs80040922*	21	coding	NS	NS	<i>UMODL</i>	.	.	.
rs61753605	6	coding	5	NS	<i>LOC100996481</i>	.	.	.
rs35665085*	22	coding	6	0	<i>CECR5</i>	.	.	.
rs143021649*	3	coding	NS	NS	<i>CNTN3</i>	.	.	.
rs6795524	3	intron	5	0.26	<i>PROS1</i>	rs76514818	3a	<i>ARL13B</i>
rs10003468	4	intergenic	NS	0.1	<i>FAT4-NUPL1P1</i>	.	.	.
rs10131142	14	intergenic	NS	0.5	<i>EDDM3A-EDDM3B</i>	.	.	.
rs3732042	2	3utr	6	0.24	<i>CNRIP1</i>	rs73935338	2b	<i>PPP3R1- CNRIP1</i>
rs34022679*	4	coding	5	0.1	<i>GRK4</i>	.	.	.
rs7829965*	8	coding	2b	0.5	<i>ADAM28</i>	.	.	.
rs7097067	10	intergenic	6	0.5	<i>PPA1-NPFFR1</i>	rs60660561	2b	<i>PPA1</i>
rs7097067	10	intergenic	6	0.5	<i>PPA1-NPFFR1</i>	rs56938544	2b	<i>NPFFR1</i>
rs35912436	7	intergenic	6	NS	<i>TMEM106B-VWDE</i>	rs2192840	2b	<i>TMEM106B-VWDE</i>
rs2160271	7	intergenic	NS	NS	<i>TMEM106B-VWDE</i>	rs2192840	2b	<i>TMEM106B-VWDE</i>
rs17588454	13	intergenic	5	NS	<i>LINC00544-LINC00384</i>	rs4534683	2b	<i>LINC00544-LINC00384</i>
rs368390	18	intron	6	0.5	<i>C18orf42</i>	.	.	.
rs17080410*	6	coding	5	0	<i>PLEKHG1</i>	.	.	.
rs61742396*	6	coding	5	NS	<i>PLEKHG1</i>	rs57264696	2a	<i>PLEKHG1-MTHFD1L</i>

Appendix Table 7 continued....

SNP	Chr	Feature	RegulomeDB Score [†]	F-SNP**	Gene/region	Correlated SNP	RegulomeDB score [†]	Gene (Correlated SNPs)
rs35672330*	1	coding	5	0	<i>EXO5</i>	.	.	.
rs1503292	4	intron	6	NS	<i>TLL1</i>	.	.	.
rs1978526	2	intergenic	6	NS	<i>KCNH7- RPL7P61</i>	rs72623141	3a	<i>KCNH7-RPL7P61</i>
rs6887604	5	intergenic	6	NS	<i>CD180- LOC101928819</i>	rs78308574	3a	<i>CD180- LOC101928819</i>
rs10063286	5	intergenic	NS	0.1	<i>DRD1-SFXN1</i>	rs201488474	3a	<i>DRD1-SFXN1</i>
rs16879126	4	intron	4	NS	<i>NT5C3</i>	rs72555715	2c	<i>NT5C3A</i>
rs34265667	8	coding	5	0.14	<i>ANK1</i>	.	.	.
rs34664882*	8	coding	5	0	<i>ANK1</i>	.	.	.
rs61731389*	10	coding	6	NS	<i>PCDH15</i>	rs72797047	3a	<i>PCDH15</i>
rs4764332	12	intergenic	NS	NS	<i>GABARAPL1- KLRD1</i>	rs73060081	2b	<i>GABARAPL1- KLRD1</i>
rs4496864	7	intergenic	NS	NS	<i>TMEM106B-VWDE</i>	rs2192840	2b	<i>TMEM106B-VWDE</i>
rs6936494	6	intergenic	NS	NS	<i>ACTBP8- LOC101928936</i>	.	.	.
rs3847262	9	coding	NS	0.87	<i>TPD52L3</i>	rs10758768	2a	<i>TPD52L3-UHRF2</i>
rs2890707	9	3utr	2b	NS	<i>TPD52L3</i>	rs10758768	2a	<i>TPD52L3-UHRF2</i>
rs7626907	3	intergenic	NS	NS	<i>KCNH8-EFHB</i>	.	.	.
rs2229528	3	coding	2b	NS	<i>ACAA1</i>	.	.	.
rs9842465	3	intron	NS	0.24	<i>SCHIP1</i>	rs13434009	3a	<i>SCHIP1</i>
rs6796558	3	intergenic	6	0.1	<i>PYDC2-FGF12</i>	.	.	.
rs55882716*	5	coding	5	NS	<i>MAST4</i>	.	.	.
rs1030270	5	intron	NS	NS	<i>CYFIP2</i>	rs61088678	3a	<i>CYFIP2</i>
rs205944	6	intron	NS	NS	<i>SLC35F1</i>	.	.	.
rs381783	6	intron	NS	NS	<i>IL20RA</i>	rs276497	2b	<i>IL20RA</i>

Appendix Table 7 continued....

SNP	Chr	Feature	RegulomeDB Score [†]	F-SNP ^{**}	Gene/region	Correlated SNP	RegulomeDB score [†]	Gene (Correlated SNPs)
rs381783	6	intron	NS	NS	<i>IL20RA</i>	rs276498	2b	<i>IL20RA</i>
rs381783	6	intron	NS	NS	<i>IL20RA</i>	rs276499	2b	<i>IL20RA</i>
rs11980237	7	intron	NS	0	<i>KDELR2</i>	.	.	.
rs720872	7	intergenic	NS	NS	<i>DGKB-AGMO</i>	rs218078	3a	<i>DGKB-AGMO</i>
rs147596194*	9	intron	4	NS	<i>RGS3</i>	rs118167986	2b	<i>RGS3</i>
rs147596194*	9	intron	4	NS	<i>RGS3</i>	rs76385691	2b	<i>RGS3</i>
rs147596194*	9	intron	4	NS	<i>RGS3</i>	rs117507747	2b	<i>RGS3</i>
rs147596194*	9	intron	4	NS	<i>RGS3</i>	rs113069800	2b	<i>RGS3</i>
rs147596194*	9	intron	4	NS	<i>RGS3</i>	rs150767530	2b	<i>RGS3- LOC100288542</i>
rs61745456*	9	coding	5	NS	<i>MAMDC4</i>	.	.	.
rs117923468*	19	coding	NS	NS	<i>WDR87</i>	.	.	.
rs182319278*	19	coding	NS	NS	<i>WDR87</i>	.	.	.
rs9305777	5	intergenic	5	NS	<i>MIR99AHG-NEK4P1</i>	.	.	.
rs8129749	21	intergenic	NS	NS	<i>LOC339622- RNA5SP489</i>	rs11909912	3a	<i>LOC339622- RNA5SP489</i>
rs985456	21	intergenic	5	NS	<i>MARCKSP1- LOC100996571</i>	rs79015379	3a	<i>LOC102724317- CYR1-ASI</i>
rs16863233	3	intron	NS	0.24	<i>LPP</i>	.	.	.
rs7037100	9	intron	5	NS	<i>ZNF782</i>	rs12349952	1f	<i>ZNF510</i>
rs7630157	3	intron	NS	0.1	<i>EGFEM1P</i>	.	.	.
rs62640905*	16	coding	5	NS	<i>OSGIN1</i>	.	.	.
rs16973890*	19	intron	4	0.62	<i>ZNF571</i>	.	.	.
rs35693261*	20	coding	5	0.1	<i>MTG2</i>	.	.	.
rs7539097	1	intron	5	NS	<i>TNR</i>	rs80216135	3a	<i>TNR</i>

Appendix Table 7 continued....

SNP	Chr	Feature	RegulomeDB Score [†]	F-SNP**	Gene/region	Correlated SNP	RegulomeDB score [†]	Gene (Correlated SNPs)
rs9493135	6	intergenic	4	NS	<i>ENPP1-CTGF</i>	rs73779142	3a	<i>ENPP1-CTGF</i>
rs9493135	6	intergenic	4	NS	<i>ENPP1-CTGF</i>	rs9493137	3a	<i>ENPP1-CTGF</i>
rs9493135	6	intergenic	4	NS	<i>ENPP1-CTGF</i>	rs57896928	3a	<i>ENPP1-CTGF</i>
rs6722598	2	5upstream	5	0.24	<i>MFF</i>	rs138676164	3a	<i>LOC654841</i>
rs6722598	2	5upstream	5	0.24	<i>MFF</i>	rs201829089	3a	<i>LOC654841</i>
rs1049894	2	coding	NS	0.37	<i>PSME4</i>	rs10180492	3a	<i>GPR75-ASB3</i>
rs1049894	2	coding	NS	0.37	<i>PSME4</i>	rs78542544	3a	<i>PSME4</i>
rs11904365	2	intergenic	6	0.1	<i>PSME4-RPL21P30</i>	.	.	.
rs10003958	4	intron	5	0.1	<i>RAB28</i>	rs7673680	3b	<i>RAB28</i>
rs9993832	4	intron	5	NS	<i>RAB28</i>	rs7673680	3b	<i>RAB28</i>
rs36041430	8	coding	NS	0	<i>ADAM28</i>	.	.	.
rs78888579*	1	coding	5	NS	<i>CROCC</i>	rs116314250	2b	<i>CROCC</i>
rs78888579*	1	coding	5	NS	<i>CROCC</i>	rs140067167	2b	<i>CROCC</i>
rs10218650	1	intergenic	NS	0.1	<i>CDC73-KCNT2</i>	.	.	.
rs13405142	2	intergenic	NS	0.1	<i>HNRNPA1P57-LDHAP3</i>	.	.	.
rs10194197	2	intergenic	6	0.1	<i>GCFC2- SUCLA2P2</i>	.	.	.
rs61741435*	2	coding	6	NS	<i>CCDC173</i>	rs79306213	2b	<i>PPIG</i>
rs4856270	3	intron	5	0.1	<i>CADM2</i>	rs6809486	3a	<i>CADM2</i>
rs2165084	4	intergenic	3a	0.27	<i>KIAA0922-WDR45P</i>	rs2118864	2a	<i>KIAA0922-WDR45P</i>
rs7703414	5	intergenic	6	0.1	<i>INTS6P1-LINC00603</i>	.	.	.
rs11751765*	6	coding	5	0.9	<i>TRERF1</i>	.	.	.
rs7797334	7	intergenic	5	NS	<i>LOC101927558-ISP</i>	.	.	.

Appendix Table 7 continued....

SNP	Chr	Feature	RegulomeDB Score [†]	F-SNP**	Gene/region	Correlated SNP	RegulomeDB score [†]	Gene (Correlated SNPs)
rs4278110	7	intergenic	5	NS	<i>LOC101927558-ISP</i>	rs6583519	3a	<i>CDC14C-LOC100533714</i>
rs11987106	8	intron	6	NS	<i>COLEC10</i>	.	.	.
rs61735202	9	coding	6	NS	<i>CCIN</i>	.	.	.
rs943811	10	intergenic	5	NS	<i>LINC01163-MGMT</i>	.	.	.
rs10430621	10	intergenic	6	NS	<i>TCERG1L-PPP2R2D</i>	.	.	.
rs11182332	12	intron	6	NS	<i>TMEM117</i>	.	.	.
rs2293624*	12	coding	NS	0.37	<i>C12orf73</i>	.	.	.
rs4770684*	13	coding	NS	0.32	<i>PARP4</i>	.	.	.
rs7182827	15	intron	6	NS	<i>UBE3A</i>	rs74946267	2b	<i>UBE3A</i>
rs12621721	2	intron	6	0.1	<i>MAP3K19/YSK4</i>	rs78265845	2b	<i>MAP3K19</i>
rs7275217	21	intergenic	6	NS	<i>KRTAP21-1-KRTAP8</i>	.	.	.
rs41299607*	1	coding	6	0.1	<i>RGSL1</i>	.	.	.
rs9282777	11	coding	5	0.37	<i>LMO2</i>	.	.	.
rs10520291	2	intergenic	NS	0.1	<i>CTNNA2-SUCLG1</i>	.	.	.
rs12037891	1	intron	6	0.1	<i>PDE4B</i>	.	.	.
rs73022563*	5	coding	5	NS	<i>PLEKHG4B</i>	.	.	.
rs130069*	6	coding	5	1	<i>CCHCR1</i>	.	.	.
rs6929434	6	5upstream	1b	0.5	<i>TCF19</i>	.	.	.
rs10975823	9	intron	NS	0	<i>KDM4C</i>	rs10118219	2a	<i>KDM4C</i>
rs4645656*	9	coding	5	0.5	<i>ZNF782</i>	rs12349952	1f	<i>ZNF510</i>
rs7848710	9	intron	NS	NS	<i>ZNF782</i>	rs12349952	1f	<i>ZNF510</i>
rs6477733	9	intron	5	0.5	<i>ZNF782</i>	rs12349952	1f	<i>ZNF510</i>

Appendix Table 7 continued....

SNP	Chr	Feature	RegulomeDB Score [†]	F-SNP ^{**}	Gene/region	Correlated SNP	RegulomeDB score [†]	Gene (Correlated SNPs)
rs17000817	9	intergenic	5	0.5	<i>RNA5P489- RPL13AP7</i>	.	.	.
rs2633820	3	intron	NS	0.1	<i>SUMF1</i>	.	.	.
rs9469223	6	intergenic	NS	NS	<i>NEDD9-HIVEP1</i>	rs17608111	3a	<i>NEDD9-HIVEP1</i>

Note: Some associated SNPs showed multiple statistically correlated functional variants

Chr = Chromosome; NS = No score; SNP = single nucleotide polymorphisms; *Missense; ^{††}SNPs change or create a binding site for transcription factors

[†]RegulomDb predicts score from 1 to 7. A score of one suggests SNPs have higher functionality and may play an important role in gene regulation. A score of 7 predicts least functionality

^{**}F-SNP predicts score from 0 to 1. A score of one suggest higher functionality and a score zero suggests no functional role of a SNP

Appendix Table 8: Expression quantitative trait locus analysis of gender-specific associated genetic risk variants

SNP	Chr	Feature	Gene	eQTL
rs7912381*	2	intergenic	<i>TCERG1L-PPP2R2D</i>	<i>FGD6</i>
rs798292*	7	intronic	<i>MAGI2</i>	<i>MYST2, ATAD2B, EIF1AX</i>
rs1550017*	4	intergenic	<i>GRIA2-LOC340017</i>	<i>FGD6</i>
rs12054636*	4	intergenic	<i>GRIA2-LOC340017</i>	<i>FGD6</i>
rs560887*	2	intronic	<i>G6PC2</i>	<i>P4HA2</i>
rs739924*	17	intronic	<i>SPATA20</i>	<i>SPATA20</i>
rs725038*	17	intronic	<i>ACACA</i>	<i>COL9A3</i>
rs12904345*	15	intergenic	<i>RPL31P55-FAM149B1P1</i>	<i>ROPN1, ROPN1B</i>
rs4299194*	17	intronic	<i>ACACA</i>	<i>LOC100131190, MX2, PLSCR1</i>
rs12461333*	19	intergenic	<i>UPK1A-ZBTB32</i>	<i>CANT1, CLPTM1,</i>
rs9913430*	17	intronic	<i>SPATA20</i>	<i>SPATA20</i>
rs9493135**	6	intergenic	<i>ENPP1-CTGF</i>	<i>NPAL2, ENOSF1, SMG1, PTPN11, ACACA, GALK2, LOC440354, LOC595101, LOC641298</i>

eQTL = expression quantitative trait loci; Chr = chromosome

*Gender-specific results based on the P value; **Gender-specific results based on the effect sizes

Appendix Table 9: Gender- and age-specific single nucleotides polymorphisms and their previous GWAS associations

SNP	Gene	Disease/trait	Results	PUBMED ID
rs552976	G6PC2	Glycated hemoglobin levels	Gender P value	20858683
rs563694	G6PC2	Fasting plasma glucose	Gender P value	18521185
rs560887	G6PC2	Glycemic traits (pregnancy)	Gender P value	23903356
rs560887	G6PC2	Metabolite levels	Gender P value	22916037
rs560887	G6PC2	Fasting glucose-related traits (interaction with BMI)	Gender P value	22581228
rs560887	G6PC2	Fasting plasma glucose	Gender P value	22508271
rs560887	G6PC2	Metabolic syndrome	Gender P value	22399527
rs560887	G6PC2	Metabolite levels	Gender P value	22286219
rs560887	G6PC2	Fasting glucose-related traits	Gender P value	20081858
rs560887	G6PC2	Fasting glucose-related traits	Gender P value	20081858
rs560887	G6PC2	Metabolic traits	Gender P value	19060910
rs560887	G6PC2	Fasting plasma glucose	Gender P value	19060907
rs560887	G6PC2	Fasting plasma glucose	Gender P value	18451265
rs12940887	ZNF652	Blood pressure	Gender P value	21909110
rs9305777	intergenic	Platelet aggregation	Gender OR	17903294
rs5028798	EHF	Volumetric brain MRI	Age P value	17903297
rs4948088	COBL	Type 1 diabetes	Age P value	19430480
rs2116078	KCNB2	Multiple sclerosis (age of onset)	Age P value	19010793
rs12188300	IL12B	Psoriatic arthritis	Age OR	20953186
rs28421666	intergenic	Nasopharyngeal carcinoma	Age OR	20512145
rs7169431	intergenic	Chronic lymphocytic leukemia	Age OR	23770605
rs7169431	intergenic	Chronic lymphocytic leukemia	Age OR	20062064

SNP = single nucleotide polymorphism; OR: odds ratio

Appendix Table 10: Genes showing gender-specific associations (ranked by their P values) and their interactions with chemicals in studies curated in the Comparative Toxicological Database

Gene/region	SNP	Chemical interaction	PubMed IDs
<i>RASSF2</i>	rs4813720	aflatoxin B1, arsenite, benzene, bisphenol A , copper sulfate, dust, ethinyl estradiol, tetrachlorodibenzodioxin, 4-hydroxy-2-nonenal, acetaminophen	22100608, 18929588, 19162166, 12075121, 12075121, 20080153, 20436886 , 17562736, 19549813, 17805423
<i>TCERG1L</i>	rs7912381* rs12219278	arsenite, fonofos, parathion, terbufos, pentachlorophenol	23974009, 22847954, 22847954, 23724009, 23892564
<i>PPP2R2D</i>	rs7912381*	benzo(a)pyrene diol epoxide, PCBs, acetaminophen, bisphenol A, tetrachlorodibenzodioxin, 2,6-dinitrotoluene, sodium selenite	20971185, 19114083, 17562736, 24534842, 21570461, 21346803, 18175754
<i>MAGI2</i>	rs798292	acetaminophen, aflatoxin B1, arsenite, benzo(a)pyrene, benzo(a)pyrene diol epoxide, bisphenol A, PCB, methoxychlor, tetrachlorodibenzodioxin, tungsten carbide, ammonium chloride, bisphenol A, dibutyl phthalate, diethylhexyl phthalate, ammonium chloride	22230336, 21632981, 22100608, 23974009, 20106945, 20382639, 21632981, 21871943, 23359474, 23303685, 21177773, 24935251, 20105288, 23829299, 19114083, 23829299, 16483693, 23359474, 16483693
<i>SLIT2</i>	rs13107783* rs4470624*	aflatoxin B1, asbestos, atrazine, benzo(a)pyrene, benzo(a)pyrene diol epoxide, estradiol, bisphenol A, estrogens, N-acetyl-4-benzoquinoneimine, tetrachlorodibenzodioxin, chlorpyrifos, dibutyl phthalate, flusilazole, hexaconazole, nitrofen, thiram, 2,6-dinitrotoluene, acetaldehyde, ammonium chloride, cyproconazole	20106945, 17331233, 22378314, 21871943, 19150397, 19484750, 22576693, 21233418, 21177773, 21296121, 17361019, 22634333, 20406850, 22634333, 16483693, 22045034
<i>FAR2</i>	rs1849374* rs17439813 rs10506041	arsenite, benzo(a)pyrene, formaldehyde, methylmercuric chloride, potassium chromate(VI), testosterone, tetrachlorodibenzodioxin, aluminum	23974009, 20064835, 23649840, 23179753, 22079256, 21592394, 21998131, 21298039
<i>TMEM244</i>	rs6904762	air pollutants	21757418

Appendix Table 10 continued....

Gene/region	SNP	Chemical interaction	PubMed IDs
<i>ACACA</i>	rs12948120 rs8081866 rs2542660 rs2542653	aflatoxin B1, dihydrotestosterone, arsenite, benzo(a)pyrene, estradiol, formaldehyde, hydrogen peroxide, niclosamide, tetrachlorodibenzodioxin, 1,4-bis(2-(3,5-dichloropyridyloxy))benzene, 2,4-dinitrotoluene, 2,6-dinitrotoluene, acetaminophen, ammonium chloride, aristolochic acids, atrazine, benzene, bisphenol A, bis(tri-n-butyltin)oxide, chlorpyrifos, decamethrin, ethanol, ethinyl estradiol, flusilazole, insecticides, lipopolysaccharides, 2,6-dinitrotoluene, ammonium chloride, ethanol, nicotine	20106945, 18801408, 23974009, 20106945, 23019147, 23649840, 21179406, 22576131, 21632981, 24878338, 21346803, 20406850, 17562736, 16483693, 21167265, 24440342, 19483382, 21932408, 22174045, 21356183, 23401056, 23692951, 24440342, 22382673, 23401056, 22025971, 20406850, 16483693, 23692951, 17635921
<i>L3MBTL3</i>	rs6904762	potassium chromate(VI), acetaminophen, estradiol, copper sulfate, tetrachlorodibenzodioxin	22079256, 17562736, 20068009, 19789285, 21570461
<i>ZNF706</i>	rs506389*	atrazine, benzo(a)pyrene, copper sulfate, bisphenol A	22378314, 20064835, 19549813, 24534842
<i>SLC6A1</i>	rs349714* rs349707*	aflatoxin B1, estradiol, agrochemicals, herbicides, lipopolysaccharides, progesterone, toluene	20106945, 20106945, 22467014, 22467014, 21219332, 20631399, 21827849
<i>HRH1</i>	rs349714* rs349707*	PCB, aflatoxin B1, asbestos, benzo(a)pyrene, benzo(a)pyrene diol epoxide, lipopolysaccharides, particulate matter, vehicle emissions, endosulfan, tetrachlorodibenzodioxin	11238657, 22100608, 22398240, 20064835, 20382639, 21255012, 10051702, 10051702, 16263506, 21570461
<i>VAPA</i>	rs206457	benzene, acetaminophen, benzo(a)pyrene, bisphenol A, dibutyl phthalate, particulate matter, tetrachlorodibenzodioxin, vehicle emissions	19162166, 17562736, 21569818, 21786754, 17379624, 17295261, 21570461, 17295261
<i>APCDD1</i>	rs206457	benzo(a)pyrene diol epoxide, copper sulfate, progesterone, tetrachlorodibenzodioxin, trichostatin A, acetaminophen, estradiol, carbon tetrachloride, toluene	20382639, 19549813, 20864642, 22298810, 24935251, 17562736, 14664709, 17484886, 22967744

Appendix Table 10 continued....

Gene/region	SNP	Chemical interaction	PubMed IDs
<i>PRLR</i>	rs37389	arsenite, azaspiracid, benzo(a)pyrene, estradiol, hydrogen peroxide, potassium chromate(VI), progesterone, methoxychlor, 2,4-dinitrotoluene, PCBs, acetaminophen, aflatoxin B1, benzene, bisphenol A, cadmium, carbon tetrachloride, clofibrate, cyproconazole, dibutyl phthalate, diethylhexyl phthalate, diethylnitrosamine, diethylstilbestrol, epoxiconazole, ethinyl estradiol, fumonisin B1, lead acetate, 2-methoxyethanol, methylmercury II, progesterone, propiconazole, sodium arsenite, sulpiride, sumatriptan, testosterone, tetrachlorodibenzodioxin, trichloroethylene	23974009, 20547569, 22316170, 20660070, 18951874, 22079256, 20660070, 19414516, 21346803, 19467301, 20959002, 17562736, 19770486, 17905399, 22349186, 24067728, 12734012, 17602206, 19770486, 22334560, 21266533, 19850644, 22129741, 22349186, 12655037, 21864555, 23303685, 21061450, 17905399, 16251485, 22937105, 18467677, 16107292, 18162529, 20844152, 21570461, 17905399
<i>FAM124A</i>	rs9563035	atrazine, benzo(a)pyrene, copper sulfate, bisphenol A, tetrachlorodibenzodioxin	22378314, 22316170, 19549813, 19770486
<i>LRP2</i>	rs2544371	bisphenol A, ethinyl estradiol, hydrogen peroxide, tetrachlorodibenzodioxin, PCB, cycloheximide, particulate matter, progesterone, pseudocumene	20170705, 20170705, 20044591, 22298810, 23994337, 20576581, 19176365, 17251523
<i>BBS5</i>	rs2544371	copper sulfate, estrogens, acetaminophen, dibutyl phthalate, dioxins, furan, progesterone, tetrachlorodibenzodioxin	19549813, 21233418, 17562736, 21266533, 20463971, 22079235, 19690047, 21570461
<i>SOX5</i>	rs7294845	benzo(a)pyrene, arsenite, benzo(a)pyrene diol epoxide, bisphenol A, copper sulfate, vomitoxin, acetaminophen, carbon tetrachloride, bis(2-ethylhexyl) phthalate, ethinyl estradiol, methylmercury, mustard gas, polychlorinated biphenyls, potassium dichromate, propiconazole, tetrachlorodibenzodioxin, tobacco smoke pollution	22316170, 23974009, 20382639, 20170705, 19549813, 23792671, 17562736, 17484886, 19850644, 17555576, 20020106, 15674844, 20020106, 23608068, 21278054, 21570461, 20133372
<i>RYBP</i>	rs11708505	acetaminophen, copper sulfate, formaldehyde, hydrogen peroxide, benzo(a)pyrene, dibutyl phthalate	21420995, 19549813, 23649840, 20044591, 20504355, 21266533

Appendix Table 10 continued....

Gene/region	SNP	Chemical interaction	PubMed IDs
<i>SHQ1</i>	rs11708505	atrazine, bisphenol A, tetrachlorodibenzodioxin	22378314, 21786754, 21570461
<i>HHAT</i>	rs6540610	aflatoxin B1, benzo(a)pyrene, copper sulfate, formaldehyde, hydrogen peroxide, tetrachlorodibenzodioxin	20106945, 20106945, 21632981, 20106945, 23649840, 23649840, 20106945, 21632981
<i>GRIA2</i>	rs1550017 rs12054636	arsenite, aflatoxin B1, estradiol, bisphenol A, chlorpyrifos, dieldrin, ethanol, lead, progesterone, tetrachlorodibenzodioxin, toluene	23974009, 23630614, 22154832, 22504913, 11772933, 23719929, 22154832, 16922920, 21827849
<i>GRIK1</i>	rs468771	benzo(a)pyrene, tetrachlorodibenzodioxin, ammonium chloride, progesterone	21802500, 21802500, 16483693, 19690047
<i>SUB1</i>	rs864674	arsenic trioxide, atrazine, formaldehyde, mercury, tetrachlorodibenzodioxin, benzo(a)pyrene, bisphenol A, dioxins, ethinyl estradiol, fipronil, nicotine	20458559, 22378314, 23649840, 19937285, 22574217, 22228805, 21786754, 20463971, 17555576, 23962444, 17456735
<i>NPR3</i>	rs864674	aflatoxin B1, benzo(a)pyrene diol, estradiol, copper sulfate, fonofos, parathion, progesterone, smoke, terbufos, PCB, acetaminophen, arsenic, benzo(a)pyrene, bisphenol A, carbon tetrachloride, lipopolysaccharides, nitrofen, ozone, tetrachlorodibenzodioxin, tobacco smoke pollution	22100608, 20382639, 23019147, 19549813, 22847954, 20864642, 21095227, 22847954, 24935251, 17562736, 19654921, 15034205, 19228888, 17484886, 22128259, 10898224, 19555225, 15034205, 20133372
<i>KMT2B</i>	rs8106959	asbestos, benzene, mercury, tetrachlorodibenzodioxin, uranium compounds, aflatoxin B1, methylcholanthrene	17331233, 19162166, 16823088, 21296121, 19654044, 19770486, 18804290
<i>GPC6</i>	rs9561489	acetaminophen, aflatoxin B1, arsenite, benzo(a)pyrene, benzo(a)pyrene diol, testosterone, carbon tetrachloride	21420995, 20106945, 23974009, 20106945, 21632981, 20382639, 20106945, 23300844, 23179753, 24383497, 24935251, 17484886
<i>MYO18A</i>	rs9897342	estradiol, bisphenol A, copper sulfate, acetaminophen, aflatoxin B1, benzo(a)pyrene, carbon tetrachloride, tetrachlorodibenzodioxin	23019147, 19549813, 17562736, 19770486, 22228805, 17484886, 21570461

Appendix Table 10 continued....

