Genetic Susceptibility to Childhood Leukemia & The Hispanic Connection

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November 16, 2011

OUTLINE

Childhood ALL Epidemiology

Genetic studies

GWAS

Dorak et al

Unpublished studies

Proposed research on the Hispanic differential in susceptibility

Childhood Cancer Epidemiology

- In the US, the incidence of childhood cancer overall is approximately 125 per million persons.

- Between 1 in 600 and 1 in 500 children in Europe develop a malignant disease before the age of 15 years.

- One third of childhood cancers are leukemias (majority ALL).

- Childhood cancer is the biggest killer disease in childhood.

- Cure rates have exceeded 80% for childhood leukemia resulting in a large cancer survivor pool in the adult population.

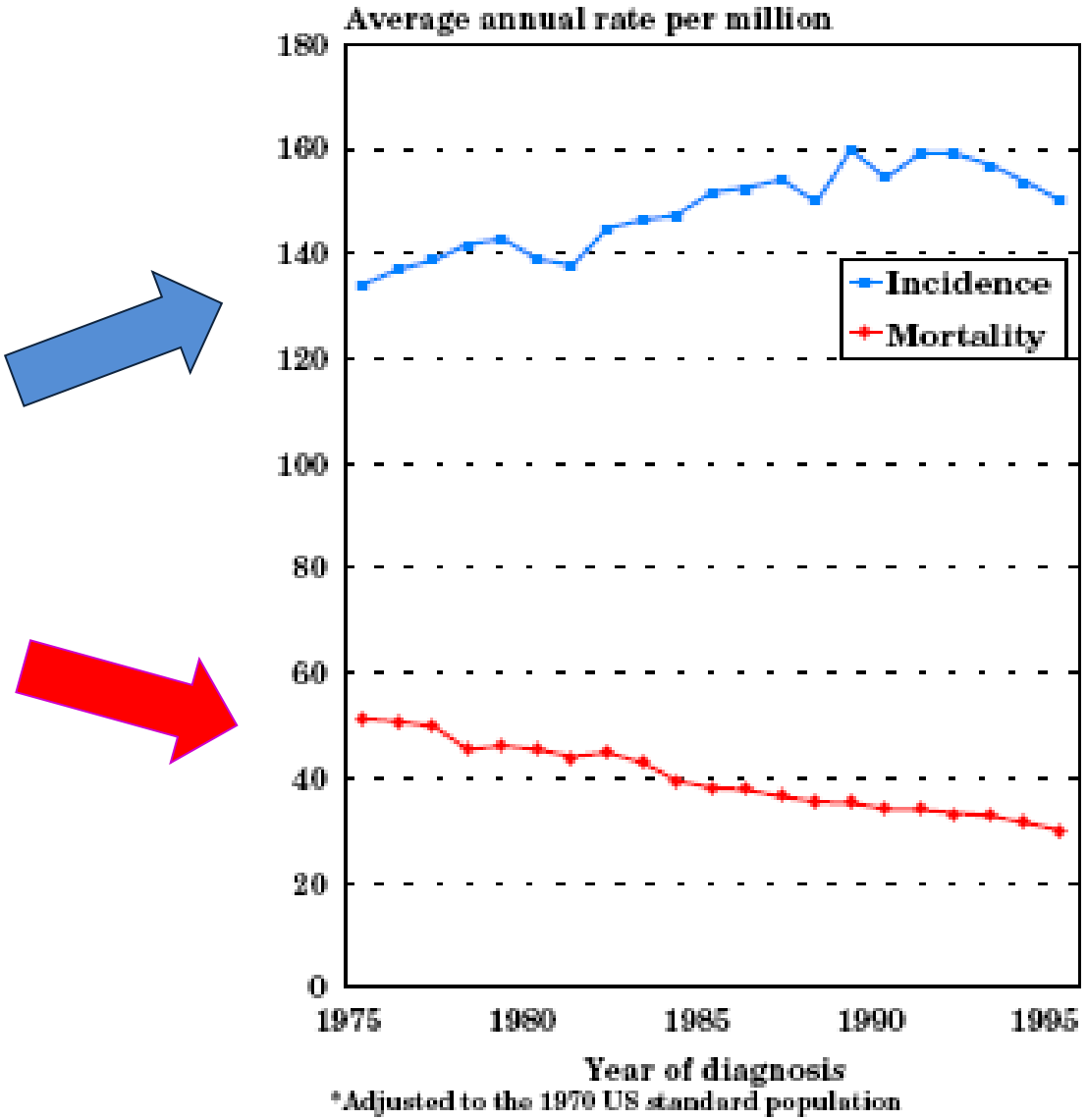
Malcolm A. Smith, Lynn A. Gloeckler Ries, James G. Gurney, Julie A. Ross

HIGHLIGHTS

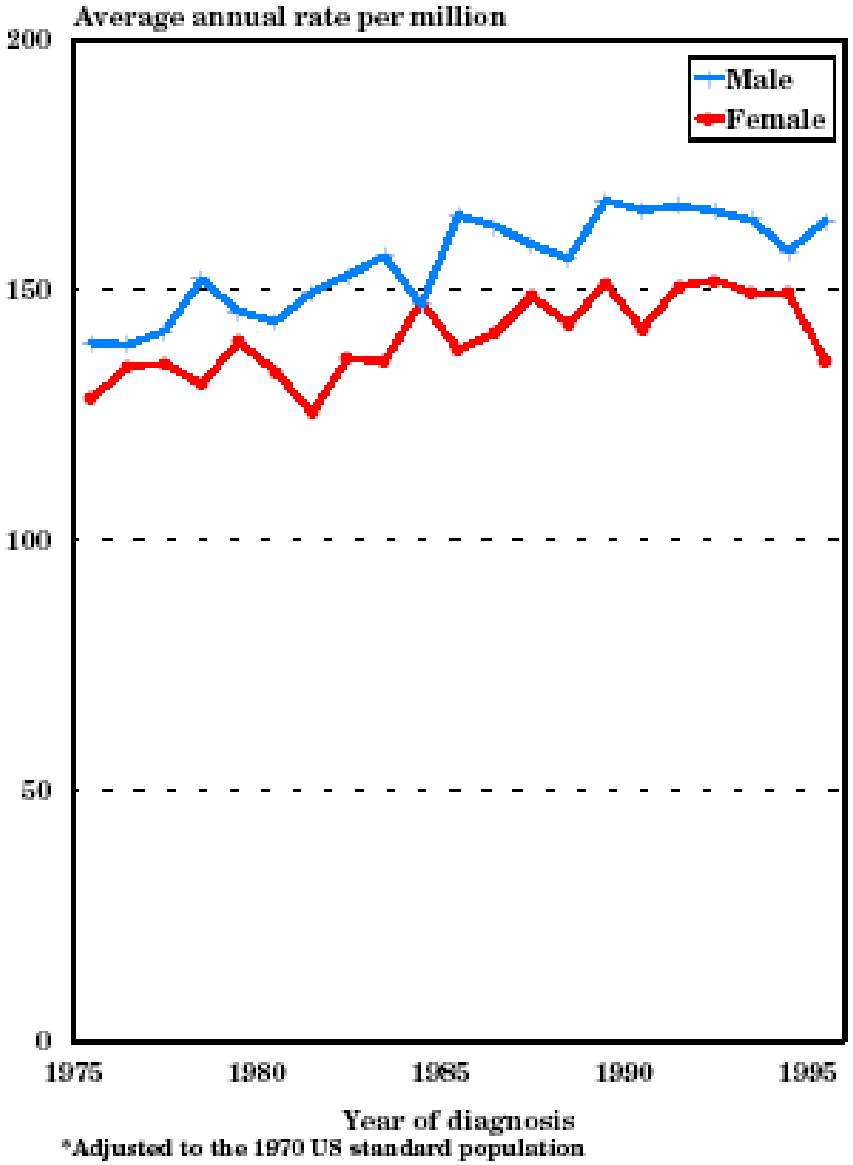
Incidence

- For the years from 1990-95, the leukemias represented 31% of all cancer cases occurring among children younger than 15 years of age and 25% of cancer cases occurring among those younger than 20 years of age. In the US there are approximately 3,250 children diagnosed each year with leukemia and 2,400 with acute lymphoblastic leukemia (ALL).
- The relative contribution of leukemia to the total childhood cancer burden varies markedly with age, being 17% in the first year of life, increasing to 46% for 2 and 3 year olds, and then decreasing to only 9% for 19 year olds (Figure I.1).
- The two major types of leukemia were ALL comprising nearly three-fourths and acute non-lymphocytic comprising 19%.
- There was a sharp peak in ALL incidence among 2-3 year olds (> 80 per million) which decreases to a rate of 20 per million for 8-10 year olds. The incidence of ALL among 2-3 year olds is approximately 4-fold greater than that for infants and is nearly 10-fold greater than that for 19 year olds (Figure I.2a).
- Leukemia rates are substantially higher for white children than for black children, with rates of 45.6 versus 27.8 per million for the period from 1986-95 for children 0-14 years old (Table I.4). This difference between white and black children is most apparent when examining rates of leukemia by single year of age (Figure I.3), with a nearly 3-fold higher incidence at 2-3 years of age for white children compared to black children.
- The incidence of leukemia among children younger than 15 years of age has shown a moderate increase in the past 20 years (Figure I.4) with the trend primarily reflecting an increase in ALL incidence during this period. The rates of leukemias other than ALL did not appear to increase from 1977 to 1995 (Figure I.5)

Figure 1: Trends in age-adjusted* SEER incidence & U.S. mortality rates for all childhood cancers age<20, all races, both sexes, 1975-95



*Adjusted to the 1970 US standard population



Boys have 1.1 to 1.4 times higher risk than girls

Magnitude of Gender Effect in Cancer

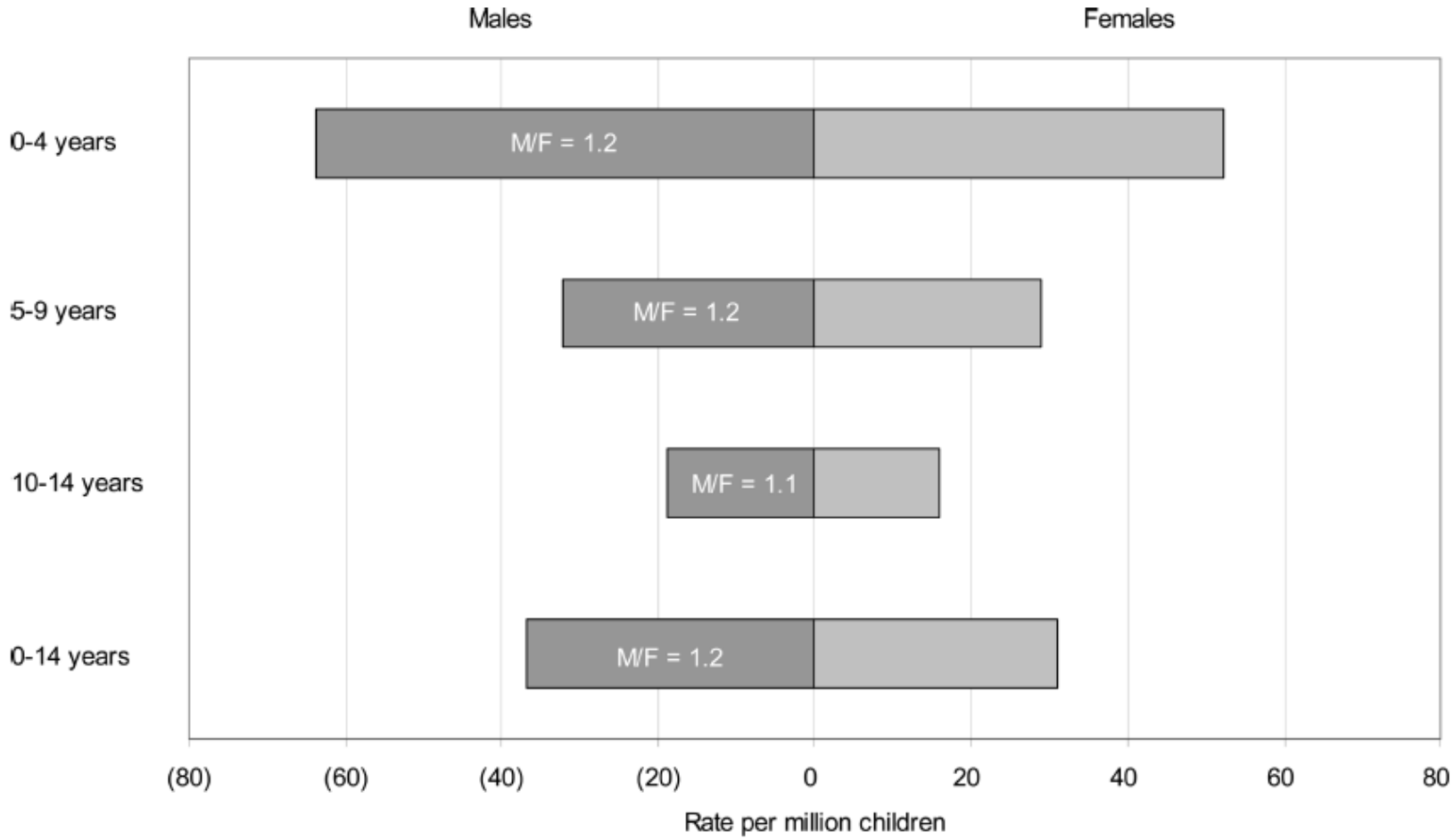


FIGURE 3 Male to female (M/F) ratios of age adjusted acute lymphoblastic leukemia rates (per million population) by age group.[3]

SEER, 1975-1995

TABLE 1. Risk Factors (Known, Suggestive, Limited) Associated With Childhood Leukemias and Lymphomas

Exposure or Characteristic	Leukemia		Lymphoma	
	Acute Lymphoblastic	Acute Myeloid	Hodgkin Disease	Non-Hodgkin Lymphoma
Known				
Gender	M:F = 1.3	M:F = 1.1	M:F = 1.3	M:F = 3.0
Age peak	2–4 years	Infancy	Adolescence	Adolescence
Age-adjusted incidence	26.3 per million	6.5 per million	13.8 per million	9.9 per million
Race	W:B = 2.0	W:B = 1.0	W:B = 1.3	W:B = 1.4
Other factors	Birth weight >4000 g		Monozygotic twins of young adults	Immunosuppressive therapy
	Ionizing radiation		Affected siblings	Congenital immunodeficiency syndromes (eg, ataxia, telangiectasia)
	Diagnostic, in utero		Epstein-Barr virus linked with some forms	AIDS
	Therapeutic, postnatal ALL and AML		Infectious mononucleosis	
	Down syndrome			
	ALL and AML M7			
	Congenital disorders, ataxia telangiectasia, Fanconi syndrome, Bloom syndrome, neurofibromatosis			
Suggestive	Maternal fetal loss	Maternal alcohol use during pregnancy		
	Mother older than 35 years at pregnancy			
	First born	Parental occupational exposures		
		- Benzene		
		- Pesticides		
Limited	Paternal smoking before conception	Maternal marijuana use during pregnancy	Residential exposures	
			Pesticides	
	Parental occupational exposures	Parental occupational exposures		
	Hydrocarbons	Pesticides		
	Paints			
	Motor vehicle exhaust			
	60-Hz magnetic fields >0.4 μT	Residential exposures		
		Pesticides		
	Postnatal chloramphenicol use			
	Clustering			
	Decreased risk associated with breastfeeding			

M:F indicates male-to-female ratio of incidence; W:B, white-to-black ratio of incidence; AML, acute myeloid leukemia; AIDS, acquired immunodeficiency syndrome.

