

Polymorphisms in *CYP1A1* and Ethnic-Specific Susceptibility to Acute Lymphoblastic Leukemia in Children

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Abstract

Background: Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy. The U.S. Surveillance Epidemiology and End Results (SEER) registry reports that Hispanic children have the highest incidence of ALL, however, it is unclear if this is due to genetic factors, unique environmental exposures, or both. Previous reports have shown an association between *CYP1A1* variants and ALL.

Methods: To explore the contribution of *CYP1A1* polymorphisms to ALL susceptibility in different ethnic groups, we conducted a case-control analysis in Caucasian, Hispanic, and African-American children.

Results: Increased risk of developing ALL was found in the whole sample group for homozygosity of variant alleles at *CYP1A1**2C (OR 2.51, 95% CI 1.18–5.33, $P = 0.016$) and *CYP1A1**2B (OR 3.24, 95% CI 1.43–7.34, $P = 0.005$). Stratified analyses showed increased risks in the Hispanic group (*CYP1A1**2A, OR 2.70, 95% CI 1.27–5.74, $P = 0.010$; *CYP1A1**2C, OR 2.47, 95% CI 1.13–5.38, $P = 0.023$; and *CYP1A1**2B, OR 3.28, 95% CI 1.40–7.69, $P = 0.006$) but not for the other ethnic groups. Hispanic control subjects were significantly more likely to be carriers of variant alleles as compared to Caucasians ($P < 0.0001$) and African Americans ($P = 0.005$).

Conclusions: Our study suggests that polymorphisms in *CYP1A1* may contribute to the increased risk of ALL in Hispanic children due to both their impact on leukemia susceptibility and the increased prevalence of the at-risk alleles in the Hispanic population.

Impact: Our study provides a novel and specific link between *CYP1A1* polymorphisms and ethnic influence on ALL risk that may help explain varying susceptibilities across groups to environmental toxins. *Cancer Epidemiol Biomarkers Prev*; 20(7); 1537–42. ©2011 AACR.

Introduction

Acute lymphoblastic leukemia (ALL) accounts for approximately 74% of the leukemia cases among children ages 0 to 19 years and an estimated 5,300 cases will be diagnosed in 2010 in the United States. Despite an 80% overall 5-year survival, ALL remains a major cause of childhood mortality (1–3). There is significant ethnic variation in incidence rates with Hispanics having the

highest rate (44/million), followed by Whites (36/million) and African Americans with the lowest rate (20/million) reported in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry (1). The causes of childhood leukemia continue to be incompletely explained but have been linked to environmental exposures and multiple low penetrance genetic factors (4, 5).

Studies of childhood cancer have suggested that genetic variants within xenobiotic metabolizing enzymes (XMEs) significantly affect susceptibility to childhood ALL (4, 6–8) and that XME polymorphisms may be significant predictors of chemotherapy response and survival for children with leukemia (4, 6, 7, 9). Previous association studies have shown that variants within cytochrome p450 1A1 (*CYP1A1*), a member of the CYP1 gene family of constitutive and inducible enzymes with a major role in the oxidative activation and/or deactivation of a wide range of xenobiotics, are associated with increased risk in ALL (6–8, 10). In particular, 2 common polymorphisms in the *CYP1A1* gene, a T6235C change within the 3' noncoding region of the gene (*2A, also known as the MspI restriction fragment length polymorphism) and an A4889G change in the heme-binding domain of exon 7 (*2C), have been previously described

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to influence enzymatic activity (11). An elevation in *CYP1A1* enzyme activity has been found with the A4889 polymorphism in exon 7 alone and when combined with the T6235C polymorphism to form the *CYP1A1*2B* genotype (12). *CYP1A1* polymorphisms have been found to be significantly associated with both an increased genetic susceptibility (8) and worse prognosis (9) for childhood ALL among French–Canadians. Another study found that *CYP1A1* polymorphisms greatly increased susceptibility of ALL among Indian children, with the homozygous *CYP1A1*2A* conferring a 6-fold risk and the *CYP1A1*2C* conferring a 4-fold risk (13). However, a possible role of *CYP1A1* polymorphisms in ALL was not confirmed in Turkish (14, 15), Brazilian (6), or Chinese (16) study groups.