Gene/region	SNP	Chemical interaction	PubMed IDs
<i>ALX3</i>	rs756134	fonofos, parathion, terbufos	22847954, 22847954, 22847954
<i>ABCB11</i>	rs552976 rs563694	acetaminophen, aflatoxin B1, diethylstilbestrol, ethinyl estradiol, lipopolysaccharides, progesterone, tetrachlorodibenzodioxin, benzo(a)pyrene, carbon tetrachloride, potassium dichromate	21420995, 22100608, 20829430, 15205115, 24014644, 16837569, 19770486, 17522070, 23608068
<i>TNFRSF19</i>	rs9510793	arsenic, benzo(a)pyrene, benzo(a)pyrene diol epoxide, estradiol, potassium chromate(VI), progesterone, tetrachlorodibenzodioxin, PCB, acetaminophen, cyproconazole, epoxiconazole, methoxychlor, methylmercuric chloride, DDT, propiconazole	24675094, 20106945, 21632981, 20382639, 23649840, 22079256, 20660070, 21632981, 24383497, 21851831, 17562736, 22334560, 23970803, 20829426, 20864626, 18925944, 21278054, 22334560, 23970803,
<i>N4BP2</i>	rs61748746	acetaminophen, aflatoxin B1, benzo(a)pyrene, formaldehyde, PCB, bisphenol A, tetrachlorodibenzodioxin	21420995, 20106945, 20106945, 23649840, 21786754, 21570461
<i>G6PC2</i>	rs563694 rs560887	cyclophosphamide	15331540
<i>SMARCA2</i>	rs7025331	acetaminophen, arsenic trioxide, benzo(a)pyrene, copper sulfate, potassium chromate(VI), PCB, bisphenol A, dibutyl phthalate, ethinyl estradiol, pentachlorophenol, tetrachlorodibenzodioxin	21420995, 20458559, 20106945, 19549813, 22079256, 19114083, 23359474, 23359474, 17942748, 24642059, 17942748
<i>DOCK1</i>	rs7917910	acetaminophen, aflatoxin B1, atrazine, benzo(a)pyrene, copper sulfate, dibutyl phthalate, lead acetate, methylmercuric chloride, progesterone, sodium arsenite, tetrachlorodibenzodioxin	17562736, 21641981, 22378314, 22316170, 19549813, 21266533, 20542052, 23103053, 19690047, 21297353, 21570461
<i>PDIA5</i>	rs9873177	acetaminophen, atrazine, diazinon, benzo(a)pyrene, bisphenol A, clofibric acid, diethylhexyl phthalate, pentachlorophenol, propiconazole, tetrachlorodibenzodioxin	21420995, 22378314, 22964155, 23179753, 24383497, 19770486, 21786754, 21318169, 21278054, 18495758

Appendix Table 10 continued....

Gene/region	SNP	Chemical interaction	PubMed IDs
<i>SPATA20</i>	rs739924	arsenic trioxide, benzo(a)pyrene, benzo(a)pyrene diol epoxide, cadmium, copper sulfate, tetrachlorodibenzodioxin, bisphenol A, chlorpyrifos, progesterone	20707922, 21632981, 19150397, 24376830, 19549813, 20106945, 21632981, 24586524, 21356183, 23012394
<i>MGMT</i>	rs1978759	aflatoxin B1, benzo(a)pyrene, ethylene dibromide, dust, fonofos, parathion, polycyclic aromatic hydrocarbon, acetaminophen, ammonium chloride, arsenite, estradiol, bisphenol A, carbon tetrachloride, diethylstilbestrol, furan, methylnitrosourea, ozone, praziquantel, sodium arsenite, tetrachlorodibenzodioxin	20106945, 20064835, 12151404, 17805423, 8823159, 23543013, 12883083, 16483693, 18929588, 20965277, 20965277, 17484886, 15890375, 22507866, 20965277, 23358140, 18636392, 15890375, 21813463, 11241755, 21215274
<i>CSRNP3</i>	rs729867	PCB, dibutyl phthalate	19114083, 21266533
<i>CSMD1</i>	rs4875742	aflatoxin B1, tetrachlorodibenzodioxin	23630614, 21570461
<i>SCN3B</i>	rs1720326	aflatoxin B1, methylcholanthrene, PCB, arsenic, benzo(a)pyrene, estradiol, bisphenol A, carbon tetrachloride, cyfluthrin, cypermethrin, dibutyl phthalate, fenvalerate, nitrofen, Ozone	20106945, 20348232, 19114083, 19654921, 21569818, 23557687, 23359474, 12629582, 18538810, 18538810, 23359474, 18538810, 20638522, 17095637
<i>ZNF202</i>	rs1720326	estradiol, formaldehyde	20106945, 20655997
<i>SORCS2</i>	rs3857193	aflatoxin B1, benzo(a)pyrene, formaldehyde, hydrogen peroxide, tetrachlorodibenzodioxin, tobacco smoke pollution	22100608, 21871943, 23649840, 20044591, 24383497, 19933214, 20133372
<i>CCDC25</i>	rs6987111	copper sulfate, acetaminophen, benzo(a)pyrene, bisphenol A, dibutyl phthalate, testosterone, tetrachlorodibenzodioxin	19549813, 17562736, 22228805, 21786754, 21266533, 20844152, 21570461
<i>ZNF611</i>	rs4801931	formaldehyde, smoke	23649840, 21095227
<i>ZNF652</i>	rs12940887 rs7225787 rs4794031 rs11079867	acetaminophen, aflatoxin B1, benzo(a)pyrene, benzo(a)pyrene diol epoxide, estradiol, copper sulfate, formaldehyde, hydrogen peroxide, progesterone, tetrachlorodibenzodioxin, dibutyl phthalate	21420995, 22100608, 22316170, 20018196, 17404688, 19549813, 20655997, 23649840, 23649840, 17404688, 20106945, 21632981, 23179753, 21266533

Appendix Table 10 continued....

Gene/region	SNP	Chemical interaction	PubMed IDs
<i>SMC4</i>	rs4680582	acetaminophen, aflatoxin B1, arsenic trioxide, benzene, benzo(a)pyrene diol epoxide, estradiol, bisphenol A, hydrogen peroxide, mercury, polychlorinated biphenyls, progesterone, testosterone, tetrachlorodibenzodioxin	22230336, 20106945, 17547211, 19162166, 19150397, 20018196, 20382639, 16474171, 19167446, 23410634, 17547211, 23649840, 16474171, 21795739, 18691609
<i>HIP1</i>	rs6962352	acetaminophen, benzo(a)pyrene, copper sulfate, potassium chromate(VI), tetrachlorodibenzodioxin, dibutyl phthalate, ethinyl estradiol,	21420995, 20106945, 19549813, 22079256, 21934132, 21266533, 20227414
<i>SYNRG</i>	rs4074605	formaldehyde, acetaminophen, chlorpyrifos, tetrachlorodibenzodioxin	20655997, 17562736, 18668222, 21570461
<i>TXNRD1</i>	rs10778311	acetaminophen, arsenic trioxide, arsenite, asbestos, benzo(a)pyrene, benzo(a)pyrene diol epoxide, estradiol, caffeine, chlorobenzene, chloropicrin, copper sulfate, cupric chloride, cycloheximide, cylindrospermopsin, diquat, epichlorohydrin, glycidamide, hydrogen peroxide, hydroquinone, mercuric chloride, mercury, methylmercuric chloride, tetrachlorodibenzodioxin, tobacco smoke pollution	21420995, 17640917, 18550526, 18687144, 20106945, 21632981, 22316170, 19150397, 23665804, 18444173, 19800902, 19549813, 21172416, 24211530, 17822822, 18951874, 15452088, 24816296, 17547211, 24816296, 22298810
<i>ZBTB16</i>	rs10128580	acetaminophen, estradiol, mercury, progesterone, arsenic, chlorpyrifos, cyproconazole, flusilazole, hexaconazole, mercuric chloride, ozone, progesterone, propiconazole, sodium arsenite, tetrachlorodibenzodioxin, tobacco smoke pollution	22230336, 17404688, 19937285, 17404688, 19654921, 20350560, 22045034, 20353558, 17460151, 17251523, 21278054, 17682005, 20055451, 20133372
<i>DLGAP1</i>	rs7243843	aflatoxin B1, formaldehyde, tetrachlorodibenzodioxin, bisphenol A, dibutyl phthalate, environmental pollutants, progesterone	22100608, 23649840, 21296121, 24820113, 21266533, 20064776, 22238285
<i>EYA4</i>	rs9373051	benzo(a)pyrene diol epoxide, estradiol, bisphenol A, lead acetate, tetrachlorodibenzodioxin, tobacco smoke pollution	19150397, 23179753, 24383497, 23557687, 21786754, 22641619, 19933214, 20133372

Appendix Table 10 continued....

Gene/region	SNP	Chemical interaction	PubMed IDs
<i>ADAMTS12</i>	rs7700370	acetaminophen, smoke, benzo(a)pyrene, carbon tetrachloride	22230336, 21095227, 24935251, 20713471, 17484886
<i>DOK5</i>	rs910850	arsenic trioxide, arsenite, PCB, benzo(a)pyrene, dibutyl phthalate, potassium chromate(VI)	20458559, 23974009, 24383497, 24935251, 23829299, 14625279, 21266533, 14625279
<i>SLC38A1</i>	rs12822012	acetaminophen, atrazine, benzo(a)pyrene, benzo(a)pyrene diol epoxide, copper sulfate, DDT, chlorpyrifos, heptachlor, lipopolysaccharides, progesterone, tetrachlorodibenzodioxin	21420995, 22378314, 20064835, 20382639, 19549813, 18204070, 18668222, 23153324, 21645290, 20726854, 19770486,
<i>CDH2</i>	rs7237664	arsenite, benzo(a)pyrene, benzo(a)pyrene diol epoxide, DDT, estrogens, hydrogen peroxide, acetaminophen, aflatoxin B1, agrochemicals, bisphenol A, dibutyl phthalate, herbicides, mercuric chloride, methylcholanthrene, pentachlorophenol, progesterone, tetrachlorodibenzodioxin, tobacco smoke pollution	23974009, 17690111, 19150397, 24820114, 15473135, 12419474, 17562736, 19770486, 22467014, 21786754, 21266533, 22467014, 21126564, 21163286, 17556502, 24680724, 20133372
<i>GOLGA8B</i>	rs7163190	DDT, hydrogen peroxide	25014179, 21179406
<i>GJD2</i>	rs7163190	tetrachlorodibenzodioxin	20055451
<i>HSD17B2</i>	rs11648233	acetaminophen, aflatoxin B1, arsenic trioxide, benzo(a)pyrene, benzo(a)pyrene diol epoxide, estradiol, copper sulfate, hydrogen peroxide, progesterone, testosterone, tetrachlorodibenzodioxin, atrazine, bisphenol A, carbon tetrachloride, hexachlorobenzene, mercuric chloride, methoxychlor	21420995, 20106945, 17547211, 20106945, 20382639, 21972996, 19549813, 20044591, 20660070, 16054388, 22298810, 16249480, 22285353, 22285353, 16239168, 15159207, 16507785, 22285353

SNP = single nucleotide polymorphism

Appendix Table 11: Genes showing gender-specific associations (ranked by their OR) and their interactions with chemicals in studies curated in the Comparative Toxicological Database

Gene/region	SNP	Chemical interaction	PubMed IDs
<i>HLA-DQA1</i>	rs12722042 rs12722039	PCB, arsenic, benzene, lipopolysaccharides, mercury, progesterone, aluminum	20638727, 18414638, 16188091, 22235868, 19690047, 21298039
<i>ADAM28</i>	rs11992342 rs7829965 rs36041430	benzo(a)pyrene, estradiol, progesterone, tetrachlorodibenzodioxin, bisphenol A	22316170, 20660070, 20660070, 22298810, 24935251, 24586524
<i>UMODL1</i>	rs80040922	tetrachlorodibenzodioxin, vehicle emissions	21570461, 23940539
<i>CECR5</i>	rs35665085	acetaminophen, 2,4-dinitrotoluene	21420995, 21346803
<i>CNTN3</i>	rs143021649	acetaminophen, aflatoxin B1, benzo(a)pyrene diol epoxide, progesterone, trichostatin A, PCB, ammonium chloride, ethinyl estradiol	21420995, 22100608, 20382639, 21795739, 24935251, 23179753, 19114083, 16483693, 17557909
<i>PROS1</i>	rs6795524	acetaminophen, benzo(a)pyrene diol, estradiol, copper sulfate, particulate matter, PCBs, tetrachlorodibenzodioxin, vehicle emissions, asbestos, benzo(a)pyrene, bisphenol A, carbon tetrachloride, diuron, fipronil, 2,4-dinitrotoluene, 2,6-dinitrotoluene, ammonium chloride, ethinyl estradiol, silicon dioxide	22230336, 20382639, 19619570, 19549813, 17987463, 21334430, 20436886, 19619570, 21934132, 24935251, 23179753, 17987463, 22352330, 22228805, 21786754, 17484886, 23962444, 21346803, 21346803, 16483693, 15288212, 19073995
<i>FAT4</i>	rs10003468	potassium chromate(VI), benzo(a)pyrene, dibutyl phthalate, tetrachlorodibenzodioxin, toluene	22079256, 21569818, 21266533, 19933214, 22967744
<i>CNRIP1</i>	rs3732042	PCB, Acetaminophen, Aflatoxin B1, trichostatin A, Valproic Acid, Tetrachlorodibenzodioxin, Tretinoin	23146750, 21420995, 22100608, 24935251, 23179753, 19654925, 20488242
<i>GRK4</i>	rs34022679	arsenic trioxide, PCBs, benzo(a)pyrene, ethinyl estradiol, tetrachlorodibenzodioxin	15761015, 19114083, 19654925, 17942748, 17942748
<i>PPA1</i>	rs7097067	acetaminophen, copper sulfate, dust, benzo(a)pyrene, estradiol, bisphenol A, furan, pentachlorophenol, progesterone, tetrachlorodibenzodioxin	22230336, 19549813, 17805423, 22228805, 19484750, 21786754, 22240984, 23018184, 21570461

Appendix Table 11 continued....

Gene/region	SNP	Chemical interaction	PubMed IDs
<i>TMEM106B</i>	rs35912436* rs2160271*	benzo(a)pyrene diol epoxide, hydrogen peroxide, testosterone, PCB, acetaminophen, aflatoxin B1, carbon tetrachloride, copper sulfate, tetrachlorodibenzodioxin	20018196, 18951874, 21592394, 22298810, 19467301, 17562736, 19770486, 17484886, 18579281, 22298810
<i>VWDE</i>	rs35912436* rs2160271*	benzo(a)pyrene, tetrachlorodibenzodioxin	22316170, 21570461
<i>KATNAL1</i>	rs17588454	acetaminophen, copper sulfate, potassium chromate(VI), bisphenol A, fipronil, tetrachlorodibenzodioxin	22230336, 19549813, 22079256, 21786754, 21570461
<i>PLEKHG1</i>	rs17080410 rs61742396	arsenic trioxide, formaldehyde, methylmercuric chloride, nicotine, acetaminophen	20458559, 23649840, 23179753, 18438686, 17562736
<i>EXO5</i>	rs35672330	acetaminophen, atrazine, copper sulfate, tetrachlorodibenzodioxin	22230336, 22378314, 19549813, 22574217,
<i>TLL1</i>	rs1503292	lipopolysaccharides, tetrachlorodibenzodioxin, thiram	12057914, 19933214, 20530235
<i>KCNH7</i>	rs1978526	uranium compounds, PCB, aflatoxin B1, carbon tetrachloride, paraquat, perfluorooctane sulfonic acid	19654044, 19114083, 23630614, 12734012, 22563483, 19162173
<i>CD180</i>	rs6887604	acetaminophen, benzo(a)pyrene, estradiol, progesterone, testosterone, biological toxins	17562736, 22228805, 19693291, 19693291, 19682533
<i>DRD1</i>	rs10063286	fonofos, parathion, terbufos, tetrachlorodibenzodioxin, formaldehyde, methoxychlor	22847954, 22847954, 19901195, 17434604
<i>SFXN1</i>	rs10063286	acetaminophen, arsenite, benzo(a)pyrene diol epoxide, bisphenol A, copper sulfate, formaldehyde, PCB, estradiol, tetrachlorodibenzodioxin	21420995, 23974009, 19150397, 22576693, 19549813, 23649840, 20959002, 16684588, 21570461
<i>NT5C3</i>	rs16879126	acetaminophen, ethinyl estradiol, fipronil, lead, tetrachlorodibenzodioxin	17562736, 17942748, 23962444, 16672222, 21570461

Appendix Table 11 continued....

Gene/region	SNP	Chemical interaction	PubMed IDs
<i>ANK1</i>	rs34265667 rs34664882	mercury, testosterone, benzo(a)pyrene, estradiol, dieldrin, tetrachlorodibenzodioxin	19937285, 21592394, 22228805, 20068009, 17942748
<i>GABARAPL1</i>	rs4764332	aflatoxin B1, air pollutants, atrazine, benzo(a)pyrene, copper sulfate, hydrogen peroxide, tetrachlorodibenzodioxin, tobacco smoke pollution, acetaminophen, benzene, dibutyl phthalate, progesterone	21641981, 21757418, 22378314, 22316170, 19549813, 20044591, 21632981, 19101580, 17562736, 15120971, 21266533
<i>KLRD1</i>	rs4764332	acetaminophen, arsenite, benzo(a)pyrene, methotrexate, estradiol, tetrachlorodibenzodioxin, tobacco smoke pollution	17093179, 23974009, 22316170, 17400583, 19484750, 21041162, 20133372
<i>KCNH8</i>	rs7626907	arsenite, lead	23974009, 19921347
<i>EFHB</i>	rs7626907	atrazine, copper sulfate, estradiol, chlorpyrifos	22378314, 19549813, 19484750, 21356183
<i>ACAA1</i>	rs2229528	acetaminophen, aflatoxin B1, copper sulfate, hydrogen peroxide, bisphenol A, cadmium, dibutyl phthalate, furan, phthalic acids, tetrachlorodibenzodioxin	22230336, 20106945, 19549813, 18951874, 19287073, 17327699, 21266533, 15120968, 15728792, 16960034
<i>SCHIP1</i>	rs9842465	acetaminophen, atrazine, benzo(a)pyrene, benzo(a)pyrene diol, copper sulfate, estrogens, aflatoxin B1, carbon tetrachloride, dibutyl phthalate, tetrachlorodibenzodioxin	21420995, 22378314, 20106945, 19150397, 19549813, 21233418, 23724009, 19770486, 17484886, 21266533, 21570461
<i>FGF12</i>	rs6796558	aflatoxin B1, arsenic, arsenic trioxide, arsenite, fonofos, methotrexate, parathion, potassium chromate(VI), terbufos, uranium compounds, PCB, benzo(a)pyrene, carbon tetrachloride	22100608, 24675094, 22521957, 23974009, 22847954, 17400583, 22847954, 22079256, 22847954, 17045167, 19654044, 23179753, 19114083, 22228805, 17484886
<i>MAST4</i>	rs55882716	acetaminophen, aflatoxin B1, cadmium chloride, copper sulfate, dibutyl phthalate, formaldehyde, smoke, testosterone, tetrachlorodibenzodioxin	17562736, 21641981, 12160620, 19549813, 21266533, 20655997, 21095227, 21592394, 22298810

Appendix Table 11 continued....

Gene/region	SNP	Chemical interaction	PubMed IDs
<i>CYFIP2</i>	rs1030270	acetaminophen, aflatoxin B1, air pollutants, arsenic trioxide, atrazine, benzo(a)pyrene, benzo(a)pyrene diol, estradiol, cupric chloride, formaldehyde, progesterone, bisphenol A, methylmercury compounds, tetrachlorodibenzodioxin	22230336, 20106945, 21757418, 15894607, 22378314, 22316170, 20382639, 20660070, 17211630, 23649840, 23649840, 23649840, 20660070, 15894607, 17183730, 21786754, 21664453, 19759094, 15901671
<i>SLC35F1</i>	rs205944	dibutyl phthalate, tetrachlorodibenzodioxin	21266533, 21570461
<i>IL20RA</i>	rs381783	estradiol, progesterone, tetrachlorodibenzodioxin, acetaminophen, benzo(a)pyrene, bisphenol A, mercuric chloride, tetrachlorodibenzodioxin	20660070, 23152189, 23724009, 17562736, 22228805, 21786754, 18496552, 21570461
<i>KDEL2</i>	rs11980237	asbestos, atrazine, copper sulfate, formaldehyde, acetaminophen, bisphenol A, cadmium sulfate, ethinyl estradiol, propiconazole, sodium arsenate, tetrachlorodibenzodioxin	18687144, 22378314, 19549813, 23649840, 21786754, 16221973, 17942748, 21278054, 16882884, 18495758
<i>DGKB</i>	rs720872	progesterone, occupational air pollutants,	21795739, 19936710
<i>AGMO</i>	rs720872	aflatoxin B1, benzo(a)pyrene, copper sulfate, acetaminophen, agrochemicals, diuron, herbicides, mercuric Chloride, tetrachlorodibenzodioxin	22100608, 21871943, 19549813, 17562736, 22467014, 21551480, 22467014, 20353558, 19770486
<i>RGS3</i>	rs147596194	acetaminophen, asbestos, benzo(a)pyrene, estradiol, diazinon, hydrogen peroxide, progesterone, arsenite, benzene, carbon tetrachloride, dibutyl phthalate, methylmercury II, tetrachlorodibenzodioxin	21420995, 17331233, 21714911, 20660070, 23410634, 21592394, 24935251, 18929588, 17905399, 17484886, 21266533, 17905399, 21570461
<i>MAMDC4</i>	rs61745456	benzo(a)pyrene, tetrachlorodibenzodioxin	22228805, 22298810
<i>WDR87</i>	rs117923468 rs182319278	tobacco smoke pollution	18087596

Appendix Table 11 continued....

Gene/region	SNP	Chemical interaction	PubMed IDs
<i>APP</i>	rs985456	benzene, benzo(a)pyrene, cadmium, estradiol, fonofos, hydrogen peroxide, ibuprofen, iron, lead, mercury, methotrexate, nicotine, ozone, parathion, particulate matter, terbufos, uranium, aluminum chloride, cadmium chloride, carbon tetrachloride, dichlorvos, diuron, fipronil, lead acetate, lipopolysaccharides, nickel, nicotine, DDT, progesterone, propiconazole, sodium arsenite, tetrachlorodibenzodioxin, toluene	15707952, 22316170, 16266835, 12963085, 22847954, 21179406, 12777371, 16308480, 22313790, 10617124, 12182891, 17400583, 16627626, 15513908, 22847954, 15513908, 18482095, 19840844, 17484886, 21551480, 23962444, 17277887, 11080519, 16230335, 22764079, 15919760, 21952557, 17135361, 17984292, 19162173, 22484513, 17988898, 21440049
<i>CYR1</i>	rs985456	arsenite, methylmercuric chloride, silicon dioxide, dibutyl phthalate, fipronil, tetrachlorodibenzodioxin, toluene	23974009, 23179753, 23806026, 21266533, 23962444, 24680724
<i>LPP</i>	rs16863233	acetaminophen, aflatoxin B1, benzo(a)pyrene, estradiol, copper sulfate, methylmercuric chloride, PCBs, tetrachlorodibenzodioxin, dibutyl phthalate	21420995, 20106945, 20064835, 19549813, 23179753, 21334430, 21632981, 21266533
<i>ZNF782</i>	rs7037100	arsenic, methylmercuric chloride	21291286, 23103053
<i>OSGIN1</i>	rs62640905	acetaminophen, benzo(a)pyrene, bisphenol A, copper sulfate, hydrogen peroxide, methylmercury compounds, particulate matter, testosterone, tetrachlorodibenzodioxin, vehicle emissions, aflatoxin B1, cadmium chloride, carbon tetrachloride, diethylhexyl phthalate, furan, mercuric chloride, propiconazole	21420995, 22316170, 20170705, 19549813, 23410634, 22129749, 20307321, 21592394, 21632981, 20307321, 19770486, 20061341, 17484886, 19850644, 24183702, 16507785, 21278054, 17963808
<i>MTG2</i>	rs35693261	arsenic, hydrogen peroxide, PCBs, dibutyl phthalate, tetrachlorodibenzodioxin	18414638, 18951874, 19114083, 21266533, 21570461
<i>TNR</i>	rs7539097	copper sulfate, lead, PCBs, arsenic, chlorpyrifos	19549813, 19921347, 19114083, 24019935, 18668222

Appendix Table 11 continued....

Gene/region	SNP	Chemical interaction	PubMed IDs
<i>ENPP1</i>	rs9493135	aflatoxin B1, benzo(a)pyrene diol epoxide, mercury, potassium dichromate, progesterone, tetrachlorodibenzodioxin, PCB, bisphenol A, carbon tetrachloride, chlorpyrifos, dibutyl phthalate, lipopolysaccharide, progesterone	22100608, 20382639, 17547211, 17547211, 20864642, 21632981, 24935251, 24383497, 23196670, 20739668, 17484886, 21356183, 21266533, 17573159, 23018184
<i>CTGF</i>	rs9493135	1-nitropyrene, acetaminophen, arsenic, asbestos, benzo(a)pyrene, benzo(a)pyrene diol epoxide, estradiol, bisphenol A, cadmium, copper sulfate, cycloheximide, diuron, dust, ethinyl estradiol, fonofos, formaldehyde, hydrogen peroxide, lipopolysaccharides, methylmercuric chloride, parathion, piroxicam, smoke, sodium arsenite, terbufos, tetrachlorodibenzodioxin, trichostatin A, aflatoxin B1, aspirin, carbon tetrachloride, chlorpyrifos, dibutyl phthalate, diuron, ethanol, nitrofen, particulate matter, progesterone, testosterone, tobacco smoke pollution, vehicle emissions	19041380, 22230336, 24675094, 22076105, 21632981, 20018196, 14699072, 20170705, 19369054, 19549813, 19684285, 24172598, 15735009, 20170705, 22847954, 23416264, 17965732, 23179753, 22847954, 23155386, 12377979, 22847954, 22298810, 19606018, 24935251, 19770486, 14586741, 19484750, 24586524, 15240111, 20371981, 14724832, 21356183, 21266533, 21551480, 19280452, 21258935, 23358140, 21708214, 23018184, 15788153, 22761892, 21258935, 19165385
<i>ZNF540</i>	rs16973890	acetaminophen	22230336
<i>ZNF571</i>	rs16973890	formaldehyde	20655997
<i>MFF</i>	rs6722598	acetaminophen, copper sulfate, hydrogen peroxide	21420995, 19549813, 20044591
<i>PSME4</i>	rs1049894	arsenic trioxide, benzene, benzo(a)pyrene, estradiol, copper sulfate, decamethrin, formaldehyde, cadmium chloride, dibutyl phthalate, lead nitrate, tetrachlorodibenzodioxin	22521957, 19162166, 23892563, 23019147, 19549813, 23892563, 19187980, 21266533, 19187980, 21570461
<i>ACYP2</i>	rs11904365	atrazine, benzo(a)pyrene, estradiol, ethinyl estradiol, copper sulfate, aflatoxin B1, arsenite, bisphenol A, lead acetate, progesterone, tetrachlorodibenzodioxin	22378314, 22316170, 23019147, 19549813, 17942748, 24935251, 19770486, 18929588, 21932408, 20542052, 23012394, 21570461

Appendix Table 11 continued....

Gene/region	SNP	Chemical interaction	PubMed IDs
<i>RAB28</i>	rs10003958 rs9993832	benzo(a)pyrene, benzo(a)pyrene diol epoxide, copper sulfate, potassium chromate(VI), dibutyl phthalate, ethinyl estradiol, methylmercuric chloride, tetrachlorodibenzodioxin	22316170, 19150397, 19549813, 22079256, 23179753, 21266533, 17942748, 23458150, 21570461, 15901671
<i>CROCC</i>	rs78888579	PCBs, benzo(a)pyrene, dibutyl phthalate, mercuric chloride, tetrachlorodibenzodioxin	21334430, 22228805, 21266533, 16507785, 21570461
<i>KCNT2</i>	rs10218650	acetaminophen, air pollutants, arsenite, progesterone, benzo(a)pyrene, ethinyl estradiol	21420995, 21757418, 23974009, 21795739, 19770486, 17557909
<i>GCFC2</i>	rs10194197	manganese, fipronil, potassium dichromate	17175027, 23962444, 23608068
<i>CCDC173</i>	rs61741435	tetrachlorodibenzodioxin	22298810
<i>CADM2</i>	rs4856270	aflatoxin B1, methylmercuric chloride, tetrachlorodibenzodioxin	20106945, 23179753, 20055451
<i>KIAA0922</i>	rs2165084	air pollutants, atrazine, benzo(a)pyrene diol epoxide, PCB, potassium chromate(VI)	21757418, 22378314, 20382639, 21334430, 22079256
<i>TRERF1</i>	rs11751765	aflatoxin B1, arsenic trioxide, asbestos, estradiol, potassium chromate(VI), Progesterone, ethinyl estradiol, furan, tetrachlorodibenzodioxin, vehicle emissions	22100608, 20458559, 17331233, 20660070, 22079256, 20660070, 24935251, 24935251, 17942748, 22079235, 17942748, 23940539
<i>MEOX2</i>	rs7797334	acetaminophen, environmental pollutants, mercury, tetrachlorodibenzodioxin, PCB, chlorine, dibutyl phthalate, diethylstilbestrol, nickel, ozone	22230336, 12655031, 16823088, 22298810, 21934132, 20959002, 18636392, 21266533, 15591538, 23153324, 12540486, 18636392,
<i>ISPD</i>	rs7797334	PCB, aflatoxin B1, benzo(a)pyrene, copper sulfate, diquat, potassium dichromate	19114083, 19770486, 19770486, 19789285, 22814884, 23608068
<i>CDC14C</i>	rs4278110	estradiol	22574217
<i>COLEC10</i>	rs11987106	arsenic trioxide, acetaminophen, benzo(a)pyrene	15761015, 17562736, 21569818
<i>CCIN</i>	rs61735202	acetaminophen, cadmium chloride, tetrachlorodibenzodioxin	17562736, 22457795, 21354282

Appendix Table 11 continued....