Interpreting Epidemiologic Research: Lessons From Studies of Childhood Cancer

Martha S. Linet, MD; Sholom Wacholder, PhD; and Shelia Hoar Zahm, ScD

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GWAS in Childhood Leukemia

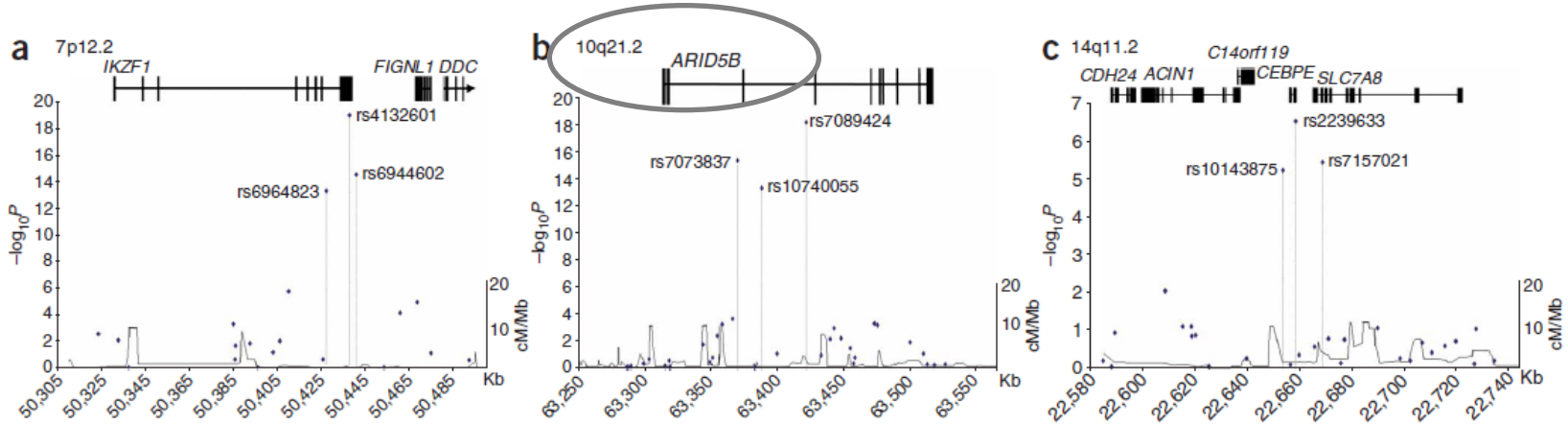


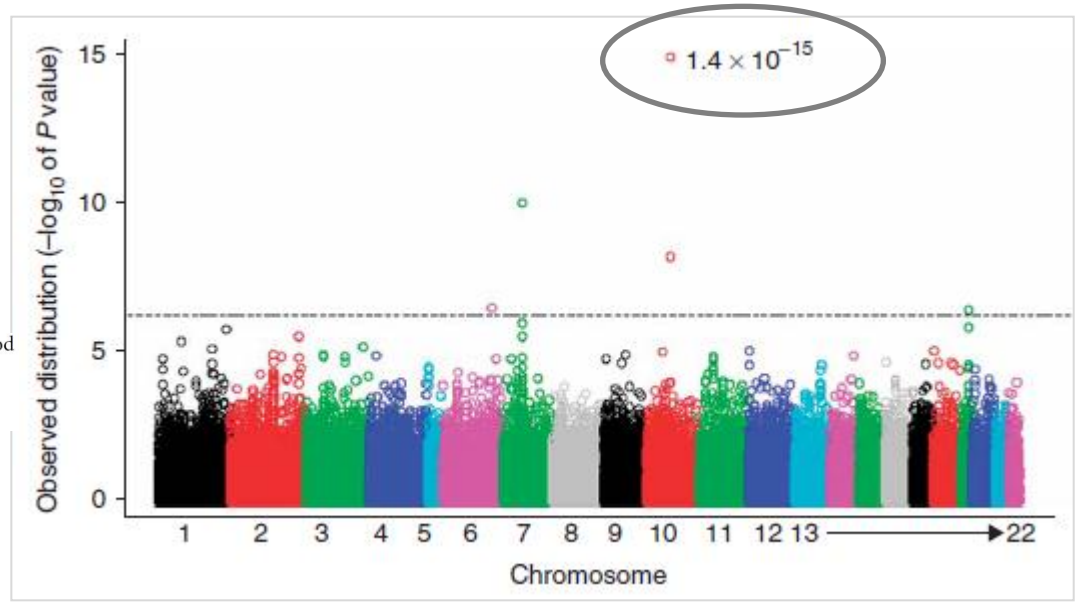
Figure 1 LD structure and association results for each of the disease-associated regions. (**a**) 7p12.2; (**b**) 10q21.2; (**c**) 14q11.2. Chromosomal positions based on NCBI build 36 coordinates, showing Ensemble (release 48) genes. Armitage trend test *P* values (as $-\log_{10}$ values; left *y* axis) are shown for SNPs analyzed. Recombination rates in HapMap CEU across the region are shown in black (right *y* axis). Also shown are the relative positions of genes mapping to each region of association. Exons of genes have been redrawn to show the relative positions in the gene; therefore, maps are not to physical scale.

Loci on 7p12.2, 10q21.2 and 14q11.2 are associated with risk of childhood acute lymphoblastic leukemia

Elli Papaemmanuil[1], Fay J Hosking[1], Jayaram Vijayakrishnan[1], Amy Price[1], Bianca Olver[1], Eammon Sheridan[2], Sally E Kinsey[3], Tracy Lightfoot[4], Eve Roman[4], Julie A E Irving[5], James M Allan[5], Ian P Tomlinson[6], Malcolm Taylor[7], Mel Greaves[8] & Richard S Houlston[1]

Germline genomic variants associated with childhood acute lymphoblastic leukemia

Lisa R Treviño[1,6], Wenjian Yang[1,6], Deborah French[1], Stephen P Hunger[2], William L Carroll[3], Meenakshi Devidas[4], Cheryl Willman[5], Geoffrey Neale[1], James Downing[1], Susana C Raimondi[1], Ching-Hon Pui[1], William E Evans[1] & Mary V Relling[1]



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GWAS in Childhood Leukemia

The *ARID5B* gene (also known as *DESRT* and *MRF2*) encodes a member of the ARID family of transcription factors and is important in embryonic development, cell type–specific gene expression and cell growth regulation[22]. Homozygous knockout mice (*Arid5b*$^{-/-}$) have abnormal thymic and splenic architecture and disrupted B cell differentiation[23–25]. *ARID5B* expression is upregulated in individuals with acute megakaryoblastic leukemia[26] and acute promyelocytic leukemia[27]. Thus, it is possible that germline variation at the *ARID5B* locus affects susceptibility to this B-lineage leukemia by altering *ARID5B* function in B-lineage development.

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GWAS & Epidemiologic Research

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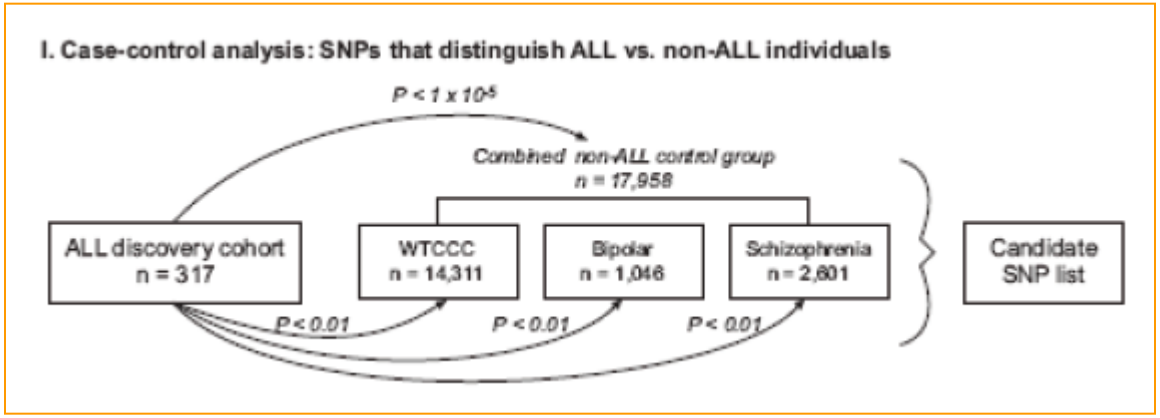

Saturday, March 29, 2008

Why do genome-wide scans fail?

High technology does not preclude the need for good research design

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Genetic Susceptibility to Leukemia

Dorak et al

Leukemia and Lymphoma, Vol. 12, pp. 211–222
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Human Major Histocompatibility Complex Contains Several Leukemia Susceptibility Genes

M. TEVFIK DORAK,* ELIZABETH A. CHALMERS,† DAIRENA GAFFNEY,‡ DAVID W. L. WILSON,§ IAN GALBRAITH,§ NANCY HENDERSON,§ MARK WORWOOD,* KEN I. MILLS* and ALAN K. BURNETT*

*Department of Haematology, University of Wales College of Medicine, Cardiff, †Department of Haematology, Western Infirmary, Glasgow, ‡Department of Pathological Biochemistry, Royal Infirmary, Glasgow, and §Tissue Typing Laboratory, Royal Infirmary, Glasgow, UK

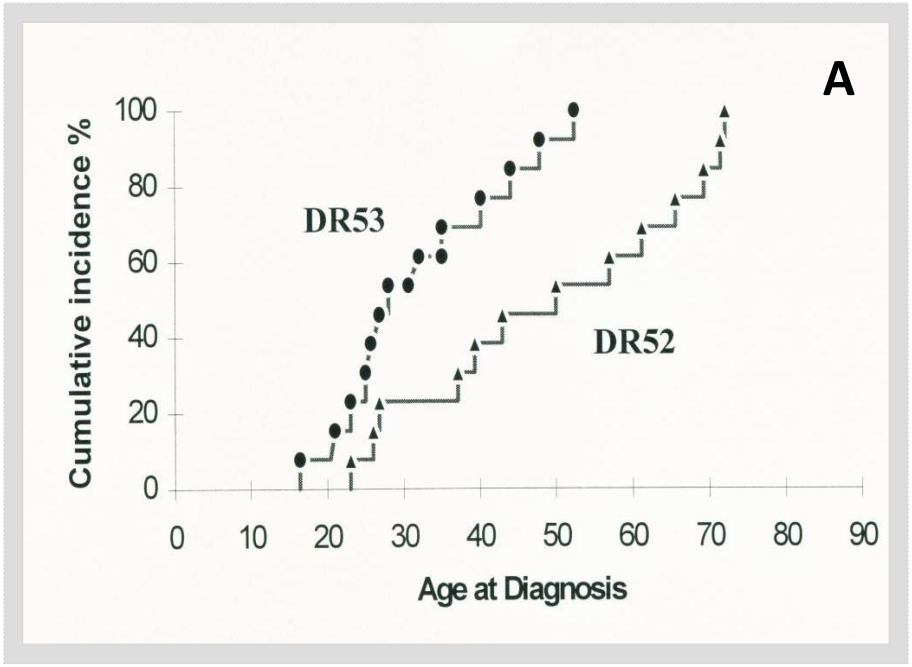
Int. J. Cancer: **65**, 134–139 (1996)

UICC Publication of the International Union Against Cancer
Publication de l'Union Internationale Contre le Cancer

INFLUENCE OF THE MAJOR HISTOCOMPATIBILITY COMPLEX ON AGE AT ONSET OF CHRONIC LYMPHOID LEUKAEMIA

M. Tevfik DORAK[1,3], Helmut K.G. MACHULLA[2], Michael HENTSCHEL[2], Ken I. MILLS[1], Jürgen LANGNER[2] and Alan K. BURNETT[1]

[1]*Department of Haematology, University of Wales College of Medicine, Cardiff, UK;* [2]*Interbranch HLA Laboratory, Martin Luther University Medical School, Halle, Germany.*



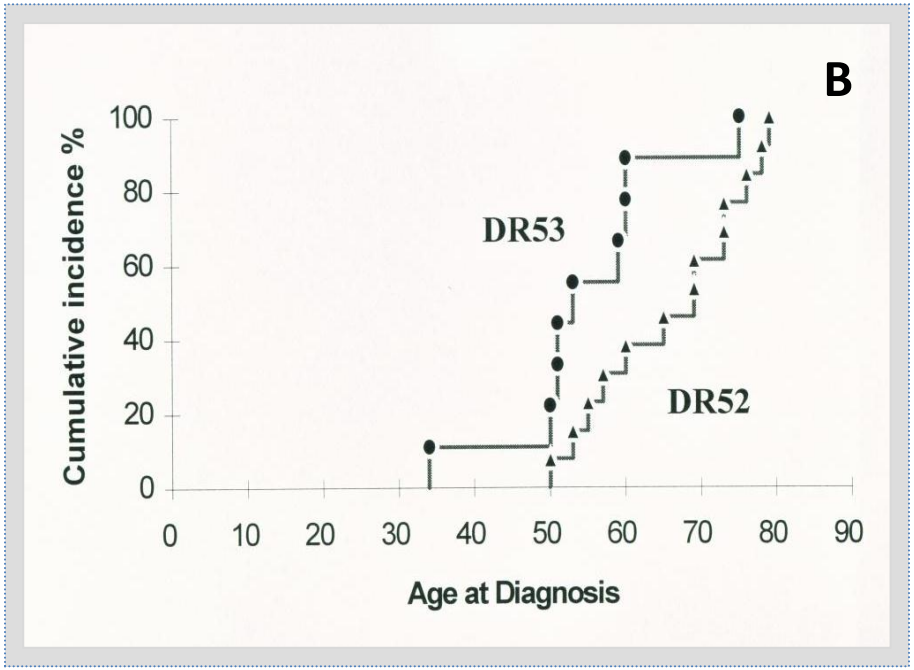


Figure 1: Age distribution of cases with two copies of DR53 and DR52 haplotypes in (A) chronic myeloid leukemia and (B) chronic lymphoid leukemia.

