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Review

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Disparities in acute lymphoblastic leukemia risk and survival across the lifespan in the United States of America

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Abstract

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer but is less frequent in adolescents and young adults (AYAs) and is rare among older adults. The 5-year survival of ALL is above 90% in children, but drops significantly in AYAs, and over half of ALL-related deaths occur in older adults. In addition to diagnosis age, the race/ethnicity of patients consistently shows association with ALL incidence and outcomes. Here, we review the racial/ethnic disparities in ALL incidence and outcomes, discuss how these vary across the age spectrum, and examine the potential causes of these disparities. In the United States, the incidence of ALL is highest in Hispanics/Latinos and lowest in Black individuals across all age groups. ALL incidence is rising fastest in Hispanics/Latinos, especially in AYAs. In addition, survival is worse in Hispanic/Latino or Black ALL patients compared to those who are non-Hispanic White. Different molecular subtypes of ALL show heterogeneities in incidence rates and survival outcomes across age groups and race/ethnicity. Several ALL risk variants are associated with genetic ancestry, and demonstrate different risk allele frequencies and/or effect sizes across populations. Moreover, non-genetic factors including socioeconomic status, access to care, and environmental exposures all likely influence the disparities in ALL risk and survival. Further studies are needed to investigate the potential joint effects and interactions of genetic and environmental risk factors. Improving survival in Hispanic/Latino and Black patients with ALL requires advances in precision medicine approaches, improved access

to care, and inclusion of more diverse populations in future clinical trials.

Keywords: Acute lymphoblastic leukemia, disparities, race/ethnicity, genetic variation, socioeconomic status, access to care, recruitment to clinical trials, children, adolescents and young adults

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a hematologic malignancy characterized by impaired differentiation, proliferation, and accumulation of B- and T-lineage lymphoid precursor cells in the bone marrow, peripheral blood, and other organs[1,2]. In the United States, the age-adjusted incidence rate (AAIR) for ALL was estimated to be 1.64 per 100,000 people[3], with approximately 5700 new cases and 1600 deaths projected to occur in 2021[4]. The incidence rate (IR) of ALL demonstrates a bimodal age pattern, in which the initial peak occurs at age 1-4 years, followed by a decline at age 20-59 years and a modest rise at ages above 60 years[5]. Indeed, ALL is the most common childhood malignancy, with approximately 2700 incident ALL cases diagnosed under age 15 each year in the United States[6].

The causes of ALL are multifactorial, and likely vary based on the molecular subtype and patient age of diagnosis[7]. Only a small proportion (< 10%) of ALL cases are attributable to known risk factors with large effects[8], namely ionizing radiation and congenital syndromes[9-13], although both common and rare genetic variants are now known to contribute to childhood ALL risk[14]. Genome-wide association studies (GWAS) of childhood ALL have identified multiple genomic regions harboring common risk alleles for ALL, including at: 7p12.2 (*IKZF1*), 8q24.21, 9p21.3 (*CDKN2A/B*), 10p12.2 (*PIP4K2A*), 10p12.31 (*BMI1*), 10p14 (*GATA3*), 10q21.2 (*ARID5B*), 10q26.13 (*LHPP*), 12q23.1 (*ELK3*), 14q11.2 (*CEBPE*), 16p13.3 (*USP7*), 17q12, and 21q22.2 (*ERG*)[15-32] [Table 1]. In addition, sequencing studies of familial and sporadic ALL have discovered rare germline variants in *PAX5*[33,34], *ETV6*[35-39], *IKZF1*[40-42], and *TP53*[43,44] that are associated with disease risk. Non-genetic factors also contribute to ALL risk; for example, there is strong epidemiological evidence supporting a role for early life infections and modulation of the developing immune system in childhood ALL etiology, which has been reviewed in detail elsewhere[45]. Studies have also reported modest associations for childhood ALL risk with several environmental exposures[46], including tobacco smoke[47-49], pesticides[50,51], paint[52,53], and air pollution[54-56]. The vast majority of epidemiologic studies for ALL have been conducted in children, and very little is known regarding potential differences in ALL etiology across age groups.