Gene/region	SNP	Chemical interaction	PubMed IDs
<i>MGMT</i>	rs943811	aflatoxin B1, benzo(a)pyrene, ethylene dibromide, dust, fonofos, parathion, polycyclic aromatic hydrocarbon, acetaminophen, ammonium chloride, arsenite, estradiol, bisphenol A, carbon tetrachloride, diethylstilbestrol, furan, methylnitrosourea, ozone, piperonyl butoxide, praziquantel, sodium arsenite, tetrachlorodibenzodioxin	20106945, 20064835, 12151404, 17805423, 8823159, 22847954, 23543013, 12883083, 16483693, 18929588, 20965277, 20965277, 17484886, 15890375, 22507866, 20965277, 23358140, 18636392, 15890375, 21813463, 11241755, 21215274, 17292431
<i>TMEM117</i>	rs11182332	aflatoxin B1, benzo(a)pyrene, benzo(a)pyrene diol epoxide, copper sulfate, diuron, potassium chromate(VI), PCB	20106945, 21714911, 19150397, 19549813, 24172598, 22079256, 23724009, 24935251, 23179753, 19114083
<i>PARP4</i>	rs4770684	acetaminophen, arsenite, estradiol, copper sulfate, hydrogen peroxide, nicotine, potassium chromate(VI), aflatoxin B1, arsenic, benzo(a)pyrene	21420995, 23974009, 22574217, 19549813, 21179406, 23825647, 22079256, 19770486, 19654921, 21839799
<i>UBE3A</i>	rs7182827	arsenic trioxide, atrazine, benzo(a)pyrene diol, estradiol, nicotine, acetaminophen, benzo(a)pyrene, bisphenol A, cadmium sulfate, tetrachlorodibenzodioxin, tobacco smoke pollution	20458559, 22378314, 19150397, 23665804, 12588870, 16140955, 17562736, 22228805, 23593014, 16221973, 21570461, 18087596
<i>KRTAP21-1</i>	rs7275217	aluminum	21298039
<i>RGSL1</i>	rs41299607	cadmium	24376830
<i>LMO2</i>	rs9282777	arsenic trioxide, Benzo(a)pyrene, Estradiol, Isotretinoin, Testosterone, Tetrachlorodibenzodioxin, Tretinoin, trichostatin A, Valproic Acid, bisphenol A, Cadmium Chloride, Carbon Tetrachloride, Dibutyl Phthalate, Ozone	19128835, 22316170, 22574217, 20436886, 21592394, 22903824, 21934132, 24935251, 24935251, 21786754, 22457795, 17484886, 21266533, 17095637
<i>CTNNA2</i>	rs10520291	acetaminophen, estradiol, progesterone, testosterone, 2,6-dinitrotoluene, bisphenol A, dibutyl phthalate, dioxins, ethinyl estradiol, ozone, tetrachlorodibenzodioxin	22230336, 20660070, 20660070, 21592394, 23179753, 20406850, 21786754, 21266533, 20463971, 17942748, 12763052, 21570461, 16211290

Appendix Table 11 continued....

Gene/region	SNP	Chemical interaction	PubMed IDs
<i>PDE4B</i>	rs12037891	arsenic, arsenic trioxide, benzo(a)pyrene, estradiol, formaldehyde, lipopolysaccharides, progesterone, smoke, testosterone, atrazine, bisphenol A, carbon tetrachloride, dibutyl phthalate, fipronil, furan, testosterone, tetrachlorodibenzodioxin	16835338, 15761015, 22316170, 14699072, 23649840, 20655997, 21854221, 21795739, 21095227, 18535249, 19541795, 21932408, 17484886, 21266533, 22079235, 18535249, 22298810
<i>CCHCR1</i>	rs130069	acetaminophen, potassium chromate(VI), benzo(a)pyrene, tetrachlorodibenzodioxin	22230336, 22228805, 21570461
<i>TCF19</i>	rs6929434	acetaminophen, aflatoxin B1, benzo(a)pyrene diol, estradiol, copper sulfate, formaldehyde, testosterone	22230336, 20106945, 20382639, 19167446, 19549813, 23649840, 23649840, 21592394
<i>KDM4C</i>	rs10975823	acetaminophen, aflatoxin B1, atrazine, benzo(a)pyrene, potassium chromate(VI)	22230336, 22378314, 22378314, 22316170, 22079256
<i>ZNF782</i>	rs4645656 rs7848710 rs6477733	arsenic, methylmercuric chloride	21291286, 23103053
<i>SUMF1</i>	rs2633820	copper sulfate, formaldehyde, hydrogen peroxide, tetrachlorodibenzodioxin, bisphenol A, dibutyl phthalate, tetrachlorodibenzodioxin	19549813, 23649840, 18951874, 22574217, 24935251, 21786754, 21266533, 21570461
<i>NEDD9</i>	rs9469223	benzene, benzo(a)pyrene, benzo(a)pyrene diol, estradiol, bisphenol A, copper sulfate, diuron, ethylbenzene, formaldehyde, methylmercuric chloride, particulate matter, PCB, smoke, tetrachlorodibenzodioxin, tobacco tar, toluene, 2,6-dinitrotoluene, acetaminophen, carbon tetrachloride, dibutyl phthalate, diethylstilbestrol, diuron, ethinyl estradiol, lipopolysaccharide, nicotine, propiconazole, sodium arsenite	20359517, 20064835, 20382639, 22574217, 20170705, 19549813, 24172598, 20359517, 23649840, 23179753, 22178795, 16474171, 21095227, 19619570, 19559774, 24383497, 20406850, 18700144, 17484886, 21266533, 21658437, 24172598, 20170705, 18930950, 17456735, 16014739, 19015723

SNP = single nucleotide polymorphism

Appendix Table 12: Top one hundred SNPs associated with childhood ALL risk with age-specificity, results based on the lowest P values

					Minor allele frequency				
SNP	Gene/region	Chr	Minor allele	Feature	1-5 year	6-10 year	OR _{allele} (95% CI)*	P value**	P value (permutation) ^{††}
rs10505918	<i>SOX5</i>	12	A	intron	0.42	0.19	3.15 (1.90 - 5.24)	9.84 x 10 ⁻⁰⁶	1 x 10 ⁻⁴
rs11997355	8q21.11	8	T	intergenic	0.05	0.19	0.22 (0.11 - 0.44)	2.74 x 10 ⁻⁰⁵	1 x 10 ⁻⁴
rs2388773	16q12.2	16	C	intergenic	0.14	0.35	0.35 (0.21 - 0.57)	3.78 x 10 ⁻⁰⁵	1 x 10 ⁻⁴
rs665159	<i>CHRM3</i>	1	T	intron	0.55	0.33	2.46 (1.58 - 3.84)	7.42 x 10 ⁻⁰⁵	2 x 10 ⁻⁴
rs3954950	9p24.2	9	T	intergenic	0.24	0.43	0.38 (0.24 - 0.62)	7.77 x 10 ⁻⁰⁵	1 x 10 ⁻⁴
rs7818844	8p12	8	T	intergenic	0.4	0.6	0.38 (0.23 - 0.61)	7.86 x 10 ⁻⁰⁵	1 x 10 ⁻⁴
rs6972158	<i>NPSRI</i>	7	G	intron	0.34	0.14	3.03 (1.74 - 5.25)	8.30 x 10 ⁻⁰⁵	1 x 10 ⁻⁴
rs7320982	8p12	13	C	intergenic	0.19	0.38	0.39 (0.24 - 0.62)	8.33 x 10 ⁻⁰⁵	1 x 10 ⁻⁴
rs7583258	2q22.3	2	G	intergenic	0.09	0.24	0.29 (0.16 - 0.54)	8.79 x 10 ⁻⁰⁵	2 x 10 ⁻⁴
rs1882591	16q12.2	16	G	intergenic	0.22	0.42	0.42 (0.27 - 0.64)	9.60 x 10 ⁻⁰⁵	2 x 10 ⁻⁴
rs7318021	13q31.3	13	T	intergenic	0.23	0.43	0.42 (0.27 - 0.66)	1.16 x 10 ⁻⁰⁴	1 x 10 ⁻⁴
rs7016929	8q31.3	8	A	intergenic	0.2	0.39	0.40 (0.25 - 0.64)	1.18 x 10 ⁻⁰⁴	1 x 10 ⁻⁴
rs10079494	5q14.1	5	A	intergenic	0.28	0.1	3.39 (1.82 - 6.32)	1.22 x 10 ⁻⁰⁴	2 x 10 ⁻⁴
rs10250709	<i>NPSRI</i>	7	A	intron	0.33	0.14	3.03 (1.72 - 5.32)	1.22 x 10 ⁻⁰⁴	1 x 10 ⁻⁴
rs7720650	5q31.2	5	A	intergenic	0.12	0.27	0.32 (0.18 - 0.57)	1.33 x 10 ⁻⁰⁴	1 x 10 ⁻⁴
rs2949827	7q31.1	7	A	intergenic	0.08	0.21	0.29 (0.16 - 0.55)	1.44 x 10 ⁻⁰⁴	2 x 10 ⁻⁴
rs2396653	7q31.1	7	A	intergenic	0.14	0.29	0.34 (0.19 - 0.59)	1.57 x 10 ⁻⁰⁴	2 x 10 ⁻⁴
rs202050948	<i>CD97</i>	19	T	intron	0.04	0.15	0.22 (0.10 - 0.48)	1.72 x 10 ⁻⁰⁴	1 x 10 ⁻⁴
rs1191818	2p24.1	2	C	intergenic	0.38	0.59	0.43 (0.28 - 0.67)	1.76 x 10 ⁻⁰⁴	6 x 10 ⁻⁴
rs3800292	<i>GNMT</i>	6	G	intron	0.02	0.11	0.13 (0.04 - 0.38)	1.87 x 10 ⁻⁰⁴	1 x 10 ⁻⁴

Appendix Table 12 continued....

					Minor allele frequency				
SNP	Gene/region	Chr	Minor allele	Feature	1-5 year	6-10 year	OR _{allele} (95% CI)*	P value**	P value (permutation) ^{††}
rs1881116	<i>C7orf50</i>	7	A	intron	0.38	0.21	2.70 (1.60 - 4.57)	2.04 x 10 ⁻⁰⁴	2 x 10 ⁻⁴
rs4821717	22q13.1	22	A	intergenic	0.45	0.26	2.46 (1.53 - 3.97)	2.06 x 10 ⁻⁰⁴	5 x 10 ⁻⁴
rs2212824	21q21.3	21	G	intergenic	0.44	0.26	2.52 (1.55 - 4.11)	2.15 x 10 ⁻⁰⁴	2 x 10 ⁻⁴
rs7157104	14q13.2	14	G	intergenic	0.15	0.3	0.36 (0.21 - 0.62)	2.28 x 10 ⁻⁰⁴	1 x 10 ⁻⁴
rs2051713	12q21.33	12	G	intergenic	0.52	0.32	2.40 (1.51 - 3.82)	2.30 x 10 ⁻⁰⁴	2 x 10 ⁻⁴
rs2125649	8p21.3	8	G	intergenic	0.07	0.19	0.28 (0.14 - 0.55)	2.32 x 10 ⁻⁰⁴	1 x 10 ⁻⁴
rs6739633	2p24.3	2	T	intergenic	0.48	0.28	2.36 (1.50 - 3.74)	2.33 x 10 ⁻⁰⁴	2 x 10 ⁻⁴
rs738027	<i>PYROXD1</i>	12	A	intron	0.43	0.24	2.45 (1.52 - 3.96)	2.55 x 10 ⁻⁰⁴	3 x 10 ⁻⁴
rs237320	17p12	17	T	intergenic	0.11	0.26	0.35 (0.20 - 0.62)	2.65 x 10 ⁻⁰⁴	1 x 10 ⁻⁴
rs139886	<i>SOX10</i>	22	C	intron	0.47	0.28	2.41 (1.50 - 3.87)	2.67 x 10 ⁻⁰⁴	2 x 10 ⁻⁴
rs13116233	4q34.3	4	C	intergenic	0.36	0.17	2.56 (1.54 - 4.25)	2.69 x 10 ⁻⁰⁴	3 x 10 ⁻⁴
rs6519091	<i>MICALL1</i>	22	C	intron	0.51	0.32	2.33 (1.48 - 3.69)	2.87 x 10 ⁻⁰⁴	5 x 10 ⁻⁴
rs6109487	20p12.1	20	A	intergenic	0.24	0.09	3.55 (1.79 - 7.03)	2.90 x 10 ⁻⁰⁴	3 x 10 ⁻⁴
rs1151277	16q12.2	16	T	intergenic	0.13	0.29	0.38 (0.23 - 0.64)	2.93 x 10 ⁻⁰⁴	1 x 10 ⁻⁴
rs6052937	<i>SLC23A2</i>	20	A	3'UTR	0.12	0.27	0.38 (0.22 - 0.64)	2.99 x 10 ⁻⁰⁴	1 x 10 ⁻⁴
rs34099167	<i>NEK1</i>	4	C	coding	0.04	0.15	0.24 (0.11 - 0.52)	3.07 x 10 ⁻⁰⁴	1 x 10 ⁻⁴
rs7722067	5q14.2	5	C	intergenic	0.16	0.31	0.38 (0.22 - 0.64)	3.08 x 10 ⁻⁰⁴	1 x 10 ⁻⁴
rs1004327	<i>CLNK</i>	4	C	intron	0.41	0.24	2.54 (1.53 - 4.22)	3.11 x 10 ⁻⁰⁴	3 x 10 ⁻⁴
rs3993401	12q21.31	12	C	intergenic	0.24	0.41	0.41 (0.25 - 0.67)	3.16 x 10 ⁻⁰⁴	3 x 10 ⁻⁴
rs6492498	13q31.3	13	A	intergenic	0.29	0.49	0.45 (0.30 - 0.70)	3.22 x 10 ⁻⁰⁴	5.9 x 10 ⁻⁴
rs2806907	13q14.13	13	T	intergenic	0.32	0.51	0.44 (0.28 - 0.69)	3.29 x 10 ⁻⁰⁴	4 x 10 ⁻⁴

Appendix Table 12 continued....

SNP	Gene/region	Chr	Minor allele	Feature	Minor allele frequency		OR _{allele} (95% CI)*	P value**	P value (permutation) ^{††}
					1-5 year	6-10 year			
rs2101919	<i>NID2</i>	14	G	coding	0.28	0.46	0.44 (0.28 - 0.69)	3.31 x 10 ⁻⁰⁴	4 x 10 ⁻⁴
rs2899293	<i>ANKRD54</i>	22	G	intron	0.51	0.32	2.32 (1.47 - 3.68)	3.32 x 10 ⁻⁰⁴	5.9 x 10 ⁻⁴
rs1028695	<i>SPATA13</i>	13	T	intron	0.14	0.29	0.38 (0.23 - 0.65)	3.38 x 10 ⁻⁰⁴	2 x 10 ⁻⁴
rs2185230	<i>PCSK5</i>	9	A	intron	0.34	0.17	2.76 (1.58 - 4.81)	3.39 x 10 ⁻⁰⁴	3 x 10 ⁻⁴
rs4254428	<i>ZNF420</i>	19	C	intron	0.43	0.63	0.45 (0.29 - 0.70)	3.41 x 10 ⁻⁰⁴	4 x 10 ⁻⁴
rs139866	<i>POLR2F</i>	22	C	intron	0.45	0.27	2.40 (1.49 - 3.88)	3.46 x 10 ⁻⁰⁴	3 x 10 ⁻⁴
rs5028798	11p13	11	T	intergenic	0.28	0.46	0.44 (0.28 - 0.69)	3.48 x 10 ⁻⁰⁴	5 x 10 ⁻⁴
rs2065212	13q31.3	13	A	intergenic	0.31	0.51	0.46 (0.30 - 0.71)	3.51 x 10 ⁻⁰⁴	5 x 10 ⁻⁴
rs222314	7p21.3	7	G	intergenic	0.2	0.05	4.52 (1.98 - 10.35)	3.52 x 10 ⁻⁰⁴	2 x 10 ⁻⁴
rs1894381	<i>TMC5</i>	16	G	intron	0.16	0.32	0.41 (0.25 - 0.67)	3.52 x 10 ⁻⁰⁴	5 x 10 ⁻⁴
rs9809647	3q28	3	T	intergenic	0.34	0.54	0.48 (0.32 - 0.72)	3.53 x 10 ⁻⁰⁴	2 x 10 ⁻⁴
rs898982	1p34.3	1	C	intergenic	0.04	0.14	0.24 (0.11 - 0.52)	3.65 x 10 ⁻⁰⁴	3 x 10 ⁻⁴
rs1868368	8q24.23	8	C	intergenic	0.19	0.35	0.41 (0.25 - 0.67)	3.74 x 10 ⁻⁰⁴	1 x 10 ⁻⁴
rs9392857	6p25.3	6	A	intergenic	0.3	0.48	0.44 (0.28 - 0.69)	3.77 x 10 ⁻⁰⁴	1 x 10 ⁻⁴
rs8014810	<i>BRMS1L</i>	14	T	intron	0.13	0.26	0.36 (0.20 - 0.63)	3.88 x 10 ⁻⁰⁴	2 x 10 ⁻⁴
rs8021355	<i>RALGAPAI</i>	14	A	intron	0.15	0.29	0.38 (0.22 - 0.65)	4.10 x 10 ⁻⁰⁴	3 x 10 ⁻⁴
rs7144565	<i>RALGAPAI</i>	14	A	intron	0.15	0.29	0.38 (0.22 - 0.65)	4.10 x 10 ⁻⁰⁴	3 x 10 ⁻⁴
rs2274068	<i>RALGAPAI</i>	14	C	coding	0.15	0.29	0.38 (0.22 - 0.65)	4.10 x 10 ⁻⁰⁴	3 x 10 ⁻⁴
rs762562	<i>ERCC1/CD3EAP</i>	19	G	3'UTR	0.19	0.36	0.43 (0.26 - 0.68)	4.22 x 10 ⁻⁰⁴	2 x 10 ⁻⁴
rs4948088	7p12.1	7	A	intergenic	0.05	0.15	0.26 (0.12 - 0.55)	4.23 x 10 ⁻⁰⁴	2 x 10 ⁻⁴
rs3850942	<i>MARK2</i>	11	C	intron	0.03	0.12	0.20 (0.09 - 0.49)	4.35 x 10 ⁻⁰⁴	1 x 10 ⁻⁴

Appendix Table 12 continued....

SNP	Gene/region	Chr	Minor allele	Feature	Minor allele frequency		OR _{allele} (95% CI)*	P value**	P value (permutation) ^{††}
					1-5 year	6-10 year			
rs2899469	15q21.2	15	G	intergenic	0.48	0.29	2.24 (1.43 - 3.52)	4.45 x 10 ⁻⁰⁴	4 x 10 ⁻⁴
rs8011343	<i>MDGA2</i>	14	C	intron	0.19	0.06	4.21 (1.89 - 9.41)	4.51 x 10 ⁻⁰⁴	5 x 10 ⁻⁴
rs2031293	13q34	13	A	intergenic	0.43	0.63	0.47 (0.30- 0.71)	4.61 x 10 ⁻⁰⁴	3 x 10 ⁻⁴
rs11171543	12q12	12	A	intergenic	0.09	0.24	0.37 (0.21 - 0.64)	4.75 x 10 ⁻⁰⁴	5.9 x 10 ⁻⁴
rs11172024	<i>KIF21A</i>	12	C	intron	0.06	0.18	0.30 (0.15 - 0.59)	4.76 x 10 ⁻⁰⁴	3 x 10 ⁻⁴
rs1510136	4q31.21	4	G	intergenic	0.19	0.35	0.44 (0.28 - 0.70)	4.80 x 10 ⁻⁰⁴	4 x 10 ⁻⁴
rs16979806	21q21.3	21	T	intergenic	0.21	0.38	0.45 (0.29 - 0.71)	4.86 x 10 ⁻⁰⁴	6.9 x 10 ⁻⁴
rs17017488	<i>CCSER1</i>	4	C	intron	0.36	0.54	0.47 (0.31 - 0.72)	5.04 x 10 ⁻⁰⁴	5.9 x 10 ⁻⁴
rs10511980	<i>MAMDC2</i>	9	A	intron	0.27	0.45	0.46 (0.30 - 0.71)	5.04 x 10 ⁻⁰⁴	5 x 10 ⁻⁴
rs2620870	12q14.1	12	G	intergenic	0.55	0.36	2.06 (1.37 - 3.10)	5.08 x 10 ⁻⁰⁴	4 x 10 ⁻⁴
rs377621	21q21.3	21	G	intergenic	0.23	0.41	0.46 (0.30 - 0.72)	5.15 x 10 ⁻⁰⁴	7.9 x 10 ⁻⁴
rs6510588	<i>ZNF420</i>	19	A	intron	0.43	0.62	0.46 (0.30 - 0.72)	5.17 x 10 ⁻⁰⁴	5 x 10 ⁻⁴
rs10739501	9q33.1	9	C	intergenic	0.34	0.52	0.46 (0.29 - 0.71)	5.18 x 10 ⁻⁰⁴	5.9 x 10 ⁻⁴
rs6834625	4q31.21	4	G	intergenic	0.17	0.33	0.44 (0.28 - 0.70)	5.22 x 10 ⁻⁰⁴	3 x 10 ⁻⁴
rs1209145	14q22.3	14	G	intergenic	0.17	0.05	4.48 (1.91 - 10.5)	5.51 x 10 ⁻⁰⁴	2 x 10 ⁻⁴
rs1481046	8q13.3	8	G	intergenic	0.3	0.15	2.71 (1.54 - 4.77)	5.57 x 10 ⁻⁰⁴	4 x 10 ⁻⁴
rs924615	5q14.2	5	T	intergenic	0.26	0.43	0.47 (0.31 - 0.72)	5.70 x 10 ⁻⁰⁴	1 x 10 ⁻⁴
rs26784	<i>MSH3</i>	5	C	intron	0.43	0.26	2.28 (1.43 - 3.65)	5.71 x 10 ⁻⁰⁴	5.9 x 10 ⁻⁴
rs11120342	<i>PTPN14</i>	1	C	intron	0.2	0.36	0.45 (0.28 - 0.71)	5.76 x 10 ⁻⁰⁴	8.9 x 10 ⁻⁴
rs2830698	21q21.3	21	T	intergenic	0.2	0.37	0.44 (0.27 - 0.70)	5.77 x 10 ⁻⁰⁴	2 x 10 ⁻⁴
rs6037033	20p11.21	20	A	intergenic	0.32	0.49	0.45 (0.29 - 0.71)	5.80 x 10 ⁻⁰⁴	5.9 x 10 ⁻⁴

Appendix Table 12 continued....

SNP	Gene/region	Chr	Minor allele	Feature	Minor allele frequency		OR _{allele} (95% CI)*	P value**	P value (permutation) ^{††}
					1-5 year	6-10 year			
rs12073211	1p32.1	1	C	intergenic	0.35	0.53	0.46 (0.30 - 0.72)	5.82 x 10 ⁻⁰⁴	4 x 10 ⁻⁴
rs3825594	NID2	14	T	intron	0.26	0.43	0.46 (0.29 - 0.72)	5.86 x 10 ⁻⁰⁴	5 x 10 ⁻⁴
rs742390	1p36.11	1	T	intron	0.38	0.21	2.43 (1.46 - 4.02)	5.87 x 10 ⁻⁰⁴	5.9 x 10 ⁻⁴
rs973358	SHISA6	17	A	intron	0.46	0.29	2.32 (1.44 - 3.75)	5.92 x 10 ⁻⁰⁴	5.9 x 10 ⁻⁴
rs10133677	MDGA2	14	G	intron	0.16	0.05	4.92 (1.98 - 12.23)	5.97 x 10 ⁻⁰⁴	3 x 10 ⁻⁴
rs1493897	16q12.2	16	A	intergenic	0.17	0.33	0.44 (0.27 - 0.70)	5.99 x 10 ⁻⁰⁴	6.9 x 10 ⁻⁴
rs9694342	AGO2	8	T	intron	0.24	0.41	0.46 (0.30 - 0.72)	6.17 x 10 ⁻⁰⁴	5.9 x 10 ⁻⁴
rs7952853	OR6C2	12	T	intron	0.28	0.46	0.45 (0.29 - 0.71)	6.20 x 10 ⁻⁰⁴	3 x 10 ⁻⁴
rs6943934	7p22.3	7	C	intergenic	0.04	0.14	0.25 (0.11 - 0.56)	6.21 x 10 ⁻⁰⁴	1 x 10 ⁻⁴
rs1610315	6q27	6	C	intergenic	0.21	0.38	0.43 (0.27 - 0.70)	6.24 x 10 ⁻⁰⁴	4 x 10 ⁻⁴
rs1521244	2p24.3	2	C	intergenic	0.43	0.26	2.26 (1.42 - 3.61)	6.26 x 10 ⁻⁰⁴	4 x 10 ⁻⁴
rs9897794	EFCAB5	17	T	coding	0.36	0.46	0.45 (0.28 - 0.71)	6.34 x 10 ⁻⁰⁴	6.9 x 10 ⁻⁴
rs877111	6p21.1	6	C	intergenic	0.4	0.23	2.40 (1.45 - 3.97)	6.36 x 10 ⁻⁰⁴	5.9 x 10 ⁻⁴
rs753712	10q26.3	10	T	intergenic	0.38	0.57	0.48 (0.31 - 0.73)	6.39 x 10 ⁻⁰⁴	5.9 x 10 ⁻⁴
rs1430838	8q13.3	8	C	intergenic	0.52	0.35	2.28 (1.42 - 3.67)	6.48 x 10 ⁻⁰⁴	5.9 x 10 ⁻⁴
rs2116078	8q13.3	8	G	intergenic	0.52	0.35	2.28 (1.42 - 3.67)	6.48 x 10 ⁻⁰⁴	5.9 x 10 ⁻⁴
rs2615874	ATRNL1	10	G	intron	0.4	0.09	3.12 (1.62 - 5.99)	6.51 x 10 ⁻⁰⁴	5 x 10 ⁻⁴

*OR_{interaction} per allele (OR_{allele}) for the additive model; **P value adjusted for genomic control; ^{††}P value permutation = point wise P value from maxT permutation analysis after 10,000 permutation

Chr = Chromosome, SNP = single nucleotide polymorphism

Appendix Table 13: List of single nucleotide polymorphisms that showed age-specific associations based on the P value and were statistically correlated

Chr A	SNP 1	Chr B	SNP 2
2	rs1521244	2	rs6739633
4	rs6834625	4	rs1510136
7	rs10250709	7	rs6972158
8	rs1430838	8	rs2116078
13	rs6492498	13	rs2065212
14	rs7157104	14	rs2274068
14	rs7157104	14	rs8021355
14	rs7157104	14	rs7144565
14	rs2274068	14	rs8021355
14	rs2274068	14	rs7144565
14	rs8021355	14	rs7144565
14	rs3825594	14	rs2101919
16	rs1151277	16	rs2388773
19	rs4254428	19	rs6510588
21	rs16979806	21	rs377621
22	rs2899293	22	rs6519091
22	rs6519091	22	rs139886
22	rs139866	22	rs139886

SNP = single nucleotide polymorphism

Note: Chromosome A and Chromosome B are same chromosome.
SNP1 and SNP2 and statistically correlated SNPs

Appendix Table 14: Top one hundred SNPs associated with childhood ALL risk with age-specificity, results based on the highest effect sizes (P < 0.05)

					Minor allele frequency				
SNP	Gene/region	Chr	Minor allele	Feature	1-5 year	6-10 year	ORAllele (95% CI)*	P value**	P value (permutation) [†]
rs17109582	<i>DIO1</i>	1	C	intron	0.09	0.007	12.46 (1.67 - 93.01)	0.01	0.006
rs7304215	<i>TMEM132D</i>	12	G	intron	0.07	0.007	11.25 (1.47 - 85.90)	0.02	0.01
rs10999147	<i>AIFM2</i>	10	G	coding	0.07	0.007	10.89 (1.43 - 83.02)	0.02	0.01
rs7330286	13q33.2	13	T	intergenic	0.07	0.007	10.01 (1.33 - 75.63)	0.03	0.01
rs41309927	<i>SEC23B</i>	20	A	coding	0.07	0.007	9.70 (1.28 - 73.39)	0.03	0.02
rs36086854	<i>CFAP99</i>	4	A	coding	0.06	0.007	9.42 (1.23 - 72.26)	0.03	0.02
rs17409162	<i>ANO10</i>	3	A	coding	0.06	0.007	9.24 (1.20 - 71.06)	0.03	0.02
rs13129052	4p16.3	4	G	intron	0.06	0.007	9.24 (1.20 - 71.06)	0.03	0.02
rs9856456	3p22.1	3	C	intergenic	0.06	0.007	8.78 (1.14 - 67.62)	0.04	0.02
rs6927353	6q26	6	A	intergenic	0.06	0.007	8.68 (1.16 - 64.90)	0.04	0.02
rs11651675	<i>TMC8</i>	17	A	coding	0.05	0.007	8.65 (1.11 - 67.50)	0.04	0.03
rs10109794	<i>TRIM55</i>	8	T	intron	0.06	0.007	8.58 (1.13 - 65.16)	0.04	0.02
rs10099957	<i>TRIM55</i>	8	A	intron	0.11	0.007	8.58 (2.00 - 36.93)	0.004	0.001
rs56291145	<i>ATP12A</i>	13	C	coding	0.06	0.007	8.40 (1.09 - 64.78)	0.04	0.02
rs2909644	18q22	18	G	intergenic	0.06	0.007	8.40 (1.09 - 64.78)	0.04	0.03
rs6093579	<i>PTPRT</i>	20	T	intron	0.06	0.007	8.40 (1.09 - 64.78)	0.04	0.02
rs17039265	1p36.21	1	A	intergenic	0.06	0.007	8.29 (1.08 - 63.96)	0.04	0.02
rs9728577	<i>PRAMEF2</i>	1	A	coding	0.06	0.007	8.29 (1.08 - 63.96)	0.04	0.02
rs75411676	<i>PRAMEF2</i>	1	T	coding	0.06	0.007	8.29 (1.08 - 63.96)	0.04	0.02
rs36068434	<i>CDS1</i>	4	T	coding	0.06	0.007	8.29 (1.08 - 63.96)	0.04	0.02

Appendix Table 14 continued....