Genetic Susceptibility to Childhood Leukemia

Dorak et al

Clues to Follow:

Animal studies

Gender effect

Miscarriages

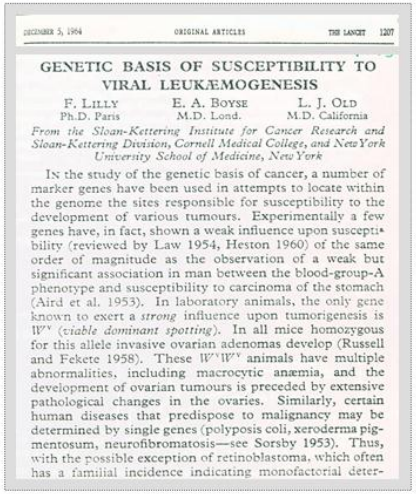
Birth weight

Multiple sclerosis

???

The first DNA-based HLA association study in childhood leukemia

Demonstration of the sex effect



DECEMBER 5, 1964 ORIGINAL ARTICLES THE LANCET 1207

GENETIC BASIS OF SUSCEPTIBILITY TO VIRAL LEUKÆMOGENESIS

F. LILLY Ph.D. Paris
E. A. BOYSE M.D. Lond.
L. J. OLD M.D. California

From the Sloan-Kettering Institute for Cancer Research and Sloan-Kettering Division, Cornell Medical College, and New York University School of Medicine, New York

IN the study of the genetic basis of cancer, a number of marker genes have been used in attempts to locate within the genome the sites responsible for susceptibility to the development of various tumours. Experimentally a few genes have, in fact, shown a weak influence upon susceptibility (reviewed by Law 1954, Heston 1960) of the same order of magnitude as the observation of a weak but significant association in man between the blood-group-A phenotype and susceptibility to carcinoma of the stomach (Aird et al. 1953). In laboratory animals, the only gene known to exert a *strong* influence upon tumorigenesis is W^v (*viable dominant spotting*). In all mice homozygous for this allele invasive ovarian adenomas develop (Russell and Fekete 1958). These W^vW^v animals have multiple abnormalities, including macrocytic anæmia, and the development of ovarian tumours is preceded by extensive pathological changes in the ovaries. Similarly, certain human diseases that predispose to malignancy may be determined by single genes (polyposis coli, xeroderma pigmentosum, neurofibromatosis—see Sorsby 1953). Thus, with the possible exception of retinoblastoma, which often has a familial incidence indicating monofactorial deter-

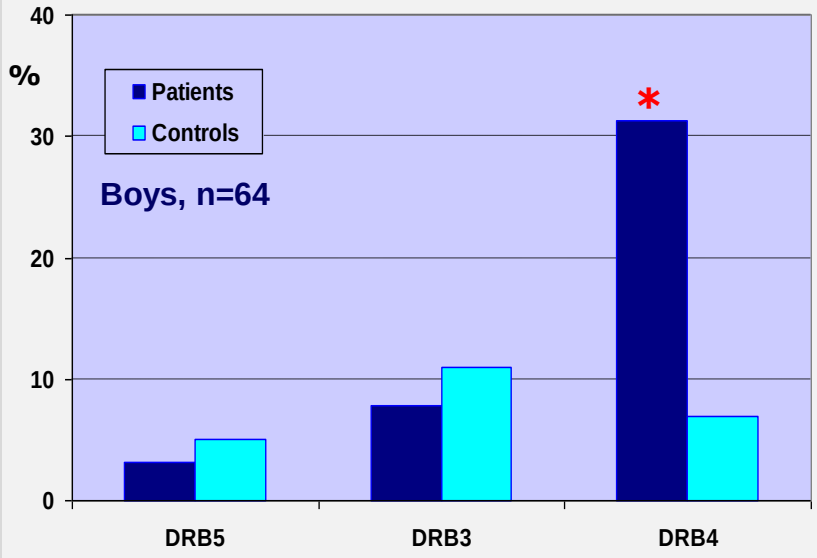
Unravelling an HLA-DR Association in Childhood Acute Lymphoblastic Leukemia

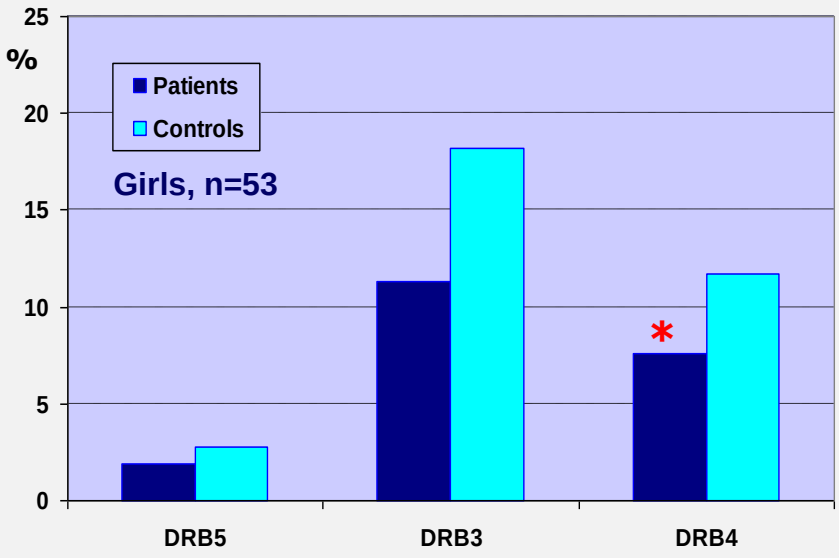
By M. Tevfik Dorak, Tom Lawson, Helmut K.G. Machulla, Chris Darke, Ken I. Mills, and Alan K. Burnett

Genetic and environmental factors play an interactive role in the development of childhood acute lymphoblastic leukemia (ALL). Since the demonstration of a major histocompatibility complex (MHC) influence on mouse leukemia in 1964, an HLA association has been considered as a possible genetic risk factor. Despite extensive efforts, however, no strong evidence comparable to the H-2^k influence on mouse leukemia has been shown. The number of negative serological studies resulted in a loss of interest and consequently, no molecular HLA-DR association study has been published to date. We reconsidered the HLA-DR association in childhood ALL in 114 patients from a single center and 325 local newborn controls by polymerase chain reaction (PCR) analysis of the HLA-DRB1/3/4/5 loci. With conventional analysis, there was a moderate allelic association with the most common allele in the HLA-DR53 group, HLA-DRB1*04, in the whole group that was stronger in males (P = .0005, odds ratio = 2.9). When the other expressed HLA-DRB loci were examined, homozygosity for HLA-DRB4*01, encoding the HLA-DR53 specificity, was increased in patients (21.1% *v* 8.3%; odds ratio = 2.9, P = .0005). Consideration of gender showed that all of these associations were reflections of a male-specific increase in homozygosity for HLA-DRB4*01 (32.8% *v* 4.0%; odds ratio = 11.7, 95% confidence interval [CI] = 4.9 to 28.0; $P = 3 \times 10^{-8}$). This highly significant result provided the long-suspected evidence for the HLA-DR influence on the development of childhood ALL while confirming the recessive nature of the MHC influence on human leukemogenesis as in experimental models. The cross-reactivity between HLA-DR53 and H-2E^k, extensive mimicry of the immunodominant epitope of HLA-DR53 by several carcinogenic viruses, and the extra amount of DNA in the vicinity of the HLA-DRB4 gene argue for the case that HLA-DRB4*01 may be one of the genetic risk factors for childhood ALL.

Blood, Vol 94, No 2 (July 15), 1999: pp 694-700

HLA-DRB4 Association in Childhood ALL





Homozygosity for *HLA-DRB4* family is associated with susceptibility to childhood ALL in boys only (*P* < 0.0001, OR = 6.1, 95% CI = 2.9 to 12.6)

*** Case-only analysis *P* = 0.002 (OR = 5.6; 95% CI = 1.8 to 17.6)**

Biochimica et Biophysica Acta 1802 (2010) 292–300

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

An intronic polymorphism of IRF4 gene influences gene transcription *in vitro* and shows a risk association with childhood acute lymphoblastic leukemia in males

Thuy N. Do, Esma Ucisik-Akkaya, Charronne F. Davis, Brittany A. Morrison, M. Tevfik Dorak *

Genomic Immunoepidemiology Laboratory, HUMIGEN LLC, The Institute for Genetic Immunology, 2439 Kuser Road, Hamilton, NJ 08690-3303, USA

Functional study of the IRF4 risk marker suggested the involvement of NF-kB pathway and estrogen

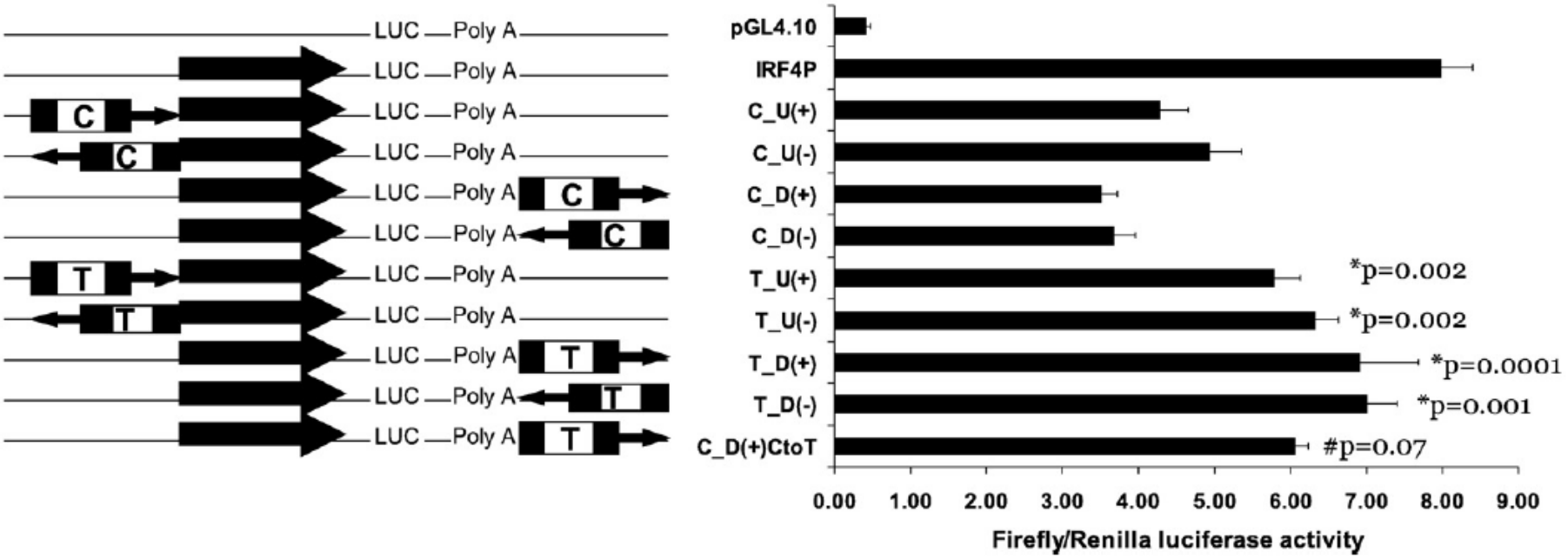


Fig. 1. IRF4 intron 4 with wild type allele C at SNP rs12203592 represses IRF4 promoter activity while IRF4 intron 4 with variant allele T significantly alleviates this repressive effect. Both work in an orientation- and position-independent manner. The full 1.2-kb fragment of intron 4 of the human IRF4 gene (contains either a wild type C or variant allele T at SNP rs12203592) was subcloned into the luciferase-reporter plasmid driven by a 2.4-kb IRF4 promoter (the big black arrow right before luciferase gene (LUC)). In all of the constructs, the LUC is used as a reporter gene whose mRNA is stabilized by a polyadenylation/splice signal from the simian virus 40 (Poly A). Raji cells were co-nucleofected with these constructs and with the internal control plasmid pGL4.13[hRenilla/SV40] and then assayed for both firefly and *Renilla* luciferases after 24 h. To adjust for differences in transfection efficiencies, firefly luciferase values were standardized to *Renilla* luciferase values. The results are from three independent experiments. The error bars represent standard errors. *Comparison between intron 4 with the variant allele T and intron 4 with the wild type allele C; #comparison between CD(+)CtoT with TD(+).

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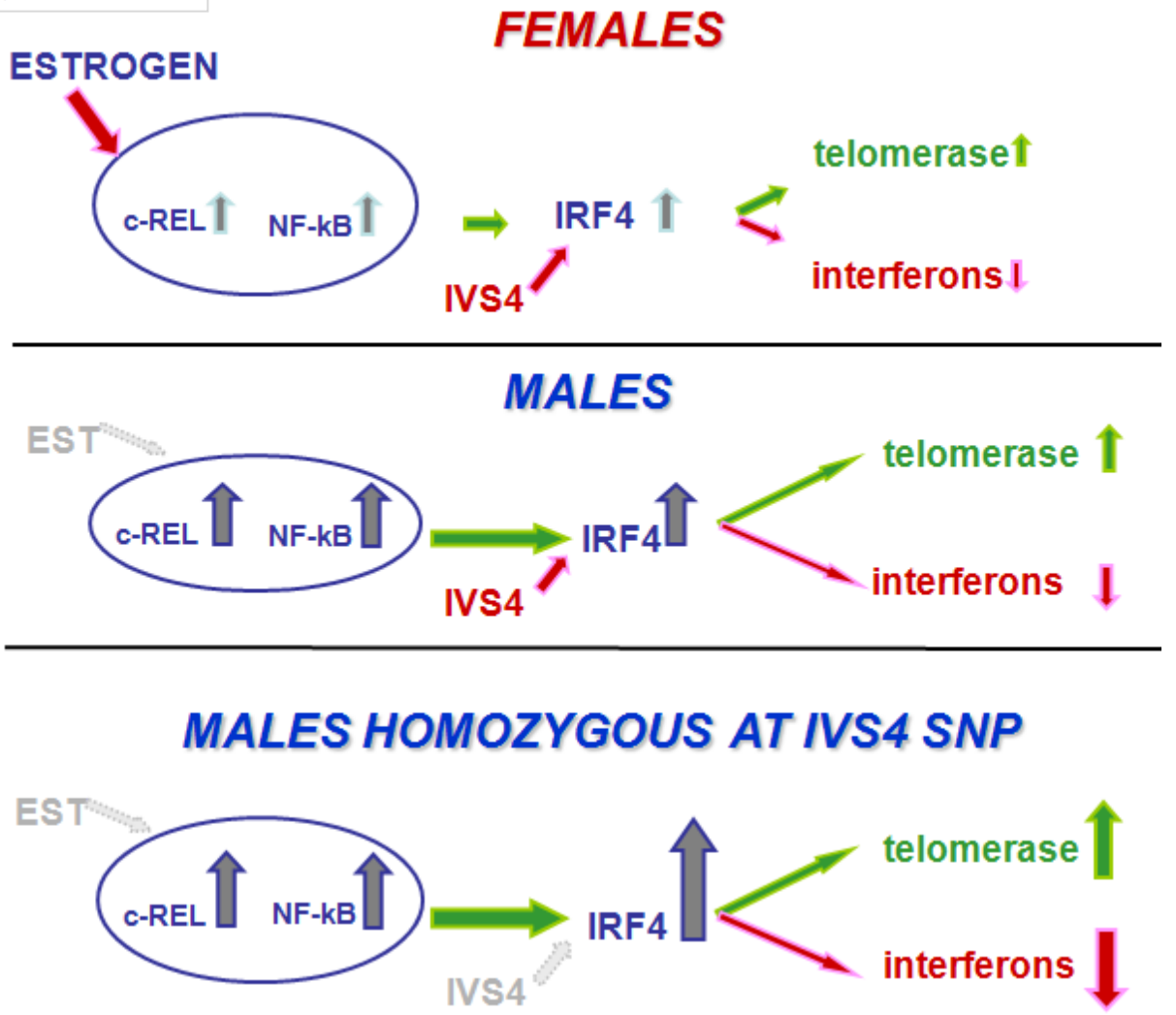