One factor that consistently shows association with ALL incidence is race/ethnicity. We acknowledge that race and ethnicity are dynamic and multifactorial concepts[60], and in this review we use the term race/ethnicity to refer to heterogeneous groups of people defined by the USA Office of Management and Budget as African Americans/Blacks (hereafter, Blacks); Hispanics/Latinos; American Indians and Alaska Natives (AI/ANs); and Asians and Native Hawaiians/other Pacific Islanders (APIs)[61]. Race/ethnicity reflects genetic ancestry, and additionally conveys important epidemiologic information as to how social determinants such as racism and discrimination, socioeconomic position, and environmental exposures can influence disease incidence and mortality[60]. In the United States, the incidence of ALL is highest in Hispanics/Latinos and lowest in Blacks, and this is consistent across age groups[5,62-66].

Race/ethnicity is also associated with ALL patient outcomes. Overall, survival of ALL patients has improved dramatically in recent decades[3], primarily in children[2,67], which can largely be attributed to improvements in combination chemotherapy protocols[2], as well as advances in the understanding of cytogenetics and genetics of the disease and, more recently, the development of immunotherapy and targeted therapies[68-70].

Table 1. Genetic variants associated with ALL risk in genome-wide association studies

Gene	Region	SNP	Ref	Alt	Risk	Trait(s)	PubMed ID	Year	First author	AF_afr	AF_amr	AF_nfe	*P*	OR (CI)
ARID5B	10q21.2	rs10821936	C	T	C	ALL	19684603	2009	Treviño LR	0.227	0.463	0.302	1.40E-15	1.91 (1.60-2.20)
ARID5B	10q21.2	rs10994982	A	G	A	ALL	19684603	2009	Treviño LR	0.565	0.560	0.467	5.70E-09	1.61 (1.30-1.90)
ARID5B	10q21.2	rs7089424	T	G	G	ALL	19684604	2009	Papaemmanuil E	0.241	0.460	0.304	7.00E-19	1.65 (1.54-1.76)
ARID5B	10q21.2	rs7089424	T	G	G	B-ALL	19684604	2009	Papaemmanuil E	0.241	0.460	0.304	1.41E-19	1.70 (1.58-1.81)
BAK1	6p21.31	rs210143	T	C	C	B-ALL (High-hyperdiploidy)	31767839	2019	Vijayakrishnan J	0.735	0.718	0.724	2.21E-08	1.30 (1.19-1.43)
BMI1	10p12.31	rs4748793	A	G	A	ALL	23512250	2013	Xu H	0.893	0.774	0.787	8.40E-09	1.40 (1.26-1.57)
BMI1	10p12.31	rs11591377	G	A	G	ALL	29923177	2018	de Smith AJ	0.905	0.767	0.793	2.07E-10	1.27 (1.20-1.35)
C5orf56	5q31.1	rs886285	T	C	T	B-ALL (High-hyperdiploidy)	31767839	2019	Vijayakrishnan J	0.647	0.304	0.343	1.56E-08	1.29 (1.18-1.41)
CCDC26	8q24.21	rs28665337	C	A,T	A	B-ALL	29632299	2018	Vijayakrishnan J	0.086	0.097	0.116	4.00E-09	1.34 (1.21-1.47)
CCDC26	8q24.21	rs4617118	A	C,G	G	ALL	29348612	2018	Wiemels JL	0.305	0.117	0.163	3.05E-09	1.27 (1.17-1.38)
CDKN2A	9p21.3	rs3731217	A	C,T	A	ALL	20453839	2010	Sherborne AL	0.902	0.898	0.867	3.01E-11	1.41 (1.28-1.56)