SNP	Gene/region	Chr	Minor allele	Feature	Minor allele frequency		ORAllele (95% CI)*	P value**	P value (permutation) [†]
					1-5 year	6-10 year			
rs11916525	CEP70	3	C	coding	0.06	0.007	8.29 (1.07 - 64.03)	0.04	0.02
rs3204798	PRAMEF2	1	G	intron	0.06	0.007	8.25 (1.07 - 63.64)	0.04	0.02
rs35340237	CEP70	3	C	coding	0.06	0.007	8.21 (1.06 - 63.41)	0.04	0.02
rs8176018	KEL	7	T	intron	0.06	0.007	8.19 (1.07 - 62.68)	0.04	0.02
rs1835154	2q24.1	2	G	intergenic	0.06	0.007	8.05 (1.06 - 61.21)	0.04	0.03
rs78323957	SLC10A5	8	G	coding	0.05	0.007	8.02 (1.03 - 62.12)	0.05	0.03
rs16909509	ZFAND1	8	T	intron	0.05	0.007	8.02 (1.03 - 62.12)	0.05	0.03
rs3729598	LIFR	5	G	intron	0.05	0.007	7.94 (1.03 - 61.48)	0.05	0.04
rs568760	HCN4	15	T	intron	0.06	0.007	7.78 (1.02 - 59.39)	0.05	0.03
rs1800141	LRP1	12	A	coding	0.05	0.007	7.75 (1.00 - 59.98)	0.05	0.04
rs35384751	FYB	5	T	coding	0.06	0.007	7.68 (1.01 - 58.62)	0.05	0.03
rs11175471	RASSF3	12	C	intron	0.1	0.01	7.56 (1.77 - 32.29)	0.006	0.004
rs2389891	4q26	4	G	intergenic	0.09	0.01	7.21 (1.66 - 31.40)	0.008	0.005
rs35424709	ATP13A4	3	A	coding	0.11	0.02	6.74 (1.95 - 23.25)	0.003	0.009
rs12188300	5q33.3	5	T	intergenic	0.08	0.01	6.58 (1.51 - 28.74)	0.01	0.007
rs7303641	RASSF3	12	G	intron	0.09	0.01	6.57 (1.54 - 28.09)	0.01	0.004
rs34139105	PRRG4	11	A	coding	0.08	0.01	6.36 (1.44 - 28.06)	0.01	0.009
rs10500248	19q12	19	C	intergenic	0.08	0.01	6.34 (1.45 - 27.77)	0.01	0.01
rs2124906	19q12	19	G	intergenic	0.08	0.01	6.34 (1.45 - 27.77)	0.01	0.01
rs7492685	14q21.3	14	C	intergenic	0.07	0.01	6.26 (1.38 - 28.46)	0.02	0.009
rs276725	19q12	19	C	intergenic	0.08	0.01	6.05 (1.38 - 26.56)	0.02	0.007

Appendix Table 14 continued....

SNP	Gene/region	Chr	Minor allele	Feature	Minor allele frequency		ORAllele (95% CI)*	P value**	P value (permutation) [†]
					1-5 year	6-10 year			
rs6851586	4p15.2	4	A	intergenic	0.09	0.01	5.87 (1.38 - 24.92)	0.02	0.01
rs16871434	KCNIP4	4	A	intron	0.08	0.01	5.79 (1.34 - 25.04)	0.02	0.01
rs28421666	6p21.3	6	G	intergenic	0.1	0.02	5.58 (1.63 - 19.06)	0.006	0.003
rs17055478	13q21.1	13	A	intergenic	0.07	0.01	5.58 (1.26 - 24.70)	0.02	0.02
rs1582274	7q31.1	7	A	intergenic	0.07	0.01	5.48 (1.24 - 24.24)	0.02	0.02
rs6572051	LOC644919	14	G	intron	0.07	0.01	5.40 (1.22 - 23.85)	0.03	0.02
rs9407838	SH3GL2	9	T	intron	0.11	0.02	5.32 (1.58 - 17.89)	0.007	0.004
rs72838683	PDZD7	10	T	3'UTR	0.07	0.01	5.31 (1.22 - 23.05)	0.03	0.02
rs11250832	10p15.3	10	T	intergenic	0.1	0.02	5.29 (1.56 - 17.97)	0.008	0.005
rs16827743	3q13.32	3	T	intergenic	0.07	0.01	5.28 (1.20 - 23.32)	0.03	0.03
rs12705300	7q22.3	7	A	intron	0.12	0.02	5.27 (1.61 - 17.30)	0.006	0.003
rs1915164	15q21.1	15	T	intergenic	0.07	0.01	5.24 (1.20 - 22.95)	0.03	0.01
rs12083795	1p34.3	1	T	intergenic	0.07	0.01	5.21 (1.18 - 23.08)	0.03	0.02
rs9861022	3q13.32	3	C	intergenic	0.07	0.01	5.14 (1.18 - 22.38)	0.03	0.02
rs16964079	C15orf41/ CSNK1A1P1	15	A	3'UTR	0.07	0.01	5.10 (1.17 - 22.22)	0.03	0.02
rs10157510	1q24.3	1	T	intergenic	0.08	0.01	5.00 (1.18 - 21.27)	0.03	0.02
rs10224856	VPS41	7	A	intron	0.07	0.01	4.95 (1.12 - 21.93)	0.04	0.03
rs1728850	15q21.3	15	G	intergenic	0.07	0.01	4.95 (1.12 - 21.93)	0.04	0.03
rs17055548	13q21.1	13	G	intergenic	0.06	0.01	4.94 (1.11 - 22.03)	0.04	0.03
rs10133677	MDGA2	14	G	intron	0.16	0.04	4.92 (1.98 - 12.23)	0.0006	0.0004
rs3130161	6p21.3	6	C	intergenic	0.07	0.01	4.89 (1.13 - 21.23)	0.03	0.04

Appendix Table 14 continued....

SNP	Gene/region	Chr	Minor allele	Feature	Minor allele frequency		ORAllele (95% CI)*	P value**	P value (permutation) [†]
					1-5 year	6-10 year			
rs1000521	<i>SLC8A3</i>	14	G	intron	0.11	0.02	4.87 (1.46 - 16.18)	0.01	0.005
rs12257453	<i>ARMC3</i>	10	G	intron	0.07	0.01	4.86 (1.12 - 21.19)	0.04	0.03
rs11833839	<i>EP400</i>	12	T	coding	0.06	0.01	4.85 (1.09 - 21.59)	0.04	0.03
rs3790126	<i>EMP2</i>	16	A	3'UTR	0.08	0.01	4.85 (1.15 - 20.38)	0.03	0.02
rs16950438	16q12.1	16	C	intergenic	0.1	0.02	4.84 (1.44 - 16.25)	0.01	0.005
rs6151599	<i>MSH3/DHFR</i>	5	G	intron	0.1	0.02	4.82 (1.45 - 16.10)	0.01	0.008
rs4546429	5p13.1	5	T	intergenic	0.07	0.01	4.79 (1.10 - 20.82)	0.04	0.03
rs11234604	<i>C11orf73</i>	11	A	5'UTR	0.06	0.01	4.78 (1.07 - 21.24)	0.04	0.03
rs6708453	2q21.1	2	C	intergenic	0.17	0.04	4.72 (1.92 - 11.62)	0.0007	0.0007
rs3805114	<i>ABCC5</i>	3	C	3'UTR	0.06	0.01	4.71 (1.06 - 20.95)	0.04	0.04
rs9328207	6p25.2	6	T	intergenic	0.06	0.01	4.71 (1.06 - 20.95)	0.04	0.04
rs2864680	<i>FSTL4</i>	5	A	intron	0.07	0.01	4.71 (1.10 - 20.10)	0.04	0.02
rs4741086	9p24.3	9	A	intergenic	0.17	0.04	4.67 (1.91 - 11.42)	0.0007	0.0009
rs10514074	18q22.3	18	C	intergenic	0.1	0.02	4.66 (1.37 - 15.88)	0.01	0.01
rs41285557	<i>MAML1</i>	5	A	coding	0.06	0.01	4.65 (1.02 - 21.12)	0.05	0.03
rs7620914	3p22.3	3	A	intron	0.14	0.04	4.64 (1.75 - 12.32)	0.002	0.001
rs7091901	10p11.22	10	T	intergenic	0.09	0.02	4.64 (1.35 - 15.96)	0.02	0.01
rs8100295	19q13.42	19	T	intergenic	0.06	0.01	4.62 (1.04 - 20.60)	0.04	0.04
rs17407084	<i>AK8</i>	9	C	coding	0.06	0.01	4.58 (1.03 - 20.51)	0.05	0.03
rs222314	7p21.3	7	G	intergenic	0.2	0.05	4.52 (1.98 - 10.35)	0.0003	0.0002
rs7770942	6p25.3	6	T	intergenic	0.09	0.02	4.51 (1.31 - 15.54)	0.05	0.01

Appendix Table 14 continued....

SNP	Gene/region	Chr	Minor allele	Feature	Minor allele frequency		ORAllele (95% CI)*	P value**	P value (permutation) [†]
					1-5 year	6-10 year			
rs16916188	<i>RBM12B</i>	8	G	coding	0.06	0.01	4.51 (1.01 - 20.12)	0.05	0.03
rs17140942	<i>RBFOX1</i>	16	G	intron	0.06	0.01	4.51 (1.01 - 20.12)	0.05	0.03
rs7172316	15q24.1	15	G	intergenic	0.07	0.02	4.49 (1.03 - 19.51)	0.05	0.03
rs1209145	14q22.3	14	G	intergenic	0.17	0.05	4.48 (1.91 - 10.50)	0.0006	0.0003
rs10902652	1p36.11	1	C	intergenic	0.06	0.01	4.46 (1.02 - 19.61)	0.05	0.04
rs1457759	5q22.3	5	C	intergenic	0.09	0.02	4.44 (1.31 - 15.08)	0.02	0.01
rs10826912	10p11.22	10	G	intergenic	0.08	0.02	4.44 (1.29 - 15.33)	0.02	0.008
rs61744122	<i>VWA3A</i>	16	A	intron	0.06	0.01	4.44 (1.02 - 19.36)	0.05	0.04
rs4748309	<i>RSU1</i>	10	A	intron	0.1	0.02	4.39 (1.33 - 14.52)	0.02	0.008
rs8013602	14q21.2	14	A	intergenic	0.06	0.01	4.39 (1.00 - 19.23)	0.05	0.04
rs9560160	13q34	13	C	intergenic	0.13	0.03	4.38 (1.54 - 12.49)	0.005	0.003
rs1755588	<i>ACOT11</i>	1	T	intron	0.09	0.02	4.36 (1.28 - 14.88)	0.02	0.01
rs10493958	1p21.2	1	A	intergenic	0.07	0.01	4.32 (1.01 - 18.51)	0.05	0.03
rs7169431	15q21.3	15	A	intergenic	0.08	0.02	4.31 (.124 - 14.96)	0.02	0.02
rs17170286	<i>BBS9</i>	7	C	intron	0.09	0.02	4.30 (1.26 - 14.68)	0.02	0.02
rs11945730	4p15.32	4	G	intergenic	0.12	0.03	4.28 (1.47 - 12.40)	0.007	0.006
rs17149645	11q14.2	11	T	intergenic	0.11	0.03	4.25 (1.45 - 12.46)	0.008	0.006

*OR_{interaction} per allele (OR_{allele}) for the additive model; **P value adjusted for genomic control; ^{††}P value permutation = point wise P value from maxT permutation analysis after 10,000 permutation

Chr = Chromosome, SNP = single nucleotide polymorphism

Appendix Table 15: List of single nucleotide polymorphisms that showed age-specific associations based on effect size and were statistically correlated

Chr A	SNP 1	Chr B	SNP 2
1	rs17039265	1	rs9728577
1	rs17039265	1	rs3204798
1	rs17039265	1	rs75411676
1	rs9728577	1	rs3204798
1	rs9728577	1	rs75411676
1	rs3204798	1	rs75411676
3	rs9861022	3	rs16827743
8	rs78323957	8	rs16909509
10	rs7091901	10	rs10826912
12	rs11175471	12	rs7303641
13	rs17055478	13	rs17055548
14	rs4502127	14	rs11157201
19	rs10500248	19	rs2124906

SNP = single nucleotide polymorphism

Note: Chromosome A and Chromosome B are same chromosome.
SNP1 and SNP2 and statistically correlated SNPs

Appendix Table 16: Bioinformatic analysis of genetic risk markers for the top one hundred age-specific associations with childhood ALL with the lowest P values

SNP	Chr	RegulomeDB score [†]	F-SNP ^{**}	Gene	Correlated SNP	RegulomeDB score [†]	Gene (correlated SNP)
rs10505918	12	NS	NS	<i>SOX5</i>	.	.	.
rs11997355	8	3a	NS	<i>HNF4G-ZFHX4</i>	.	.	.
rs2388773	16	5	NS	<i>IRX-CRNDE3</i>	.	.	.
rs665159	1	5	0.5	<i>CHRM3</i>	rs112493720	2b	<i>CHRM3</i>
rs3954950	9	5	NS	<i>RFX-GLIS33</i>	.	.	.
rs7818844	8	5	NS	<i>CYCSP3-RPL10AP3</i>	.	.	.
rs6972158 ^{**††}	7	5	0.41	<i>NPSR1</i>	.	.	.
rs7320982	13	5	NS	<i>MIRHG1-GPC5</i>	.	.	.
rs7583258	2	5	0.1	<i>TEX41-ACVR2A</i>	.	.	.
rs1882591	16	NS	NS	<i>IRX-CRNDE3</i>	rs1151271	3a	<i>IRX3-CRNDE</i>
rs7318021	13	NS	NS	<i>KRT18P27-RNU6-75P</i>	rs7996128	3a	<i>KRT18P27-RNU6-75P</i>
rs7016929	8	5	NS	<i>KHDRBS3-LOC101927892</i>	.	.	.
rs10079494	5	4	NS	<i>MSH3-RASGRF2</i>	rs7708505	2b	<i>MSH3-RASGRF2</i>
rs10250709	7	5	0.18	<i>NPSR1</i>	.	.	.
rs7720650	5	5	NS	<i>WNT8A-NME5</i>	rs56331448	2b	<i>WNT8A-NME5</i>
rs2949827	7	NS	NS	<i>GPR85-PPP1R3A</i>	.	.	.
rs2396653	7	6	NS	<i>GPR85-PPP1R3A</i>	.	.	.
rs202050948	19	5	NS	<i>CD97</i>	.	.	.
rs1191818	2	2a	0.1	<i>MATN3-LAPTM4A</i>	.	.	.
rs3800292	6	5	0.21	<i>GNMT</i>	rs3831135	2b	<i>PEX6</i>
rs3800292	6	5	0.21	<i>GNMT</i>	rs2274518	2b	<i>PEX6</i>

Appendix Table 16 continued....

SNP	Chr	RegulomeDB score [†]	F-SNP**	Gene	Correlated SNP	RegulomeDB score [†]	Gene (correlated SNP)
rs3800292	6	5	0.21	<i>GNMT</i>	rs8540	2b	<i>KLHDC3</i>
rs1881116	7	5	NS	<i>C7orf50</i>	.	.	.
rs4821717	22	5	0.5	<i>GCAT-GALR3</i>	rs139852	1b	<i>EIF3EIP</i>
rs4821717	22	5	0.5	<i>GCAT-GALR3</i>	rs7290156	1f	<i>GALR3</i>
rs2212824	21	6	NS	<i>ADAMTS5-GXP2</i>	.	.	.
rs7157104	14	6	NS	<i>KRT18P6-INSM2</i>	.	.	.
rs2051713	12	6	NS	<i>MRPL2P1-C12orf37</i>	.	.	.
rs2125649	8	NS	NS	<i>RP11-24P4.1-GFRA2</i>	.	.	.
rs6739633	2	6	0.1	<i>TRIB2-FAM84A</i>	.	.	.
rs738027	12	6	NS	<i>PYROXD1</i>	rs7133853	3a	<i>PYROXD1</i>
rs237320	17	5	NS	<i>MAP2K4-MYOCD</i>	rs237318 ^{††}	2b	<i>MAP2K4-MYOCD</i>
rs139886	22	1f	0.18	<i>SOX10</i>	rs139892	1f	<i>POLR2F</i>
rs13116233	4	6	0.1	<i>AGA-LINC01098</i>	.	.	.
rs6519091	22	2b	NS	<i>MICALL1</i>	rs4821723	1f	<i>MICALL1</i>
rs6109487	20	5	NS	<i>PA2G4P2-SPTLC3</i>	rs73088401	2c	<i>PA2G4P2-SPTLC3</i>
rs1151277	16	6	NS	<i>IRX-CRNDE3</i>	.	.	.
rs6052937	20	5	NS	<i>SLC23A2</i>	.	.	.
rs34099167*	4	NS	0	<i>NEK1</i>	rs6818590	2b	<i>NEK1</i>
rs7722067	5	NS	0.1	<i>ATP6AP1L-RPL5P16</i>	.	.	.
rs1004327	4	3a	0.24	<i>CLNK</i>	.	.	.
rs3993401	12	NS	NS	<i>C12orf26- TMTC2</i>	.	.	.
rs6492498	13	4	NS	<i>KRT18P27-LINC01049</i>	.	.	.
rs2806907	13	6	NS	<i>SIAH3-ZC3H13</i>	rs9522975	3a	<i>KRT18P27 - LINC01049</i>

Appendix Table 16 continued....

SNP	Chr	RegulomeDB score [†]	F-SNP ^{**}	Gene	Correlated SNP	RegulomeDB score [†]	Gene (correlated SNP)
rs2101919 ^{*††}	14	6	0.37	<i>NID2</i>	.	.	.
rs2899293	22	6	0.5	<i>ANKRD54</i>	.	.	.
rs1028695	13	NS	0.5	<i>SPATA13</i>	rs4821722	1f	<i>EIF3L</i>
rs1028695	13	NS	0.5	<i>SPATA13</i>	rs4821723	1f	<i>MICALL1</i>
rs2185230	9	NS	0.5	<i>PCSK5</i>	.	.	.
rs4254428	19	NS	NS	<i>ZNF420</i>	rs2562599	1f	<i>ZNF568-ZNF420</i>
rs4254428	19	NS	NS	<i>ZNF420</i>	rs1402468	1f	<i>ZNF420</i>
rs4254428	19	NS	NS	<i>ZNF420</i>	rs11666786	1f	<i>ZNF420-ZNF585A</i>
rs4254428	19	NS	NS	<i>ZNF420</i>	rs7245882	1f	<i>ZNF420</i>
rs139866	22	NS	NS	<i>POLR2F</i>	rs139886	1f	<i>SOX10</i>
rs139866	22	NS	NS	<i>POLR2F</i>	rs139892	1f	<i>POLR2F</i>
rs5028798	11	5	NS	<i>ELF5- EHF</i>	rs12793417	2b	<i>ELF5- EHF</i>
rs2065212	13	NS	NS	<i>KRT18P27-LINC01049</i>	rs9522975	3a	<i>KRT18P27-LINC01049</i>
rs222314	7	NS	NS	<i>LOC340268-HSPA8P8</i>	.	.	.
rs1894381	16	NS	NS	<i>TMC5</i>	.	.	.
rs9809647	3	6	0.24	<i>PYDC2-FGF12</i>	.	.	.
rs898982	1	5	0.1	<i>POU3F1- RRAGC</i>	rs77420329	2a	<i>POU3F1- RRAGC</i>
rs1868368	8	5	NS	<i>KHDRBS3- LOC101927892</i>	.	.	.
rs9392857	6	5	NS	<i>EXOC2-OC101927691</i>	.	.	.
rs8014810	14	NS	NS	<i>BRMS1L</i>	rs7152711	3a	<i>GARNL1</i>
rs8014810	14	NS	NS	<i>BRMS1L</i>	rs10146494	3a	<i>BRMS1L</i>
rs8014810	14	NS	NS	<i>BRMS1L</i>	rs71124724	3a	<i>BRMS1L-LOC644584</i>

Appendix Table 16 continued....

SNP	Chr	RegulomeDB score [†]	F-SNP**	Gene	Correlated SNP	RegulomeDB score [†]	Gene (correlated SNP)
rs8021355	14	6	NS	<i>RALGAP1</i>	.	.	.
rs7144565	14	6	NS	<i>RALGAP1</i>	.	.	.
rs2274068*	14	4	0.65	<i>RALGAP1</i>	.	.	.
rs762562*	19	NS	0.09	<i>ERCC1/CD3EAP</i>	.	.	.
rs4948088	7	5	NS	<i>GRB10-COBL</i>	.	.	.
rs3850942	11	4	NS	<i>MARK2</i>	rs61886104	2b	<i>MARK2</i>
rs2899469	15	5	NS	<i>TNFAIP8L3-CYP19A1</i>	rs4551976	2b	<i>TNFAIP8L3-CYP19A1</i>
rs8011343	14	NS	0.5	<i>MDGA2</i>	rs10133677	3a	<i>MDGA2</i>
rs2031293	13	5	NS	<i>C13orf16-SOX1</i>	.	.	.
rs11171543	12	NS	NS	<i>CPNE8- KIF21A</i>	.	.	.
rs11172024	12	6	NS	<i>KIF21A</i>	rs11171955	3a	<i>KIF21A</i>
rs11172024	12	6	NS	<i>KIF21A</i>	rs11171957	3a	<i>KIF21A</i>
rs11172024	12	6	NS	<i>KIF21A</i>	rs12228664	3a	<i>KIF21A-BCD2</i>
rs1510136	4	5	NS	<i>INPP4B-USP38</i>	rs11306676	2b	<i>INPP4B-USP38</i>
rs16979806	21	4	NS	<i>ADAMTS5- LOC102724355</i>	.	.	.
rs17017488	4	5	0.5	<i>CCSER1</i>	.	.	.
rs10511980	9	NS	NS	<i>MAMDC2</i>	rs2209779	2b	<i>MAMDC2</i>
rs2620870	12	NS	NS	<i>SLC16A7- USP15</i>	.	.	.
rs377621	21	NS	NS	<i>ADAMTS5- LOC102724355</i>	rs368477	2b	<i>ADAMTS5- LOC102724355</i>
rs6510588	19	6	NS	<i>ZNF420</i>	rs2562599	1f	<i>ZNF568-ZNF420</i>
rs6510588	19	6	NS	<i>ZNF420</i>	rs1402468	1f	<i>ZNF420</i>
rs6510588	19	6	NS	<i>ZNF420</i>	rs11666786	1f	<i>ZNF420-ZNF585A</i>

Appendix Table 16 continued....

SNP	Chr	RegulomeDB score [†]	F-SNP**	Gene	Correlated SNP	RegulomeDB score [†]	Gene (correlated SNP)
rs6510588	19	6	NS	<i>ZNF420</i>	rs7245882	1f	<i>ZNF420</i>
rs10739501	9	NS	NS	<i>TLR4-BRINP1</i>	.	.	.
rs6834625	4	NS	0.1	<i>INPP4B-USP38</i>	rs11306676	2b	<i>INPP4B-USP38</i>
rs1209145	14	6	NS	<i>C14orf105-SLC35F4</i>	rs373690	1f	<i>C14orf105-SLC35F4</i>
rs1481046	8	6	NS	<i>NCOA2-TRAM1</i>	rs10096078	2c	<i>NCOA2-TRAM1</i>
rs924615	5	NS	NS	<i>FLJ41309-RPL5P16</i>	.	.	.
rs26784	5	6	0.27	<i>MSH3</i>	.	.	.
rs11120342	1	NS	0.24	<i>PTPN14</i>	.	.	.
rs2830698	21	NS	NS	<i>ADAMTS5- LOC102724355</i>	rs2830715	3a	<i>ADAMTS5- LOC102724355</i>
rs6037033	20	5	NS	<i>VSX1- ENTDP6</i>	rs4815392	2b	<i>ENTDP6</i>
rs12073211	1	NS	0.1	<i>MYSM1-JUN</i>	rs11207297	2b	<i>MYSM1</i>
rs3825594	14	NS	NS	<i>NID2</i>	.	.	.
rs742390	1	4	NS	<i>RUNX3-SYF2</i>	.	.	.
rs973358	17	5	NS	<i>SHISA6</i>	.	.	.
rs10133677	14	3a	0	<i>MDGA2</i>	.	.	.
rs1493897	16	6	NS	<i>IRX3-CRNDE</i>	.	.	.
rs9694342	8	2b	0	<i>AGO2</i>	.	.	.
rs7952853	12	6	0.4	<i>OR6C2</i>	.	.	.
rs6943934	7	5	NS	<i>C7orf50-ZFAND2A</i>	rs73264941	2b	<i>C7orf50-ZFAND2A</i>
rs1610315	6	6	NS	<i>GNG5P1-PRR18</i>	.	.	.
rs1521244	2	5	NS	<i>TRIB2-LOC100506474</i>	.	.	.
rs9897794*	17	1f	0.37	<i>EFCAB5</i>	rs9890205	1d	<i>EFCAB5</i>

Appendix Table 16 continued....

SNP	Chr	RegulomeDB score [†]	F-SNP ^{**}	Gene	Correlated SNP	RegulomeDB score [†]	Gene (correlated SNP)
rs877111	6	6	0.5	<i>C6orf223-MRPL14</i>	rs7770652	1f	<i>MRPL14</i>
rs877111	6	6	0.5	<i>C6orf223-MRPL14</i>	rs4714739	1f	<i>C6orf223-MRPL14</i>
rs877111	6	6	0.5	<i>C6orf223-MRPL14</i>	rs4714741	1f	<i>C6orf223-MRPL14</i>
rs877111	6	6	0.5	<i>C6orf223-MRPL14</i>	rs1321097	1f	<i>C6orf223-MRPL14</i>
rs877111	6	6	0.5	<i>C6orf223-MRPL14</i>	rs910616	1f	<i>C6orf223-MRPL14</i>
rs877111	6	6	0.5	<i>C6orf223-MRPL14</i>	rs4714745	1f	<i>C6orf223-MRPL14</i>
rs877111	6	6	0.5	<i>C6orf223-MRPL14</i>	rs4714742	1f	<i>C6orf223-MRPL14</i>
rs877111	6	6	0.5	<i>C6orf223-MRPL14</i>	rs6883	1f	<i>MRPL14</i>
rs877111	6	6	0.5	<i>C6orf223-MRPL14</i>	rs4711767	1f	<i>MRPL14</i>
rs877111	6	6	0.5	<i>C6orf223-MRPL14</i>	rs910616	1f	<i>C6orf223-MRPL14</i>
rs877111	6	6	0.5	<i>C6orf223-MRPL14</i>	rs1935611	1f	<i>MRPL14</i>
rs877111	6	6	0.5	<i>C6orf223-MRPL14</i>	rs9462964	1f	<i>TMEM63B</i>
rs877111	6	6	0.5	<i>C6orf223-MRPL14</i>	rs4714755	1f	<i>TMEM63B</i>
rs753712	10	6	NS	<i>MKI67-MGMT</i>	.	.	.
rs1430838	8	NS	NS	<i>TRPA1-KCNB2</i>	.	.	.
rs2116078	8	5	NS	<i>TRPA1-KCNB2</i>	.	.	.
rs2615874	10	5	NS	<i>ATRNL1</i>	.	.	.

Note: Some associated SNPs showed multiple correlated functional variants

Chr = Chromosome; NS = No score; SNP = single nucleotide polymorphism; *Missense; ^{††}SNPs change or create a binding site for transcription factors

[†]RegulomDb predicts score from 1 to 7. A score of one suggests SNPs have higher functionality and may play an important role in gene regulation. A score of 7 predicts least functionality

^{**}F-SNP predicts score from 0 to 1. A score of one suggest higher functionality and a score zero suggests no functional role of a SNP

Appendix Table 17: Bioinformatic analysis of genetic risk markers for the top one hundred age-specific associations with childhood ALL with the highest effect sizes ($P < 0.05$)

SNP	Chr	RegulomeDB score [†]	F-SNP**	Gene	Correlated SNP	RegulomeDB score [†]	Gene (correlated SNP)
rs17109582	1	5	NS	<i>DIO1</i>	rs76114672	2b	<i>DIO1-HSPB11</i>
rs17109582	1	5	NS	<i>DIO1</i>	rs77840912	2b	<i>HSPB11</i>
rs7304215	12	NS	NS	<i>TMEM132D</i>	.	.	.
rs10999147*	10	4	0.31	<i>AIFM2</i>	.	.	.
rs7330286	13	6	NS	<i>LINC00343-RNA5SP38</i>	.	.	.
rs41309927*††	20	7	NS	<i>SEC23B</i>	.	.	.
rs36086854*	4	4	0.07	<i>CFAP99</i>	.	.	.
rs17409162*	3	5	0.37	<i>ANO10</i>	rs9856765	2a	<i>ANO10-ABHD5</i>
rs13129052	4	5	0.1	<i>RGS12</i>	rs994425	2b	<i>C4orf44-RGS12</i>
rs13129052	4	5	0.1	<i>RGS12</i>	rs61211078	2b	<i>C4orf44-RGS12</i>
rs9856456	3	NS	0.1	<i>LOC101926953-IGSF11</i>	.	.	.
rs6927353	6	6	NS	<i>TCP10-LOC401286</i>	.	.	.
rs11651675*	17	2a	0.5	<i>TMC8</i>	rs117626020	2a	<i>TMC8</i>
rs10109794	8	3a	NS	<i>TRIM55</i>	rs112477862	2b	<i>LOC101060153</i>
rs10099957	8	4	NS	<i>TRIM55</i>	rs7846184	2b	<i>DNAJC5B-TRIM55</i>
rs10099957	8	4	NS	<i>TRIM55</i>	rs7843038	2b	<i>TRIM55</i>
rs56291145*	13	4	NS	<i>ATP12A</i>	.	.	.
rs2909644	18	NS	NS	<i>RP11-146N18.1-LOC101927404</i>	.	.	.
rs6093579††	20	6	0.27	<i>PTPRT</i>	rs6093581	3a	<i>PTPRT</i>
rs17039265	1	5	0.27	<i>HNRNPCL1-PRAMEF2</i>	rs138700801	Missense	<i>HNRNPCL1</i>

Appendix Table 17 continued....

