



The Impact Of Genetic Ancestry On The Biology And Prognosis Of Childhood Acute Lymphoblastic Leukemia

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Background

Although cure rates of childhood acute lymphoblastic leukemia (ALL) have improved significantly with risk-adapted therapy, stark racial disparities persist in both the incidence and treatment outcomes of ALL. There is a paucity of data describing the genetic basis of these disparities, especially in relation to modern ALL molecular taxonomy and in the context of contemporary treatment regimens.

Objective

To determine the associations of genetic ancestry with ALL biology, and the relevance of genetic ancestry to survival outcomes of modern ALL therapy.

Methodology

This was a multi-national genomic study of 2,428 children with ALL on front-line trials from United States (SJRGH: Total XV, Total XVI; COG: P9906, AALL0232, AALL0331, AALL0932, and AALL1131), Singapore and Malaysia (Ma-Spore 2003 and 2010), and Guatemala (LLAG-0707), representing diverse populations of European (EUR), African (AFR), Native American (NA), East Asian (EAS), and South Asian (SAS) descent.

We performed RNA-sequencing to characterize ALL molecular subtype and genetic ancestry. For categorization of patients into racial groups, individuals were classified based on composition of genetic ancestry as: “white” [EUR >90%], “black” [AFR >70%], “Hispanic” [NA >10% and NA greater than AFR], “East Asian” [EAS >90%], “South Asian” [SAS >70%], with the rest defined as “Other”. Because the “Other” category comprised a highly heterogenous group, we further sub-classified them by the dominant ancestral component. Admixed patients with majority EAS or SAS were categorized into “Other-Asian”, and admixed patients with majority EUR or AFR or NA >10% with NA less than AFR, were categorized into “Other-US”. We then evaluated associations of genetic ancestries with ALL biology and treatment outcomes.

Conclusions

ALL biology and prognosis are highly associated with genetic ancestry, pointing to a genetic basis for racial disparities in ALL. Therefore, biology-driven treatment individualization is needed to eliminate racial gaps in cure rates of this cancer.

Results

Association of genetic ancestry with ALL molecular subtype

We first evaluated the percentage of genetic ancestry as a continuous variable for association with ALL subtype using European ancestry as the reference group.

African ancestry (AFR) showed the strongest association with *TCF3-PBX1*, and was also related to *MEF2D* fusion, while it was negatively correlated with the frequency of *DUX4* rearrangements and hyperdiploidy.

Native American (NA) ancestry was related to an increased occurrence of *CRLF2* rearrangement and marginally with *ETV6-RUNX1*-like, whereas it was negatively correlated with the frequency of hyperdiploid ALL, *ETV6-RUNX1*, and T-ALL.

East Asian ancestry (EAS) was associated with a higher frequency of *DUX4* rearrangement, *ZNF384* fusion, *PAX5* alteration, and *TCF3-PBX1*, while it was protective against the occurrence of *BCR-ABL1*-like, *CRLF2* rearrangement, and T-ALL.

South Asian ancestry (SAS) was linked to *DUX4* ALL and associated with a lower prevalence of hyperdiploidy.

Association of genetic ancestry with ALL treatment outcomes

We then evaluated the association of genetic ancestry with prognosis. Here we found that survival outcomes differed significantly by genetic ancestry, where AFR and NA ancestries were both associated with poorer outcomes.

Event-free survival (Univariable analysis)

%AFR: **HR 2.3** (95% CI 1.4 – 3.8), **P=0.001**

%NA: **HR 2.5** (95% CI 1.0 – 5.9), **P=0.044**

Overall survival (Univariable analysis)

%AFR: **HR, 2.4** (95% CI, 1.2 – 4.7), **P=0.012**

%NA: **HR, 3.3** (95% CI, 1.1 – 10.0), **P=0.033**.

We also examined outcomes across racial categories. White, East Asian and South Asian children overall had more favorable outcomes compared to their black and Hispanic counterparts. Specifically, Hispanics had the poorest 5-year EFS (72.1 ± 4.2 %) and OS (82.3 ± 3.6 %), whereas South Asians had the highest EFS (94.6 ± 3.6 %) and OS (98.2 ± 2.1 %). Relapse risk trended in parallel with that of EFS and OS, with South Asians having one of the lowest CIR of 3.7 ± 2.6 %, and Hispanics having the highest at 22.8 ± 2.9 %.