CDKN2A	9p21.3	rs3731249	C	T	T	ALL	26527286	2015	Walsh K	0.004	0.016	0.033	1.69E-13	2.97 (2.22-3.96)
CDKN2B	9p21.3	rs77728904	A	C,G	C	B-ALL	26868379	2016	Hungate EA	0.094	0.059	0.080	3.32E-15	1.72 (1.50-1.97)
CEBPE	14q11.2	rs2239633	G	A	G	B-ALL (ETV6-RUNX1)	22076464	2012	Ellinghaus E	0.787	0.599	0.519	4.00E-10	1.35 (1.22-1.47)
CEBPE	14q11.2	rs4982731	C	T	C	ALL	23512250	2013	Xu H	0.396	0.368	0.278	9.00E-12	1.36 (1.24-1.48)
CPSF2	14q32.12	rs189434316	A	T	T	B-ALL (Normal cytogenetic)	29296818	2017	Clay-Gilmour AI	0.011	0.027	0.066	6.00E-09	3.70 (2.50-6.20)
ELK3	12q23.1	rs4762284	A	T	T	B-ALL	27694927	2017	Vijayakrishnan J	0.449	0.480	0.299	8.00E-09	1.19 (1.12-1.26)
ERG	21q22.2	rs2836365	A	G	G	B-ALL	30510082	2019	Qian M	0.197	0.360	0.329	3.76E-08	1.56 (1.33-1.83)
ERG	21q22.2	rs8131436	G	C	C	ALL	31296947	2019	de Smith AJ	0.196	0.363	0.331	8.76E-09	1.23 (1.16-1.31)
GATA3	10p14	rs3824662	C	A,T	A	B-ALL	23996088	2013	Migliorini G	0.094	0.395	0.172	8.62E-12	1.31 (1.21-1.41)
GATA3	10p14	rs3824662	C	A,T	A	B-ALL (Ph-like)	24141364	2013	Perez-Andreu V	0.094	0.395	0.172	2.17E-14	3.85 (2.71-5.47)
IGF2BP1	17q21.32	rs10853104	C	G,T	T	B-ALL (ETV6-RUNX1)	31767839	2019	Vijayakrishnan J	0.663	0.420	0.508	1.82E-08	1.33 (1.21-1.47)
IKZF1	7p12.2	rs11978267	A	G	G	ALL	19684603	2009	Treviño LR	0.193	0.241	0.277	8.80E-11	1.69 (1.40-1.90)
IKZF1	7p12.2	rs4132601	T	G	G	ALL	19684604	2009	Papaemmanuil E	0.193	0.242	0.275	1.00E-19	1.69 (1.58-1.81)
IKZF1	7p12.2	rs4132601	T	G	G	B-ALL	19684604	2009	Papaemmanuil E	0.193	0.242	0.275	9.31E-20	1.73 (1.61-1.85)
IKZF3	17q21.1	rs2290400	T	C	T	ALL	29348612	2018	Wiemels JL	0.518	0.619	0.510	2.05E-08	1.18 (1.11-1.25)
LHPP	10q26.13	rs35837782	A	G	G	B-ALL	27694927	2017	Vijayakrishnan J	0.654	0.504	0.631	1.00E-11	1.21 (1.15-1.28)
OR8U8	11q12.1	rs1945213	C	G,T	C	B-ALL (ETV6-RUNX1)	22076464	2012	Ellinghaus E	0.218	0.184	0.285	3.89E-08	1.28 (1.14-1.45)
PIP4K2A	11q12.1	rs10828317	T	C	T	B-ALL	23996088	2013	Migliorini G	0.908	0.835	0.698	2.30E-09	1.23 (1.15-1.32)
PIP4K2A	10p12.2	rs7088318	C	A	A	ALL	23512250	2013	Xu H	0.400	0.751	0.616	1.13E-11	1.40 (1.28-1.53)
PIP4K2A	10p12.2	rs4748812	G	A	A	ALL	29923177	2018	de Smith AJ	0.360	0.742	0.626	1.30E-15	1.31 (1.25-1.38)
RPL6P5	2q22.3	rs17481869	C	A	A	B-ALL (ETV6-RUNX1)	29632299	2018	Vijayakrishnan J	0.020	0.036	0.079	3.20E-08	2.14 (1.64-2.80)

SP4	7p15.3	rs2390536	G	A	A	ALL	29348612	2018	Wiemels JL	0.083	0.184	0.368	3.59E-08	1.20 (1.13-1.29)
TLE1	9q21.31	rs76925697	A	T	A	B-ALL	31767839	2019	Vijayakrishnan J	0.964	0.969	0.962	2.11E-08	1.52 (1.31-1.76)
TP63	3q28	rs17505102	G	C	C	B-ALL (ETV6-RUNX1)	22076464	2012	Ellinghaus E	0.053	0.064	0.128	8.94E-09	1.59 (1.33-1.92)
USP7	16p13.2	rs74010351	A	C,G	G	T-ALL	30938820	2019	Qian M	0.178	0.060	0.060	4.51E-08	1.44 (1.27-1.65)