SNP	Chr	RegulomeDB score [†]	F-SNP ^{**}	Gene	Correlated SNP	RegulomeDB score [†]	Gene (correlated SNP)
rs17039265	1	5	0.27	<i>HNRNPCL1-PRAMEF2</i>	rs141872266	Missense	<i>HNRNPCL1</i>
rs17039265	1	5	0.27	<i>HNRNPCL1-PRAMEF2</i>	rs41279492	Missense	<i>HNRNPCL1</i>
rs17039265	1	5	0.27	<i>HNRNPCL1-PRAMEF2</i>	rs9728577	Missense	<i>PRAMEF2</i>
rs9728577*	1	6	0.27	<i>PRAMEF2</i>	.	.	.
rs75411676**	1	NS	NS	<i>PRAMEF2</i>	.	.	.
rs36068434*	4	5	0.1	<i>CDS1</i>	rs148100862	2b	<i>CDS1</i>
rs36068434*	4	5	0.1	<i>CDS1</i>	rs113914543	2b	<i>CDS1</i>
rs11916525	3	5	NS	<i>CEP70</i>	rs12632793	1d	<i>CEP70</i>
rs11916525	3	5	NS	<i>CEP70</i>	rs12632794	1d	<i>CEP70</i>
rs11916525	3	5	NS	<i>CEP70</i>	rs9049	1f	<i>CEP70</i>
rs11916525	3	5	NS	<i>CEP70</i>	rs1563615	1f	<i>CEP70</i>
rs3204798*	1	6	0.91	<i>PRAMEF2</i>	.	.	.
rs35340237*	3	NS	NS	<i>CEP70</i>	rs35537868 ^{††}	Missense	<i>FAM62C</i>
rs8176018	7	4	0	<i>KEL</i>	rs7810229	2b	<i>KEL</i>
rs1835154	2	3a	NS	<i>GALNT13-KCNJ3</i>	rs16837893	3a	<i>GALNT13-KCNJ3</i>
rs78323957*	8	4	NS	<i>SLC10A5</i>	rs16909527	1f	<i>CHMP4C</i>
rs16909509*	8	NS	NS	<i>ZFAND1</i>	rs16909527	1f	<i>CHMP4C</i>
rs3729598	5	6	0.27	<i>LIFR</i>	rs76127780	3a	<i>LIFR</i>
rs568760	15	5	0	<i>HCN4</i>	.	.	.
rs1800141 ^{††}	12	4	0.27	<i>LRP1/MIR1228</i>	.	.	.
rs35384751 ^{*††}	5	4	0.64	<i>FYB</i>	.	.	.
rs11175471	12	NS	0	<i>RASSF3</i>	rs17223244	2b	<i>RASSF3</i>
rs2389891	4	NS	NS	<i>PDE5A</i>	.	.	.

Appendix Table 17 continued....

SNP	Chr	RegulomeDB score [†]	F-SNP ^{**}	Gene	Correlated SNP	RegulomeDB score [†]	Gene (correlated SNP)
rs35424709*	3	5	0.1	<i>ATP13A4</i>	.	.	.
rs12188300	5	4	NS	<i>IL12B-LOC285627</i>	.	.	.
rs7303641	12	NS	0	<i>RASSF3</i>	rs7959471	2b	<i>RASSF3</i>
rs34139105*	11	NS	0	<i>PRRG4</i>	.	.	.
rs10500248	19	NS	NS	<i>ZNF536- LOC101927254</i>	.	.	.
rs2124906	19	NS	NS	<i>ZNF536- LOC101927254</i>	.	.	.
rs7492685	14	6	NS	<i>RPL18P1-ATP5G2P2</i>	.	.	.
rs276725	19	NS	NS	<i>ZNF536- LOC101927254</i>	.	.	.
rs6851586	4	5	0.1	<i>ANAPC4-LOC645433</i>	.	.	.
rs16871434	4	6	0.1	<i>KCNIP4</i>	.	.	.
rs28421666	6	3a	NS	<i>HLA-DRB1-HLA- DQA1</i>	rs2395226	3a	<i>HLA-DRB1- HLA-DQA1</i>
rs17055478	13	NS	NS	<i>DNAJA1P1- HMG2P39</i>	.	.	.
rs1582274	7	NS	NS	<i>IMMP2L- DOCK4</i>	rs75469463	3a	<i>IMMP2L-DOCK4</i>
rs6572051	14	6	NS	<i>LOC644919</i>	.	.	.
rs9407838	9	6	0.5	<i>SH3GL2</i>	.	.	.
rs72838683*	10	4	NS	<i>PDZD7</i>	.	.	.
rs11250832	10	6	NS	<i>ADARB2- LINC00700</i>	.	.	.
rs16827743	3	5	0.1	<i>LOC101926953- LOC101926968</i>	.	.	.
rs12705300	7	4	NS	<i>SRPK2</i>	.	.	.
rs1915164	15	NS	NS	<i>SQRDL-LOC729316</i>	.	.	.
rs12083795	1	5	0.1	<i>POU3F1- RRAGC</i>	rs72663642	2a	<i>POU3F1- RRAGC</i>

Appendix Table 17 continued....

SNP	Chr	RegulomeDB score [†]	F-SNP**	Gene	Correlated SNP	RegulomeDB score [†]	Gene (correlated SNP)
rs9861022	3	4	0.1	<i>LOC101926953-IGSF11</i>	.	.	.
rs16964079	15	6	NS	<i>C15orf41/CSNK1A1P1</i>	rs28659969	3a	<i>C15orf41</i>
rs16964079	15	6	NS	<i>C15orf41/CSNK1A1P1</i>	rs28480404	3a	<i>C15orf41</i>
rs16964079	15	6	NS	<i>C15orf41/CSNK1A1P1</i>	rs28629456	3a	<i>C15orf41</i>
rs16964079	15	6	NS	<i>C15orf41/CSNK1A1P1</i>	rs12903299	3a	<i>C15orf41</i>
rs16964079	15	6	NS	<i>C15orf41/CSNK1A1P1</i>	rs77483951	3a	<i>CSNK1A1P1</i>
rs16964079	15	6	NS	<i>C15orf41/CSNK1A1P1</i>	rs8031162	3a	<i>C15orf41</i>
rs16964079	15	6	NS	<i>C15orf41/CSNK1A1P1</i>	rs12595212	3a	<i>CSNK1A1P1</i>
rs10157510	1	4	NS	<i>VAMP4-METTL13</i>	rs10913576	2b	<i>VAMP4</i>
rs10224856	7	NS	NS	<i>VPS41</i>	rs2214668	2b	<i>VPS41</i>
rs1728850	15	5	NS	<i>UNC13C-RSL24D1</i>	rs183003270	3a	<i>UNC13C-RSL24D1</i>
rs1728850	15	5	NS	<i>UNC13C-RSL24D1</i>	rs139840085	3a	<i>UNC13C-RSL24D1</i>
rs17055548	13	6	NS	<i>DNAJA1P1- HMG2P39</i>	.	.	.
rs10133677	14	3a	0	<i>MDGA2</i>	.	.	.
rs3130161	6	5	0.5	<i>HLA-DPB1-COL11A2</i>	rs3129203	2b	<i>HLA-DPB1- COL11A2</i>
rs1000521	14	NS	NS	<i>SLC8A3</i>	rs8011824	2b	<i>SLC8A3</i>
rs1000521	14	NS	NS	<i>SLC8A3</i>	rs17107699 ^{††}	2b	<i>SLC8A3</i>
rs12257453	10	6	NS	<i>ARMC3</i>	.	.	.
rs11833839	12	6	NS	<i>EP400</i>	rs1127023	2b	<i>EP400</i>
rs3790126	16	4	0.18	<i>EMP2</i>	rs12598331	2a	<i>ATF7IP2-EMP2</i>
rs16950438	16	5	NS	<i>LINC01571-C16orf97</i>	.	.	.

Appendix Table 17 continued....

SNP	Chr	RegulomeDB score [†]	F-SNP ^{**}	Gene	Correlated SNP	RegulomeDB score [†]	Gene (correlated SNP)
rs6151599	5	4	0.27	<i>MSH3/DHFR</i>	rs11749051	3a	<i>DHFR</i>
rs4546429	5	5	0.1	<i>LINC00603- PTGER4</i>	.	.	.
rs11234604	11	2b	NS	<i>C11orf73</i>	.	.	.
rs6708453	2	5	0.1	<i>TEKT4P3-TRNAE26</i>	rs55872863	3a	<i>IMP4</i>
rs3805114	3	5	0.24	<i>ABCC5</i>	.	.	.
rs9328207	6	5	0.5	<i>TDGFIP4-LOC728344</i>	.	.	.
rs2864680	5	NS	NS	<i>FSTL4</i>	.	.	.
rs4741086	9	NS	NS	<i>DMRT2-RPS27AP14</i>	.	.	.
rs10514074	18	NS	NS	<i>LOC100505817- FBXO15</i>	.	.	.
rs41285557*	5	4	NS	<i>MAML1</i>	.	.	.
rs7620914	3	NS	0.1	<i>LOC101928135</i>	.	.	.
rs7091901	10	5	NS	<i>ZNF438-ZEB1</i>	rs10826908	2c	<i>ZNF438- LOC100129789</i>
rs8100295	19	4	NS	<i>ZNF331-DPRX</i>	.	.	.
rs17407084*	9	5	0.56	<i>AK8</i>	rs73550647	2a	<i>AK8</i>
rs222314	7	NS	NS	<i>LOC340268-HSPA8P8</i>	.	.	.
rs7770942	6	2b	NS	<i>EXOC2- LOC101927691</i>	rs6900976	2b	<i>EXOC2-LOC285768</i>
rs16916188*	8	5	0.5	<i>RBM12B</i>	.	.	.
rs17140942	16	NS	0.5	<i>RBFOX1</i>	.	.	.
rs7172316	15	2b	NS	<i>NPM1P42- NEO1</i>	.	.	.
rs1209145	14	5	NS	<i>C14orf105- SLC35F4</i>	rs373690	1f	<i>C14orf105-SLC35F4</i>
rs10902652	1	NS	0.1	<i>SNRPEP7-WDTC1</i>	.	.	.
rs1457759	5	NS	0.1	<i>LOC101927041- KCNN2</i>	.	.	.

Appendix Table 17 continued....

SNP	Chr	RegulomeDB score [†]	F-SNP ^{**}	Gene	Correlated SNP	RegulomeDB score [†]	Gene (correlated SNP)
rs10826912	10	5	NS	<i>ZNF438-ZEB1</i>	rs10826908	2c	<i>ZNF438-ZEB1</i>
rs61744122*	16	NS	NS	<i>VWA3A</i>	.	.	.
rs4748309 ^{††}	10	6	NS	<i>RSU1</i>	.	.	.
rs8013602	14	6	NS	<i>HNRNPUP1-KRT8P2</i>	.	.	.
rs9560160	13	5	NS	<i>LOC102724489- LOC102724510</i>	.	.	.
rs1755588	1	4	0.07	<i>ACOT11</i>	rs1655527	2b	<i>ACOT11</i>
rs1755588	1	4	0.07	<i>ACOT11</i>	rs114205182	2b	<i>ACOT11</i>
rs1755588	1	4	0.07	<i>ACOT11</i>	rs116752923	2b	<i>ACOT11</i>
rs1755588	1	4	0.07	<i>ACOT11</i>	rs41313244	2b	<i>ACOT11</i>
rs1755588	1	4	0.07	<i>ACOT11</i>	rs60613980	2b	<i>ACOT11</i>
rs10493958 ^{††}	1	3a	NS	<i>LOC102723784-OLFM3</i>	rs12724739	3a	<i>LOC102723784- OLFM3</i>
rs7169431	15	5	NS	<i>NEDD4-RFX7</i>	.	.	.
rs17170286 ^{††}	7	5	0.50	<i>BBS9</i>	.	.	.
rs11945730	4	3a	0.27	<i>BST1-CD38</i>	.	.	.
rs17149645	11	NS	NS	<i>LOC100506368- TMEM135</i>	.	.	.

Note: Some associated SNPs showed multiple correlated functional variants

Chr = Chromosome; NS = No score; SNP = single nucleotide polymorphism; *Missense; **Nonsense; ^{††}SNPs change or create a binding site for transcription factors

[†]RegulomDb predicts score from 1 to 7. A score of one suggests SNPs have higher functionality and may play an important role in gene regulation. A score of 7 predicts least functionality

^{**}F-SNP predicts score from 0 to 1. A score of one suggest higher functionality and a score zero suggests no functional role of a SNP

Appendix Table 18: Expression quantitative trait locus analysis of age-specific associated genetic risk variants

SNP	Chr	Feature	Gene	eQTL
rs7320982*	13	intergenic	<i>MIRHG1-GPC5</i>	<i>ADM, GNB4</i>
rs2212824*	21	intergenic	<i>ADAMTS5-GPXP2</i>	<i>CRIPAK, MTG1</i>
rs2051713*	12	intergenic	<i>MRPL2P1-C12orf37</i>	<i>H1FX</i>
rs6519091*	22	intron	<i>MICALL1</i>	<i>LMF1, MYD88</i>
rs2899293*	22	intron	<i>ANKRD54</i>	<i>LMF1</i>
rs139866*	22	intron	<i>POLR2F</i>	<i>CNPY3</i>
rs6510588*	19	intron	<i>ZNF420</i>	<i>ZNF420</i>
rs1209145*	14	intergenic	<i>C14orf105-SLC35F4</i>	<i>CCR10</i>
rs973358*	17	intron	<i>SHISA6</i>	<i>WDTC1</i>
rs7952853*	12	intron	<i>OR6C2</i>	<i>PAG1</i>
rs877111*	6	intergenic	<i>C6orf223</i>	<i>MRPL14</i>
rs4821723*	22	5' upstream	<i>MICALL1</i>	<i>LMF1</i>
rs2562599*	19	intergenic	<i>ZNF568-ZNF420</i>	<i>SLC13A2, ZNF420</i>
rs735482*	19	3'UTR	<i>ERCC1/CD3EAP</i>	<i>HDGFL1, ERCC1</i>
rs4714739*	6	intergenic	<i>C6orf223-MRPL14</i>	<i>MRPL14</i>
rs4714755*	6	intron	<i>TMEM63B</i>	<i>MRPL14</i>
rs1321097*	6	intergenic	<i>C6orf223-MRPL14</i>	<i>MRPL14</i>
rs910616*	6	intergenic	<i>C6orf223-MRPL14</i>	<i>MRPL14</i>
rs4711767*	6	intron	<i>MRPL14</i>	<i>MRPL14</i>
rs9462964*	6	intron	<i>TMEM63B</i>	<i>MRPL14</i>
rs1935611*	6	intron	<i>MRPL14</i>	<i>MRPL14</i>
rs4714741*	6	intergenic	<i>C6orf223-MRPL14</i>	<i>MRPL14</i>
rs7770652*	6	intron	<i>MRPL14</i>	<i>MRPL14</i>
rs7304215**	12	intron	<i>TMEM132D</i>	<i>BCR, FLJ42953, LOC728468</i>
rs10514074**	18	intergenic	<i>LOC100505817-FBXO15</i>	<i>ZC3H7A, KIF5B, CORO1A, LOC606724, APRT, STX10, ARHGEF1, AGPAT9, CHTF18, C16orf24</i>
rs1209145**	14	intergenic	<i>C14orf105-SLC35F4</i>	<i>CCR10</i>

eQTL = expression quantitative trait loci; Chr = chromosome

*Age-specific results based on P value; **Age-specific results based on effect size

Appendix Table 19: Genes showing age-specific associations (ranked by their P values) and their interactions with chemicals in studies curated in the Comparative Toxicological Database

Gene/region	SNP	Chemical interaction	PUBMED ID
<i>SOX5</i>	rs10505918	arsenite, benzo(a)pyrene, benzo(a)pyrene diol epoxide, bisphenol A, copper sulfate, acetaminophen, carbon tetrachloride, diethylhexyl phthalate, ethinyl estradiol, methylmercury compounds, PCB, potassium dichromate, propiconazole, tetrachlorodibenzodioxin, tobacco smoke pollution	23974009, 22316170, 20382639, 20170705, 19549813, 17562736, 17484886, 19850644, 17555576, 20020106, 20020106, 23608068, 21570461, 17942748, 20133372
<i>HNF4G</i>	rs11997355*	acetaminophen, aflatoxin B1, air pollutants, benzo(a)pyrene, formaldehyde, tetrachlorodibenzodioxin, lead acetate, diethylnitrosamine, chlordane	22230336, 20106945, 21632981, 23649840, 21632981, 22609695, 22129741, 20403969
<i>ZFHX4</i>	rs11997355*	atrazine, benzo(a)pyrene, benzo(a)pyrene diol epoxide, carbon tetrachloride, diethylnitrosamine, propiconazole, tobacco smoke pollution	22378314, 22316170, 20382639, 17484886, 22129741, 21278054, 20133372
<i>IRX3</i>	rs2388773* rs1151277* rs1882591* rs1493897*	estradiol, copper sulfate, formaldehyde, smoke, tetrachlorodibenzodioxin, aflatoxin B1, benzo(a)pyrene, caffeine, nicotine, nitrofen	21185374, 19549813, 20655997, 21095227, 21632981, 19770486, 22228805, 20230807, 20230807, 21238641
<i>CHRM3</i>	rs665159	lead, silicon dioxide, testosterone, PCB, aflatoxin B1, ammonium chloride, carbon tetrachloride, chlorpyrifos, diazinon, dibutyl phthalate, dichlorvos, dimethoate, disulfoton, environmental pollutants, chlorinated hydrocarbons, methyl parathion, potassium dichromate, progesterone, trinitrotoluene	19921347, 23806026, 21592394, 19114083, 23630614, 16483693, 16644059, 17666426, 16207942, 15620428, 19100812, 15033006, 22872703, 22872703, 17666426, 23608068, 15900516, 21346803
<i>RFX3</i>	rs3954950*	arsenic, atrazine, diazinon, formaldehyde, potassium chromate(VI), PCB, benzo(a)pyrene	16835338, 22378314, 22964155, 23649840, 22079256, 19114083, 19770486
<i>GLIS3</i>	rs3954950*	asbestos, benzo(a)pyrene, estradiol, potassium chromate(VI), carbon tetrachloride	17331233, 20106945, 20106945, 22079256, 17484886
<i>RNF122</i>	rs7818844*	benzo(a)pyrene, dibutyl phthalate	22228805, 21266533
<i>NPSR1</i>	rs6972158 rs10250709	atrazine, cadmium, lead acetate, tetrachlorodibenzodioxin	22378314, 24376830, 22641619, 21570461

Appendix Table 19 continued....

Gene/region	SNP	Chemical interaction	PUBMED ID
<i>GPC5</i>	rs7320982*	PCB, atrazine, benzo(a)pyrene, cocaine, diethylnitrosamine	23829299, 22378314, 20106945, 18355967, 22129741
<i>GPC5</i>	rs7320982*	PCB, atrazine, benzo(a)pyrene, cocaine, diethylnitrosamine	23829299, 22378314, 20106945, 18355967, 22129741
<i>KHDRBS3</i>	rs7016929* rs1868368*	acetaminophen, cobaltous chloride, tetrachlorodibenzodioxin, PCB, aflatoxin B1, benzo(a)pyrene, carbon tetrachloride	21420995, 19320972, 22574217, 19114083, 19770486, 19770486
<i>MSH3</i>	rs10079494* rs26784	benzo(a)pyrene, copper sulfate, tetrachlorodibenzodioxin, tobacco smoke pollution, PCB, aflatoxin B1, cadmium chloride, propiconazole	21632981, 19549813, 11007951, 22623965, 19114083, 19770486, 11958953, 21278054
<i>RASGRF2</i>	rs10079494*	arsenite, copper sulfate, PCB, acetaminophen, benzo(a)pyrene, dibutyl phthalate, tobacco smoke pollution	23974009, 19549813, 19114083, 17585979, 21839799, 18087596, 21266533
<i>WNT8A</i>	rs7720650*	bisphenol A	21786754
<i>NME5</i>	rs7720650*	PCB, tetrachlorodibenzodioxin	21334430, 19933214
<i>GPR85</i>	rs2949827* rs2396653*	carbon tetrachloride, chlorpyrifos, copper sulfate, tetrachlorodibenzodioxin	17484886, 18668222, 18579281, 21570461
<i>PPP1R3A</i>	rs2949827* rs2396653*	acetaminophen, bisphenol A, copper sulfate	17562736, 17706920, 18579281
<i>CD97</i>	rs202050948	aflatoxin B1, arsenic trioxide, benzo(a)pyrene, estradiol, copper sulfate, hydrogen peroxide, lithium chloride, PCB, 2,6-dinitrotoluene, acetaminophen, tetrachlorodibenzodioxin, toluene	20106945, 19128835, 20064835, 23019147, 19549813, 20044591, 23527032, 19114083, 21346803, 17562736, 24680724, 22967744
<i>MATN3</i>	rs1191818*	aflatoxin B1, atrazine, benzo(a)pyrene, copper sulfate, diuron, ethanol, fonofos, hydrogen peroxide, parathion, terbufos, testosterone, tetrachlorodibenzodioxin	21632981, 22378314, 21632981, 19549813, 24172598, 20621659, 22847954, 20044591, 22847954, 22847954, 21592394, 21632981
<i>LAPTM4A</i>	rs1191818*	atrazine, potassium dichromate, lipopolysaccharides, pentachlorophenol, Tetrachlorodibenzodioxin	22378314, 23718831, 10975854, 23892564, 21570461
<i>GNMT</i>	rs3800292	aflatoxin B1, benzo(a)pyrene, estradiol, copper sulfate, dioxins, methylcholanthrene, testosterone, tetrachlorodibenzodioxin, acetaminophen, carbon tetrachloride, lipopolysaccharide, tetrachlorodibenzodioxin	20106945, 22100608, 20106945, 19549813, 22100608, 22100608, 21592394, 22298810, 17562736, 18346771, 18346771, 16214954

Appendix Table 19 continued....

Gene/region	SNP	Chemical interaction	PUBMED ID
<i>C7orf50</i>	rs1881116	arsenic, benzene, benzo(a)pyrene, cobaltous chloride	18414638, 19162166, 21632981, 19320972
<i>GCAT</i>	rs4821717*	copper sulfate, diazinon, tetrachlorodibenzodioxin, 2,4-dinitrotoluene, acetaminophen, aflatoxin B1, benzo(a)pyrene, carbon tetrachloride, dibutyl phthalate, testosterone, tetrachlorodibenzodioxin	19549813, 22964155, 21632981, 21346803, 17562736, 19770486, 23735875, 17484886, 17361019, 20403060, 19770486
<i>GALR3</i>	rs4821717*	aflatoxin B1, lead, methylmercuric chloride, PCB, acetaminophen	22100608, 19921347, 21385734, 19114083, 17562736
<i>ADAMTS5</i>	rs2212824*	acetaminophen, arsenic trioxide, benzo(a)pyrene diol epoxide, fonofos, parathion, particulate matter, potassium chromate(VI), terbufos, PCB, aflatoxin B1, carbon tetrachloride, diuron, tetrachlorodibenzodioxin	21420995, 25258189, 20382639, 22847954, 22847954, 23085030, 22079256, 22847954, 23196670, 23630614, 17484886, 25152437, 19465110
<i>INSM2</i>	rs7157104*	atrazine, copper sulfate, tetrachlorodibenzodioxin	22378314, 19549813, 21354282
<i>GFRA2</i>	rs2125649*	atrazine, cobaltous chloride, PCB, carbon tetrachloride, chlorpyrifos, cocaine, paraquat, progesterone	22378314, 17553155, 19114083, 17805973, 17452286, 12358776, 18198484, 22238285
<i>TRIB2</i>	rs6739633*	acetaminophen, arsenic trioxide, asbestos, atrazine, benzo(a)pyrene diol epoxide, estradiol, formaldehyde, nicotine, progesterone, smoke, tetrachlorodibenzodioxin, benzo(a)pyrene, dibutyl phthalate, lead acetate, paraquat, potassium dichromate	21420995, 20458559, 17331233, 22378314, 20382639, 14699072, 23649840, 16949557, 20660070, 21095227, 21296121, 22610609, 21266533, 21829687, 21371552, 23608068
<i>FAM84A</i>	rs6739633*	acetaminophen, benzo(a)pyrene, estradiol, dibutyl phthalate, propiconazole	17562736, 19770486, 19484750, 21266533, 21278054
<i>MAP2K4</i>	rs237320*	arsenic trioxide, benzo(a)pyrene diol epoxide, estradiol, cadmium chloride, hydrogen peroxide, lipopolysaccharides, acetaminophen, cocaine, diethylnitrosamine, lipopolysaccharides, methylmercury compounds, tetrachlorodibenzodioxin, tobacco smoke pollution	14701702, 19150397, 23094148, 18703135, 16707465, 21112663, 17562736, 18355967, 18691550, 21548916, 19666049, 21570461, 15289447
<i>MYOCD</i>	rs237320*	asbestos, benzo(a)pyrene, benzo(a)pyrene diol epoxide, fonofos, parathion, progesterone, terbufos, PCB, tetrachlorodibenzodioxin, tobacco smoke pollution	18687144, 22178795, , 20382639, 22847954, 22847954, 20864642, 22847954, 19114083, 17942748, 20133372
<i>SOX10</i>	rs139886	lead, diethylnitrosamine, progesterone	19921347, 20360939, 17478888

Appendix Table 19 continued....

Gene/region	SNP	Chemical interaction	PUBMED ID
<i>AGA</i>	rs13116233*	cobaltous chloride, fonofos, parathion, terbufos, 2,6-dinitrotoluene, acetaminophen, benzo(a)pyrene, dibutyl phthalate, vehicle emissions	19376846, 22847954, 22847954, 22847954, 21346803, 17562736, 21715664, 21266533, 19165385
<i>MICALL1</i>	rs6519091	acetaminophen, aflatoxin B1, benzo(a)pyrene, estradiol, cobaltous chloride, formaldehyde, methylmercuric chloride	22230336, 20106945, 21632981, 20106945, 19320972, 23649840, 23179753
<i>SPTLC3</i>	rs6109487*	acetaminophen, aflatoxin B1, air pollutants, benzo(a)pyrene, copper sulfate, formaldehyde, nicotine, PCB, tetrachlorodibenzodioxin	21420995, 20106945, 21757418, 22316170, 19549813, 23649840, 23825647, 21334430, 21632981
<i>SLC23A2</i>	rs6052937	acetaminophen, air pollutants, arsenite, benzo(a)pyrene, estradiol, cobaltous chloride, progesterone, tetrachlorodibenzodioxin, carbon tetrachloride, iron, ozone, paraquat, propiconazole, toluene	21420995, 21757418, 23974009, 21632981, 17092984, 19376846, 17092984, 21632981, 17484886, 16629162, 20417186, 22558179, 22334560, 18653662
<i>NEK1</i>	rs34099167	acetaminophen, arsenic trioxide, benzo(a)pyrene, cobaltous chloride, copper sulfate, hydrogen peroxide, potassium chromate(VI)	22230336, 22521957, 20064835, 19376846, 19549813, 18951874, 22079256
<i>ATP6AP1L</i>	rs7722067*	aflatoxin B1, benzo(a)pyrene	23630614, 21839799
<i>CLNK</i>	rs1004327	potassium dichromate, tetrachlorodibenzodioxin	23608068, 21570461
<i>TMTC2</i>	rs3993401*	atrazine, benzo(a)pyrene, formaldehyde, hydrogen peroxide, lead, methylcholanthrene, smoke, tetrachlorodibenzodioxin, acetaminophen, aflatoxin B1, arsenic, dibutyl phthalate, tobacco smoke pollution	22378314, 22316170, 23649840, 18951874, 19921347, 20348232, 21095227, 22903824, 17562736, 19770486, 19654921, 21266533, 20133372
<i>ZC3H13</i>	rs2806907*	formaldehyde, acetaminophen, diuron, ethanol, tetrachlorodibenzodioxin	23649840, 17562736, 25152437, 17618662, 21889950
<i>NID2</i>	rs2101919 rs3825594	air pollutants, arsenates, arsenite, atrazine, PCB, benzo(a)pyrene, estradiol, carbon tetrachloride, diethylnitrosamine, diuron, testosterone, tetrachlorodibenzodioxin	21757418, 18585445, 23974009, 18585445, 23196670, 22228805, 19484750, 17484886, 18164116, 20032058, 21570461
<i>ANKRD54</i>	rs2899293	copper sulfate, aflatoxin B1, dibutyl phthalate, nickel monoxide, tetrachlorodibenzodioxin	19549813, 19770486, 21266533, 19167457, 21570461

Appendix Table 19 continued....

Gene/region	SNP	Chemical interaction	PUBMED ID
<i>SPATA13</i>	rs1028695	arsenic trioxide, benzo(a)pyrene diol epoxide, estradiol, copper sulfate, aflatoxin B1, ciguatoxins, dibutyl phthalate, propiconazole	20458559, 19150397, 17962382, 19549813, 19770486, 18353800, 21266533, 21278054
<i>PCSK5</i>	rs2185230	PCB, arsenic trioxide, benzene, benzo(a)pyrene, estradiol, copper sulfate, progesterone, tetrachlorodibenzodioxin, 2,4-dinitrotoluene, acetaminophen, aflatoxin B1, carbon tetrachloride, dibutyl phthalate, diuron, propiconazole	19692669, 15761015, 19162166, 22316170, 20660070, 19549813, 20660070, 22298810, 21346803, 17585979, 19770486, 17484886, 21266533, 25152437, 21278054
<i>ZNF420</i>	rs4254428	arsenite, formaldehyde	23974009, 20655997
<i>POLR2F</i>	rs139866	cobaltous chloride, copper sulfate, diazinon, hydrogen peroxide, PCB, 2,6-dinitrotoluene, dibutyl phthalate, tetrachlorodibenzodioxin	19376846, 19549813, 22964155, 18951874, 19114083, 21346803, 21266533, 21570461
<i>ELF</i>	rs5028798*	copper sulfate	16973896
<i>EHF</i>	rs5028798*	arsenite, asbestos, estradiol, formaldehyde, progesterone, smoke, tetrachlorodibenzodioxin, aflatoxin B1, furan, tobacco smoke pollution	23974009, 17331233, 20660070, 23649840, 20660070, 21095227, 23152189, 23630614, 22079235, 20133372
<i>TMC5</i>	rs1894381	air pollutants, arsenic trioxide, benzo(a)pyrene diol epoxide, copper sulfate, hydrogen peroxide, smoke, tetrachlorodibenzodioxin, tobacco smoke pollution	21757418, 20707922, 20018196, 19549813, 18951874, 21095227, 21570461, 20133372
<i>FGF12</i>	rs9809647*	aflatoxin B1, arsenic, arsenic trioxide, arsenite, fonofos, parathion, potassium chromate(VI), terbufos, uranium compounds	22100608, 24675094, 22521957, 23974009, 22847954, 22847954, 22079256, 22847954, 19654044
<i>POU3F1</i>	rs898982*	diazinon, lead, PCB, acetaminophen, arsenite, diethylnitrosamine, diuron, potassium dichromate, tetrachlorodibenzodioxin	22964155, 19921347, 24046277, 17562736, 18929588, 18164116, 25152437, 23608068, 22298810
<i>RRAGC</i>	rs898982*	acetaminophen, asbestos, benzene, cobaltous chloride, copper sulfate, formaldehyde, benzo(a)pyrene, tetrachlorodibenzodioxin	22230336, 18687144, 19162166, 19376846, 19549813, 23649840, 20504355, 21570461
<i>EXOC2</i>	rs9392857*	benzo(a)pyrene, potassium chromate(VI), PCB, 2,4-dinitrotoluene, cadmium chloride, dibutyl phthalate, diethylnitrosamine, tetrachlorodibenzodioxin	22316170, 22079256, 19114083, 21346803, 22457795, 21266533, 23968726, 21570461

Appendix Table 19 continued....