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ELSEVIER

Cancer Genetics and Cytogenetics 195 (2009) 31–36

Cancer Genetics and Cytogenetics

TP53 R72P and *MDM2* SNP309 polymorphisms in modification of childhood acute lymphoblastic leukemia susceptibility

Thuy N. Do, Esma Ucisik-Akkaya, Charronne F. Davis, Brittany A. Morrison, M. Tevfik Dorak*

Genomic Immunoepidemiology Laboratory, HUMIGEN LLC, Institute for Genetic Immunology, 2439 Kuser Road, Hamilton, NJ 08690-3303

MDM2 SNP309 is associated with earlier age-at-onset in leukemia as in breast cancer

Table 3
Median age at diagnosis of childhood acute lymphoblastic leukemia by *MDM2* SNP309 genotype

	Age, mo (sample size)			
	TT, wild type	GT, heterozygosity	GG, minor allele homozygosity	GT + GG, minor allele positivity
Total	68 (n=42)	56 (n=51)	66 (n=12)	52 (n=63)
Male	78 (n=19)	66 (n=31)	77 (n=7)	60 (n=38)
Female	59 (n=23)	44 (n=20)	32 (n=5)	36 (n=25)
P-value[a]	1.0	0.008	0.16	0.002

[a] The P-value is for age distribution differences between male and female cases (Kruskal–Wallis test).

The association with earlier age-at-onset was observed only in females, as has been noted also in adult cancers. This effect is attributed to estrogen activity.

The associations of IRF4 and MDM2 implicate estrogen action in childhood ALL and raises the possibility of mediation of "fetal programming of childhood ALL susceptibility" by sex hormones.

"Fetal programming of adult disease susceptibility" has been shown in several diseases and equally applies to childhood leukemia.

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Miscarriages

Cancer Causes Control
DOI 10.1007/s10552-006-0093-8

ORIGINAL PAPER

Examination of gender effect in birth weight and miscarriage associations with childhood cancer (United Kingdom)

M. Tevfik Dorak · Mark S. Pearce · Donna M. Hammal · Richard J. Q. McNally · Louise Parker

	Odds Ratio	P	[95% Conf.	Interval]
bw100	1.05	0.02	1.01	1.09
mcyn	1.47	0.05	1.00	2.16
sex	19.12	0.004	2.52	145.30
sex X bw100	0.91	0.004	0.86	0.97

Birth weight and miscarriages both have independent risk associations with childhood ALL (in boys only)

Molecular Human Reproduction, Vol.16, No.10 pp. 770–777, 2010
Advanced Access publication on June 29, 2010 doi:10.1093/molehr/gaq047

MHR Basic science of reproductive medicine

ORIGINAL RESEARCH

Examination of genetic polymorphisms in newborns for signatures of sex-specific prenatal selection

Esma Ucisik-Akkaya[1], Charronne F. Davis[1], Thuy N. Do[1], Brittany A. Morrison[1], Shlomo M. Stemmer[2], William J. Amadio[3], and M. Tevfik Dorak[1,4,*]

Table III The final set of independent markers of sex-specific prenatal selection.

Marker	OR (95% CI)[a]	P^a (adjusted)	P^b (permutation)
HIST1H1T rs198844	0.43 (0.25–0.74)	0.002	0.015
RXRB rs2076310	0.48 (0.30–0.76)	0.002	0.009
IFNG rs2069727	0.54 (0.29–1.01)	0.055	0.035
KLRK1 rs10772266	0.58 (0.34–1.00)	0.048	0.037
HSPA1B-DRA-DQA1 haplotype homozygosity	0.36 (0.16–0.82)	0.015	0.004
IRF4 heterozygosity	0.41 (0.21–0.79)	0.008	0.013

[a]*P*-values and ORs were obtained from multivariable logistic regression model containing these six markers.
[b]*P*-values were obtained from Monte Carlo permutation test (100 000 simulations).

Birth weight

Int. J. Cancer: **124,** 2658–2670 (2009)

Birth weight and childhood leukemia: A meta-analysis and review of the current evidence

Robert W. Caughey[1] and Karin B. Michels[1,2]*

[1]*Department of Epidemiology, Harvard School of Public Health, Boston, MA*
[2]*Obstetrics and Gynecology Epidemiology Center, Department of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*

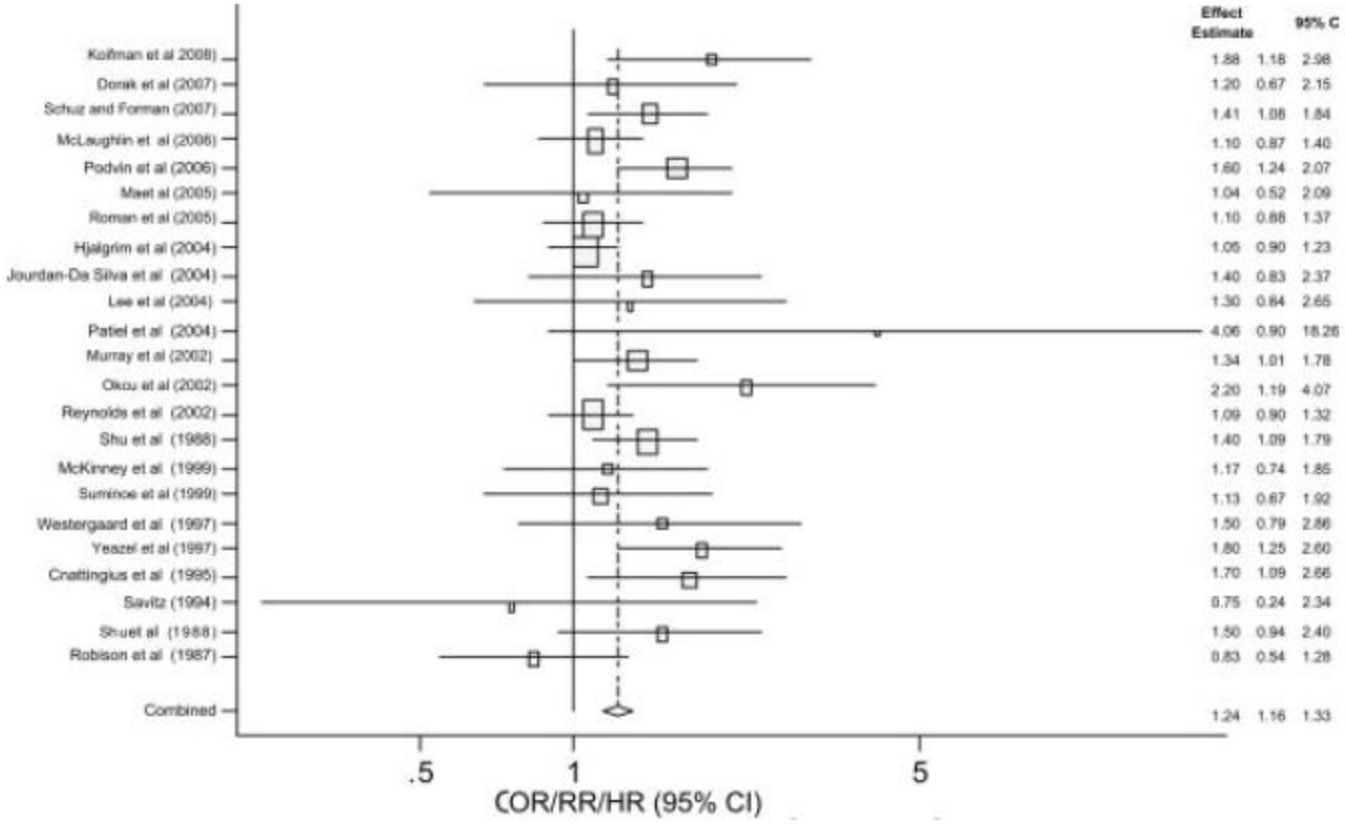

FIGURE 2 – Studies on the risk of ALL associated with high birth weight. OR, odds ratio; RR, relative risk; HR, hazard ratio; CI, confidence interval. The square indicates the OR, RR, or HR; the size of the square represents the statistical weight of each study; the bars represent 95% CIs.

Early Life Exposure to Iron and Childhood Leukemia Risk

Cancer Causes Control
DOI 10.1007/s10552-006-0093-8

ORIGINAL PAPER

Examination of gender effect in birth weight and miscarriage associations with childhood cancer (United Kingdom)

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	Odds Ratio	P	[95% Conf.	Interval]
bw100	1.05	0.02	1.01	1.09
mcyn	1.47	0.05	1.00	2.16
sex	19.12	0.004	2.52	145.30
sex X bw100	0.91	0.004	0.86	0.97

Both have independent risk associations with childhood ALL (in boys only)

of malignant transformation [3]. At present, this is the most parsimonious explanation and may have a genetic as well as an environmental basis. These two hypotheses are not mutually exclusive and a common genetic basis for increased growth factor production and high birth weight is plausible. One other growth factor for both fetal [45, 46] and cancer cell growth [47] is iron. The HFE gene shows a replicated association with childhood ALL in boys only [26], which is likely to be due to the effect of this mutation on body iron content [48]. Iron excess is also linked with gestational diabetes [49] and recently, an HFE association in gestational diabetes has been reported [50]. As gestational diabetes has been proposed one of the possible biological mechanisms of birth weight association with childhood cancer [2], and given the parallels in the epidemiology of diabetes and childhood leukemia, including the sex effect [51], the iron and diabetes connection is also noteworthy. These observations suggest that just like IGF-1, iron may also be connected with both birth weight and leukemia risk.

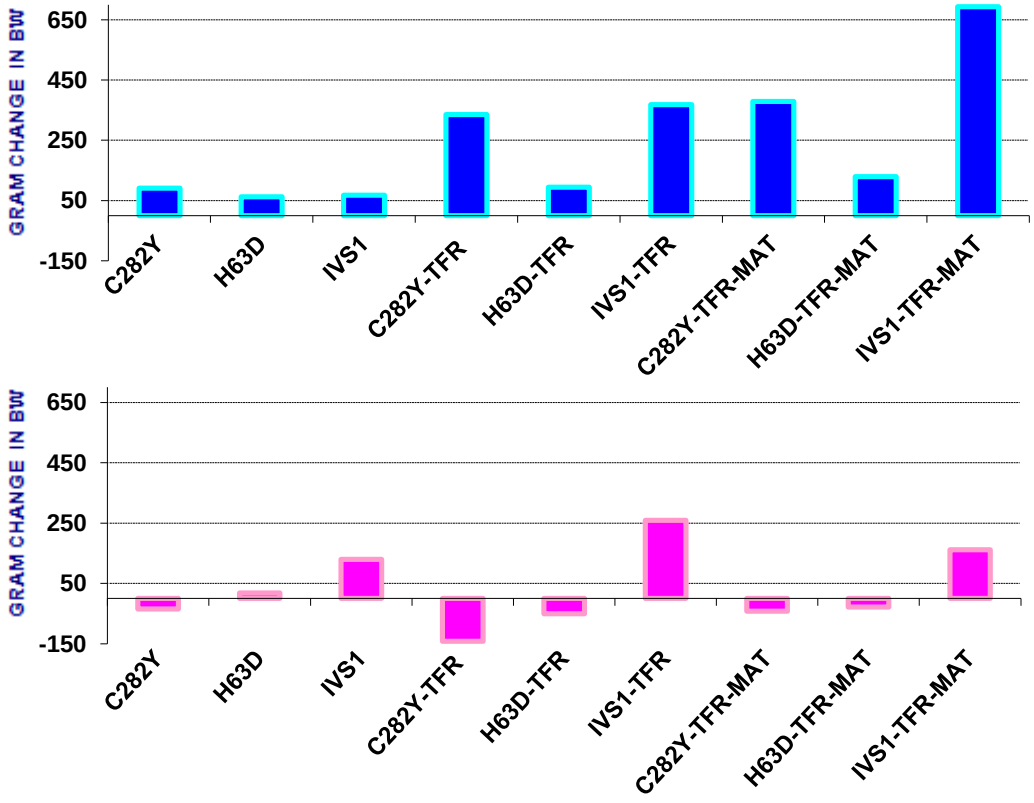
Early Life Exposure to Iron and Childhood Leukemia Risk

Mean Birth Weight (g) in Relation to HFE - TFRC Genotypes in Newborn Boys and Maternal HFE Status

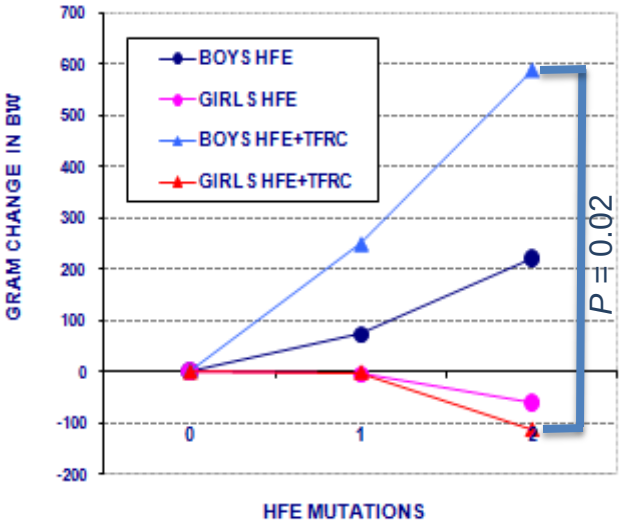
Child (boys only)	Mother	
HFE wild-type	*HFE* wild-type	3480.4 *(n=140)*
HFE-variant-positive and *TFRC* S142G homozygote	*HFE* wild-type	3590.0 *(n=14)*
HFE-variant-positive and *TFRC* S142G homozygote	*HFE* variant-positive	3749.0 *(n=21)*
	P value for trend	0.02

