

Short Communication

Cytogenetics of Hispanic and White Children with Acute Lymphoblastic Leukemia in California

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Abstract

Epidemiologic studies of childhood leukemia have made limited use of tumor genetic characteristics, which may be related to disease etiology. We characterized the cytogenetics of 543 childhood leukemia patients (0-14 years of age) enrolled in the Northern California Childhood Leukemia Study, an approximately population-based study comprised primarily of Hispanics (42%) and non-Hispanic Whites (41%), and compared the cytogenetic profiles between these two ethnic groups. Subjects were classified by immunophenotype, conventional cytogenetic characteristics, and fluorescence *in situ* hybridization findings. The ploidy levels most frequently observed among acute lymphoblastic leukemia patients were high hyperdiploidy (51-67 chromosomes) and pseudodiploidy

(34% and 27%, respectively). No ethnic differences in the frequency of 11q23/*MLL* rearrangements were observed between Hispanics and non-Hispanic Whites. Among B-lineage acute lymphoblastic leukemia patients, the percentage of *TEL-AML1* translocations was significantly lower in Hispanics (13%) than in non-Hispanic Whites (24%; $P = 0.01$). This is the first time that this ethnic variation has been observed in a large number of patients in a defined geographic region, which is consistent with findings from smaller international studies. The mechanistic basis for this 2-fold variation in frequency of *TEL-AML1* may be due to ethnic-specific risk factors or genetics and should be explored further. (Cancer Epidemiol Biomarkers Prev 2006;15(3):578-81)

Introduction

Leukemia is the most common malignancy diagnosed among children in the United States. Chromosomal and molecular markers have identified children with favorable and unfavorable prognoses, which may be indicative of subtypes with distinct leukemogenic mechanisms (1). Cytogenetic subtypes, however, are not commonly used for disease classification in epidemiologic studies and inadequate classification may have contributed to the limited understanding of the etiology of childhood leukemia.

International studies suggest the frequency of genetic abnormalities in childhood leukemia vary by ethnicity and geographic region (e.g., *TEL/AML1*; Table 1). Published studies from the United States often include primarily Caucasian and African American populations and have limited details describing cytogenetic abnormalities among Hispanics. Yet, interestingly, Hispanics are reported to have a higher incidence of acute lymphoblastic leukemia (ALL) than non-Hispanics (43 per 10⁶ versus 28 per 10⁶; ref. 2). Because data are sparse describing cytogenetic patterns among Hispanic populations, it is unclear whether Hispanics present more frequently than Whites with aberrations typically associated with poor and favorable prognoses. Given that the Hispanic population is expected to increase in size more than any other group over

future decades, a comprehensive description of differences in disease characteristics of Hispanics is increasingly important in the interpretation of disease incidence and outcome. We describe the cytogenetic characteristics of 543 cases enrolled sequentially in the Northern California Childhood Leukemia Study (NCCLS), with a focus on common abnormalities and two ethnic groups (Hispanics and non-Hispanic Whites).

Patients and Methods

Study Population. Newly diagnosed childhood leukemia patients presenting at collaborating pediatric hospitals located in the San Francisco Bay Area and the Central Valley of California were prospectively identified from nine participating hospitals during the period December 1995 to December 2002 using rapid case ascertainment procedures developed by the NCCLS. Incident patients were eligible for participation if they (a) were 0 to 14 years of age, (b) were diagnosed with childhood leukemia according to International Classification of Diseases for Oncology criteria, (c) had no prior diagnosis of malignancy, (d) had an English or Spanish speaking parent/guardian, and (e) resided within the 35-county study region at the time of hospital admission. A comparison with the population-based statewide California Cancer Registry (2000) showed that the NCCLS identified 95% of incident childhood leukemia cases in the San Francisco-Oakland metropolitan statistical region and 76% of cases in the remaining 30 counties. As of December 2002, parents or guardians of 543 study-eligible pediatric leukemia patients provided written informed consent, representing an overall participation rate of 86%.