Gene/region	SNP	Chemical interaction	PUBMED ID
<i>BRMS1L</i>	rs8014810	acetaminophen, aflatoxin B1, benzo(a)pyrene, benzo(a)pyrene diol epoxide, formaldehyde, dibutyl phthalate, particulate matter, pentachlorophenol	22230336, 21641981, 22316170, 19150397, 23649840, 21266533, 19176365, 23892564
<i>RALGAP1</i>	rs8021355 rs7144565 rs2274068	arsenic trioxide, benzo(a)pyrene, benzo(a)pyrene diol epoxide, copper sulfate, hydrogen peroxide, mercury, 2,6-dinitrotoluene, acetaminophen, lead acetate, sodium arsenate	20458559, 20064835, 19150397, 19549813, 21179406, 19937285, 21346803, 17562736, 20542052, 21795629
<i>ERCC1</i>	rs762562	aflatoxin B1, arsenic, asbestos, benzene, benzo(a)pyrene diol epoxide, benzo(a)pyrene, estradiol, cobaltous chloride, copper sulfate, lipopolysaccharides, paraquat, 2,4-dinitrotoluene, acetaminophen, benzo(a)pyrene, carbon tetrachloride, furan, lead nitrate, particulate matter, tetrachlorodibenzodioxin, vehicle emissions	22100608, 16882524, 20855422, 16188086, 23203453, 20624995, 22082530, 19376846, 19549813, 22777745, 23613995, 21346803, 17562736, 22641617, 15056808, 22079235, 11891201, 12919963, 21570461, 12919963
<i>CD3EAP</i>	rs762562	aflatoxin B1, cobaltous chloride, formaldehyde, hydrogen peroxide, acetaminophen, benzo(a)pyrene	22100608, 19320972, 23649840, 20044591, 17562736, 21715664
<i>GRB10</i>	rs4948088*	arsenic trioxide, benzo(a)pyrene, benzo(a)pyrene diol epoxide, estradiol, cobaltous chloride, copper sulfate, progesterone, PCB, aflatoxin B1, carbon tetrachloride, chlorpyrifos, diuron, lead acetate, particulate matter, testosterone, vehicle emissions	20458559, 22316170, 20382639, 14699072, 19320972, 19549813, 21795739, 19114083, 19770486, 17484886, 20350560, 25152437, 25270620, 21222557, 20403060, 21222557
<i>COBL</i>	rs4948088*	acetaminophen, aflatoxin B1, benzo(a)pyrene, benzo(a)pyrene diol epoxide, estradiol, copper sulfate, smoke, caffeine, copper sulfate, diuron, lipopolysaccharides, propiconazole, tetrachlorodibenzodioxin	22230336, 20106945, 22316170, 20018196, 23019147, 19549813, 21095227, 20864626, 18579281, 21551480, 12057914, 21278054, 19933214
<i>MARK2</i>	rs3850942	copper sulfate, 2,4-dinitrotoluene, 2,6-dinitrotoluene, acetaminophen, propiconazole	19549813, 21346803, 21346803, 17562736, 22228805, 16730040
<i>TNFAIP8L</i>	rs2899469*	aflatoxin B1, benzo(a)pyrene, tetrachlorodibenzodioxin	22100608, 20064835, 21889950

Appendix Table 19 continued....

Gene/region	SNP	Chemical interaction	PUBMED ID
<i>CYP19A1</i>	rs2899469*	PCB, aflatoxin B1, atrazine, benzo(a)pyrene, estradiol, bisphenol A, cadmium, chlordan, copper sulfate, dicofol, endosulfan, estrogens, flusilazole, heptachlor, hexaconazole, Ibuprofen, lipopolysaccharides, methoxychlor, progesterone, propiconazole, testosterone, tetrachlorodibenzodioxin	16216300, 23402939, 11675267, 24361490, 12839940, 22120136, 24376830, 16996190, 19549813, 10806373, 16996190, 16054421, 15554355, 16996190, 12127262, 15964185, 10657851, 22120136, 22130322, 16996190, 12628686, 19147701
<i>MDGA2</i>	rs8011343 rs10133677 rs10133677	sodium arsenite, benzo(a)pyrene, tetrachlorodibenzodioxin	21925251, 22228805, 21570461
<i>SOX1</i>	rs2031293*	benzo(a)pyrene, hydralazine, dibutyl phthalate, tetrachlorodibenzodioxin	22316170, 17183730, 21266533, 24680724
<i>CPNE8</i>	rs11171543*	benzo(a)pyrene, benzo(a)pyrene diol epoxide, potassium chromate(VI), smoke, tetrachlorodibenzodioxin, acetaminophen, cocaine, tetrachlorodibenzodioxin	21632981, 20018196, 22079256, 21095227, 21632981, 17562736, 17898221, 21570461
<i>KIF21A</i>	rs11171543* rs11172024	aspirin, benzo(a)pyrene diol epoxide, estradiol, cobaltous chloride, hydrogen peroxide, 2,6-dinitrotoluene, benzo(a)pyrene, tetrachlorodibenzodioxin	11906190, 19150397, 20404318, 19320972, 21179406, 21346803, 22228805, 21570461
<i>INPP4B</i>	rs1510136* rs6834625*	atrazine, benzene, benzo(a)pyrene, benzo(a)pyrene diol epoxide, estradiol, progesterone, tetrachlorodibenzodioxin, 2,4-dinitrotoluene, 2,6-dinitrotoluene, paraquat	22378314, 19162166, 22316170, 20382639, 23019147, 21795739, 20106945, 21346803, 21346803, 18198484
<i>USP38</i>	rs1510136* rs6834625*	atrazine, benzo(a)pyrene diol epoxide, cobaltous chloride, copper sulfate, formaldehyde, 2,6-dinitrotoluene	22378314, 20018196, 19320972, 19549813, 20655997, 21346803
<i>ADAMTS5</i>	rs16979806* rs377621* rs2830698*	acetaminophen, arsenic trioxide, benzo(a)pyrene diol epoxide, fonofos, parathion, particulate matter, potassium chromate(VI), terbufos, PCB, aflatoxin B1, carbon tetrachloride, diuron, tetrachlorodibenzodioxin	21420995, 25258189, 20382639, 22847954, 22847954, 23085030, 22079256, 22847954, 23196670, 23630614, 17484886, 25152437, 19465110
<i>CCSER1</i>	rs17017488	cocaine	18438686

Appendix Table 19 continued....

Gene/region	SNP	Chemical interaction	PUBMED ID
<i>MAMDC2</i>	rs10511980	benzo(a)pyrene, benzo(a)pyrene diol epoxide, progesterone, acetaminophen, carbon tetrachloride, diuron, lead acetate, tetrachlorodibenzodioxin	22316170, 20382639, 21795739, 17562736, 17484886, 25152437, 22641619, 19654925
<i>SLC16A7</i>	rs2620870*	acetaminophen, air pollutants, benzo(a)pyrene diol epoxide, estradiol, copper sulfate, progesterone, smoke, tetrachlorodibenzodioxin, 2,4-dinitrotoluene, acetaminophen, aflatoxin B1, ethanol, heptachlor, hydrogen peroxide, tetrachlorodibenzodioxin	21420995, 21757418, 20018196, 19619570, 19549813, 21795739, 21095227, 19619570, 21346803, 17562736, 19770486, 19167417, 23153324, 16766717, 20702594
<i>USP15</i>	rs2620870*	aspirin, cobaltous chloride, formaldehyde, PCB, 2,6-dinitrotoluene, acetaminophen, benzo(a)pyrene, tetrachlorodibenzodioxin	11906190, 19376846, 23649840, 21334430, 21346803, 17942131, 15034205, 15034205
<i>TLR4</i>	rs10739501*	PCB, aflatoxin B1, arsenic, lipopolysaccharides, progesterone, smoke, tobacco smoke pollution, acetaminophen, benzo(a)pyrene, carbon tetrachloride, ethanol, ozone, paraquat, particulate matter, tetrachlorodibenzodioxin, tobacco smoke pollution, vehicle emissions	21703328, 22100608, 19945496, 22014880, 22014880, 22516759, 24269501, 17562736, 22228805, 17484886, 16439473, 17626835, 23969119, 12832678, 21653731, 24612634, 20362647
<i>BRINP1</i>	rs10739501*	arsenic trioxide, PCB	15761015, 23196670
<i>C14orf105</i>	rs1209145*	acetaminophen, aflatoxin B1, arsenic trioxide, benzo(a)pyrene, formaldehyde, tetrachlorodibenzodioxin	21420995, 20106945, 15761015, 20106945, 23649840, 20106945
<i>SLC35F4</i>	rs1209145*	acetaminophen, potassium dichromate	17562736, 23608068
<i>NCOA2</i>	rs1481046*	aflatoxin B1, air pollutants, arsenic trioxide, benzo(a)pyrene, estradiol, bisphenol A, lipopolysaccharides, potassium chromate(VI), tetrachlorodibenzodioxin, furan, lead acetate, lipopolysaccharides, progesterone	20106945, 21757418, 19131511, 21632981, 17962382, 23583298, 21370964, 22079256, 18842620, 22079235, 22641619, 16847310, 17556502
<i>TRAM1</i>	rs1481046*	benzo(a)pyrene diol epoxide, copper sulfate, PCB, estradiol	20018196, 19549813, 19114083, 20068009

Appendix Table 19 continued....

Gene/region	SNP	Chemical interaction	PUBMED ID
<i>PTPN14</i>	rs11120342	cobaltous chloride, copper sulfate, PCB, benzo(a)pyrene, dibutyl phthalate, diuron, lead acetate, ozone, tetrachlorodibenzodioxin	19320972, 19549813, 19114083, 21569818, 21266533, 25152437, 25270620, 17095637, 21570461
<i>VSX1</i>	rs6037033*	acetaminophen, arsenite, copper sulfate, hydrogen peroxide, aflatoxin B1	22230336, 23974009, 19549813, 18951874, 23630614
<i>ENTPD6</i>	rs6037033*	acetaminophen	21420995
<i>MYSM1</i>	rs12073211*	formaldehyde, potassium chromate(VI), tetrachlorodibenzodioxin, 2,4-dinitrotoluene, 2,6-dinitrotoluene, benzo(a)pyrene, propiconazole, tetrachlorodibenzodioxin	20655997, 22079256, 22298810, 21346803, 21346803, 19770486, 21278054, 21570461
<i>JUN</i>	rs12073211*	PCB, aflatoxin B1, air pollutants, arsenic trioxide, arsenite, asbestos, aspirin, atrazine, benzene, benzo(a)pyrene, benzo(a)pyrene diol epoxide, estradiol, cadmium chloride, cocaine, copper sulfate, diquat, endosulfan, heptachlor, hydrogen peroxide, lipopolysaccharides, nicotine, paraquat, particulate matter, potassium dichromate, tetrachlorodibenzodioxin	16611624, 22100608, 21757418, 18633430, 22260869, 18687144, 16600694, 22378314, 17119257, 16041517, 20382639, 15930183, 11341981, 15814102, 19549813, 21172416, 22146149, 15888667, 8853906, 24149798, 11592233, 16237197, 22178795, 20493934, 15019843
<i>RUNX3</i>	rs742390*	arsenite, benzo(a)pyrene, estradiol, diazinon, fonofos, parathion, terbufos, tetrachlorodibenzodioxin, tobacco smoke pollution, 4-amino-2,6-dinitrotoluene, acetaminophen	23974009, 20064835, 20404318, 22964155, 22847954, 22847954, 22847954, 22298810, 23724145, 21346803, 17562736
<i>SYF2</i>	rs742390*	atrazine, copper sulfate, formaldehyde, potassium chromate(VI), PCB, acetaminophen, benzo(a)pyrene, tetrachlorodibenzodioxin	22378314, 19549813, 23649840, 22079256, 17562736, 22228805, 24680724
<i>SHISA6</i>	rs973358	Tretinoin	21934132

Appendix Table 19 continued....

Gene/region	SNP	Chemical interaction	PUBMED ID
<i>AGO2</i>	rs9694342	benzo(a)pyrene diol epoxide, estradiol, copper sulfate, diazinon, formaldehyde, 2,4-dinitrotoluene, acetaminophen, cocaine, mercuric chloride, tetrachlorodibenzodioxin	20018196, 23019147, 19549813, 22964155, 20655997, 21346803, 17562736, 20643829, 16507785, 21570461
<i>ZFAND2A</i>	rs6943934*	acetaminophen, benzo(a)pyrene, benzo(a)pyrene diol epoxide, estradiol, cobaltous chloride, copper sulfate, diazinon, formaldehyde, potassium chromate(VI), tobacco smoke pollution, aflatoxin B1, arsenite, bisphenol A, dibutyl phthalate, tetrachlorodibenzodioxin	21420995, 21632981, 19150397, 20106945, 19320972, 19549813, 22964155, 23649840, 22079256, 22363418, 19770486, 16973439, 21932408, 21266533, 21570461
<i>TRIB2</i>	rs1521244*	acetaminophen, arsenic trioxide, asbestos, atrazine, benzo(a)pyrene diol epoxide, estradiol, formaldehyde, hydralazine, nicotine, progesterone, smoke, tetrachlorodibenzodioxin, benzo(a)pyrene, dibutyl phthalate, lead acetate, paraquat	21420995, 20458559, 17331233, 22378314, 20382639, 14699072, 23649840, 17183730, 16949557, 20660070, 21095227, 21296121, 22610609, 21266533, 21829687, 21371552
<i>EFCAB5</i>	rs9897794	potassium dichromate, tetrachlorodibenzodioxin	23608068, 21570461
<i>C6orf223</i>	rs877111	acetaminophen, formaldehyde	22230336, 23649840
<i>MKI67</i>	rs753712	acetaminophen, aflatoxin B1, atrazine, benzene, benzo(a)pyrene diol epoxide, estradiol, copper sulfate, methylmercuric chloride, PCB, progesterone, benzo(a)pyrene, bisphenol A, carbon tetrachloride, diazinon, diethylnitrosamine, propiconazole, asbestos	22230336, 20106945, 18585445, 21843810, 21776270, 19167446, 19549813, 23179753, 21334430, 16888808, 21569818, 22875908, 17484886, 22546817, 24012840, 21278054, 17200189
<i>TRPA1</i>	rs1430838 rs2116078	benzene, benzo(a)pyrene diol epoxide, coal ash, dibutyl phthalate, formaldehyde, ozone, particulate matter, smoke	21591660, 20382639, 22155782, 22935519, 21591660, 20008466, 23541125, 23541125
<i>ATRNL1</i>	rs2615874	atrazine, estradiol, fonofos, parathion, terbufos, tetrachlorodibenzodioxin	22378314, 19619570, 22847954, 22847954, 22847954, 19619570

SNP = single nucleotide polymorphism

Appendix Table 20: Genes showing age-specific associations (ranked by their OR) and their interactions with chemicals in studies curated in the Comparative Toxicological Database

Gene/region	SNP	Chemical interaction	PUBMED ID
<i>DIO1</i>	rs17109582	aflatoxin B1, benzo(a)pyrene, estradiol, copper sulfate, tetrachlorodibenzodioxin, PCB, 2,4-dinitrotoluene, acetaminophen, arsenic, cobaltous chloride, diethylnitrosamine, ethanol, fipronil, furan, hexachlorobenzene, lead acetate, methoxychlor, pentachlorophenol	20106945, 21871943, 20106945, 19549813, 22298810, 15254343, 20959002, 21346803, 17562736, 18288313, 21139344, 17602206, 15353170, 23962444, 22079235, 15664263, 22609695, 7574712
<i>TMEM132D</i>	rs7304215	fonofos, parathion, terbufos, potassium dichromate	22847954, 22847954, 22847954, 23608068
<i>AIFM2</i>	rs10999147	benzo(a)pyrene, cobaltous chloride, copper sulfate, tetrachlorodibenzodioxin, cadmium, hydrogen peroxide	21632981, 19320972, 19549813, 24067728, 14987999
<i>SEC23B</i>	rs41309927	atrazine, cobaltous chloride, 2,6-dinitrotoluene	22378314, 19376846, 21346803
<i>ANO10</i>	rs17409162	formaldehyde, testosterone, aflatoxin B1, dibutyl phthalate, tetrachlorodibenzodioxin	23649840, 21592394, 19770486, 21266533, 21570461
<i>RGS12</i>	rs13129052	acetaminophen, benzo(a)pyrene, copper sulfate, aflatoxin B1, benzo(a)pyrene, dibutyl phthalate, diethylnitrosamine, ethinyl estradiol, propiconazole, tetrachlorodibenzodioxin	22230336, 20064835, 19549813, 19770486, 22228805, 21266533, 18164116, 17108234, 21278054, 21570461
<i>IGSF11</i>	rs9856456* rs9861022*	estradiol, PCB, acetaminophen, benzo(a)pyrene, chlorpyrifos, diethylnitrosamine, tetrachlorodibenzodioxin	20404318, 19114083, 17562736, 19770486, 18668222, 17602206, 21570461
<i>TMC8</i>	rs11651675	arsenic, copper sulfate, tetrachlorodibenzodioxin	18414638, 19549813, 21570461
<i>TRIM55</i>	rs10109794 rs10099957	methylcholanthrene, acetaminophen, coal ash,	20348232, 17562736, 19000753
<i>ATP12A</i>	rs56291145	tetrachlorodibenzodioxin, estradiol, lead acetate, smoke	23152189, 19484750, 25270620, 23693141
<i>PTPRT</i>	rs6093579	fonofos, parathion, terbufos, acetaminophen, aflatoxin B1, diethylnitrosamine	22847954, 22847954, 22847954, 17562736, 23630614, 22129741

Appendix Table 20 continued....

Gene/region	SNP	Chemical interaction	PUBMED ID
<i>PRAMEF2</i>	rs17039265* rs9728577 rs75411676 rs3204798	aflatoxin B1	22100608
<i>CDS1</i>	rs36068434	estradiol, nicotine, benzo(a)pyrene, tetrachlorodibenzodioxin, PCB, 2,4-dinitrotoluene, tetrachlorodibenzodioxin	19167446, 23825647, 22228805, 17942748, 19114083, 21346803, 21215274
<i>CEP70</i>	rs11916525 rs35340237	acetaminophen, aflatoxin B1, air pollutants, arsenic trioxide, atrazine, Benzo(a)pyrene, benzo(a)pyrene diol epoxide, copper sulfate, potassium chromate(VI), 3-dinitrobenzene	22230336, 22100608, 21757418, 20458559, 22378314, 21632981, 20018196, 19549813, 22079256, 21983209
<i>KEL</i>	rs8176018	formaldehyde, acetaminophen, potassium dichromate, tetrachlorodibenzodioxin	23649840, 17562736, 23608068, 19465110
<i>GALNT13</i>	rs1835154*	copper sulfate, PCB, estradiol	19549813, 19114083, 19484750
<i>KCNJ3</i>	rs1835154*	benzo(a)pyrene, carbon tetrachloride, ethanol	22316170, 16644059, 22164246
<i>SLC10A5</i>	rs78323957	arsenic	21291286
<i>ZFAND1</i>	rs16909509	tetrachlorodibenzodioxin, acetaminophen, dibutyl phthalate	21632981, 17562736, 21266533
<i>LIFR</i>	rs3729598	aflatoxin B1, arsenic, asbestos, benzo(a)pyrene, benzo(a)pyrene diol epoxide, estradiol, methylmercuric chloride, PCBs, testosterone, tetrachlorodibenzodioxin, 2,6-dinitrotoluene, acetaminophen, arsenite, carbon tetrachloride, furan, lipopolysaccharides, maneb, paraquat, progesterone	22100608, 24675094, 17297452, 21632981, 20018196, 21185374, 23179753, 21334430, 21592394, 20106945, 21346803, 17585979, 18929588, 17484886, 22079235, 17321000, 22563483, 22563483, 21770760
<i>HCN4</i>	rs568760	aflatoxin B1, diazinon, methoxychlor	22100608, 22964155, 23303685
<i>LRP1</i>	rs1800141*	air pollutants, arsenic trioxide, copper sulfate, hydrogen peroxide, 2,4-dinitrotoluene, 2,6-dinitrotoluene, acetaminophen, aflatoxin B1, benzo(a)pyrene, estradiol, dibutyl phthalate, diethylnitrosamine, lipopolysaccharide, propiconazole, tetrachlorodibenzodioxin	21757418, 22521957, 19549813, 23410634, 21346803, 21346803, 17585979, 19770486, 22228805, 16977382, 21266533, 17942915, 16977382, 21278054, 21570461

Appendix Table 20 continued....

Gene/region	SNP	Chemical interaction	PUBMED ID
<i>FYB</i>	rs35384751	arsenic trioxide, benzo(a)pyrene, cobaltous chloride, diuron, fonofos, parathion, terbufos, acetaminophen, tetrachlorodibenzodioxin	15761015, 20064835, 19376846, 24172598, 22847954, 22847954, 22847954, 17562736, 20702594
<i>RASSF3</i>	rs11175471 rs7303641	acetaminophen, benzo(a)pyrene, carbon tetrachloride, tetrachlorodibenzodioxin	17562736, 19770486, 17484886, 21570461
<i>PDE5A</i>	rs2389891*	benzo(a)pyrene, benzo(a)pyrene diol epoxide, estradiol, PCB, caffeine, carbon tetrachloride, chlorpyrifos, diazinon, methylmercuric chloride, testosterone, tetrachlorodibenzodioxin, tobacco smoke pollution	22316170, 20382639, 22574217, 23196670, 20864626, 16644059, 17452286, 17452286, 20864626, 17138653, 24680724, 20133372
<i>ATP13A4</i>	rs35424709	hydralazine, aflatoxin B1, diethylnitrosamine, tetrachlorodibenzodioxin, tobacco smoke pollution	17183730, 19770486, 17942915, 19770486, 20133372
<i>IL12B</i>	rs12188300*	estradiol, lipopolysaccharides, progesterone, PCB, acetaminophen, aflatoxin B1, benzene, benzo(a)pyrene, bisphenol A, diazinon, diethylnitrosamine, ethanol, formaldehyde, hydrogen peroxide, methoxychlor, nicotine, ozone, particulate matter, progesterone, tetrachlorodibenzodioxin, tobacco smoke pollution, vehicle emissions	20130130, 19211157, 20130130, 19114083, 22575169, 22445859, 15894107, 17275222, 18569609, 17499902, 25051504, 20624996, 12161283, 15723204, 22842586, 21237301, 18929643, 19805405, 21977998, 21097750, 20133372, 19805405
<i>PRRG4</i>	rs34139105	benzo(a)pyrene diol epoxide, formaldehyde, smoke, tetrachlorodibenzodioxin, acetaminophen, aflatoxin B1, benzo(a)pyrene, diethylnitrosamine	22101062, 23649840, 21095227, 22298810, 17562736, 23630614, 19770486, 22129741
<i>ANAPC4</i>	rs6851586*	arsenite, potassium chromate(VI), 2,4-dinitrotoluene, 2,6-dinitrotoluene, acetaminophen, benzo(a)pyrene, ethanol, tetrachlorodibenzodioxin	23974009, 22079256, 21346803, 21346803, 17562736, 22228805, 17618662, 21570461
<i>KCNIP4</i>	rs16871434	benzo(a)pyrene, copper sulfate, furan, progesterone, testosterone, tobacco smoke pollution	22316170, 19549813, 22079235, 22238285, 19693291, 19969065
<i>HLA-DRB1</i>	rs28421666*	arsenic, aspirin, benzo(a)pyrene, estradiol, lead, progesterone, smoke	18414638, 20485159, 20106945, 20660070, 19921347, 20660070, 21095227
<i>HLA-DQA1</i>	rs28421666*	PCB, Arsenic, Benzene, Lipopolysaccharides, Mercury, Progesterone, Aluminum	20638727, 18414638, 16188091, 22235868, 19690047, 21298039

Appendix Table 20 continued....

Gene/region	SNP	Chemical interaction	PUBMED ID
<i>IMMP2L</i>	rs1582274*	aflatoxin B1, benzo(a)pyrene, copper sulfate, formaldehyde, acetaminophen, estradiol, tetrachlorodibenzodioxin	20106945, 22316170, 19549813, 23649840, 17562736, 19484750, 21570461
<i>DOCK4</i>	rs1582274*	aflatoxin B1, asbestos, benzo(a)pyrene, benzo(a)pyrene diol epoxide, diazinon, hydrogen peroxide, progesterone, potassium dichromate, tetrachlorodibenzodioxin	20106945, 18687144, 21714911, 19150397, 22964155, 18951874, 21795739, 23608068, 19465110
<i>SH3GL2</i>	rs9407838	aflatoxin B1, arsenic trioxide, benzo(a)pyrene, fonofos, parathion, terbufos, tetrachlorodibenzodioxin, PCB, dibutyl phthalate, paraquat, potassium dichromate	20106945, 15761015, 20106945, 22847954, 22847954, 22847954, 20106945, 21673325, 21266533, 21371552, 23608068
<i>PDZD7</i>	rs72838683	arsenic trioxide, copper sulfate	20458559, 19549813
<i>ADARB2</i>	rs11250832*	acetaminophen, aflatoxin B1, PCB, tetrachlorodibenzodioxin	22230336, 22100608, 19114083, 21570461
<i>SRPK2</i>	rs12705300	acetaminophen, arsenite, benzo(a)pyrene, benzo(a)pyrene diol epoxide, paraquat, potassium chromate(VI), 2,4-dinitrotoluene, 2,6-dinitrotoluene, aflatoxin B1, carbon tetrachloride, chlorpyrifos, lipopolysaccharides, potassium dichromate, propiconazole, toluene	22230336, 23974009, 20106945, 19150397, 23613995, 22079256, 21346803, 21346803, 19770486, 17484886, 18668222, 12057914, 23608068, 21278054, 22166486
<i>SQRDL</i>	rs1915164*	acetaminophen, benzo(a)pyrene, estradiol, copper sulfate, hydrogen peroxide, potassium chromate(VI), progesterone, tetrachlorodibenzodioxin, propiconazole	21420995, 22316170, 22574217, 19549813, 23410634, 22079256, 21795739, 21632981, 21278054
<i>POU3F1</i>	rs12083795*	diazinon, lead, PCB, acetaminophen, arsenite, diethylnitrosamine, diuron, potassium dichromate, tetrachlorodibenzodioxin	22964155, 19921347, 19114083, 17562736, 18929588, 18164116, 25152437, 23608068, 24046277
<i>RRAGC</i>	rs12083795*	acetaminophen, asbestos, benzene, copper sulfate, formaldehyde, benzo(a)pyrene, tetrachlorodibenzodioxin	22230336, 18687144, 19162166, 19549813, 23649840, 20504355, 21570461
<i>C15orf41</i>	rs16964079	potassium chromate(VI)	22079256
<i>VAMP4</i>	rs10157510*	arsenic trioxide, cobaltous chloride, copper sulfate, formaldehyde, aflatoxin B1, benzo(a)pyrene, nicotine, tetrachlorodibenzodioxin	20458559, 19376846, 19549813, 23649840, 19770486, 15034205, 17997037, 15034205
<i>METTL13</i>	rs10157510*	acetaminophen, atrazine, copper sulfate, tetrachlorodibenzodioxin	21420995, 22378314, 19549813, 19654925

Appendix Table 20 continued....