Although current research has elucidated tumorigenic characteristics of *CYP1A1* polymorphisms, these studies have not examined the impact of ethnicity on these variants and ALL risk. No study has investigated the importance of *CYP1A1* polymorphisms and ethnic status by comparing Caucasian, Hispanic, and African-American children. Furthermore, no studies have explained the increased incidence of ALL in the U.S. Hispanic population.

We determined the association between 6 tagging single nucleotide polymorphisms (SNPs) in *CYP1A1* as well as the combined *CYP1A1*2B* variant and the risk of developing ALL using a case–control group consisting of children diagnosed with ALL and children without malignancy matched by sex, age, and ethnicity. We present results for the whole study population as well as from a stratified analysis by ethnic groups.

Materials and Methods

Subjects

Consecutive case samples were obtained via blood draw from 258 unrelated children (145 Caucasians, 79 Hispanics, and 34 African Americans) diagnosed with B-lineage ALL during the study period between 1990 and 2005 at Children’s Medical Center of Dallas ($n = 246$) and from a pilot study project between 2007 and 2009 at the University of Texas Health Science Center at San Antonio ($n = 12$). The case sample consisted of 137 males and 121 females, with a mean age at diagnosis of 6.3 years. Approval from Institutional Review Board at both universities was attained and the parents of each child signed consent to participate in genetic studies. A total of 646 age, gender, and ethnicity-matched unrelated control samples were obtained from surplus de-identified blood samples from children after emergency room treatment for diagnoses other than cancer at the laboratory services of Children’s Medical Center including 274 Caucasians, 206 Hispanics and 166 African Americans. Exclusion criteria for the controls consisted of any history of malignancy as confirmed by review of medical records. Ethnicity was self-reported as determined by parental report. The Hispa-

nics were primarily children of Mexican descent. The use of DNA samples from both leukemia patients and from leftover blood samples from children without malignancy was approved by the Institutional Review Board. All samples underwent standard DNA preparation procedures and were stored at 4°C until genotyping was performed.

Genotyping

We used Haploview to select 6 tagging SNPs encompassing *CYP1A1*. Genotyping of these SNPs was performed with the Golden Gate Assay of the VeraCode technology using the BeadXpress reader System according to the manufacturer’s protocol (Illumina). Duplicate samples were included as quality controls and a 99.8% reproducibility rate was obtained. Allele status for *CYP1A1*2B*, designated by the combination of *CYP1A1*2A* (rs4646903) and *CYP1A1*2C* (rs1048943), was described as homozygous for variant (VV), homozygous for wild type (WW), and heterozygous variant/wild type (VW).

Statistical analyses

Allele frequencies among the cases and controls in each ethnic group were compared using the Chi-square test (χ^2). To measure the magnitude of the association, the OR and its 95% CI were estimated by logistic regression using R statistical software. Tests were 2-sided and a $P < 0.05$ was considered significant. We used additive, dominant, and recessive models in the test analysis and chose the model with strongest association for presentation (i.e., model with smallest P value). Analyses were performed on the whole sample group and also stratified by ethnicity. Haploview was used to measure linkage disequilibrium (LD) and to define the block structure between the tagging SNPs for each ethnicity (17). Estimates of each individual’s genetic ancestry in Hispanics were derived from 96 ancestral informative markers using a maximum likelihood method implemented in the program Maximum Likelihood Individual Admixture Estimation, as described previously (18). The ancestral proportions were estimated at 46% European, 47% Native American, and 7% West-African. Genetic ancestry was used as a covariate in the association analysis.