Clinical Data and Fluorescence *In situ* Hybridization. Pretreatment karyotype [conventional banding and occasional fluorescence *in situ* hybridization (FISH)] and pertinent clinical data were abstracted from patient records shortly after

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Note: J. Wiemels is a scholar of the Leukemia and Lymphoma Society of America.

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Table 1. Frequency of *TEL-AML1* among B-lineage ALL by geographic location

Author	Year	Country	n	B-lineage ALL (%)
Rubnitz et al. (21)	1997	U.S.	188	26
Eguchi-Ishimae et al. (22)	1998	Japan	74	10
Inamdar et al. (23)	1998	India	46	9
Avigad et al. (24)	1999	Israel	98	24
Garcia-Sanz et al. (18)	1999	Spain	41	3
Spathas et al. (25)	1999	United Kingdom	31	13
Jamil et al. (26)	2000	U.S.	86	17
Magalhaes et al. (27)	2000	Brazil	67	20
Tsang et al. (28)	2001	China	67	18
Liang et al. (29)	2002	Taiwan	165	18
Ozbek et al. (30)	2003	Turkey	219	28
Sazawal et al. (31)	2004	India	35	0
Hill et al. (32)	2005	India	42	7

diagnosis. All abstracted data were reviewed for accuracy by a consulting clinical oncologist. Using probes for chromosome 12p13 (*TEL*), chromosome 21q22 (*AML1*), and the centromere of chromosome X (Vysis, Downers Grove, IL), we used a FISH assay in our molecular laboratory at the University of California Berkeley to allow simultaneous detection of *TEL-AML1* and high hyperdiploidy among B-lineage ALL cases (>1 year of age; ref. 3). Additional probes for chromosomes 6, 10, and 18 were applied to cases ambiguous for hyperdiploidy. Cases with available bone marrow aspirate smears were selected for University of California Berkeley FISH analysis if the diagnostic cytogenetic report did not show either hyperdiploidy or a common translocation. An *a priori* algorithm describing selection criteria for FISH analysis was applied systematically to ensure completeness of reporting.

Race/Ethnicity Information. Race information was obtained from a questionnaire administered during an interview with the primary caregiver, usually the biological mother. Hispanic status was assessed from the child's birth certificate (a child was considered Hispanic if either parent was identified as Hispanic). Race/ethnicity information was missing for 19 cases.

Immunophenotype. Immunophenotype was determined for ALL cases using flow cytometry profiles. Those positive for CD19 or CD10 ($\geq 20\%$) were classified as B-lineage and those expressing CD2, CD3, CD4, CD5, CD7, or CD8 ($\geq 20\%$) were classified as T-lineage (4). B-lineage patients were classified as standard or high-risk according to the National Cancer Institute/Rome criteria for therapy protocol assignment (5).

Classification of Cytogenetic Abnormalities. Diagnostic karyotype for each patient was classified according to clonal genetic aberrations using the International System for Human Cytogenetic Nomenclature 1995 criteria (6). Cases having chromosome gains or structural abnormalities required two or more metaphases for designation of clonality, whereas loss of chromosomes necessitated a minimum of three metaphases. Patients having translocations, inversions, deletions, or insertions involving the 11q23/*MLL* chromosome region were classified as having 11q23/*MLL* rearrangements. Patients with diploid karyotypes required a minimum of 20 banded metaphases. Cases with inadequate cytogenetic samples were removed from analyses ($n = 66$), resulting in a total of 477 leukemia cases for detailed cytogenetic characterization.

Classification of ploidy level was made according to the simplest clone. Conventional cytogenetics was used to assign ploidy status, unless the patient had available FISH data and a normal karyotype (or no available sample), whereby FISH was used to assign ploidy. Among the ALL cases with adequate karyotypes ($n = 389$), G-banding assigned ploidy to 63% ($n = 245$) of cases and FISH (done by either a collaborating

hospital or University of California Berkeley) assigned ploidy for the remaining 37% ($n = 144$) of cases. All classifications were reviewed by two individuals (M. Aldrich and X. Ma) separately and inconsistencies were resolved after discussion, blinded to ethnicity.