Gene/region	SNP	Chemical interaction	PUBMED ID
<i>VPS41</i>	rs10224856	atrazine, benzo(a)pyrene, bisphenol A, copper sulfate, hydrogen peroxide, caffeine, dibutyl phthalate, nicotine, tetrachlorodibenzodioxin	22378314, 20064835, 22576693, 19549813, 21179406, 21266533, 20230807, 21570461
<i>UNC13C</i>	rs1728850*	formaldehyde, benzo(a)pyrene, furan, paraquat, testosterone	23649840, 21839799, 22079235, 22563483, 20403060
<i>RSL24D1</i>	rs1728850*	acetaminophen, benzo(a)pyrene diol epoxide, copper sulfate	22230336, 20018196, 19549813
<i>MDGA2</i>	rs10133677	sodium arsenite, benzo(a)pyrene, tetrachlorodibenzodioxin	21925251, 22228805, 21570461
<i>HLA-DPB1</i>	rs3130161*	benzene, benzo(a)pyrene, tetrachlorodibenzodioxin	16188091, 15034205, 15034205
<i>COL11A2</i>	rs3130161*	copper sulfate, diuron, tetrachlorodibenzodioxin	19549813, 21551480, 21570461
<i>SLC8A3</i>	rs1000521	PCB, bisphenol A, fonofos, parathion, terbufos, ethanol	23146750, 23146750, 22847954, 22847954, 22847954, 20655511
<i>ARMC3</i>	rs12257453	benzo(a)pyrene	22316170
<i>EP400</i>	rs11833839	cobaltous chloride, copper sulfate, formaldehyde, 2,6-dinitrotoluene, acetaminophen, benzo(a)pyrene, propiconazole, tetrachlorodibenzodioxin	19320972, 19549813, 23649840, 21346803, 17562736, 20504355, 21278054, 21570461
<i>EMP2</i>	rs3790126	acetaminophen, benzo(a)pyrene, benzo(a)pyrene diol epoxide, estradiol, bisphenol A, copper sulfate, progesterone, tetrachlorodibenzodioxin, PCB, dibutyl phthalate, furan	22230336, 22316170, 20382639, 16474171, 16474171, 19549813, 20864642, 22574217, 19114083, 21266533, 24183702
<i>MSH3</i>	rs6151599	benzo(a)pyrene, copper sulfate, tetrachlorodibenzodioxin, tobacco smoke pollution, PCB, aflatoxin B1, cadmium chloride, propiconazole	21632981, 19549813, 11007951, 22623965, 19114083, 19770486, 11958953, 21278054
<i>DHFR</i>	rs6151599	acetaminophen, air pollutants, benzo(a)pyrene, benzo(a)pyrene diol epoxide, estradiol, cobaltous chloride, copper sulfate, formaldehyde, nicotine, potassium chromate(VI), PCB, aflatoxin B1, arsenite, carbon tetrachloride, dibutyl phthalate, diethylnitrosamine, tetrachlorodibenzodioxin	22230336, 21757418, 20064835, 20018196, 19167446, 19376846, 19549813, 23649840, 12588870, 22079256, 20005886, 19770486, 18929588, 17484886, 21266533, 20360939, 21570461
<i>PTGER4</i>	rs4546429*	benzo(a)pyrene, benzo(a)pyrene diol epoxide, estradiol, cobaltous chloride, diuron, formaldehyde, particulate matter, polychlorinated biphenyls, tetrachlorodibenzodioxin, ammonium chloride, bisphenol A, carbon tetrachloride, dibutyl phthalate, diuron, hydrazine, progesterone	22316170, 20382639, 19619570, 19320972, 24172598, 20655997, 22178795, 21334430, 19619570, 16483693, 20096755, 17484886, 15620428, 21551480, 15282401,

Appendix Table 20 continued....

Gene/region	SNP	Chemical interaction	PUBMED ID
<i>C11orf73</i>	rs11234604	copper sulfate, potassium chromate(VI)	19549813, 22079256
<i>ABCC5</i>	rs3805114	acetaminophen, arsenic trioxide, aspirin, benzo(a)pyrene, estradiol, estrogens, formaldehyde, hydrogen peroxide, potassium chromate(VI), tetrachlorodibenzodioxin, PCB, dibutyl phthalate, diethylnitrosamine, testosterone	17627974, 20458559, 21900887, 21871943, 15072547, 21233418, 23649840, 21179406, 22079256, 19619570, 15833929, 21266533, 17602206, 20403060
<i>FSTL4</i>	rs2864680	arsenic trioxide, benzo(a)pyrene, potassium dichromate	15894607, 22228805, 23608068
<i>DMRT2</i>	rs4741086*	arsenite, cobalt, cobaltous chloride, fonofos, parathion, terbufos, lead acetate,	23974009, 20105288, 20105288, 22847954, 22847954, 22847954, 21829687
<i>FBXO15</i>	rs10514074*	aflatoxin B1, tetrachlorodibenzodioxin	22100608, 22298810
<i>MAML1</i>	rs41285557	arsenic trioxide, asbestos, acetaminophen, benzo(a)pyrene, propiconazole, tetrachlorodibenzodioxin	20458559, 17331233, 17562736, 22228805, 21278054, 21570461
<i>ZNF438</i>	rs7091901* rs10826912*	cobaltous chloride, copper sulfate, potassium chromate(VI)	20105288, 19549813, 22079256
<i>ZEB1</i>	rs7091901* rs10826912*	acetaminophen, arsenic trioxide, benzo(a)pyrene diol epoxide, estradiol, cobaltous chloride, copper sulfate, estrogens, formaldehyde, progesterone, benzo(a)pyrene, chlorpyrifos, diuron, mercuric chloride, tetrachlorodibenzodioxin	21420995, 20707922, 19150397, 12154049, 19376846, 19549813, 18622689, 23649840, 20864642, 15034205, 20350560, 25152437, 16507785, 15034205
<i>ZNF331</i>	rs8100295*	arsenic, atrazine, benzene, lead	16835338, 22378314, 17119257, 19921347
<i>AK8</i>	rs17407084	benzo(a)pyrene, cadmium chloride	22228805, 22457795
<i>EXOC2</i>	rs7770942*	benzo(a)pyrene, potassium chromate(VI), PCB, 2,4-dinitrotoluene, dibutyl phthalate, tetrachlorodibenzodioxin	22316170, 22079256, 19114083, 21346803, 21266533, 21570461
<i>RBM12B</i>	rs16916188	atrazine, formaldehyde, aflatoxin B1, tetrachlorodibenzodioxin	22378314, 20655997, 19770486, 21215274
<i>RBFOX1</i>	rs17140942	PCB, dibutyl phthalate, tetrachlorodibenzodioxin	19933214, 17361019, 19933214
<i>NEO1</i>	rs7172316*	acetaminophen, atrazine, benzo(a)pyrene, estradiol, hydrogen peroxide, progesterone, progesterone, 2,4-dinitrotoluene, aflatoxin B1, carbon tetrachloride, cocaine, dibutyl phthalate, formaldehyde, tetrachlorodibenzodioxin	22230336, 22378314, 21632981, 20660070, 20044591, 20660070, 20660070, 21346803, 19770486, 17484886, 15056714, 21266533, 12679049, 21570461

Appendix Table 20 continued....

Gene/region	SNP	Chemical interaction	PUBMED ID
<i>C14orf105</i>	rs1209145*	acetaminophen, aflatoxin B1, arsenic trioxide, benzo(a)pyrene, formaldehyde, tetrachlorodibenzodioxin	21420995, 20106945, 15761015, 20106945, 23649840, 20106945
<i>SLC35F4</i>	rs1209145*	acetaminophen, potassium dichromate	17562736, 23608068
<i>WDTC1</i>	rs10902652*	acetaminophen, diazinon, tetrachlorodibenzodioxin, 2,4-dinitrotoluene, propiconazole, tetrachlorodibenzodioxin	22230336, 22964155, 22298810, 21346803, 21278054, 24680724
<i>KCNN2</i>	rs1457759*	arsenite, benzo(a)pyrene, benzo(a)pyrene diol epoxide, testosterone, tetrachlorodibenzodioxin, PCB, acetaminophen, aflatoxin B1, ammonium chloride, bisphenol A, dibutyl phthalate, diethylnitrosamine, methoxychlor, tobacco smoke pollution	23974009, 21802500, 20382639, 21592394, 22298810, 19114083, 17562736, 19770486, 16483693, 23359474, 23359474, 15833021, 23303685, 18087596
<i>VWA3A</i>	rs61744122	copper sulfate, tetrachlorodibenzodioxin	19549813, 21570461
<i>RSU1</i>	rs4748309	arsenite, estradiol, PCB, aflatoxin B1, benzo(a)pyrene, tetrachlorodibenzodioxin	23974009, 19167446, 19114083, 19770486, 21715664, 21570461
<i>ACOT11</i>	rs1755588	aflatoxin B1, atrazine, benzo(a)pyrene, copper sulfate, fonofos, hydrogen peroxide, parathion, terbufos, testosterone	21641981, 22378314, 22316170, 19549813, 22847954, 20044591, 22847954, 22847954, 21592394
<i>OLFM3</i>	rs10493958*	atrazine, benzo(a)pyrene, acetaminophen	22378314, 22316170, 17562736
<i>NEDD4</i>	rs7169431*	acetaminophen, arsenite, copper sulfate, potassium chromate(VI), benzo(a)pyrene, diuron, ethinyl estradiol, testosterone, tetrachlorodibenzodioxin	21420995, 23974009, 19549813, 22079256, 20127859, 25152437, 17555576, 21669218, 21570461
<i>RFX7</i>	rs7169431*	atrazine, estradiol, copper sulfate, formaldehyde	22378314, 22574217, 19549813, 20655997
<i>BBS9</i>	rs17170286	aflatoxin B1, air pollutants, arsenic trioxide, benzo(a)pyrene, cobaltous chloride, formaldehyde, tetrachlorodibenzodioxin	20106945, 21757418, 20458559, 21632981, 19320972, 23649840, 21570461
<i>BST1</i>	rs11945730*	aflatoxin B1, benzo(a)pyrene diol epoxide, cobaltous chloride, tetrachlorodibenzodioxin, acetaminophen, arsenic, chlorpyrifos, cocaine, diazinon, ethanol, testosterone, tobacco smoke pollution	22100608, 20382639, 19320972, 17101203, 17562736, 19654921, 21968025, 20187946, 21968025, 15353170, 15788153, 20133372

Appendix Table 20 continued....

Gene/region	SNP	Chemical interaction	PUBMED ID
<i>CD38</i>	rs11945730*	arsenic trioxide, parathion, progesterone, terbufos, arsenic, estradiol, paraquat, particulate matter, progesterone, testosterone, tetrachlorodibenzodioxin	18297255, 22847954, 21768398, 22847954, 19654921, 21840325, 18198484, 23638009, 21770760, 21840325, 21570461
<i>TMEM135</i>	rs17149645*	acetaminophen, aflatoxin B1, benzo(a)pyrene, copper sulfate, potassium chromate(VI), PCB, tetrachlorodibenzodioxin	22230336, 20106945, 21632981, 19549813, 22079256, 19114083, 24680724

SNP = single nucleotide polymorphism

Appendix Table 21: Deleterious effect of missense variations associated with gender-specificity in childhood ALL risk

SNP (missense variations)	Gender-specific results	SIFT score	SIFT prediction	SIFT confidence	PolyPhen score	PolyPhen prediction
rs9913430	Gender P value	0.74	tolerated	high	0	benign
rs61748746	Gender P value	0.25	tolerated	high	0.24	possibly damaging
rs61748749	Gender P value	0.43	tolerated	high	0.24	possibly damaging
rs35693261	Gender OR	0.01	damaging	high	0.01	benign
rs4770684	Gender OR	0.63	tolerated	high	0.03	benign
rs35665085	Gender OR	0.13	tolerated	high	0.01	benign
rs3847262	Gender OR	0.05	damaging	high	0.93	probably damaging
rs17080410	Gender OR	1	tolerated	low	0	benign
rs61742396	Gender OR	1	tolerated	low	0	benign
rs35672330	Gender OR	0	damaging	high	1	probably damaging
rs11751765	Gender OR	0.16	tolerated	high	0.91	probably damaging
rs73022563	Gender OR	0.05	damaging	high	0.96	probably damaging
rs61731389	Gender OR	0.06	tolerated	high	0.86	probably damaging
rs143021649	Gender OR	0.29	tolerated	high	0.01	benign
rs61745456	Gender OR	0.97	tolerated	high	0.98	probably damaging
rs36041430	Gender OR	0.22	tolerated	high	0.001	benign
rs7829965	Gender OR	0.72	tolerated	high	0	benign
rs34022679	Gender OR	0	damaging	high	1	probably damaging
rs2293624	Gender OR	0.11	tolerated	low	0.003	benign
rs62640905	Gender OR	0.36	tolerated	high	0.52	possibly damaging
rs16973890	Gender OR	0.08	tolerated	high	0.52	possibly damaging

Appendix Table 21 continued....

SNP (missense variations)	Gender- specific results	SIFT score	SIFT prediction	SIFT confidence	PolyPhen score	PolyPhen prediction
rs117923468	Gender OR	0.5	tolerated	high	0.21	possibly damaging
rs182319278	Gender OR	0.97	tolerated	low	0	benign
rs4645656	Gender OR	0.04	tolerated	high	0.56	possibly damaging
rs12722039	Gender OR	0.5	tolerated	low	0	benign
rs12722042	Gender OR	0.66	tolerated	low	0.36	possibly damaging
rs130069	Gender OR	0.47	tolerated	high	0.24	possibly damaging
rs78888579	Gender OR	0.51	tolerated	high	0	benign
rs56278097	Gender OR	0.22	tolerated	high	0	benign
rs2229528	Gender OR	0.05	tolerated	high	0.48	possibly damaging
rs55882716	Gender OR	0.43	tolerated	low	0	benign
rs34664882	Gender OR	0.02	damaging	high	0.003	benign
rs80040922	Gender OR	0.02	damaging	high	0.96	probably damaging
rs61741435	Gender OR	0.71	tolerated	high	0.91	probably damaging
rs147596194	Gender OR	0	damaging	low	0	benign

SNP = single nucleotide polymorphisms; SIFT & PolyPhen: databases for missense SNP prediction

Appendix Table 22: Deleterious effect of missense variations associated with age-specificity in childhood ALL risk

SNP (missense variations)	Age-specific results	SIFT score	SIFT prediction	SIFT confidence	PolyPhe score	PolyPhen prediction
rs2274068	Age P value	0.45	Tolerated	High	0	Benign
rs762562	Age P value	1	Tolerated	High	0	Benign
rs735482	Age P value	0.56	Tolerated	High	0	Benign
rs9897794	Age P value	0.34	Tolerated	High	0.003	Benign
rs2101919	Age P value	0.57	Tolerated	High	0	Benign
rs6972158	Age P value	0.43	Tolerated	High	0	Benign
rs56291145	Age OR	0.16	Tolerated	Low	0.02	Benign
rs35384751	Age OR	0	Damaging	High	0.63	Possibly damaging
rs10999147	Age OR	0.4	Tolerated	High	0.24	Possibly damaging
rs17409162	Age OR	0.22	Tolerated	High	0.97	Probably damaging
rs16916188	Age OR	0.09	Tolerated	High	0.14	Benign
rs35537868	Age OR	0.82	Tolerated	High	0.08	Benign
rs35340237	Age OR	0.84	Tolerated	High	0	Benign
rs17407084	Age OR	0	Damaging	High	1	Probably damaging
rs41309927	Age OR	0.34	Tolerated	High	0	Benign
rs36086854	Age OR	0.34	Tolerated	High	0.05	Benign
rs34139105	Age OR	0.29	Tolerated	High	0.4	Possibly damaging
rs36068434	Age OR	0.02	Tolerated	Low	0	Benign
rs11651675	Age OR	0.62	Tolerated	High	0.001	Benign
rs41279492	effect size	0.35	Tolerated	High	0	Benign

Appendix Table 22 continued....

SNP (missense variations)	Age-specific results	SIFT score	SIFT prediction	SIFT confidence	PolyPhe score	PolyPhen prediction
rs141872266	Age OR	0.01	Damaging	High	0.04	Benign
rs138700801	Age OR	0.19	Tolerated	High	0.08	Benign
rs9728577	Age OR	0.05	Damaging	High	0.006	Benign
rs3204798	Age OR	0.11	Tolerated	High	0	Benign
rs41285557	Age OR	0.68	Tolerated	High	0.001	Benign
rs35424709	Age OR	0.39	Tolerated	High	1	Probably damaging
rs61744122	Age OR	0.33	Tolerated	High	0.16	Benign
rs78323957	Age OR	0.13	Tolerated	High	0.001	Benign
rs35384751	Age OR	0.02	Damaging	High	0.63	Possibly damaging
rs35340237	Age OR	1	Tolerated	High	0	Benign

SNP = single nucleotide polymorphisms; SIFT & PolyPhen: databases for missense SNP prediction

Appendix Table 23: Time-to-event analysis of identified gender- and age-specific childhood ALL risk markers

		Overall		Male		Female	
SNP	Log rank P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
rs10505918 ^{(D)*}	< 1 x 10 ⁻⁴	1.69 (1.27 - 2.24)	< 1 x 10 ⁻³	1.55 (1.06 - 2.25)	0.02	1.93 (1.25 - 2.96)	3 x 10 ⁻³
rs2949827 ^{(D)*}	< 1 x 10 ⁻⁴	0.54 (0.38 - 0.77)	1 x 10 ⁻³	0.72 (0.46 - 1.12)	0.15	0.39 (0.23 - 0.66)	< 1 x 10 ⁻³
rs2212824 ^{(D)*}	< 1 x 10 ⁻⁴	1.76 (1.30 - 2.38)	< 1 x 10 ⁻³	1.76 (1.20 - 2.59)	4 x 10 ⁻³	1.76 (1.09 - 2.83)	0.02
rs1209145 ^{(D)*}	< 1 x 10 ⁻⁴	1.80 (1.31 - 2.48)	< 1 x 10 ⁻³	1.62 (1.05 - 2.51)	0.03	2.05 (1.28 - 3.27)	3 x 10 ⁻³
rs1209145 ^{(D)*}	< 1 x 10 ⁻⁴	1.76 (1.28 - 2.41)	< 1 x 10 ⁻³	1.62 (1.05 - 2.51)	0.03	2.05 (1.28 - 3.27)	3 x 10 ⁻³
rs738027 ^{(D)*}	< 1 x 10 ⁻⁴	1.62 (1.22 - 2.15)	1 x 10 ⁻³	1.62 (1.10 - 2.38)	0.01	1.62 (1.06 - 2.47)	0.03
rs2101919 ^{(D)*}	< 1 x 10 ⁻⁴	0.61 (0.46 - 0.80)	1 x 10 ⁻³	0.64 (0.44 - 0.94)	0.02	0.56 (0.37 - 0.86)	8 x 10 ⁻³
rs9809647 ^{(D)*}	< 1 x 10 ⁻⁴	0.60 (0.45 - 0.78)	1 x 10 ⁻³	0.57 (0.39 - 0.84)	4 x 10 ⁻³	0.64 (0.42 - 0.98)	0.04
rs10133677 ^{(D)*}	< 1 x 10 ⁻⁴	1.78 (1.28 - 2.46)	1 x 10 ⁻³	1.65 (1.05 - 2.61)	0.03	1.92 (1.21 - 3.06)	6 x 10 ⁻³
rs10999147 ^{(D)**}	< 1 x 10 ⁻⁴	2.55 (1.59 - 4.08)	< 1 x 10 ⁻³	2.01 (1.09 - 3.71)	0.03	3.90 (1.85 - 8.22)	< 1 x 10 ⁻³
rs1882591 ^{(D)*}	1 x 10 ⁻⁴	0.63 (0.48 - 0.83)	1 x 10 ⁻³	0.55 (0.38 - 0.81)	2 x 10 ⁻³	0.75 (0.49 - 1.13)	0.17
rs10099957 ^{(D)**}	1 x 10 ⁻⁴	2.00 (1.35 - 2.95)	< 1 x 10 ⁻³	2.32 (1.36 - 3.95)	2 x 10 ⁻³	1.70 (0.95 - 3.02)	0.07
rs4741086 ^{(D)**}	1 x 10 ⁻⁴	1.75 (1.26 - 2.44)	1 x 10 ⁻³	1.48 (0.98 - 2.24)	0.06	2.39 (1.40 - 4.08)	1 x 10 ⁻³
rs7091901 ^{(D)**}	1 x 10 ⁻⁴	2.00 (1.33 - 3.01)	1 x 10 ⁻³	1.76 (1.01 - 3.06)	0.05	2.38 (1.30 - 4.35)	5 x 10 ⁻³
rs1457759 ^{(D)**}	1 x 10 ⁻⁴	2.05 (1.37 - 3.06)	< 1 x 10 ⁻³	2.43 (1.43 - 4.16)	1 x 10 ⁻³	1.67 (0.90 - 3.09)	0.10
rs10826912 ^{(D)**}	1 x 10 ⁻⁴	2.00 (1.32 - 3.02)	1 x 10 ⁻³	1.74 (0.98 - 3.06)	0.06	2.38 (1.30 - 4.35)	5 x 10 ⁻³
rs237320 ^{(D)*}	2 x 10 ⁻⁴	0.62 (0.45 - 0.84)	2 x 10 ⁻³	0.65 (0.42 - 1.00)	0.05	0.58 (0.38 - 0.91)	0.02
rs17109582 ^{(D)**}	2 x 10 ⁻⁴	2.05 (1.33 - 3.16)	1 x 10 ⁻³	2.13 (1.21 - 3.74)	9 x 10 ⁻³	1.96 (1.00 - 3.82)	0.05
rs9856456 ^{(D)**}	2 x 10 ⁻⁴	2.27 (1.37 - 3.75)	1 x 10 ⁻³	1.89 (1.05 - 3.40)	0.03	4.36 (1.68 - 11.32)	2 x 10 ⁻³
rs1894381 ^{(D)*}	3 x 10 ⁻⁴	0.63 (0.47 - 0.85)	2 x 10 ⁻³	0.54 (0.36 - 0.80)	2 x 10 ⁻³	0.78 (0.51 - 1.20)	0.26
rs10079494 ^{(D)*}	4 x 10 ⁻⁴	1.53 (1.16 - 2.03)	3 x 10 ⁻³	1.44 (0.99 - 2.10)	0.06	1.69 (1.11 - 2.59)	0.02

Appendix Table 23 continued....

		Overall		Male		Female	
SNP	Log rank P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
rs35424709 ^{(D)**}	4 x 10 ⁻⁴	1.83 (1.24 - 2.68)	2 x 10 ⁻³	1.79 (0.98 - 3.28)	0.06	1.85 (1.13 - 3.05)	0.02
rs2388773 ^{(D)*}	5 x 10 ⁻⁴	0.65 (0.49 - 0.87)	4 x 10 ⁻³	0.58 (0.39 - 0.86)	6 x 10 ⁻³	0.77 (0.51 - 1.17)	0.22
rs9694342 ^{(D)*}	6 x 10 ⁻⁴	0.66 (0.50 - 0.87)	3 x 10 ⁻³	0.63 (0.43 - 0.92)	0.02	0.69 (0.45 - 1.04)	0.08
rs16827743 ^{(D)**}	6 x 10 ⁻⁴	2.00 (1.27 - 3.14)	3 x 10 ⁻³	1.81 (1.02 - 3.20)	0.04	2.40 (1.14 - 5.06)	0.02
rs8011343 ^{(D)*}	7 x 10 ⁻⁴	1.57 (1.16 - 2.13)	4 x 10 ⁻³	1.78 (1.16 - 2.74)	9 x 10 ⁻³	1.40 (0.90 - 2.17)	0.13
rs1493897 ^{(D)*}	7 x 10 ⁻⁴	0.67 (0.50 - 0.88)	5 x 10 ⁻³	0.59 (0.40 - 0.86)	6 x 10 ⁻³	0.79 (0.52 - 1.21)	0.27
rs1915164 ^{(D)**}	7 x 10 ⁻⁴	2.00 (1.26 - 3.19)	3 x 10 ⁻³	1.75 (0.84 - 3.66)	0.13	2.21 (1.21 - 4.03)	0.01
rs11014598 ^{(D)††}	8 x 10 ⁻⁴	0.45 (0.25 - 0.81)	8 x 10 ⁻³	0.47 (0.24 - 0.90)	0.02	0.38 (0.09 - 1.54)	0.18
rs6972158 ^{(D)*}	8 x 10 ⁻⁴	1.50 (1.14 - 1.98)	4 x 10 ⁻³	1.59 (1.09 - 2.31)	0.02	1.39 (0.92 - 2.10)	0.12
rs7320982 ^{(D)*}	8 x 10 ⁻⁴	0.66 (0.50 - 0.88)	5 x 10 ⁻³	0.85 (0.59 - 1.23)	0.39	0.48 (0.31 - 0.74)	1 x 10 ⁻³
rs6492498 ^{(D)*}	8 x 10 ⁻⁴	0.66 (0.50 - 0.88)	4 x 10 ⁻³	0.61 (0.42 - 0.89)	0.01	0.74 (0.49 - 1.13)	0.16
rs10250709 ^{(D)*}	8 x 10 ⁻⁴	1.50 (1.14 - 1.98)	4 x 10 ⁻³	1.59 (1.09 - 2.31)	0.02	1.39 (0.92 - 2.10)	0.12
rs1191818 ^{(D)*}	8 x 10 ⁻⁴	0.65 (0.48 - 0.87)	4 x 10 ⁻³	0.65 (0.44 - 0.96)	0.03	0.66 (0.41 - 1.05)	0.08
rs2909644 ^{(D)**}	8 x 10 ⁻⁴	2.10 (1.26 - 3.48)	4 x 10 ⁻³	1.70 (0.89 - 3.27)	0.11	3.14 (1.39 - 7.11)	6 x 10 ⁻³
rs6708453 ^{(D)**}	8 x 10 ⁻⁴	1.61 (1.17 - 2.22)	4 x 10 ⁻³	1.86 (1.23 - 2.83)	4 x 10 ⁻³	1.31 (0.78 - 2.20)	0.31
rs222314 ^{(D)*}	8 x 10 ⁻⁴	1.56 (1.15 - 2.13)	4 x 10 ⁻³	1.47 (0.98 - 2.20)	0.06	1.72 (1.06 - 2.78)	0.03
rs139886 ^{(D)*}	8 x 10 ⁻⁴	1.51 (1.13 - 2.02)	5 x 10 ⁻³	1.32 (0.90 - 1.93)	0.16	1.84 (1.16 - 2.81)	9 x 10 ⁻³
rs17409162 ^{(D)**}	8 x 10 ⁻⁴	2.09 (1.27 - 3.44)	4 x 10 ⁻³	2.06 (1.03 - 4.11)	0.04	2.13 (1.04 - 4.33)	0.04
rs9560160 ^{(D)**}	8 x 10 ⁻⁴	1.73 (1.19 - 2.52)	4 x 10 ⁻³	1.35 (0.81 - 2.23)	0.25	2.50 (1.43 - 4.36)	1 x 10 ⁻³
rs7791037 ^{(R)†}	1 x 10 ⁻³	1.66 (1.17 - 2.37)	4 x 10 ⁻³	1.78 (1.04 - 3.06)	0.04	1.59 (1.00 - 2.51)	0.05
rs1881116 ^{(D)*}	1 x 10 ⁻³	1.48 (1.12 - 1.95)	6 x 10 ⁻³	1.17 (0.81 - 1.68)	0.41	2.29 (1.46 - 3.60)	< 1 x 10 ⁻³

Appendix Table 23 continued....

		Overall		Male		Female	
SNP	Log rank P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
rs11997355 ^{(D)*}	1 x 10 ⁻³	0.61 (0.43 - 0.87)	7 x 10 ⁻³	0.62 (0.38 - 0.98)	0.04	0.61 (0.36 - 1.04)	0.07
rs7720650 ^{(D)*}	1 x 10 ⁻³	0.65 (0.48 - 0.88)	6 x 10 ⁻³	0.76 (0.50 - 1.16)	0.20	0.55 (0.35 - 0.85)	7 x 10 ⁻³
rs2396653 ^{(D)*}	1 x 10 ⁻³	0.66 (0.50 - 0.89)	6 x 10 ⁻³	0.82 (0.55 - 1.20)	0.31	0.52 (0.33 - 0.80)	3 x 10 ⁻³
rs1151277 ^{(D)*}	1 x 10 ⁻³	0.66 (0.49 - 0.89)	7 x 10 ⁻³	0.55 (0.37 - 0.82)	4 x 10 ⁻³	0.84 (0.54 - 1.31)	0.44
rs12073211 ^{(D)*}	1 x 10 ⁻³	0.67 (0.50 - 0.90)	7 x 10 ⁻³	0.75 (0.51 - 1.10)	0.14	0.58 (0.37 - 0.89)	0.01
rs3825594 ^{(D)*}	1 x 10 ⁻³	0.67 (0.51 - 0.89)	5 x 10 ⁻³	0.75 (0.51 - 1.08)	0.12	0.59 (0.39 - 0.89)	0.01
rs1610315 ^{(D)*}	1 x 10 ⁻³	0.68 (0.51 - 0.89)	6 x 10 ⁻³	0.57 (0.39 - 0.84)	4 x 10 ⁻³	0.83 (0.55 - 1.24)	0.36
rs9897794 ^{(D)*}	1 x 10 ⁻³	0.66 (0.49 - 0.89)	6 x 10 ⁻³	0.76 (0.52 - 1.12)	0.17	0.49 (0.31 - 0.80)	4 x 10 ⁻³
rs8014810 ^{(D)*}	1 x 10 ⁻³	0.67 (0.50 - 0.90)	7 x 10 ⁻³	0.69 (0.46 - 1.02)	0.06	0.64 (0.41 - 0.98)	0.04
rs3954950 ^{(D)*}	1 x 10 ⁻³	0.68 (0.51 - 0.89)	6 x 10 ⁻³	0.67 (0.46 - 0.98)	0.04	0.67 (0.44 - 1.02)	0.06
rs56291145 ^{(D)**}	1 x 10 ⁻³	2.06 (1.24 - 3.43)	5 x 10 ⁻³	1.90 (0.98 - 3.68)	0.06	2.34 (1.06 - 5.20)	0.04
rs9861022 ^{(D)**}	1 x 10 ⁻³	1.94 (1.23 - 3.05)	4 x 10 ⁻³	1.73 (0.98 - 3.07)	0.06	2.40 (1.14 - 5.06)	0.02
rs10493958 ^{(D)**}	1 x 10 ⁻³	1.99 (1.23 - 3.21)	5 x 10 ⁻³	1.95 (0.98 - 3.87)	0.06	2.03 (1.04 - 3.97)	0.04
rs9392857 ^{(D)*}	2 x 10 ⁻³	0.68 (0.51 - 0.90)	8 x 10 ⁻³	0.77 (0.52 - 1.13)	0.18	0.55 (0.36 - 0.85)	8 x 10 ⁻³
rs4948088 ^{(D)*}	2 x 10 ⁻³	0.61 (0.42 - 0.90)	8 x 10 ⁻³	0.72 (0.43 - 1.21)	0.21	0.49 (0.28 - 0.86)	0.01
rs7583258 ^{(D)*}	2 x 10 ⁻³	0.66 (0.48 - 0.91)	0.01	0.55 (0.36 - 0.84)	5 x 10 ⁻³	0.85 (0.53 - 1.35)	0.49
rs7722067 ^{(D)*}	2 x 10 ⁻³	0.68 (0.51 - 0.91)	9 x 10 ⁻³	0.74 (0.51 - 1.08)	0.12	0.61 (0.40 - 0.94)	0.03
rs2065212 ^{(D)*}	2 x 10 ⁻³	0.68 (0.52 - 0.91)	8 x 10 ⁻³	0.64 (0.44 - 0.93)	0.02	0.74 (0.49 - 1.13)	0.17
rs2830698 ^{(R)*}	2 x 10 ⁻³	0.51 (0.30 - 0.87)	0.01	0.53 (0.25 - 1.11)	0.09	0.49 (0.22 - 1.07)	0.08
rs4748309 ^{(D)**}	2 x 10 ⁻³	1.78 (1.18 - 2.65)	6 x 10 ⁻³	1.51 (0.87 - 2.62)	0.14	2.18 (1.20 - 3.98)	0.01
rs11945730 ^{(D)**}	2 x 10 ⁻³	1.66 (1.15 - 2.41)	7 x 10 ⁻³	1.42 (0.88 - 2.31)	0.16	2.13 (1.20 - 3.81)	0.01
rs7294845 ^{(D)†}	3 x 10 ⁻³	1.43 (1.08 - 1.89)	0.01	1.32 (0.90 - 1.93)	0.15	1.57 (1.04 - 2.38)	0.03

Appendix Table 23 continued....