Early Life Exposure to Iron and Childhood Leukemia Risk

HFE **variants are associated with birth weight with sex effect and maternal effect, and in interaction with TFRC**



HFE **variants interact with a *TFRC* variant and show gene-dosage effect**



Pediatr Blood Cancer 2009;53:1242–1248

Hereditary Hemochromatosis Gene (*HFE*) Variants Are Associated With Birth Weight and Childhood Leukemia Risk

M. Tevfik Dorak, MD, PhD,[1]* Rachel K. Mackay, BSc,[1] Caroline L. Relton, PhD,[2] Mark Worwood, PhD,[3] Louise Parker, PhD,[4] and Andrew G. Hall, MBBS, PhD[1]

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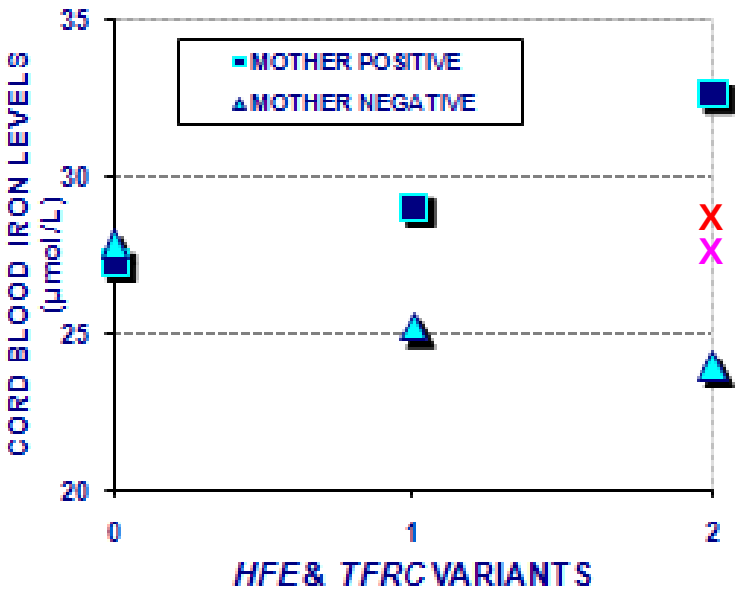
Early Life Exposure to Iron and Childhood Leukemia Risk

Cord blood iron levels correlate with HFE / TFRC
genotypes in boys only



- Maternal-fetal iron transport dynamics may differ in male and female pregnancies
- Iron overload associated genotypes increase birth weight in males, and leukemia risk in males and females
- Leukemia associations are stronger in females
- We postulate that (1) females cannot offset iron excess by increasing their weight, (2) the high risk genotype combinations result in extreme iron levels in males and cause very high birth weight and high leukemia risk.

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Hereditary Hemochromatosis Gene (*HFE*) Variants Are Associated With Birth Weight and Childhood Leukemia Risk

M. Tevfik Dorak, MD, PhD,[1]* Rachel K. Mackay, BSc,[1] Caroline L. Relton, PhD,[2] Mark Worwood, PhD,[3] Louise Parker, PhD,[4] and Andrew G. Hall, MBBS, PhD[1]

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Genetic Susceptibility to Childhood Leukemia

Dorak et al

Clues to Follow:

Animal studies

Gender effect

Miscarriages

Birth weight

Multiple sclerosis

???

Autoimmunity, December 2010; 43(8): 690–697

ISSN 0891-6934 print/1607-842X online
DOI: 10.3109/08916930903567492

informa
healthcare

Multiple sclerosis risk markers in HLA-DRA, HLA-C, and IFNG genes are associated with sex-specific childhood leukemia risk

BRITTANY A. MORRISON[1], ESMA UCISIK-AKKAYA[1], HILARIO FLORES[2], CARMEN ALAEZ[2], CLARA GORODEZKY[2], & M. TEVFIK DORAK[1]

Table III. Individual and pooled sex-specific association test results (dominant model) in the Welsh and Mexican case–control studies.*

SNP	Welsh (OR and 95% CI)	Mexican (OR and 95% CI)	Homogeneity test (*P*)	Pooled (OR and 95% CI)
HLA-DRA† (rs3135388)	2.86 (1.41–5.77)	1.83 (0.48–6.49)	0.50	2.56 (1.46–4.49), $P = 0.0009$
SKIV2L† (rs419788)	2.11 (1.03–4.47)	1.44 (0.65–3.22)	0.46	1.78 (1.09–2.92), $P = 0.02$
HLA-C† (rs9264942)	0.47 (0.23–0.98)	0.32 (0.14–0.73)	0.45	0.40 (0.24–0.66), $P = 0.0003$
IFNG‡ (rs2069727)	0.53 (0.28–1.02)	0.72 (0.36–1.40)	0.50	0.62 (0.40–0.96), $P = 0.03$

*OR and *P* values were estimated by Mantel–Haenszel test; †Female-specific association; ‡Male-specific association.

OUTLINE

Childhood ALL Epidemiology

Genetic studies

GWAS

Dorak et al

Unpublished studies

Proposed research on the Hispanic differential in susceptibility

GENETIC ASSOCIATIONS IN CHILDHOOD LEUKEMIA AND INTERACTIONS WITH SEX

M Tevfik Dorak, Esma Ucisik-Akkaya, Charronne Davis, Brittany A Morrison, Thuy Do
Genomic Immunoepidemiology Lab, HUMIGEN LLC, The Institute for Genetic Immunology, Hamilton, NJ 08690
e-mail: [illegible]

INTRODUCTION

[illegible]

SUBJECTS and METHODS

[illegible]

Table 1. Genetic Associations in Childhood ALL

[illegible]

REFERENCES

[illegible]

RESULTS

[illegible]

Table 2. Heterozygosity rates of variants in extended HLA loci

[illegible]

[illegible]

ACKNOWLEDGEMENT

This study is internally funded by HUMIGEN LLC, The Institute for Genetic Immunology. All authors are employees of HUMIGEN LLC.

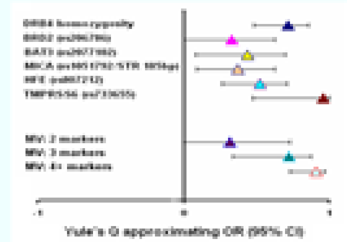


Figure 1. Statistically independent univariable associations and multivariable (MV) additive risk models in childhood ALL in males.

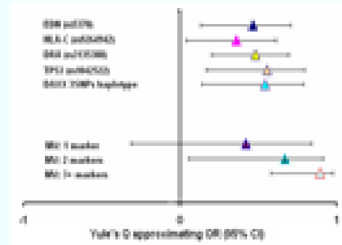
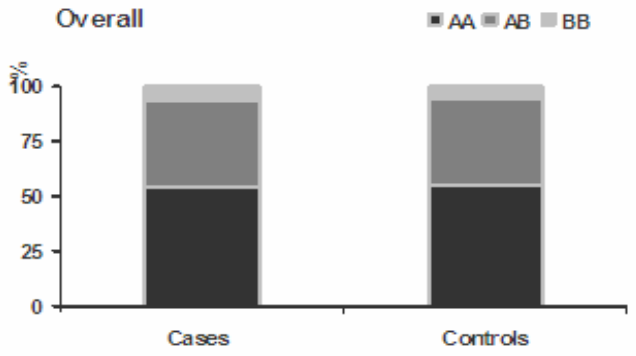


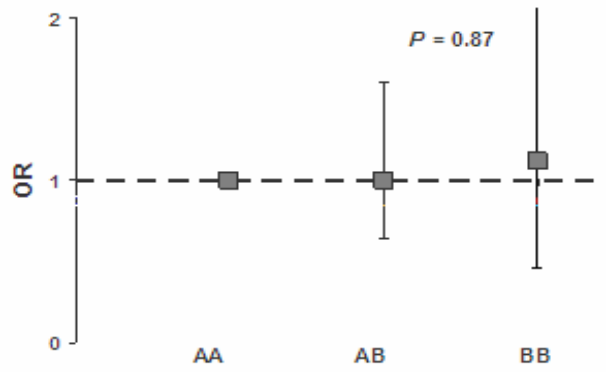
Figure 2. Statistically independent univariable associations and multivariable (MV) additive risk models in childhood ALL in females.

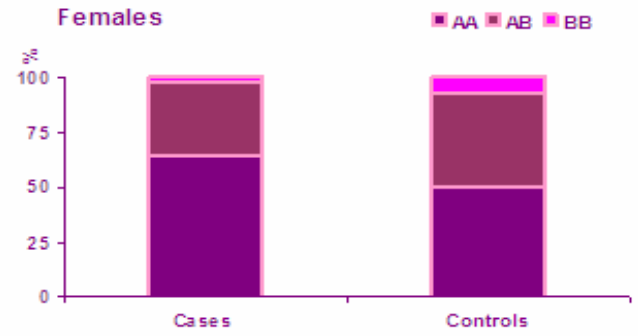
CONCLUSIONS

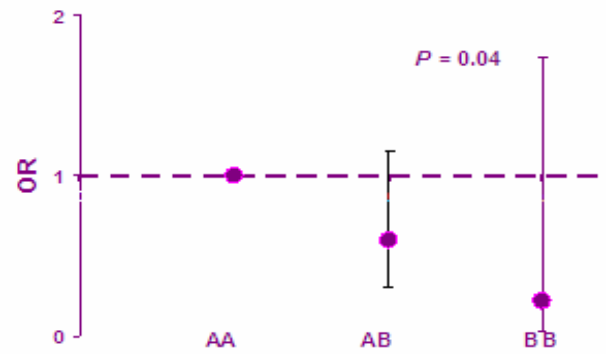
[illegible]

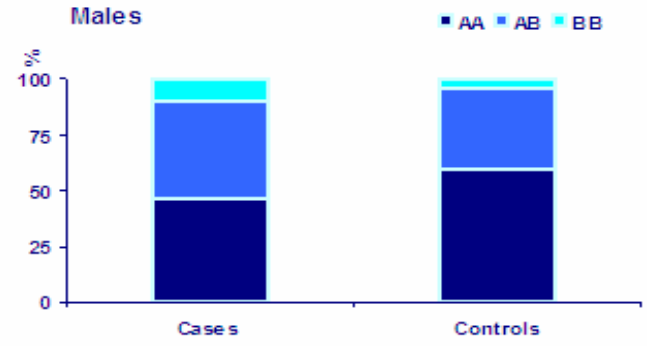
NRAMP2 rs422982 Have Different Associations when Stratified by Sex

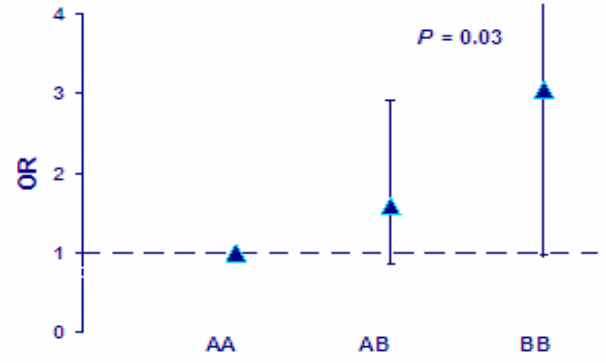




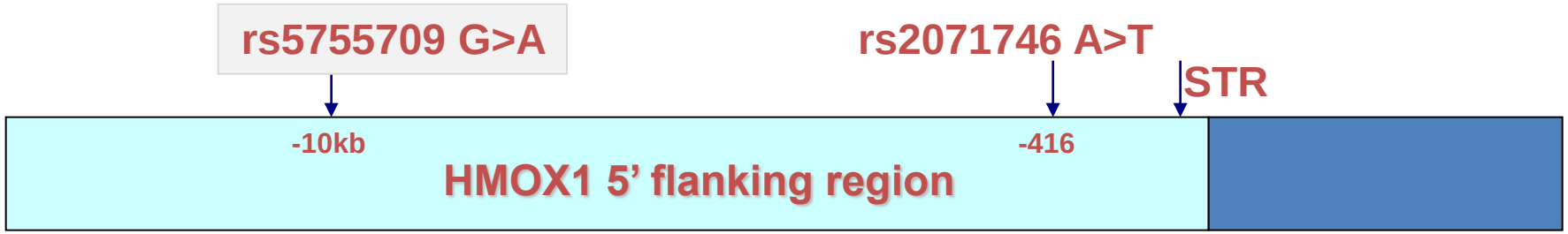


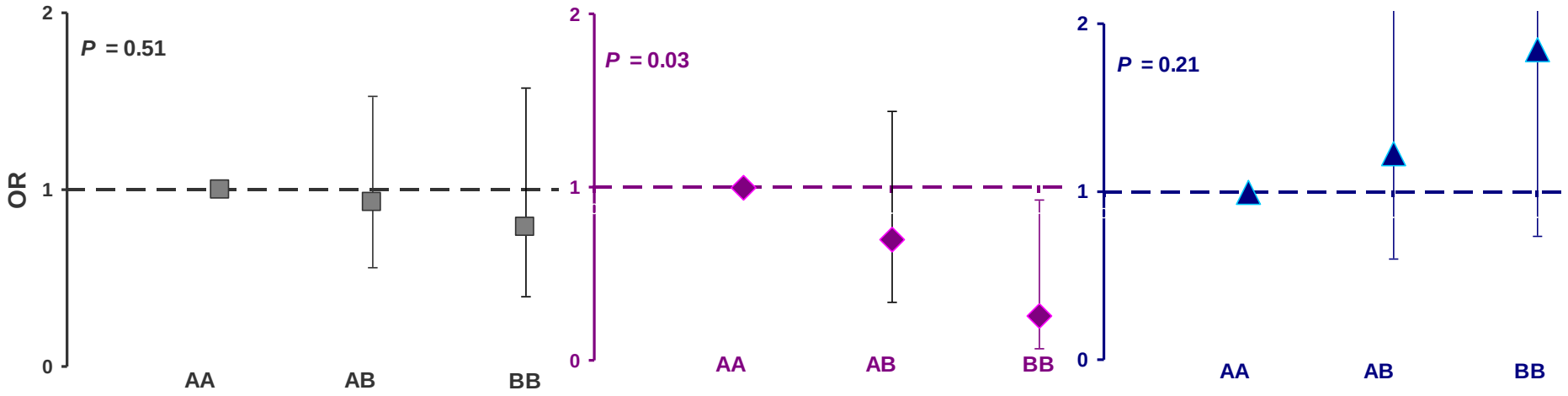






HMOX1 rs5755709 Have Different Associations when Stratified by Sex





P (sex) = 0.015

P (sex; case-only) = 0.01

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Genetic Susceptibility to Childhood Leukemia