Results

A total of 258 ALL cases and 646 controls were genotyped at 6 tagging SNPs across *CYP1A1*. Not all SNPs were successfully genotyped in every sample, thus the numbers reported for specific polymorphisms may vary from the total. The 6 markers analyzed did not depart significantly from Hardy–Weinberg equilibrium in the controls of each ethnic group. The allele frequency distribution in the cases and controls of each ethnicity are shown in Table 1. Strong LD, with $D' > 0.93$ overall, was found between the 6 markers in the controls of each sample. In Caucasians

Table 1. Minor alleles in controls and cases of each ethnicity

Gene/SNP location	SNP	Major/minor allele	Caucasians			Hispanics			African Americans		
			Controls	Cases	<i>P</i>	Controls	Cases	<i>P</i>	Controls	Cases	<i>P</i>
<i>CYP1A1</i> *2A	rs4646903	T/C	0.11	0.15	0.11	0.37	0.46	0.11	0.25	0.20	0.40
<i>CYP1A1</i> *2C	rs1048943	A/G	0.04	0.06	0.15	0.31	0.37	0.17	0.03	0.00	0.20
	rs2470893	G/A	0.33	0.27	0.18	0.10	0.14	0.34	0.05	0.07	0.69
	rs12441817	A/G	0.10	0.11	0.63	0.38	0.39	0.84	0.20	0.12	0.16
	rs4886605	G/A	0.16	0.22	0.04	0.47	0.47	0.97	0.53	0.42	0.11
	rs2472297	G/A	0.25	0.25	0.90	0.06	0.09	0.24	0.03	0.05	0.46

NOTE: Significant results are in bold.

Table 2. Significant results from SNP effects on ALL risk

Marker	Genotype	Controls/cases	OR ^a (95% CI)	<i>P</i>	Controls/cases ^b	OR ^c (95% CI)	<i>P</i>
Whole sample							
<i>CYP1A1</i> *2C	AA	505/188	Ref				
	GG	18/14	2.48 (1.14–5.39)	0.022			
	AG	118/40	0.97 (0.62–1.52)	0.899			
	GG vs. AG/AA		2.51 (1.18–5.33)	0.016			
<i>CYP1A1</i> *2B	WW	314/131	Ref				
	VV	14/13	3.45 (1.48–8.02)	0.004			
	VW	201/71	1.11 (0.77–1.60)	0.582			
	VV vs. VW/WW		3.24 (1.43–7.34)	0.005			
Caucasians							
rs4886605	GG	179/83	Ref				
	AA	9/7	1.68 (0.60–4.66)	0.321			
	AG	62/45	1.57 (0.98–2.49)	0.058			
	AA/AG vs. GG		1.58 (1.01–2.46)	0.043			
Hispanics							
<i>CYP1A1</i> *2A	TT	64/21	Ref		57/19	Ref	
	CC	19/15	2.41 (1.04–5.56)	0.040	17/14	3.55 (1.37–9.17)	0.009
	CT	90/24	0.81 (0.42–1.58)	0.543	85/19	0.84 (0.39–1.78)	0.644
	CC vs. CT/TT		2.70 (1.27–5.74)	0.010		3.96 (1.72–9.12)	0.001
<i>CYP1A1</i> *2C	AA	96/33	Ref		89/25	Ref	
	GG	17/13	2.22 (0.98–5.07)	0.057	15/13	5.81 (2.17–15.6)	0.0005
	AG	91/25	0.80 (0.44–1.45)	0.459	86/20	1.19 (0.58–2.44)	0.632
	GG vs. AG/AA		2.47 (1.13–5.38)	0.023		5.24 (2.17–12.6)	0.0002
<i>CYP1A1</i> *2B	WW	63/19	Ref		56/17	Ref	
	VV	13/12	3.06 (1.20–7.82)	0.019	11/12	6.32 (2.11–18.9)	0.001
	VW	97/26	0.89 (0.45–1.74)	0.731	92/20	0.92 (0.43–1.99)	0.839
	VV vs. VW/WW		3.28 (1.40–7.69)	0.006		6.67 (2.53–17.6)	0.0001

NOTE: Significant results are in bold.

WW, both major alleles of *2A and *2C; VV, both minor alleles of *2A and *2C.

^aAdjusted for ethnicity in whole sample, unadjusted when stratified by ethnicity.^bAncestry information was not available on all samples.^cAdjusted for individual Native American ancestry estimates.