Classification of Cytogenetic Abnormalities by FISH. When FISH assays conducted at University of California Berkeley identified extra copies of chromosomes 21 and X, assignment of high hyperdiploid status (modal number, 51-67 chromosomes) was made because high hyperdiploid patients often have predominantly concomitant copies of chromosomes 21 and X (7, 8). Patients exhibiting additional copies of chromosomes 6, 10, and 18 detected by our FISH assay were also classified as high hyperdiploid. Clinical FISH results demonstrating trisomy for chromosomes 4 and 10 permitted high hyperdiploid classification, because gains of these chromosomes are frequently found among patients with high hyperdiploidy (9-11). Identification of one to four extra copies of chromosome 21 or an extra X chromosome allowed assignment of low hyperdiploid (modal number, 47-50). Cases exhibiting loss of an X chromosome in >25% of cells were classified as hypodiploid 45. Deletions of chromosome 12p were classified as having the structural change del(12p). *TEL-AML1* translocations were identified by the fusion of the *TEL* and *AML1* loci.

Statistical Analysis. The relationship between ethnicity and frequency of cytogenetic abnormalities was described by a series of 2×2 contingency tables and analyzed using the Pearson approximate χ^2 statistic or Fisher's exact test for expected cell counts of five or less. These tables, however, produce a number of nonindependent χ^2 statistics, which contain small numbers of observations and should be interpreted with caution.

Results

Of the 543 patients (92% born in California), 83% ($n = 451$) were diagnosed with ALL and 16% ($n = 87$) with acute myelogenous leukemia (AML). Hispanics and non-Hispanic Whites comprised 42% ($n = 220$) and 41% ($n = 214$) of the study population, respectively. Figure 1 presents patients classified according subtype and immunophenotype. Comparisons of frequencies between Hispanics and non-Hispanic Whites of subtypes *MLL*, ALL (B and T lineages), and acute myelogenous leukemia did not differ significantly (data not shown). Cases meeting National Cancer Institute/Rome standard-risk criteria comprised 73% of children with B-lineage ALL and the

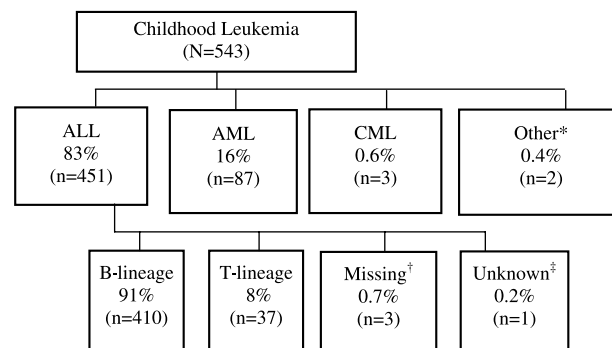


Figure 1. Classification of childhood leukemia patients. Patients were classified according to subtype followed by immunophenotype. There were no patients with chronic lymphocytic leukemia. *CML*, chronic myelogenous leukemia. * other subtypes include one juvenile myelomonocytic leukemia and one acute biphenotypic leukemia. † missing immunophenotype data. ‡ unknown immunophenotype.