Dorak et al

Summary

Most previously observed epidemiologic associations can be tested at the genetic level using genetic epidemiology as a probe for disease biology

When examined a sex effect can be found, and this approach may unmask associations that may be otherwise missed

Genetic Susceptibility to Childhood Leukemia

Dorak et al

Clues to Follow:

Animal studies

Gender effect

Miscarriages

Birth weight

Multiple sclerosis

Hispanic Differential

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Cancer Facts & Figures for Hispanics/Latinos 2006-2008

American Cancer Society

Table 4. Childhood Cancer Incidence Rates* and Ratios† by Hispanic Origin, Both Sexes Combined, 2000-2003

	Age 0-14 years			Age 15-19 years		
	Hispanic	Non-Hispanic White	Ratio	Hispanic	Non-Hispanic White	Ratio
All sites	14.8	16.1	0.9	19.1	24.1	0.8
Leukemia	5.8	4.8	1.2	4.0	2.9	1.4
Lymphoid leukemia	4.8	3.8	1.3	2.6	1.6	1.6
Acute myeloid leukemia	0.8	0.8	1.0	1.1	0.9	1.2
Brain & other nervous system	2.7	3.7	0.7	1.6	2.4	0.7
Lymphoma	1.5	1.6	0.9	3.9	5.8	0.7
Non-Hodgkin lymphoma (except Burkitt lymphoma)	0.6	0.6	1.0	1.2	1.7	0.7
Hodgkin lymphoma	0.6	0.6	1.0	2.3	3.7	0.6
Burkitt lymphoma	0.2	0.3	0.7	‡	0.3	–
Soft-tissue sarcomas	1.1	1.1	1.0	1.5	1.7	0.9
Bone tumors	0.7	0.6	1.1	1.4	1.7	0.8
Osteosarcoma	0.5	0.3	1.4	0.8	0.9	1.0
Germ cell tumors	0.6	0.5	1.2	3.6	2.9	1.2
Malignant gonadal	0.3	0.2	1.6	2.8	2.4	1.2
Intracranial & intraspinal	0.2	0.2	1.1	‡	0.3	–
Neuroblastoma	0.6	1.3	0.5	‡	‡	–
Renal tumors	0.6	0.9	0.7	‡	‡	–
Retinoblastoma	0.4	0.4	1.0	‡	‡	–
Hepatic tumors	0.2	0.3	0.9	‡	‡	–

*Rates are per 100,000 and age-adjusted to the 2000 US standard population. †Ratios are calculated as Hispanic incidence rate divided by non-Hispanic white incidence rate. ‡Data supressed due to fewer than 25 cases during 2000-2003.

Note: Hispanics are not mutually exclusive from whites, African Americans, Asian/Pacific Islanders, and American Indians/Alaska Natives.

Source: Surveillance, Epidemiology, and End Results (SEER) Program, 17 SEER registries, 2000 to 2003, Division of Cancer Control and Population Sciences, National Cancer Institute, 2006. Incidence data for Hispanics and non-Hispanic whites are based on the NAACCR Hispanic Identification Algorithm (NHIA) and exclude cases from Hawaii, Seattle, Alaska Native Registry, and Kentucky.

TABLE 1. Total counts of cancer cases, annual cancer age-standardized incidence rates (ASIRs) per 10^6 person-years, and standardized incidence ratios (SIRs) for Hispanic and non-Hispanic white children < 15 years of age, 1988–1998, for both states (California and Florida) and both genders combined

ICCC[a] major diagnostic groups and selected subgroups	Hispanic			Non-Hispanic white				
	Count	ASIR	SE[b]	Count	ASIR	SE	SIR[c]	95% CI[d]
All cancers combined	5 197	152.7	2.1	7 755	149.5	1.7	1.02	0.99, 1.05
Leukemia	2 096	61.5	1.3	2 505	48.8	1.0	1.26	1.19, 1.34
Lymphoid leukemia	1 731	50.8	1.2	2 024	39.5	0.9	1.29	1.21, 1.38
Acute nonlymphocytic leukemia	280	8.2	0.5	366	7.1	0.4	1.15	0.98, 1.35
Lymphoma & reticuloendothelial	493	14.5	0.7	760	14.0	0.5	1.04	0.91, 1.19
Hodgkin's lymphoma	211	6.2	0.4	268	4.8	0.3	1.29	1.08, 1.54
Non-Hodgkin's lymphoma	173	5.1	0.4	317	5.9	0.3	0.86	0.71, 1.03
Burkitt's lymphoma	74	2.2	0.3	136	2.5	0.2	0.88	0.65, 1.19
CNS[e], misc., intracranial, intraspinal	803	23.6	0.8	1 706	32.6	0.8	0.72	0.66, 0.78
Ependymoma	69	2.0	0.2	138	2.7	0.2	0.74	0.58, 0.94
Astrocytoma	338	9.9	0.5	905	17.2	0.6	0.58	0.52, 0.65
PNET[f]	248	7.3	0.5	421	8.1	0.4	0.90	0.76, 1.06
Sympathetic nervous system	295	8.7	0.5	564	11.5	0.5	0.76	0.66, 0.87
Retinoblastoma	190	5.6	0.4	212	4.4	0.3	1.27	1.04, 1.54
Renal tumors	270	7.9	0.5	448	9.0	0.4	0.88	0.76, 1.02
Hepatic tumors	72	2.1	0.2	103	2.1	0.2	1.00	—
Malignant bone tumors	208	6.1	0.4	348	6.3	0.3	0.97	0.84, 1.13
Osteosarcoma	129	3.8	0.3	170	3.0	0.2	1.27	1.03, 1.57
Ewing's sarcoma	59	1.7	0.2	157	2.8	0.2	0.61	0.48, 0.78
Soft tissue sarcomas	333	9.8	0.5	477	9.1	0.4	1.08	0.94, 1.24
Rhabdomyosarcoma	144	4.2	0.4	246	4.8	0.3	0.88	0.71, 1.08
Germ-cell, trophoblastic, other	259	7.6	0.5	245	4.7	0.3	1.62	1.34, 1.96
Carcinomas, other epithelial	117	3.5	0.3	314	5.7	0.3	0.61	0.51, 0.74
Other and unspecified malignancy	16	0.5	0.1	34	0.7	0.1	0.71	0.44, 1.14

[a] ICCC = International Classification of Childhood Cancer.
[b] SE = standard error.
[c] The standardized incidence ratio (SIR) is referenced to non-Hispanic white children.
[d] CI = confidence interval.
[e] CNS = central nervous system.
[f] PNET = primitive neuroectodermal tumor.

Cancer incidence among Hispanic children in the United States

James D. Wilkinson,[1, 2, 3] *Alex Gonzalez,*[2] *Brad Wohler-Torres,*[1, 3] *Lora E. Fleming,*[1, 2, 3] *Jill MacKinnon,*[1, 3] *Edward Trapido,*[1, 2, 3] *Jaclyn Button,*[1, 3] *and Steven Peace*[1, 3]

Suggested citation Wilkinson JD, Gonzalez A, Wohler-Torres B, Fleming LE, MacKinnon J, Trapido E, Button J, Peace S. Cancer incidence among Hispanic children in the United States. Rev Panam Salud Publica. 2005; 18(1):5–13.

TABLE 2. Annual cancer age-standardized incidence rates (ASIRs) per 10^6 person-years for Hispanic and non-Hispanic white children < 15 years of age, 1988–1998, by gender for both states (California and Florida) combined

ICCC[a] major diagnostic groups and selected subgroups	Male				Female			
	Hispanic		Non-Hispanic white		Hispanic		Non-Hispanic white	
	ASIR	SE[b]	ASIR	SE	ASIR	SE	ASIR	SE
All cancers combined	163.0	3.1	159.8	2.5	142.0	2.9	138.6	2.3
Leukemia	68.0	2.0	51.6	1.4	54.8	1.8	45.8	1.4
Lymphoid leukemia	56.8	1.8	42.5	1.3	44.6	1.6	36.3	1.2
Acute nonlymphocytic leukemia	8.7	0.7	6.9	0.5	7.7	0.7	7.3	0.5
Lymphoma & reticuloendothelial	19.4	1.1	18.2	0.8	9.3	0.7	9.6	0.6
Hodgkin's lymphoma	8.1	0.7	5.3	0.4	4.2	0.5	4.3	0.4
Non-Hodgkin's lymphoma	6.8	0.6	7.8	0.5	3.2	0.4	3.8	0.4
Burkitt's lymphoma	3.3	0.4	4.1	0.4	1.0	0.2	0.9	0.2
CNS[c], misc., intracranial, intraspinal	24.7	1.2	35.1	1.1	22.4	1.2	29.8	1.1
Ependymoma	2.5	0.4	2.8	0.3	1.6	0.3	2.6	0.3
Astrocytoma	9.4	0.7	18.1	0.8	10.5	0.8	16.2	0.8
PNET[d]	8.6	0.7	9.6	0.6	5.9	0.6	6.5	0.5
Sympathetic nervous system	9.5	0.7	12.7	0.7	7.8	0.7	10.2	0.7
Retinoblastoma	5.8	0.6	4.7	0.4	5.3	0.6	4.0	0.4
Renal tumors	6.8	0.6	8.1	0.6	9.1	0.7	9.9	0.6
Hepatic tumors	2.2	0.4	2.5	0.3	2.0	0.4	1.7	0.3
Malignant bone tumors	5.4	0.6	6.2	0.5	6.9	0.6	6.3	0.5
Osteosarcoma	2.9	0.4	3.1	0.3	4.7	0.5	3.0	0.3
Ewing's sarcoma	1.9	0.3	2.9	0.3	1.6	0.3	2.8	0.3
Soft tissue sarcomas	10.3	0.8	10.0	0.6	9.3	0.7	8.1	0.6
Rhabdomyosarcoma	4.1	0.5	5.8	0.5	4.4	0.5	3.7	0.4
Germ-cell, trophoblastic, other	7.2	0.6	4.4	0.4	8.1	0.7	5.1	0.4
Carcinomas, other epithelial	2.1	0.3	4.8	0.4	4.9	0.5	6.6	0.5
Other and unspecified malignancy	0.5	0.2	0.7	0.2	0.5	0.2	0.7	0.2

[a] ICCC = International Classification of Childhood Cancer.
[b] SE = standard error.
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Cancer incidence among Hispanic children in the United States

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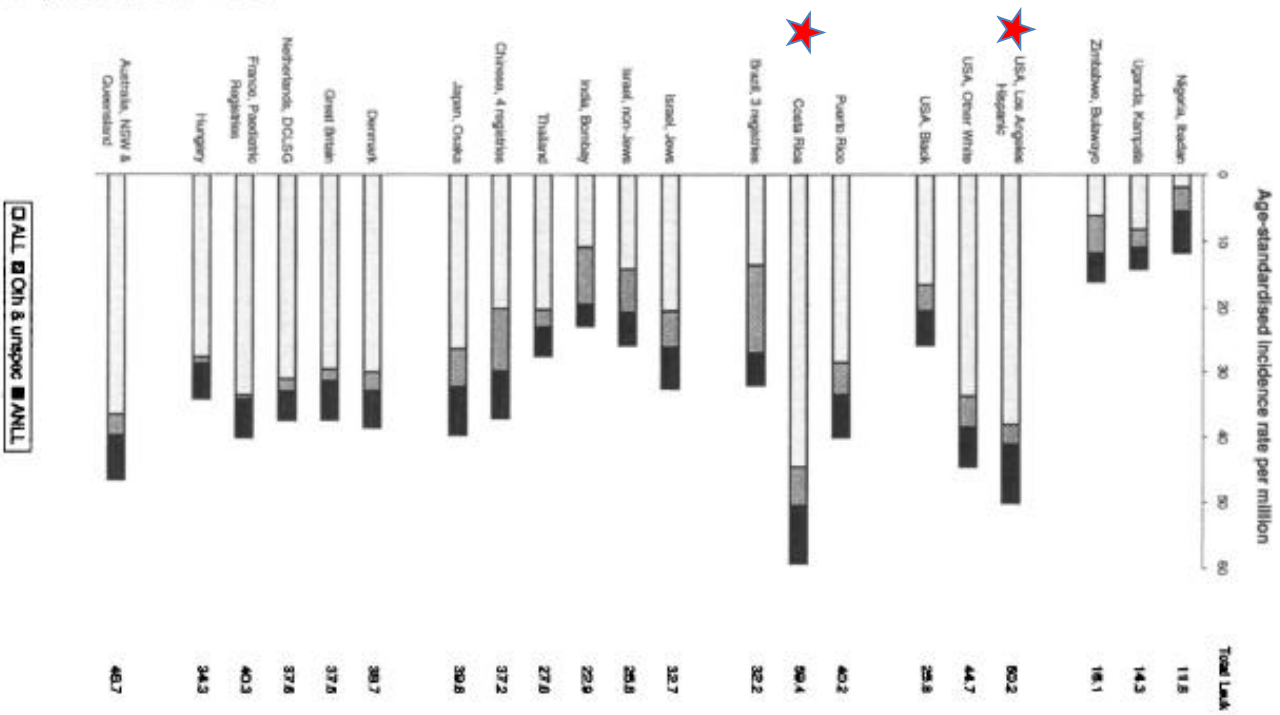


Fig. 1 Age standardised incidence rates (world standard) per million for acute lymphoblastic leukaemia, acute non-lymphocytic leukaemia and other and unspecified leukaemia in children aged 0–14 years. Source[3] except Thailand[52] and Japan, Osaka[6].