Importantly, even **after adjusting for biological subtypes and clinical features**, Native American and African ancestries remained independently associated with poor prognosis.

Event-free survival (Multivariable analysis)

%AFR: **HR 2.1** (95% CI 1.2 – 3.5), P=0.005

%NA: **HR 2.6** (95% CI, 1.0 – 6.7), P=0.044

Overall survival (Multivariable analysis)

%AFR: **HR 2.1** (95% CI 1.0 – 4.2), P=0.040

%NA: **HR 3.4** (95% CI 1.0 – 11.5), P=0.047

	%Native American			%East Asian			%South Asian			%African		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Hyperdiploid	0.53	0.36 to 0.78	0.001	0.82	0.61 to 1.10	0.197	0.48	0.24 to 0.89	0.026	0.34	0.20 to 0.55	<0.001
<i>ETV6-RUNX1</i>	0.41	0.24 to 0.67	<0.001	0.91	0.64 to 1.27	0.574	1.42	0.75 to 2.55	0.260	1.32	0.84 to 2.04	0.225
B Other	3.02	1.96 to 4.62	<0.001	0.843	0.51 to 1.35	0.492	0.53	0.15 to 1.43	0.265	0.75	0.36 to 1.44	0.410
<i>BCR-ABL1</i> -like	1.54	0.91 to 2.54	0.096	0.38	0.18 to 0.70	0.004	0.37	0.07 to 1.19	0.152	0.48	0.20 to 1.03	0.080
<i>PAX5</i> alt	1.42	0.74 to 2.58	0.270	1.77	1.09 to 2.82	0.019	1.88	0.72 to 4.25	0.161	1.72	0.85 to 3.31	0.116
<i>DUX4</i>	1.06	0.51 to 2.05	0.879	2.84	1.83 to 4.37	<0.001	2.50	1.05 to 5.34	0.040	0.21	0.04 to 0.69	0.025
<i>CRLF2</i>	4.79	2.76 to 8.22	<0.001	0.41	0.15 to 0.94	0.052	1.75	0.51 to 4.63	0.312	0.33	0.07 to 1.06	0.100
<i>TCF3-PBX1</i>	2.79	1.38 to 5.43	0.003	1.98	1.05 to 3.61	0.029	0.91	0.15 to 3.29	0.901	4.84	2.40 to 9.49	<0.001
B-ALL	0.51	0.15 to 1.39	0.228	0.75	0.31 to 1.59	0.476	1.72	0.43 to 4.97	0.371	1.35	0.49 to 3.26	0.531
<i>BCR-ABL1</i>	0.57	0.18 to 1.54	0.310	1.09	0.49 to 2.19	0.829	0.54	0.05 to 2.47	0.516	0.79	0.22 to 2.22	0.686
<i>ETV6-RUNX1</i> -like	2.17	0.93 to 4.75	0.061	0.89	0.35 to 1.99	0.797	1.65	0.33 to 5.40	0.470	0.17	0.01 to 0.98	0.105
<i>ZNF384</i>	1.33	0.40 to 3.75	0.615	3.91	1.97 to 7.73	<0.001	1.45	0.21 to 5.85	0.650	1.24	0.28 to 4.13	0.751
<i>MEF2D</i>	1.68	0.53 to 4.66	0.358	1.34	0.41 to 3.53	0.592	3.6E-06	3.6E-27 to 1.17	0.062	3.55	1.25 to 9.25	0.019
Near haploid	0.06	0.001 to 0.58	0.057	0.43	0.09 to 1.39	0.215	0.98	0.07 to 4.82	0.980	1.1	0.24 to 3.66	0.886
Low hypodiploid	1.3	0.25 to 4.98	0.728	0.75	0.12 to 2.92	0.712	0.16	1.7E-5 to 4.16	0.499	2.65	0.60 to 9.47	0.157
<i>PAX5</i> P80R	2.31	0.58 to 7.67	0.193	0.14	0.002 to 1.11	0.163	1.74	0.09 to 9.82	0.613	0.33	0.01 to 2.75	0.415
<i>NUTM1</i>	1.16	0.09 to 7.90	0.894	1.97	0.38 to 8.23	0.369	2.43	0.07 to 19.5	0.497	3.62	0.49 to 19.7	0.156
T-ALL	0.08	0.02 to 0.19	<0.001	0.41	0.25 to 0.64	<0.001	0.85	0.36 to 1.76	0.694	2.16	1.31 to 3.53	0.002