Table 3. Differences in *CYP1A1* minor allele prevalence in the controls of different ethnic groups

Allele	Caucasians		Hispanics		$P_{H/C}$	African Americans		$P_{H/AA}$	$P_{C/AA}$
	N	Prevalence of minor allele(s)	N	Prevalence of minor allele(s)		N	Prevalence of minor allele(s)		
<i>CYP1A1</i> *2A	212	4 (1.89%)	173	19 (10.98%)	$P < 0.001$	144	12 (8.33%)	0.571	0.008
<i>CYP1A1</i> *2C	271	0 (0.00%)	204	17 (8.33%)	$P < 0.001$	166	1 (0.60%)	0.001	0.38
<i>CYP1A1</i> *2B	212	0 (0.00%)	173	13 (7.51%)	$P < 0.001$	144	1 (0.69%)	0.005	0.41

NOTE: Significant results are in bold.

H/C, Hispanics/Caucasians; H/AA, Hispanics/African-Americans; C/AA, Caucasians/African Americans.

markers rs2470893–rs12441817–rs4886605–rs2472297 were part of 1 haplotype block. In Hispanics 2 haplotype blocks were defined, one including rs4646903 to rs1048943 and the second extending from rs12441817 to rs4886605. One haplotype block encompassing rs12441817 to rs4886605 was found in African Americans.

Single SNP analysis in whole sample

Of the 6 variants genotyped, only cases homozygous for *CYP1A1**2C exhibited a significant association with ALL risk as shown in Table 2. Homozygous carriers of the GG variant genotype showed an increased susceptibility to ALL (OR = 2.51, 95% CI 1.18–5.33, $P = 0.016$). Furthermore, subjects that were homozygous for both variant alleles, designated as the *CYP1A1**2B, showed a greater increase in risk of ALL under the recessive model (OR = 3.24, 95% CI 1.43–7.34, $P = 0.005$; Table 2). To determine the importance of ethnicity in the increased susceptibility for ALL, we performed a similar analysis for each ethnic group.

Single SNP analysis in each ethnic group

An increased risk associated with homozygosity of *CYP1A1**2A and *2C variant alleles was found in Hispanics. Homozygous carriers of *CYP1A1**2A variant alleles showed a 2.70-fold increased risk for ALL (OR = 2.70, 95% CI 1.27–5.74, $P = 0.010$; Table 2). An increased OR for this variant was not seen in the aggregate analysis. Individuals homozygous for *CYP1A1**2C also exhibited an increased susceptibility. The calculated OR (2.47, 95% CI 1.13–5.38, $P = 0.023$) was similar to that observed in the whole study population. The combined variant genotype *CYP1A1**B showed a more than 3-fold increase in risk for ALL (OR = 3.28, 95% CI 1.40–7.69, $P = 0.006$; Table 2). One SNP (rs4886605) was significantly associated with case–control status in the Caucasians ($P = 0.043$) whereas in African Americans no statistically significant associations were found. Of note is that no homozygous variant controls were identified in Caucasians for *CYP1A1**2C and thus ORs are undefined for this marker as well as for the combined variant genotype. In African Americans, no homozygous variant cases were found for these 2 variants, and no ORs could be calculated (Supplementary Table S1).

High LD was found between the markers analyzed, and no additional haplotype analysis was performed to delineate the boundaries of the causal variant(s).

To determine whether the associations observed in Hispanics were true associations and not due to population stratification and admixture, we estimated individual ancestry and used the estimate as covariate in the association. After accounting for Native American ancestry, the associations with ALL risk were increased in Hispanics (Table 2). A similar increase in risk was found after adjusting for European ancestry, whereas the increase in risk was less pronounced, although still present, when accounting for West African ancestry (data not shown).

Allele frequency distribution in controls of each ethnic group

We noticed a significant difference in carriers of the minor allele frequencies at *CYP1A1**2A, *2C, and the combined variant *2B in the controls between ethnicities (Table 3). In particular, *CYP1A1**2A is found in 11% of our Hispanic controls compared to less than 2% in our Caucasian controls ($P < 0.001$). The prevalence of *CYP1A1**2C and *2B are 8.33% and 7.51%, respectively, in Hispanic controls as compared to 0% in Caucasian controls ($P < 0.001$). A similar difference was seen between controls of Hispanic and African American samples, with highly significant differences between the variant allele frequencies of *2C and *2B ($P = 0.001$ and 0.005, respectively).