Geographic and ethnic variations in the incidence of childhood cancer

C A Stiller* and **D M Parkin†**

**Childhood Cancer Research Group, University of Oxford, Oxford, UK;*
†Unit of Descriptive Epidemiology, International Agency for Research on Cancer, Lyon, France

Table 3. Comparison of annual age-adjusted rates of lymphoid leukemias per million for Mexican and Salvadoran children with those for Hispanic children from three U.S. Cancer Registries and for children from Costa Rica (Mejia-Arangure, 2005)

Leukemia type	*SEER 2001 All races* (30)	*Mexico City, IMSS*	*Texas* (34)	*California* (3)	*SEER 1992–1998 Hispanics* (29)	*El Salvador*	*Florida* (4)	*Costa Rica* (5)
Lymphoid leukemia	33.2	44.9	46.8	44.0	43.0	34.2*	49.7	43.1

(3) (Glazer, 1999)
(4) (Wilkinson, 2001)
(5) (Monge, 2002)
(34) (American Cancer Society, 2008: Texas Cancer Facts & Figures 2008. Austin, TX)

BMC Cancer

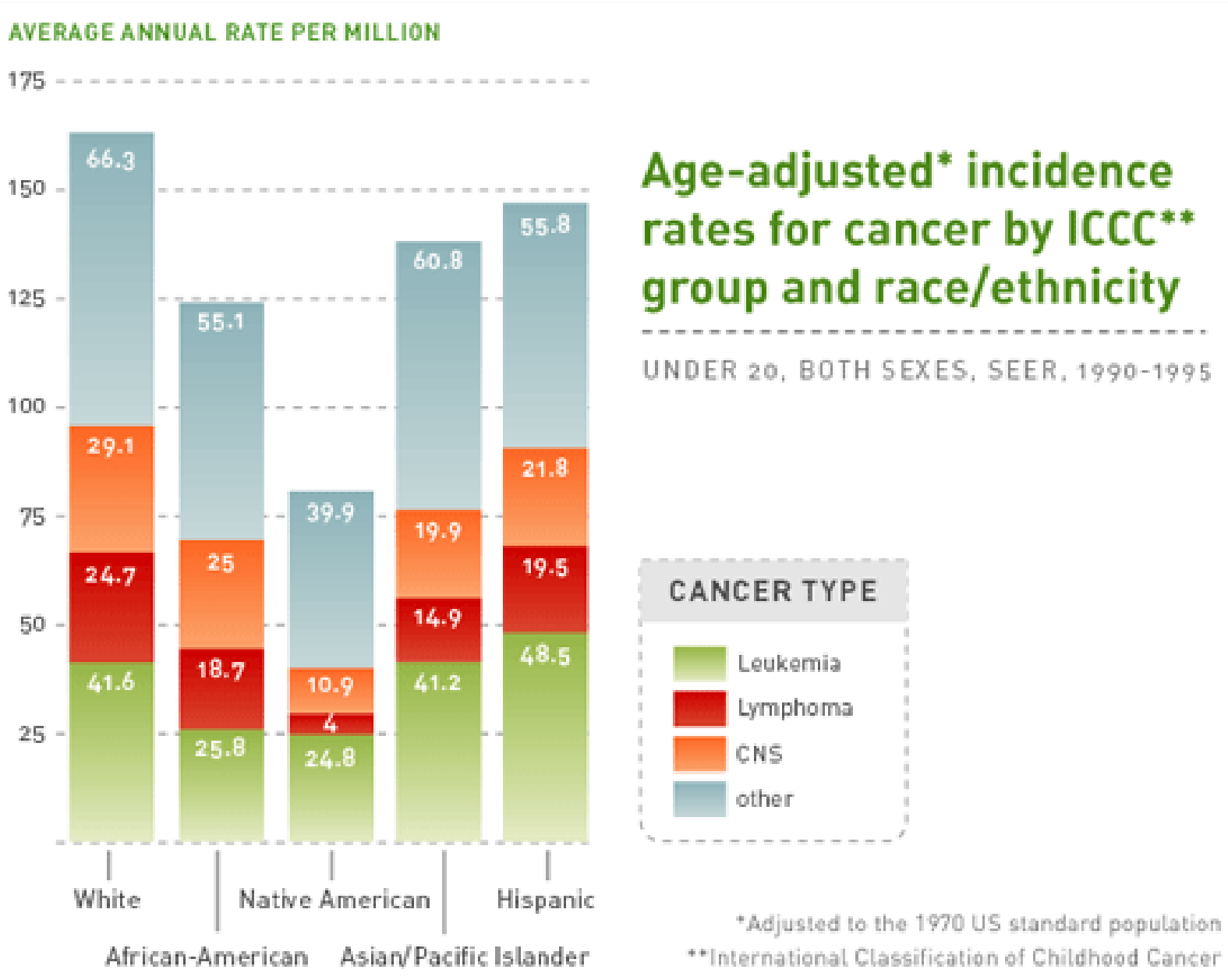
BioMed Central

Research article

Open Access

Incidence of leukemias in children from El Salvador and Mexico City between 1996 and 2000: Population-based data

Juan Manuel Mejía-Aranguré*[1], Miguel Bonilla[2,3], Rodolpho Lorenzana[4], Servando Juárez-Ocaña[1], Gladys de Reyes[2], María Luisa Pérez-Saldivar[1], Guadalupe González-Miranda[1], Roberto Bernáldez-Ríos[5], Antonio Ortiz-Fernández[6], Manuel Ortega-Alvarez[1], María del Carmen Martínez-García[1] and Arturo Fajardo-Gutiérrez[1]


AVERAGE ANNUAL RATE PER MILLION
175
150
125
100
75
50
25
66.3
29.1
24.7
41.6
55.1
25
18.7
25.8
39.9
10.9
4
24.8
60.8
19.9
14.9
41.2
55.8
21.8
19.5
48.5
White
African-American
Native American
Asian/Pacific Islander
Hispanic
Age-adjusted* incidence rates for cancer by ICCC** group and race/ethnicity
UNDER 20, BOTH SEXES, SEER, 1990-1995
CANCER TYPE
Leukemia
Lymphoma
CNS
other
*Adjusted to the 1970 US standard population
**International Classification of Childhood Cancer

Texas Cancer Facts & Figures, 2008 Report

A sourcebook for planning and implementing programs for cancer prevention and control

- View Report (.pdf, 4.43 MB)

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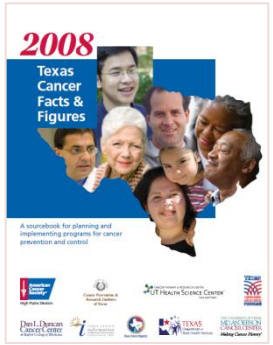
More ALL but less non-ALL Cancer in Hispanic Children in Texas

Table 28. Three Leading Childhood Cancer Sites by Race and Ethnicity, Texas, 2001-2005

	Lymphoid Leukemia		Astrocytoma		Neuroblastoma and Ganglioneuroblastoma		Total Childhood Cancers	
	Cases	Rate*	Cases	Rate*	Cases	Rate*	Cases	Rate*
Non-Hispanic White	375	36.0	203	19.5	146	13.9	1,707	163.2
Hispanic	545	46.8	130	11.6	100	7.7	1,864	161.0
Black	64	18.8	40	11.8	33	9.6	394	115.1
Asian/Pacific Islander	22	26.4	7	8.2	4	4.5	85	103.3
All Races	1,028	39.3	390	15.2	289	10.5	4,150	158.7

Note: Number of cases is a five-year total.
Childhood cancer sites are among children 0-14 years old.
Hispanic ethnicity is derived from the NAACCR Hispanic Identification Algorithm (NHIA) and may be of any race, thus categories are not mutually exclusive.
Children of other and unknown race are included in the All Races total.
*Rates are per 1,000,000 and age-adjusted to the 2000 U.S. standard population.

Source: Texas Department of State Health Services, Cancer Epidemiology and Surveillance Branch, Texas Cancer Registry, 1995-2005 Incidence, Based on 2008 NPCR-CSS Submission, 1-31-2008.



Genome-wide patterns of population structure and admixture among Hispanic/Latino populations

Katarzyna Bryc[a,1], Christopher Velez[b,1], Tatiana Karafet[c], Andres Moreno-Estrada[a,d], Andy Reynolds[a], Adam Auton[a,2], Michael Hammer[c], Carlos D. Bustamante[a,d,3,4], and Harry Ostrer[b,3,4]

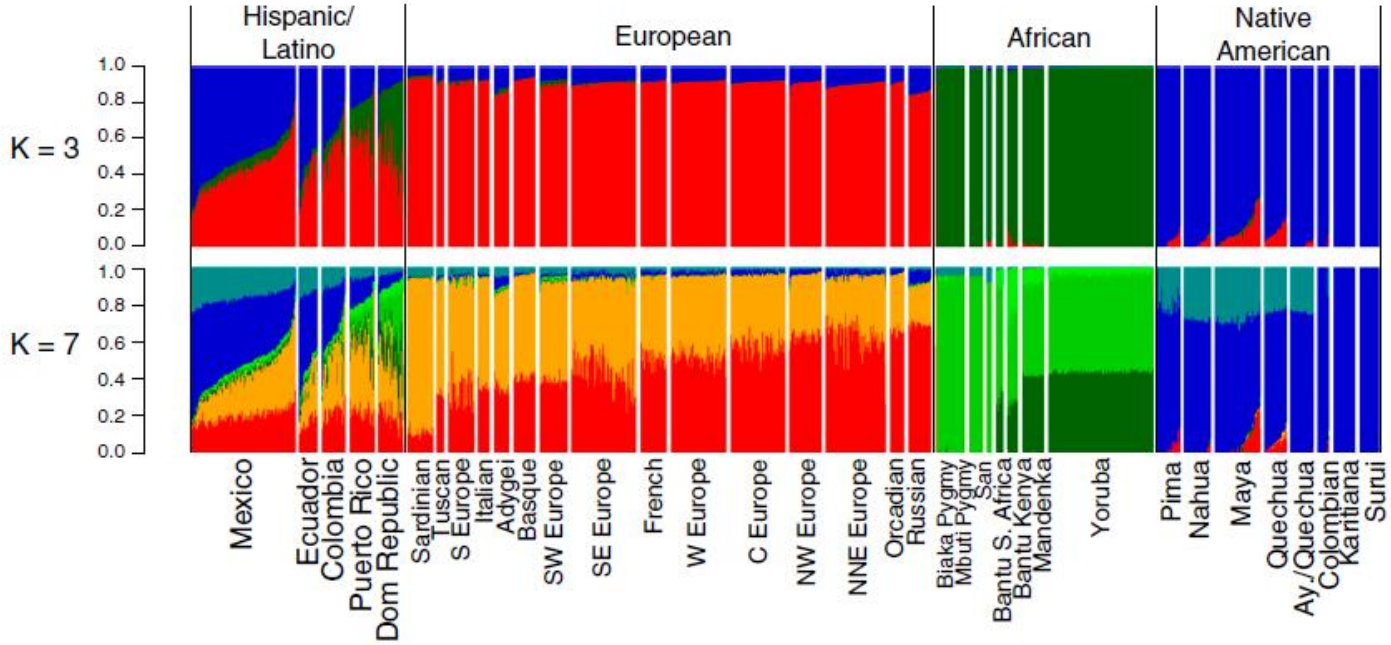
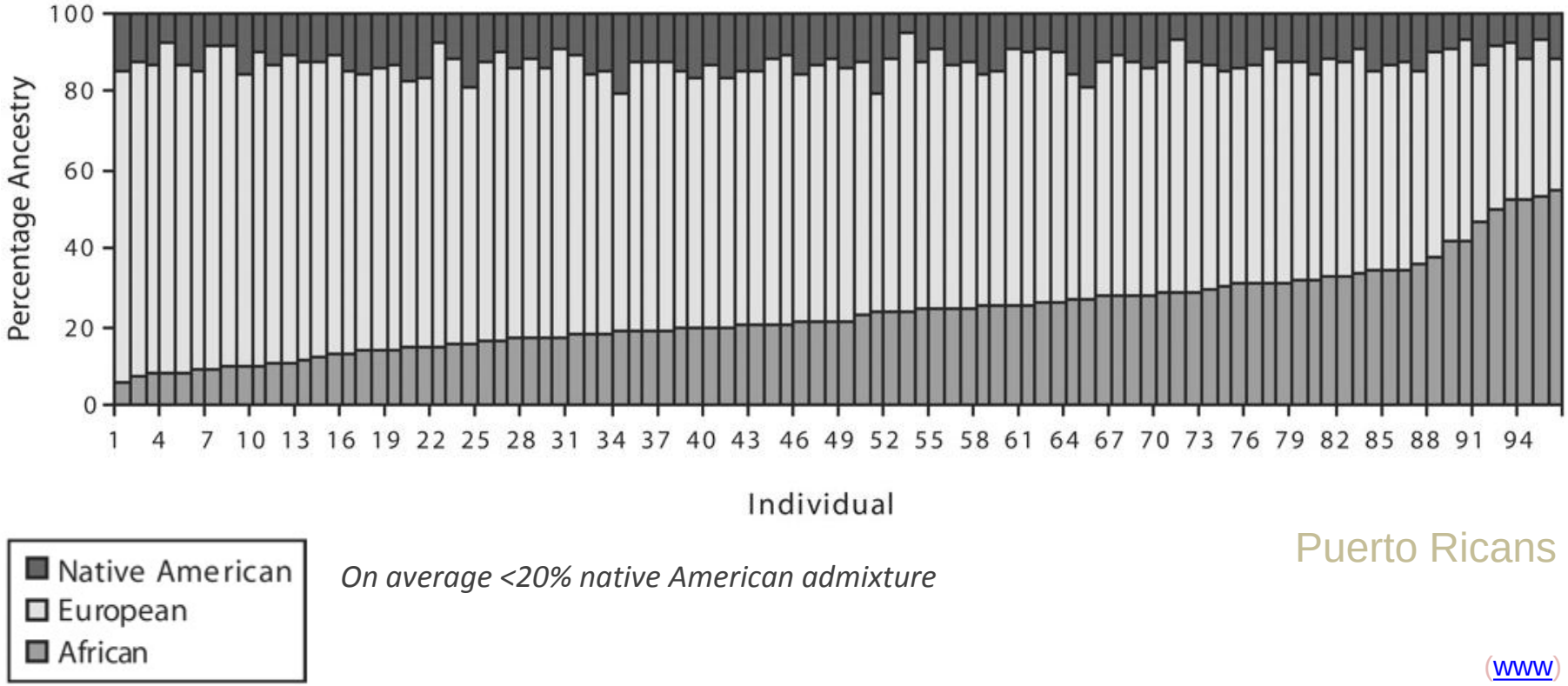


Fig. 1. *Frappe* clustering illustrating the admixed ancestry of Hispanic/Latinos shown for $K = 3$ and $K = 7$. Individuals are shown as vertical bars colored in proportion to their estimated ancestry within each cluster. Native American populations are listed in order geographically, from North to South.