		Overall		Male		Female	
SNP	Log rank P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
rs6739633 ^{(D)*}	3 x 10 ⁻³	1.44 (1.08 - 1.91)	0.01	1.23 (0.83 - 1.81)	0.30	1.85 (1.18 - 2.88)	7 x 10 ⁻³
rs139866 ^{(D)*}	3 x 10 ⁻³	1.44 (1.08 - 1.92)	0.01	1.27 (0.87 - 1.86)	0.22	1.73 (1.11 - 2.69)	0.02
rs3800292 ^{(D)*}	3 x 10 ⁻³	0.55 (0.34 - 0.88)	0.02	0.58 (0.25 - 1.32)	0.19	0.54 (0.30 - 0.96)	0.04
rs36068434 ^{(D)**}	3 x 10 ⁻³	1.93 (1.17 - 3.20)	0.01	1.96 (1.05 - 3.69)	0.04	1.88 (0.81 - 4.38)	0.14
rs16909509 ^{(D)**}	3 x 10 ⁻³	1.86 (1.10 - 3.13)	0.02	2.17 (1.03 - 4.55)	0.04	1.62 (0.78 - 3.37)	0.20
rs12705300 ^{(D)**}	3 x 10 ⁻³	1.64 (1.12 - 2.40)	0.01	1.83 (1.10 - 3.07)	0.02	1.44 (0.81 - 2.56)	0.21
rs4821717 ^{(D)*}	4 x 10 ⁻³	1.42 (1.07 - 1.88)	0.02	1.35 (0.92 - 1.96)	0.12	1.51 (0.98 - 2.33)	0.06
rs7157104 ^{(D)*}	4 x 10 ⁻³	0.71 (0.53 - 0.94)	0.02	0.76 (0.52 - 1.12)	0.12	0.64 (0.42 - 0.98)	0.04
rs973358 ^{(D)*}	4 x 10 ⁻³	1.44 (1.07 - 1.92)	0.02	1.66 (1.12 - 2.46)	0.01	1.18 (0.76 - 1.83)	0.46
rs41309927 ^{(D)**}	4 x 10 ⁻³	1.85 (1.15 - 2.99)	0.01	1.52 (0.84 - 2.74)	0.17	2.93 (1.32 - 6.52)	8 x 10 ⁻³
rs276725 ^{(D)**}	4 x 10 ⁻³	1.75 (1.14 - 2.71)	0.01	2.28 (1.26 - 4.15)	7 x 10 ⁻³	1.37 (0.72 - 2.58)	0.33
rs11250832 ^{(D)**}	4 x 10 ⁻³	1.64 (1.11 - 2.42)	0.01	1.54 (0.97 - 2.46)	0.07	1.89 (0.94 - 3.80)	0.08
rs2899293 ^{(D)*}	5 x 10 ⁻³	1.43 (1.06 - 1.93)	0.02	1.26 (0.86 - 1.86)	0.24	1.76 (1.10 - 2.83)	0.02
rs7318021 ^{(D)*}	5 x 10 ⁻³	0.72 (0.55 - 0.94)	0.02	0.61 (0.42 - 0.89)	0.01	0.86 (0.57 - 1.29)	0.46
rs8021355 ^{(D)*}	5 x 10 ⁻³	0.71 (0.53 - 0.94)	0.02	0.77 (0.53 - 1.13)	0.19	0.63 (0.41 - 0.96)	0.02
rs7144565 ^{(D)*}	5 x 10 ⁻³	0.71 (0.53 - 0.94)	0.02	0.77 (0.53 - 1.13)	0.19	0.63 (0.41 - 0.96)	0.02
rs2274068 ^{(D)*}	5 x 10 ⁻³	0.71 (0.53 - 0.94)	0.02	0.77 (0.53 - 1.13)	0.19	0.63 (0.41 - 0.96)	0.02
rs17017488 ^{(D)*}	5 x 10 ⁻³	0.71 (0.53 - 0.94)	0.02	0.75 (0.50 - 1.11)	0.15	0.66 (0.44 - 1.01)	0.06
rs10511980 ^{(D)*}	5 x 10 ⁻³	0.69 (0.52 - 0.90)	8 x 10 ⁻³	0.66 (0.46 - 0.96)	0.03	0.72 (0.47 - 1.09)	0.12
rs11172024 ^{(D)*}	5 x 10 ⁻³	0.66 (0.46 - 0.93)	0.02	0.61 (0.37 - 1.00)	0.05	0.71 (0.42 - 1.17)	0.18
rs6052937 ^{(D)*}	5 x 10 ⁻³	0.70 (0.52 - 0.94)	0.02	0.73 (0.48 - 1.13)	0.16	0.65 (0.42 - 1.01)	0.054
rs10500248 ^{(D)**}	5 x 10 ⁻³	1.70 (1.11 - 2.61)	0.01	1.81 (1.02 - 3.21)	0.04	1.59 (0.84 - 3.00)	0.16

Appendix Table 23 continued....

		Overall		Male		Female	
SNP	Log rank P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
rs2124906 ^{(D)**}	5 x 10 ⁻³	1.70 (1.11 - 2.61)	0.01	1.81 (1.02 - 3.21)	0.04	1.59 (0.84 - 3.00)	0.16
rs6572051 ^{(D)**}	5 x 10 ⁻³	1.75 (1.12 - 2.73)	0.02	1.55 (0.85 - 2.84)	0.15	2.05 (1.05 - 4.02)	0.04
rs17149645 ^{(D)**}	5 x 10 ⁻³	1.79 (1.22 - 2.62)	3 x 10 ⁻³	2.03 (1.13 - 3.66)	0.02	1.68 (1.01 - 2.77)	0.05
rs6037033 ^{(D)*}	6 x 10 ⁻³	0.71 (0.53 - 0.94)	0.02	0.63 (0.43 - 0.93)	0.02	0.81 (0.53 - 1.23)	0.33
rs1521244 ^{(D)*}	6 x 10 ⁻³	1.41 (1.06 - 1.88)	0.02	1.18 (0.81 - 1.72)	0.4	1.75 (1.14 - 2.70)	0.01
rs1430838 ^{(R)*}	6 x 10 ⁻³	1.56 (1.09 - 2.25)	0.02	1.25 (0.79 - 1.97)	0.34	2.44 (1.36 - 4.39)	0.19
rs2116078 ^{(R)*}	6 x 10 ⁻³	1.56 (1.09 - 2.25)	0.02	1.25 (0.79 - 1.97)	0.34	2.44 (1.36 - 4.39)	0.19
rs10157510 ^{(D)**}	6 x 10 ⁻³	1.72 (1.10 - 2.71)	0.02	1.61 (0.90 - 2.88)	0.11	1.93 (0.95 - 3.92)	0.07
rs13116233 ^{(D)*}	7 x 10 ⁻³	1.37 (1.04 - 1.81)	0.02	1.41 (0.98 - 2.05)	0.07	1.32 (0.87 - 1.99)	0.19
rs6519091 ^{(D)*}	7 x 10 ⁻³	1.51 (1.12 - 2.04)	7 x 10 ⁻³	1.35 (0.91 - 2.00)	0.13	1.76 (1.10 - 2.83)	0.02
rs2185230 ^{(A)*}	7 x 10 ⁻³	1.33 (1.05 - 1.68)	0.02	1.09 (0.81 - 1.47)	0.58	1.93 (1.30 - 2.88)	1 x 10 ⁻³
rs7620914 ^{(D)**}	7 x 10 ⁻³	1.50 (1.06 - 2.11)	0.02	1.84 (1.16 - 2.90)	9 x 10 ⁻³	1.18 (0.70 - 1.99)	0.53
rs3850942 ^{(D)*}	8 x 10 ⁻³	0.62 (0.40 - 0.95)	0.03	0.65 (0.35 - 1.22)	0.18	0.59 (0.33 - 1.07)	0.08
rs3993401 ^{(D)*}	8 x 10 ⁻³	0.73 (0.56 - 0.96)	0.03	0.69 (0.48 - 0.99)	0.05	0.79 (0.52 - 1.20)	0.28
rs13129052 ^{(D)**}	8 x 10 ⁻³	1.78 (1.08 - 2.91)	0.02	1.87 (0.93 - 3.76)	0.08	1.69 (0.84 - 3.41)	0.14
rs6093579 ^{(D)**}	8 x 10 ⁻³	1.80 (1.08 - 2.98)	0.02	2.38 (1.21 - 4.68)	0.01	1.34 (0.62 - 2.91)	0.62
rs78323957 ^{(D)**}	8 x 10 ⁻³	1.86 (1.10 - 3.13)	0.02	2.17 (1.03 - 4.55)	0.04	1.62 (0.78 - 3.37)	0.2
rs16950438 ^{(D)**}	8 x 10 ⁻³	1.59 (1.07 - 2.37)	0.02	1.78 (1.03 - 3.03)	0.04	1.42 (0.78 - 2.57)	0.25
rs2125649 ^{(D)*}	9 x 10 ⁻³	0.69 (0.50 - 0.96)	0.03	0.70 (0.44 - 1.10)	0.12	0.69 (0.43 - 1.10)	0.12
rs5028798 ^{(D)*}	9 x 10 ⁻³	0.73 (0.55 - 0.96)	0.03	0.62 (0.43 - 0.90)	0.01	0.90 (0.59 - 1.36)	0.6
rs6151599 ^{(D)**}	9 x 10 ⁻³	1.57 (1.06 - 2.32)	0.03	1.65 (0.96 - 2.84)	0.07	1.49 (0.84 - 2.63)	0.17
rs7492685 ^{(D)†}	0.01	1.72 (1.07 - 2.77)	0.03	1.54 (0.49 - 4.89)	0.46	1.76 (1.04 - 2.99)	0.04

Appendix Table 23 continued....

		Overall		Male		Female	
SNP	Log rank P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
rs13387046 ^{(D)††}	0.01	0.58 (0.34 - 0.97)	0.04	0.57 (0.32 - 1.01)	0.05	0.62 (0.20 - 1.98)	0.42
rs4254428 ^{(D)*}	0.01	0.71 (0.53 - 0.97)	0.03	0.73 (0.50 - 1.08)	0.12	0.69 (0.42 - 1.16)	0.16
rs6510588 ^{(D)*}	0.01	0.71 (0.53 - 0.97)	0.03	0.73 (0.50 - 1.08)	0.12	0.69 (0.42 - 1.16)	0.16
rs2051713 ^{(D)*}	0.01	1.42 (1.04 - 1.98)	0.03	1.15 (0.75 - 1.77)	0.52	1.74 (1.12 - 2.73)	0.02
rs6109487 ^{(D)*}	0.01	1.38 (1.03 - 1.84)	0.03	1.39 (0.94 - 2.06)	0.1	1.36 (0.89 - 2.08)	0.16
rs16979806 ^{(R)*}	0.01	0.61 (0.38 - 0.99)	0.04	0.64 (0.34 - 1.21)	0.14	0.57 (0.27 - 1.19)	0.14
rs11120342 ^{(D)*}	0.01	0.73 (0.56 - 0.97)	0.03	0.69 (0.48 - 1.01)	0.06	0.79 (0.52 - 1.20)	0.27
rs1481046 ^{(D)*}	0.01	1.36 (1.03 - 1.79)	0.03	1.31 (0.91 - 1.90)	0.15	1.43 (0.94 - 2.17)	0.09
rs753712 ^{(D)*}	0.01	0.72 (0.54 - 0.97)	0.03	0.70 (0.47 - 1.04)	0.07	0.75 (0.48 - 1.18)	0.17
rs6927353 ^{(D)**}	0.01	1.68 (1.04 - 2.73)	0.04	1.41 (0.79 - 2.53)	0.25	2.70 (1.15 - 6.35)	0.02
rs1800141 ^{(D)**}	0.01	1.76 (1.04 - 2.98)	0.04	1.26 (0.65 - 2.43)	0.49	4.65 (1.91 - 11.32)	1 x 10 ⁻³
rs2389891 ^{(D)**}	0.01	1.57 (1.05 - 2.37)	0.03	1.92 (1.14 - 3.26)	0.02	1.20 (0.62 - 2.33)	0.59
rs12188300 ^{(D)**}	0.01	1.57 (1.03 - 2.39)	0.04	1.85 (1.08 - 3.19)	0.03	1.25 (0.64 - 2.46)	0.52
rs7303641 ^{(D)**}	0.01	1.60 (1.06 - 2.42)	0.03	1.84 (1.06 - 3.19)	0.03	1.35 (0.72 - 2.55)	0.35
rs34139105 ^{(D)**}	0.01	1.64 (1.06 - 2.55)	0.03	2.16 (1.11 - 4.21)	0.02	1.38 (0.78 - 2.46)	0.27
rs9328207 ^{(D)**}	0.01	1.70 (1.06 - 2.73)	0.03	1.57 (0.86 - 2.88)	0.15	1.94 (0.91 - 4.15)	0.09
rs10514074 ^{(D)**}	0.01	1.60 (1.07 - 2.38)	0.02	1.66 (1.01 - 2.71)	0.05	1.49 (0.75 - 2.98)	0.26
rs61744122 ^{(D)**}	0.01	1.68 (1.05 - 2.69)	0.03	1.63 (0.82 - 3.27)	0.17	1.72 (0.90 - 3.28)	0.10
rs17170286 ^{(D)**}	0.01	1.60 (1.06 - 2.42)	0.03	2.36 (1.34 - 4.16)	3 x 10 ⁻³	1.12 (0.61 - 2.06)	0.72
rs7776264 ^{(D)†}	0.02	1.33 (1.01 - 1.76)	0.04	1.23 (0.84 - 1.79)	0.28	1.47 (0.97 - 2.24)	0.07
rs468771 ^{(R)†}	0.02	1.77 (1.03 - 3.05)	0.04	1.64 (0.91 - 2.94)	0.10	3.32 (0.79 - 13.88)	0.10
rs1713676 ^{(D)†}	0.02	1.56 (1.03 - 2.37)	0.04	1.68 (1.03 - 2.74)	0.04	1.29 (0.56 - 2.96)	0.55

Appendix Table 23 continued....

		Overall		Male		Female	
SNP	Log rank P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
rs349714 ^{(R)†}	0.02	0.70 (0.50 - 0.98)	0.04	0.68 (0.40 - 1.14)	0.15	0.72 (0.47 - 1.11)	0.14
rs2229528 ^{(D)††}	0.02	1.78 (1.02 - 3.12)	0.04	1.64 (0.90 - 3.00)	0.11	3.32 (0.79 - 13.88)	0.10
rs35693261 ^{(D)††}	0.02	1.76 (1.00 - 3.08)	0.05	1.53 (0.84 - 2.80)	0.17	8.41 (1.94 - 36.47)	4 x 10 ⁻³
rs368390 ^{(D)††}	0.02	0.63 (0.40 - 1.01)	0.053	0.59 (0.36 - 0.97)	0.04	1.06 (0.33 - 3.38)	0.92
rs6936494 ^{(D)††}	0.02	0.66 (0.44 - 1.00)	0.053	0.66 (0.42 - 1.04)	0.07	0.69 (0.24 - 1.95)	0.48
rs9842465 ^{(D)††}	0.02	1.75 (1.00 - 3.06)	0.05	1.75 (0.95 - 3.21)	0.07	1.77 (0.43 - 7.26)	0.43
rs665159 ^{(D)*}	0.02	1.35 (1.00 - 1.82)	0.05	1.19 (0.80 - 1.78)	0.38	1.65 (1.04 - 2.63)	0.03
rs924615 ^{(D)*}	0.02	0.75 (0.57 - 0.99)	0.04	0.73 (0.50 - 1.06)	0.10	0.78 (0.52 - 1.19)	0.25
rs877111 ^{(D)*}	0.02	1.31 (1.00 - 1.73)	0.052	1.30 (0.90 - 1.89)	0.17	1.30 (0.86 - 1.96)	0.21
rs742390 ^{(D)*}	0.02	1.33 (1.01 - 1.75)	0.04	1.36 (0.94 - 1.96)	0.10	1.31 (0.87 - 1.98)	0.20
rs2620870 ^{(D)*}	0.02	1.35 (1.01 - 1.82)	0.05	1.40 (0.94 - 2.08)	0.10	1.28 (0.82 - 2.01)	0.28
rs1868368 ^{(D)*}	0.02	0.76 (0.58 - 1.01)	0.054	0.67 (0.46 - 0.97)	0.04	0.89 (0.59 - 1.34)	0.58
rs762562 ^{(D)*}	0.02	0.76 (0.58 - 1.00)	0.05	0.78 (0.54 - 1.14)	0.20	0.71 (0.47 - 1.07)	0.10
rs11171543 ^{(D)*}	0.02	0.73 (0.53 - 1.00)	0.051	0.65 (0.42 - 0.99)	0.05	0.85 (0.53 - 1.36)	0.50
rs36086854 ^{(D)**}	0.02	1.65 (1.02 - 2.68)	0.04	1.54 (0.86 - 2.78)	0.15	1.92 (0.82 - 4.48)	0.13
rs1835154 ^{(D)**}	0.02	1.71 (1.03 - 2.84)	0.04	2.00 (1.03 - 3.88)	0.04	1.42 (0.65 - 3.11)	0.37
rs11175471 ^{(D)**}	0.02	1.50 (1.01 - 2.22)	0.04	1.44 (0.86 - 2.41)	0.16	1.59 (0.86 - 2.94)	0.14
rs28421666 ^{(D)**}	0.02	1.47 (1.00 - 2.15)	0.05	1.46 (0.87 - 2.46)	0.15	1.48 (0.84 - 2.59)	0.18
rs17055478 ^{(D)**}	0.02	1.58 (1.01 - 2.48)	0.05	1.97 (1.01 - 3.84)	0.05	1.35 (0.73 - 2.48)	0.34
rs3805114 ^{(D)**}	0.02	1.62 (1.01 - 2.58)	0.04	1.84 (0.99 - 3.40)	0.05	1.37 (0.66 - 2.85)	0.39
rs17140942 ^{(D)**}	0.02	1.65 (1.02 - 2.66)	0.04	1.46 (0.76 - 2.82)	0.26	1.92 (0.95 - 3.85)	0.07
rs6696657 ^{(D)†}	0.03	1.31 (0.99 - 1.74)	0.06	1.32 (0.99 - 1.76)	0.06	0.61 (0.05 - 6.73)	0.69

Appendix Table 23 continued....

		Overall		Male		Female	
SNP	Log rank P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
rs3857193 ^{(D)†}	0.03	0.76 (0.56 - 1.01)	0.06	0.82 (0.56 - 1.20)	0.30	0.68 (0.44 - 1.06)	0.09
rs117923468 ^{(D)††}	0.03	1.71 (0.98 - 3.00)	0.06	1.58 (0.86 - 2.90)	0.14	3.01 (0.73 - 12.40)	0.13
rs16973890 ^{(D)††}	0.03	1.71 (0.98 - 3.00)	0.06	1.58 (0.86 - 2.90)	0.14	3.01 (0.73 - 12.40)	0.13
rs182319278 ^{(D)††}	0.03	1.71 (0.98 - 3.00)	0.06	1.58 (0.86 - 2.90)	0.14	3.01 (0.73 - 12.40)	0.13
rs7818844 ^{(D)*}	0.03	0.74 (0.54 - 1.01)	0.06	0.76 (0.49 - 1.16)	0.20	0.72 (0.45 - 1.14)	0.16
rs2899469 ^{(D)*}	0.03	1.30 (0.98 - 1.73)	0.07	1.08 (0.74 - 1.60)	0.68	1.71 (1.12 - 2.62)	0.01
rs202050948 ^{(D)*}	0.03	0.70 (0.49 - 1.02)	0.06	0.67 (0.40 - 1.11)	0.12	0.74 (0.42 - 1.31)	0.30
rs7330286 ^{(D)**}	0.03	1.55 (0.97 - 2.48)	0.07	1.18 (0.61 - 2.28)	0.61	1.66 (0.98 - 2.82)	0.06
rs11651675 ^{(D)**}	0.03	1.69 (1.00 - 2.87)	0.05	1.41 (0.57 - 3.46)	0.46	1.89 (0.98 - 3.65)	0.06
rs10109794 ^{(D)**}	0.03	1.60 (0.98 - 2.61)	0.06	1.83 (0.97 - 3.46)	0.06	1.34 (0.62 - 2.90)	0.46
rs568760 ^{(D)**}	0.03	1.65 (0.99 - 2.74)	0.06	1.58 (0.90 - 2.78)	0.11	1.98 (0.62 - 6.33)	0.25
rs6851586 ^{(D)**}	0.03	1.49 (0.97 - 2.29)	0.07	1.06 (0.60 - 1.86)	0.85	2.93 (1.51 - 5.71)	2 x 10 ⁻³
rs3790126 ^{(D)**}	0.03	1.59 (1.00 - 2.53)	0.05	2.15 (1.07 - 4.31)	0.03	1.30 (0.71 - 2.41)	0.40
rs41285557 ^{(D)**}	0.03	1.63 (0.99 - 2.69)	0.05	1.66 (0.67 - 4.10)	0.28	1.63 (0.90 - 2.94)	0.11
rs17407084 ^{(D)**}	0.03	1.58 (0.98 - 2.56)	0.06	1.43 (0.72 - 2.83)	0.31	1.77 (0.90 - 3.47)	0.10
rs7172316 ^{(D)**}	0.03	1.57 (0.98 - 2.51)	0.06	1.40 (0.75 - 2.64)	0.29	1.82 (0.90 - 3.69)	0.10
rs10902652 ^{(D)**}	0.03	1.58 (0.98 - 2.56)	0.06	1.27 (0.64 - 2.51)	0.50	2.07 (1.04 - 4.13)	0.04
rs8013602 ^{(D)**}	0.03	1.57 (0.97 - 2.52)	0.06	1.29 (0.67 - 2.47)	0.45	2.06 (1.03 - 4.13)	0.04
rs4680582 ^{(D)†}	0.04	1.30 (0.97 - 1.75)	0.08	1.34 (0.88 - 2.04)	0.17	1.26 (0.83 - 1.91)	0.28
rs4792149 ^{(D)†}	0.04	1.33 (0.96 - 1.84)	0.09	1.35 (0.92 - 1.99)	0.13	1.27 (0.69 - 2.34)	0.44
rs2874641 ^{(D)†}	0.04	1.30 (0.98 - 1.72)	0.07	1.24 (0.84 - 1.83)	0.11	1.36 (0.90 - 2.08)	0.15
rs1550017 ^{(A)†}	0.04	1.36 (0.99 - 1.88)	0.06	1.36 (0.95 - 1.95)	0.10	1.38 (0.69 - 2.77)	0.36

Appendix Table 23 continued....

		Overall		Male		Female	
SNP	Log rank P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
rs34022679 ^{(D)††}	0.04	1.58 (0.96 – 2.59)	0.07	1.77 (1.03 – 3.03)	0.04	0.90 (0.22 – 3.66)	0.88
rs2031293 ^{(D)*}	0.04	0.76 (0.56 – 1.03)	0.08	0.99 (0.65 – 1.53)	0.99	0.48 (0.30 – 0.76)	2 x 10 ⁻³
rs7016929 ^{(D)*}	0.04	0.78 (0.59 – 1.03)	0.08	0.84 (0.63 – 1.13)	0.25	0.81 (0.56 – 1.17)	0.27
rs1004327 ^{(A)*}	0.04	1.25 (1.01 -1.26)	0.04	1.19 (0.88 – 1.60)	0.25	1.34 (0.97 – 1.85)	0.08
rs377621 ^{(G)*}	0.04	0.68 (0.44 – 1.05)	0.08	0.76 (0.44 – 1.31)	0.32	0.57 (0.27 – 1.19)	0.14
rs7304215 ^{(D)**}	0.04	1.53 (0.97 – 2.44)	0.07	2.00 (1.03 – 3.88)	0.04	1.25 (0.66 – 2.36)	0.50
rs17039265 ^{(D)**}	0.04	1.58 (0.95 – 2.63)	0.08	1.39 (0.74 – 2.62)	0.31	2.08 (0.89 – 4.84)	0.09
rs9728577 ^{(D)**}	0.04	1.58 (0.95 – 2.63)	0.08	1.39 (0.74 – 2.62)	0.31	2.08 (0.89 – 4.84)	0.09
rs75411676 ^{(D)**}	0.04	1.58 (0.95 – 2.63)	0.08	1.39 (0.74 – 2.62)	0.31	2.08 (0.89 – 4.84)	0.09
rs8176018 ^{(D)**}	0.04	1.62 (0.96 – 2.72)	0.07	0.94 (0.38 – 2.30)	0.89	2.51 (1.29 – 4.86)	7 x 10 ⁻³
rs9407838 ^{(D)**}	0.04	1.41 (0.96 -2.08)	0.08	1.35 (0.81 – 2.24)	0.25	1.51 (0.84 – 2.73)	0.17
rs16964079 ^{(D)**}	0.04	1.48 (0.94 -2.32)	0.09	1.50 (0.87 – 2.60)	0.15	1.44 (0.66 -3.14)	0.36
rs3130161 ^{(D)**}	0.04	1.52 (0.86 -2.41)	0.07	2.06 (1.11 – 3.82)	0.02	1.13 (0.56 – 2.25)	0.73
rs12257453 ^{(D)**}	0.04	1.53 (0.97 – 2.43)	0.07	1.55 (0.86 – 2.81)	0.15	1.51 (0.73 – 3.14)	0.27
rs11833839 ^{(D)**}	0.04	1.51 (0.94 -2.42)	0.09	1.71 (0.89 -3.30)	0.11	1.34 (0.68 – 2.64)	0.40
rs6904762 ^{(G)†}	0.05	0.70 (0.46 – 1.07)	0.10	0.54 (0.26 – 1.11)	0.10	0.83 (0.49 – 1.41)	0.48
rs26784 ^{(A)*}	0.05	1.23 (1.00 – 1.50)	0.05	1.26 (0.93 – 1.70)	0.14	1.20 (0.91- 1.59)	0.19
rs3204798 ^{(D)**}	0.05	1.57 (0.94 – 2.62)	0.08	1.39 (0.74 – 2.62)	0.31	2.03 (0.87 – 4.74)	0.10
rs3729598 ^{(D)**}	0.05	1.58 (0.94 – 2.66)	0.08	1.26 (0.64 – 2.51)	0.51	2.31 (1.05 – 5.13)	0.04
rs35384751 ^{(D)**}	0.05	1.58 (0.94 -2.65)	0.08	1.99 (0.96 – 4.13)	0.07	1.31 (0.63 – 2.71)	0.47

Appendix Table 23 continued....

		Overall		Male		Female	
SNP	Log rank P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
rs11234604 ^{(D)**}	0.05	1.51 (0.94 – 2.40)	0.09	1.39 (0.74 – 2.60)	0.31	1.68 (0.84 – 3.36)	0.15
rs2864680 ^{(D)**}	0.05	1.53 (1.03 – 2.28)	0.03	1.42 (0.84 – 2.40)	0.19	1.71 (0.95 -3.09)	0.08

(D): Dominant genetic model; (A): Additive genetic model; (R): Recessive genetic model

*SNPs yielded age-specific associations results based on the P values; ** SNPs yielded age-specific associations results based on the effect sizes

[†]SNPs yielded gender-specific associations results based on the P values; ^{††}SNPs yielded gender-specific associations results based on the effect sizes

SNP = single nucleotide polymorphism; HR = hazard ratio; CI = confidence interval

Appendix Table 24. Previously identified gender-specific genetic risk markers in childhood ALL and their evidence in the present study

SNP	Gene	Previous association (P interaction)	Gender-specificity/risk	P value* (present study)
rs10994982	<i>ARID5B</i>	0.01	Male-specific	0.91
rs10740055	<i>ARID5B</i>	0.03	Male-specific	0.91
rs2395185	<i>HLA-DRB9</i>	0.001	association differs in direction	0.58
rs7192	<i>HLA-DRA</i>	0.03	association differs in direction	0.85
rs419788	<i>SKIV2L</i>	0.04	association differs in direction	0.06
rs224589	<i>SLC11A2</i>	0.02	association differs in direction	0.08
rs3130342	<i>TNXB</i>	0.04	association differs in direction	0.47
rs422982	<i>NRAMP2</i>	0.007	association differs in direction	0.92
rs807212	<i>HFE</i>	0.05	association differs in direction	0.46

ALL = acute lymphoblastic leukemia; SNP = single nucleotide polymorphism

*P value represents statistical interaction

Appendix Figure 1. Genotype failure rate versus heterozygosity rate across all individuals in the study. Shading indicates sample density and dashed line denote quality control threshold. X-axis represents proportion of missing genotypes on log scale and Y-axis represents heterozygosity rates.

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PUBLICATIONS AND PRESENTATIONS (ABRIDGED LIST)

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