Discussion

Both the incidence and survival rate of childhood B-precursor ALL has been found to differ between ethnic groups. Our study attempted to build on that knowledge while providing a new perspective on the importance of the role of ethnicity. We examined 6 tagging SNPs within *CYP1A1*, including 2 functional polymorphisms (A4889G or *2A and T6235C or *2C) known to affect cancer risk, and performed a stratified analysis by ethnic status (Caucasian, Hispanic, and African American).

Our findings show that *CYP1A1**2C and *CYP1A1**2B confer an increased risk of childhood ALL among the

subjects in our study. A stratified analysis showed that the associations were only statistically significant in Hispanic children; the 2 functional polymorphisms significantly affect ALL susceptibility, with a stronger association found when the 2 polymorphisms are combined in the form of *CYP1A1**2B, suggesting that the 2 variants may act synergistically. Adjusting for individual ancestral estimates further increased the strength of these associations, which indicates that both variants are true risk factors and that the association is not confounded by population stratification. To our knowledge this is the first investigation that links *CYP1A1* polymorphisms to the increased susceptibility of ALL in Hispanic children. Two other studies have found increased risk of cancer susceptibility and *CYP1A1* polymorphisms in the Hispanic population, however, both studies report on adult patients with ALL (19, 20).

The prevalence of the *CYP1A1**2A and *2C polymorphisms has been shown to vary among different ethnic groups (21, 22). We found an increased prevalence of the variant alleles in the Hispanic control population as compared to Caucasian controls. In particular, the combined *CYP1A1**2B risk alleles, showing the strongest risk effect, is found in 7.5% of our Hispanic population compared with less than 1% of our African-American population, and absent in our Caucasian controls. The finding that *CYP1A1* polymorphisms confer specifically increased risk in our Hispanic population from Texas, combined with the higher prevalence of the polymorphisms in this population, corroborate a genetic predisposition to developing childhood ALL which could contribute to explaining the higher incidence rate of ALL among Hispanic children from Texas, as compared to other ethnicities. Because of the absence or low frequency of the risk allele in Caucasians and African Americans, respectively, we could not determine whether an interaction exists between the risk allele and ethnicity. Therefore, further studies are warranted to identify the ethnic specific effects of the risk allele. It is also not known if our findings would generalize to the Hispanic population from other geographical regions in the United States, in particular because the Hispanic population in the United States is genetically heterogeneous. A recent study by Gallegos-Arreola and colleagues (2008) in a Mexican population of adult ALL cases and controls showed a frequency of the at risk alleles of *CYP1A1**2A of 8% in the controls and 42% in the cases (20), whereas the frequency in our Hispanic controls and cases were 11% and 25%, respectively. Furthermore, Frago and colleagues (2005) showed distinct differ-

ences among Mexican subpopulations of the *CYP1A1* variants (23).

The *CYP1A1**2A allele, whether or not combined with *2C, is associated with increased enzymatic activity (12). Consequently, individuals carrying the at-risk alleles are likely to be at higher risk when exposed to carcinogens. Socio-economically disadvantaged populations, such as Hispanic migrant workers employed in oil refinery, agriculture, and textiles, are often exposed to greater levels of occupational contaminants than other subgroups of the population (24, 25), and studies on migrants have reported increased cancer susceptibility attributed to either genetic or environmental factors (26). Mexico has been identified as the agricultural zone with the highest association of pesticide-induced health damage, which might suggest that migrant workers already carry a history of childhood exposure to an array of pesticides prior to any occupational exposure due to jobs acquired in the United States (27). The combination of a greater genetic susceptibility with increased environmental exposure in vulnerable populations may uniquely enhance the susceptibility to malignancy in our Hispanic population.

Our study provides a novel and specific link between *CYP1A1* polymorphisms and ethnic influence on risk to develop childhood ALL that may help explain varying susceptibilities across groups to environmental toxins. However, further investigations of larger sample size are necessary and suggested to confirm our findings. In addition, a thorough study of genetic polymorphisms coupled with information on specific occupational and environmental exposures is needed to determine whether specific gene-environment interactions may augment risk of developing leukemia in children. Our study provides a basis for future research to elucidate the possible influence of ethnicity in conferring genetic susceptibility to cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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