Latino Populations: A Unique Opportunity for the Study of Race, Genetics, and Social Environment in Epidemiological Research

Esteban González Burchard, MD, Luisa N. Borrell, DDS, PhD, Shweta Choudhry, PhD, Mariam Naqvi, BS, Hui-Ju Tsai, PhD, Jose R. Rodriguez-Santana, MD, Rocio Chapela, MD, Scott D. Rogers, MPH, Rui Mei, PhD, William Rodriguez-Cintron, MD, Jose F. Arena, MD, PhD, Rick Kittles, PhD, Eliseo J. Perez-Stable, MD, Elad Ziv, MD, and Neil Risch, PhD



On average <20% native American admixture

Puerto Ricans

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PLoS one

Genetic Admixture and Population Substructure in Guanacaste Costa Rica

Zhaoming Wang[1,2], Allan Hildesheim[1], Sophia S. Wang[1,3], Rolando Herrero[4], Paula Gonzalez[4], Laurie Burdette[1,2], Amy Hutchinson[1,2], Gilles Thomas[5], Stephen J. Chanock[1], Kai Yu[1]*

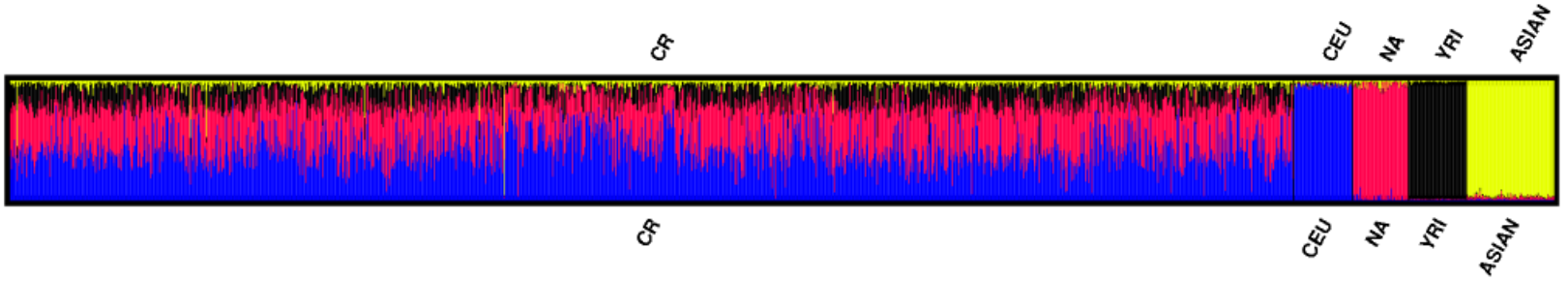

Figure 2. Spectrum plot of admixture coefficients. The admixture coefficient for each sample was the average of 10 independent unsupervised STRUCTURE runs, all with K = 4, which turned out to be the optimal K for the total sample set including CR samples and four continental reference populations (see Figure S1).
doi:10.1371/journal.pone.0013336.g002

The population of Costa Rica (CR) represents an admixture of major continental populations. An investigation of the CR population structure would provide an important foundation for mapping genetic variants underlying common diseases and traits. We conducted an analysis of 1,301 women from the Guanacaste region of CR using 27,904 single nucleotide polymorphisms (SNPs) genotyped on a custom Illumina InfiniumII iSelect chip. The program STRUCTURE was used to compare the CR Guanacaste sample with four continental reference samples, including HapMap Europeans (CEU), East Asians (JPT+CHB), West African Yoruba (YRI), as well as Native Americans (NA) from the Illumina iControl database. Our results show that the CR Guanacaste sample comprises a three-way admixture estimated to be 43% European, 38% Native American and 15% West African. An estimated 4% residual Asian ancestry may be within the error range. Results from principal components analysis reveal a correlation between genetic and geographic distance. The magnitude of linkage disequilibrium (LD) measured by the number of tagging SNPs required to cover the same region in the genome in the CR Guanacaste sample appeared to be weaker than that observed in CEU, JPT+CHB and NA reference samples but stronger than that of the HapMap YRI sample. Based on the clustering pattern observed in both STRUCTURE and principal components analysis, two subpopulations were identified that differ by approximately 20% in LD block size averaged over all LD blocks identified by Haploview. We also show in a simulated association study conducted within the two subpopulations, that the failure to account for population stratification (PS) could lead to a noticeable inflation in the false positive rate. However, we further demonstrate that existing PS adjustment approaches can reduce the inflation to an acceptable level for gene discovery.

nature genetics

Ancestry and pharmacogenomics of relapse in acute lymphoblastic leukemia

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Table 2 Average genetic ancestry by self-reported designations

	Genetic ancestry[a]			
	% European	% African	% Asian	% Native American
Self-reported white (n = 1,687)	96.7	0.9	1.0	1.4
Self-reported black (n = 250)	19.3	79.0	0.8	0.9
Self-reported Hispanic (n = 405)	51.6	6.1	1.5	40.8
Self-reported Asian (n = 76)	32.3	1.0	63.8	2.9
Other (n = 116)	55.8	9.4	19.3	15.5

[a]Genetic ancestry was estimated using STRUCTURE, as described in the **Supplementary Note**.

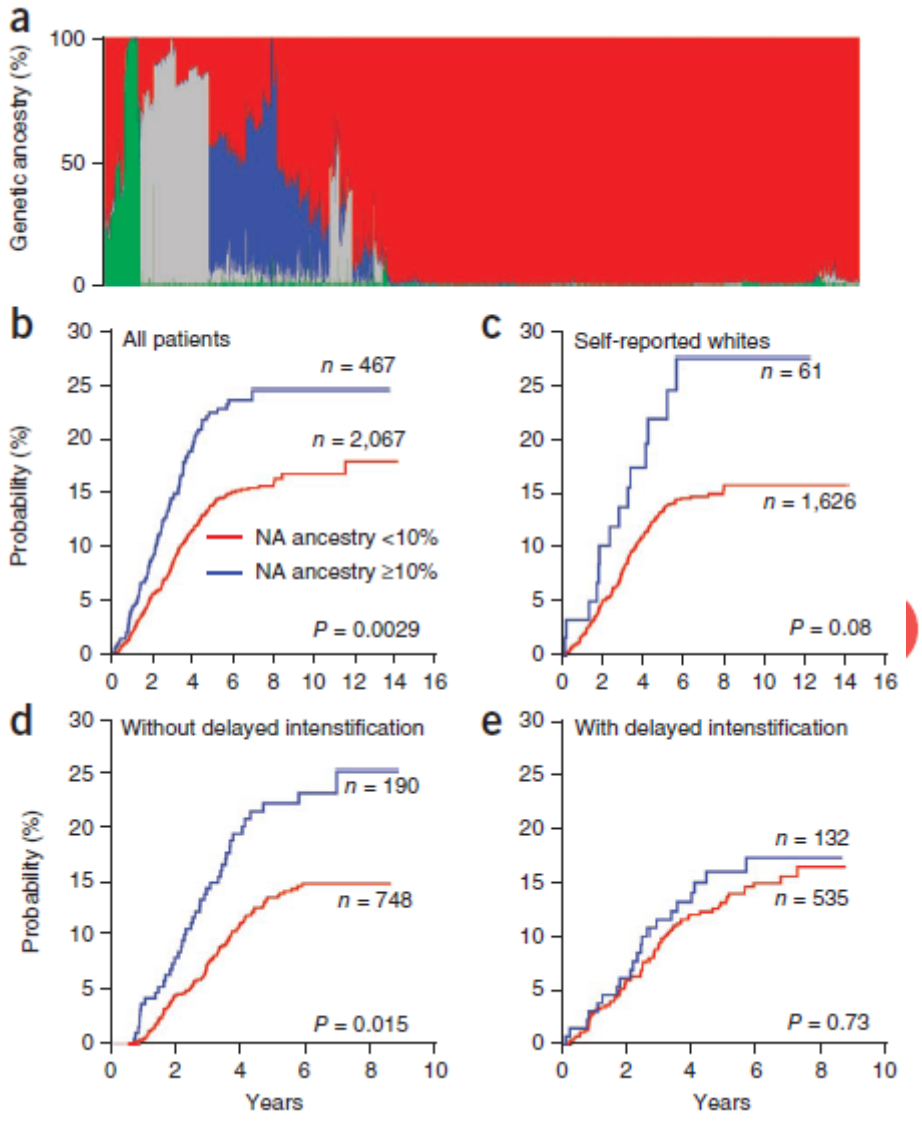

Figure 2 Genetic ancestry and risk of relapse in childhood ALL. (**a**) Genetic ancestral composition of 2,534 children with ALL. Each patient's ancestry is shown as a column and the color represents the proportion of ancestry estimated for that patient (European, red; African, gray; Asian, green; Native American, blue). Genetic ancestry was estimated using STRUCTURE. Patients were clustered using the Ward clustering method based on dissimilarity in genetic ancestry measured by 1-minus pair-wise correlation (**Supplementary Note**). (**b**–**e**) Higher levels of Native American (NA) ancestry were linked to increased risk of relapse in all patients (**b**) and within the self-reported whites (**c**) and for those who did not receive delayed intensification (**d**) but not within those who did receive delayed intensification in the COG P9904/9905 trial (**e**). Although cumulative incidence of relapse is plotted separately for patients with <10% (red) versus ≥10% (blue) Native American ancestry, we estimated all *P* values using a Fine and Gray's cumulative incidence hazard regression model treating Native American ancestry as a continuous variable (see the **Supplementary Note** for details on the Native American ancestry dichotomization).

Table 3 Multivariate analysis for risk of ALL relapse

Patient characteristics	*P*[a]	Hazard ratio[b] (95% CI)
MRD positive	1×10^{-12}	3.73 (2.98–4.68)
Leukocyte count at diagnosis (≥50,000 per μl)	6.00×10^{-6}	1.93 (1.45–2.57)
DNA index (≥1.16)	2.58×10^{-4}	0.59 (0.45–0.79)
Native American ancestry	0.017	1.84 (1.12–3.04)
Age at diagnosis (≥10 years)	0.010	1.39 (1.08–1.78)
ETV6-RUNX1[c]	0.012	0.67 (0.49–0.91)
T-cell lineage[c]	0.146	0.67 (0.40–1.15)
BCR-ABL[c]	0.454	1.48 (0.53–4.12)
TCF3-PBX1[c]	0.793	0.93 (0.53–1.63)
MLL rearrangements[c]	0.935	0.96 (0.41–2.25)

All prognostic features are dichotomized for presence versus absence of the patient characteristic except for Native American ancestry, which is treated as a continuous variable. **Supplementary Table 2** includes identical multivariate analyses with dichotomized variables used for all variables, including ancestry.

MRD: minimal residual disease; CI: confidence interval.

[a]Associations with risk of relapse (any relapse) were assessed using the Fine and Gray's regression model. [b]Hazard ratio, the relative difference (increase or decrease) in risk of ALL relapse when the patient is positive for the clinical feature of interest (for example, a 1.84-fold increase in relapse risk for every 100% increase in Native American ancestry). [c]Terms refer to cancer characteristics of the ALL cells that may have prognostic significance and are used to subdivide cases.

Genetic Markers for Ethnicity-specific Susceptibility to Childhood Leukemia

Hypothesis

Ethnic disparity is due to genetic differences which influence susceptibility either directly or via effect modification of unknown environmental exposures

Material

Texas Children's Cancer Center Case-Control Study
SOUTH FLORIDA CHILDHOOD LEUKEMIA STUDY
California Childhood Leukemia Study

ACKNOWLEDGMENTS

Anyone who has ever taught me anything

My current team:
Amy and Sandeep (& Malar)

Florida International University
RSCPHSW
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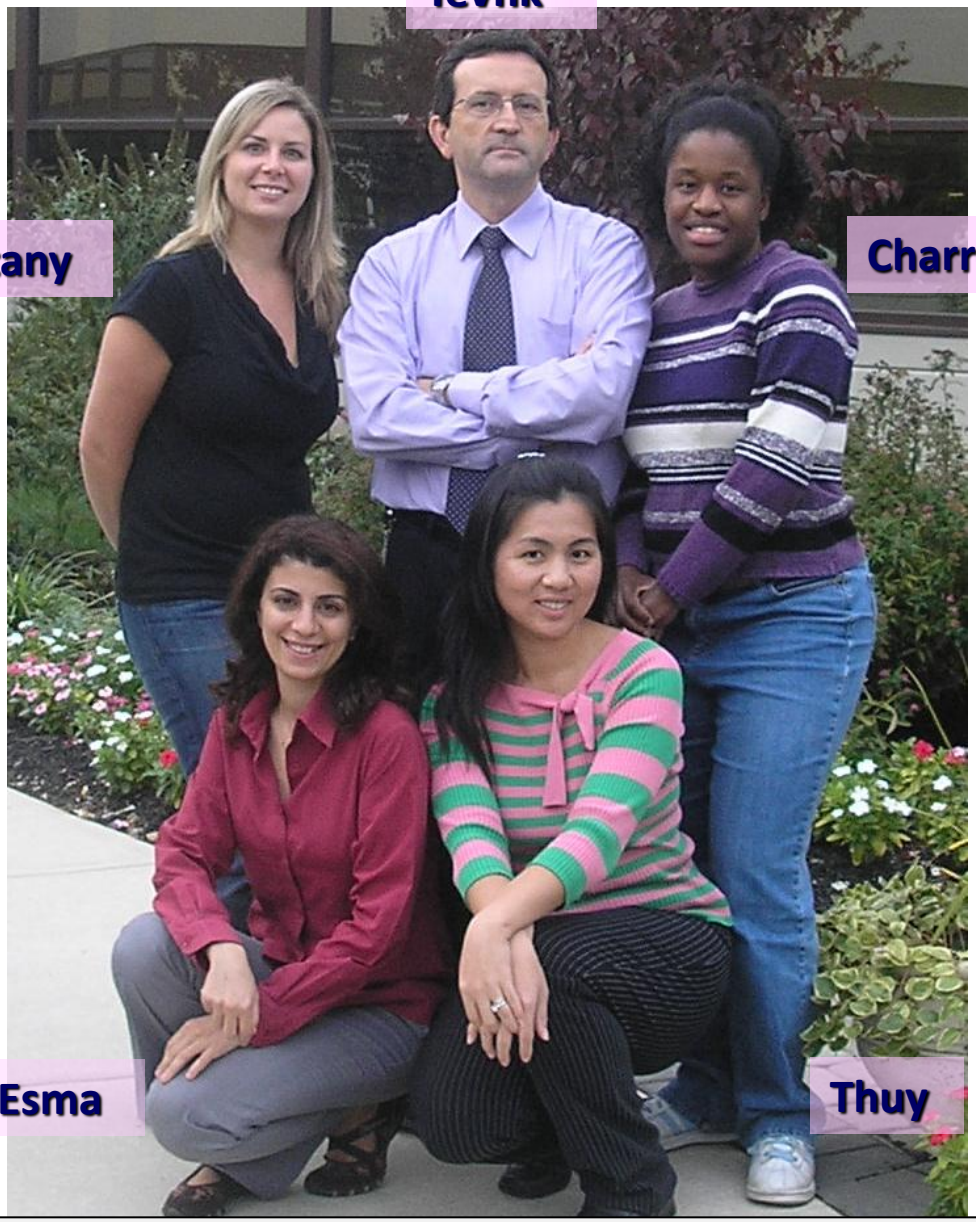
FIU | FLORIDA INTERNATIONAL UNIVERSITY

Tevfik

Brittany

Charronne



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