Risk allele frequencies for the 33 ALL-associated SNPs are global frequencies obtained from gnomAD v2.1.1.[57]. Ref, alt, AF_af, AF_amr, and AF_nfe were annotated through ANNOVAR[58]. AF_af, AF_amr, and AF_nfe were transformed to indicate the allele frequency of the risk alleles. Other information was extracted from the GWAS Catalog and was confirmed in each publication. Gene: Nearest gene; SNP: single nucleotide polymorphism; ref: reference allele; alt: alternative allele; risk: risk allele; AF: allele frequency; afr: African/African American; amr: American Admixed/Latino; nfe: Non-Finnish European; OR: odds ratio; CI: 95% confidence interval; ALL: acute lymphoblastic leukemia. Two SNPs, rs10821936 and rs10994982, were identified within the same region by the same study and are included in this table as the causal variant is unknown[59].

Although in children the overall 5-year survival rate of ALL has risen above 90%[71,72], it remains inferior in later age groups, with 60%-85% in adolescents and young adults (AYAs, age range varies by studies, between 15-39 years)[73-76], and under 30% in older adults[77-82]. In addition, ALL patients who are Hispanic/Latino or Black show worse outcomes compared to those who are non-Hispanic White (NHW)[83-89].

Here, we review the racial/ethnic disparities in ALL incidence and outcomes, and discuss how these vary across the different age groups of patients: children, AYAs, and older adults. We also examine the potential causes of these disparities, including genetic and non-genetic risk factors, and how epidemiologic studies across populations are essential to our understanding the causes of ALL.

DISPARITIES IN ALL INCIDENCE ACROSS THE LIFESPAN

ALL incidence initially peaks in the first decade of childhood, ranging from 1-4 years to < 9 years in different studies[5,64-66], declines at age 20-59 years, and rises again modestly among older adults aged 60 or above, with the highest second peak among Hispanic/Latino adults[90]. The initial peak of ALL incidence occurs earlier for B-cell ALL (B-ALL) at 1-4 years compared to T-cell ALL (T-ALL) at 5-14 years, and with a less prominent peak in the latter[5]. ALL develops more often in males than females with an incidence rate ratio (IRR) of 1.29 overall[3], and 2.20 and 1.20 for T-ALL and for B-ALL, respectively[5].

Incidence of ALL is highest in Hispanics/Latinos

Hispanic/Latino children are more likely to be diagnosed with ALL compared to NHW, Black or Asian children in both genders and across all age groups[5]. The reported Hispanic/Latino-to-NHW IRR of childhood ALL ranges from 1.25 to 1.65 for all subtypes combined[5,62,64-66], and appears to be more prominent for B-ALL (IRR = 1.64), but close to unity for T-ALL (IRR = 0.94)[5]. Moreover, the disparity in ALL IRs between Hispanic/Latino and NHW children increases with increased age from < 1 year to 19 years[64]. This disparity in ALL risk corresponds to what has been observed geographically. For instance, Latin American countries, including Mexico and Costa Rica, have some of the highest incidences of childhood ALL in the world[91,92]. Meanwhile, the highest incidence of childhood ALL in the United States is found in the West United States Census Region, where a high proportion of residents are Hispanics/Latinos[65]. On the contrary, compared to NHWs, Black children have lower IRs of nearly all ALL subtypes in all age groups[5,62,64-66], and API children also have lower IRs[93].

Among API regional groups, East Asians have a significantly higher IR of childhood ALL compared to Southeast Asians (IRR = 1.59), and Oceanians have the highest IR[93].

Among AYAs aged 15-39 years (age range defined by the National Cancer Institute), the overall ALL AAIR was 0.98 (95%CI: 0.96-1.01) per 100,000 during 2000-2016, with the highest incidence being observed in Hispanics/Latinos [AAIR = 1.63 (95%CI: 1.56-1.70)], followed by AI/ANs [AAIR = 1.16 (95%CI: 0.86-1.52)], NHWs [AAIR = 0.79 (95%CI: 0.76-0.83)], APIs [AAIR = 0.78 (95%CI: 0.70, 0.86)], and Blacks [AAIR = 0.53 (95%CI: 0.47, 0.59)][66] [Figure 1]. A similar trend has been found in B-ALL specifically, with the highest incidence seen in Hispanics/Latinos and the lowest in Blacks[94].