Table 2. Cytogenetic characteristics of patients by Hispanic status

Cytogenetic characteristic	B-lineage ALL				Total N = 356 n (%)
	ALL N = 389 n (%)	Hispanic N = 151 n (%)	Non-Hispanic White N = 140 n (%)	P	
Structural changes					
t(12;21)	74 (19.0)	19 (12.6)	34 (24.3)	0.01	72 (20.2)
t(9;22)	7 (1.8)	2 (1.3)	1 (0.7)	1.0	7 (2.0)
E2A translocation	15 (3.9)	7 (4.6)	6 (4.3)	0.89	15 (4.2)
11q23/MLL rearrangements	14 (3.6)	3 (2.0)	4 (2.9)	0.71	14 (3.9)
del(12p)	13 (3.3)	3 (2.0)	3 (2.1)	1.0	11 (3.1)
del(11q)	3 (0.8)	0 (0)	2 (1.4)	0.14	2 (0.6)
del(9p)	13 (3.3)	4 (2.7)	4 (2.9)	1.0	10 (2.8)
del(7p)	1 (0.3)	0 (0)	0 (0)	—	1 (0.3)
del(7q)	1 (0.3)	1 (0.7)	0 (0)	1.0	1 (0.3)
del(6q)	18 (4.6)	6 (4.0)	6 (4.3)	0.89	14 (3.9)
del(5q)	2 (0.5)	0 (0)	1 (0.7)	0.48	1 (0.3)
Any deletion	47 (12.1)	16 (10.6)	16 (11.4)	0.82	39 (11.0)
Total structural changes	209 (53.7)	69 (45.7)	79 (56.4)	0.07	194 (54.5)
Numerical changes					
Constitutional trisomy 21	14 (3.6)	8 (5.3)	5 (3.6)	0.48	14 (3.9)
Trisomy 8	31 (8.0)	16 (10.6)	11 (7.9)	0.42	30 (8.4)
-Y	5 (1.3)	2 (1.3)	2 (1.4)	1.0	5 (1.4)
Monosomy 7	9 (2.3)	1 (0.7)	5 (3.6)	0.11	7 (2.0)
Total numerical changes	250 (64.3)	106 (70.2)	95 (67.9)	0.67	241 (67.7)
Ploidy level*					
Diploid	61 (15.7)	23 (15.2)	17 (12.1)	0.44	45 (12.6)
Hyperdiploid (47-67)	196 (50.4)	83 (55.0)	73 (52.1)	0.63	190 (53.4)
High hyperdiploid (51-67)	133 (34.2)	62 (41.1)	47 (33.6)	0.19	133 (37.3)
Low hyperdiploid (47-50)	63 (16.2)	21 (13.9)	26 (18.6)	0.28	57 (16.0)
Hypodiploid 45	22 (5.7)	8 (5.3)	10 (7.1)	0.51	21 (5.9)
Hypodiploid <45	4 (1.0)	1 (0.7)	2 (1.4)	0.61	3 (0.8)
Pseudodiploid	103 (26.5)	34 (22.5)	37 (26.4)	0.44	94 (26.4)
Near triploid (68-80)	3 (0.8)	2 (1.3)	1 (0.7)	1.0	3 (0.8)

NOTE: Percentages do not add to 100% because patients may have more than one abnormality. Cases with inadequate karyotypes are not displayed: total, $n = 62$; too few, $n = 2$; no bone marrow sample, $n = 15$; diploid with fewer than 20 metaphases counted, $n = 40$; only FISH analysis was done and no aberration was identified, $n = 5$. For B-lineage ALL cases, a total of 65 cases having other ethnicities ($n = 54$) or unknown ethnicity ($n = 11$) are not displayed. P values are from Pearson's χ^2 statistic or Fisher's exact test (two-tailed probabilities) when expected cell frequencies were five or less.

*Pearson's χ^2 analysis comparing Hispanics and non-Hispanics: $\chi^2 = 4.10$, degrees of freedom = 6, $P = 0.66$.

remaining 27% met National Cancer Institute/Rome high-risk criteria. The distribution of National Cancer Institute/Rome risk criteria by ethnicity revealed no remarkable differences between Hispanics and Whites.

B-lineage ALL cases ($n = 187$) with an available bone marrow sample were selected for FISH analysis by our laboratory at University of California Berkeley. Among ALL patients with acceptable karyotypes, FISH assays conducted at the University of California Berkeley laboratory enhanced the detection of subjects harboring *TEL-AML1* and high hyperdiploid abnormalities [$n = 46$ (62%) and $n = 51$ (38%), respectively]. Of the 63 low hyperdiploid (modal number 47-50) patients, 24 (38%) were identified by University of California Berkeley FISH analyses, whereas 25% ($n = 16$) were detected by clinical FISH. Among the 22 hypodiploid modal number 45 patients, 16 (73%) were identified by conventional banding and the remaining 6 (27%) were identified by FISH at University of California Berkeley. Of the 103 pseudodiploid patients, the majority (59%) were assigned by G-banding, whereas, FISH done by University of California Berkeley and hospitals enabled the detection of 25% ($n = 26$) and 16% ($n = 16$), respectively.