Among older adults, ALL incidence again predominates among Hispanics/Latinos[5]. For those aged 40 or older, Hispanics/Latinos had the highest AAIR [AAIR = 1.76 (95%CI: 1.67-1.86)], followed by AI/ANs [AAIR = 1.17 (95%CI: 0.87-1.54)], NHWs [AAIR = 0.97 (95%CI: 0.94-1.00)], APIs [AAIR = 0.85 (95%CI: 0.78-0.93)], and Blacks [AAIR = 0.77 (95%CI: 0.70-0.84)][66] [Figure 1].

Furthermore, Philadelphia chromosome-like (Ph-like) ALL [patients with a similar gene expression pattern as those with t(9;22), *BCR-ABL1* translocations, i.e., Ph+], a subtype of B-ALL associated with poor outcomes[95], is more common in AYAs (19%-27%) and older adults (20%) than in children (10%)[96-99]. In addition, patients with Ph-like ALL or with its subtype carrying *CRLF2* rearrangement (also associated with poor outcomes)[99] are more likely to be Hispanics/Latinos compared to other races/ethnicities (68% in Ph-like ALL and 85% in Ph-like ALL with *CRLF2* rearrangement)[99].

Intriguingly, a higher percentage of residents born in a foreign country at the county level contributes to a higher incidence of ALL among both NHWs and Blacks, but was contradictorily associated with a lower incidence of ALL among Hispanics/Latinos[66]. For United States-based API children, ALL IRs were similar to rates seen in originating countries[93]. The inverse association between percent foreign-born and the incidence of ALL in Hispanics/Latinos represents an example of the "Hispanic paradox"[100,101], which refers to the observation that foreign-born Hispanics/Latinos have better health outcomes when compared to United States-born Hispanics/Latinos.

Incidence of ALL is rising fastest in Hispanics/Latinos

During 1992-2013, the incidence of ALL increased significantly by approximately 2% per year for Hispanic/Latino children diagnosed from age 10-14 years (APC = 2.09), and by 3% for those 15-19 years of age (APC = 2.67), while no significant increases were observed in NHW, Black, or Asian children in the same age groups[64]. In the United States Cancer Statistics database, the IR of ALL in both overall children and Hispanic children aged below 20 years increased significantly during 2001-2008, with the largest increase being observed in Hispanic/Latino children (APC = 2.5), and which remained stable during 2008-2014[65].

Despite of the relatively low AAIR of ALL compared to other age groups, AYA had the greatest increase of ALL AAIR during 2000-2016 [overall APC = 1.56 (95%CI: 1.03-2.09)][66] [Figure 1]. Hispanics/Latinos had significant increase of AAIR across all age groups [APC = 1.18 (95%CI: 0.76-1.60)], with the greatest increase found in AYAs [APC = 2.02 (95%CI: 1.17-2.88)][66]. Across all age groups, AYA is the only group in which AI/ANs had a significant increase of AAIR [APC = 9.79 (95%CI: 5.65-14.09)][66]. Given the small population size of AI/ANs, the substantial interregional differences of incidence rates and misclassification of AI/ANs in central registries that were observed in SEER data[102], a note of caution should be offered in interpreting rates and trends for the AI/AN population. The AAIR of ALL also increased significantly