Table 2 summarizes the cytogenetic characteristics of ALL cases and compares abnormalities of B-lineage ALL Hispanics and non-Hispanic Whites. The most frequently observed structural abnormality was *TEL-AML1*, whereas hyperdiploidy was the most frequently observed change in ploidy. Hispanics were significantly less likely than non-Hispanic Whites to have *TEL-AML1* translocations ($P = 0.01$). When the sample was restricted to common ALL (ALL diagnosed in children ages 2-5 years and expression of surface antigens CD10 and CD19), the association was no longer present ($P = 0.15$), although the

overall pattern remained. Among children with two Hispanic parents, the frequency of *TEL-AML1* was 16%, whereas the frequency among children with one Hispanic parent was 8%. Overall, a comparison of ploidy between Hispanics and non-Hispanic Whites did not reveal differences between these two ethnic groups ($P = 0.66$; footnote, Table 2).

Discussion

Although cytogenetic data are important to therapeutic advances, such data have not yet helped unravel leukemia etiology with the exception of the 11q23/MLL patient subgroup for which epidemiologic evidence suggests *in utero* exposure to topoisomerase II inhibitors may give rise to these *MLL* abnormalities (12-15). To better establish risk factors and understand biological mechanisms for this heterogeneous disease, cytogenetic subgroups may be more informative than FAB phenotypes as different tumor genetic pathways can result in similar morphology. Limited information is available describing cytogenetically defined subgroups of childhood leukemia among Hispanic populations. When this information is available (16, 17), details of cytogenetic abnormalities among Hispanics are narrow in scope, lacking comparisons of the frequency of specific cytogenetic abnormalities.

We compared frequencies of cytogenetic events among prospectively ascertained incident childhood leukemia patients participating in an approximately population-based epidemiologic study in California. Although our classification of cases into cytogenetic subgroups is characterized by small numbers of observations constraining our interpretation, these subgroups are more homogeneous than the broad leukemia subtypes, such

as ALL, facilitating elucidation of risk factors for leukemia. Our data suggest that Hispanic childhood leukemia patients born in California have fewer *TEL-AML1* translocations than non-Hispanic Whites. The observed lower frequency of *TEL-AML1* in Hispanics is mirrored in a population from Spain (18). This finding is particularly interesting in light of evidence suggesting that *TEL-AML1* may arise prenatally in some cases as shown by its detection in neonatal blood spots (19), suggesting *in utero* exposures may differ between Hispanics and non-Hispanic Whites with this gene fusion. This frequency in Hispanics contrasts with other studies in the United States, where typically 20% to 25% of ALL patients harbor this translocation (20). Perhaps this difference occurs because most studies have been conducted in primarily Caucasian and African American populations. This observed disparity may be occurring by chance or may be worth noting; thus, additional studies are required for confirmation.

It is possible that ethnicity of the child may be misclassified; however, there was a high concordance (94%) between child's Hispanic ethnicity assessed by interview and birth certificate. A strength of the NCCLS is its population-based approach to acquiring prospective incident cases. Most published descriptions of cytogenetic events in leukemia children are drawn from hospital case series, potentially unrepresentative of a geographically defined target population and not likely to be population based. Because the NCCLS identifies most incident leukemia cases in the study region and participation rates are high among this case series, it is unlikely that selection affected the results of this analysis. The inclusion of large numbers of Hispanic respondents by using Spanish-speaking interviewers, Spanish language documents, and culturally appropriate protocols is a strength of this study. Finally, the addition of our systematically applied FISH assay enabled the detection of otherwise obscure abnormalities and improved conventional G-banding characterization.

This is the first study of primarily Hispanic and non-Hispanic White childhood leukemia patients to compare frequencies of cytogenetic events. Owing to the heterogeneity of leukemia in children, it is possible that cytogenetic subgroups may have unique etiologies and risk factors that otherwise would be missed with the broad leukemia subtypes presently used in epidemiologic analyses.

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