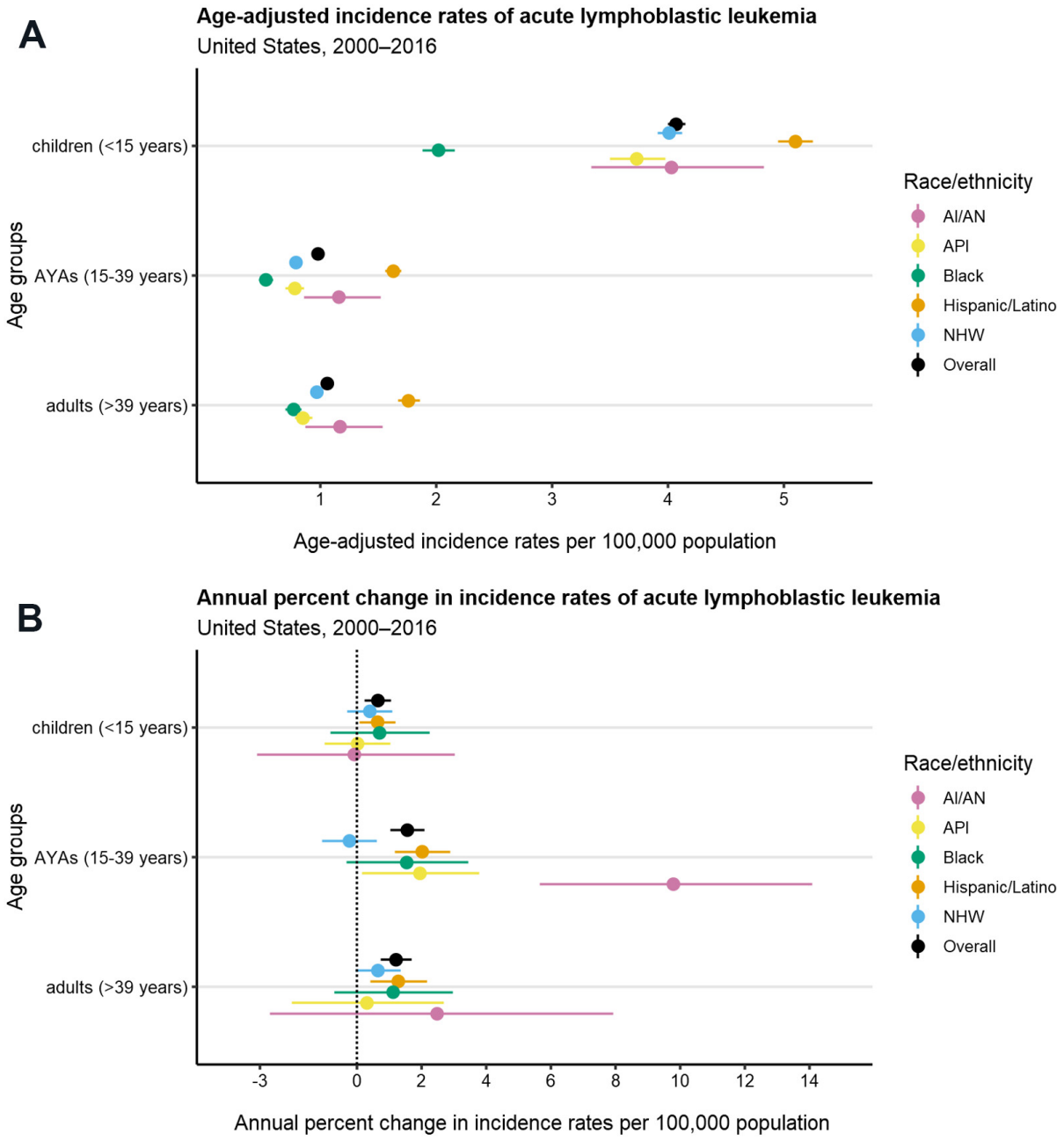

Figure 1. Disparities in acute lymphoblastic leukemia (ALL) incidence across the lifespan. Data extracted from Tables 1 and 2 from Feng *et al.*[66]. Age-adjusted incidence rate per 100,000 population was derived from the Surveillance, Epidemiology, and End Results Registry, version 18. Centers of points and horizontal bars indicate point estimates and 95% confidence intervals. (A) Age-adjusted incidence rates of ALL by age group and race/ethnicity, United States, 2000-2016. (B) Annual Percent Change in incidence rates of ALL by age group and race/ethnicity, United States, 2000-2016. AI/AN: American Indian and Alaska Native; API: Asian and Pacific Islander; Black: African American/Black; NHW: non-Hispanic White; AYAs: adolescents and young adults.

among API AYAs [APC = 1.95 (95%CI: 0.15-3.79)][66]. Among older adults, the incidence of ALL increased significantly only among Hispanics/Latinos during 2000-2016[66]. The trend of AAIR remained stable among NHWs and Blacks across all age groups over time[66].

DISPARITIES IN SURVIVAL OF ALL PATIENTS

In this section, we summarize disparities in the overall survival rates of ALL patients, though we do not review potential disparities in long-term outcomes, such as treatment-related morbidities, which have been described elsewhere[103-106].

Children

Among children, the survival of ALL is lowest in infants (< 1 year), highest in those aged 1-9 years, and thereafter, decreases with increased age[5,83]. Girls have better survival than boys overall[83]. Hispanic/Latino children have inferior outcomes compared to NHWs[83-87], with a 5%-15% difference in overall survival rate being persistently seen in SEER data[84,85,87]. Furthermore, in Hispanics/Latinos, childhood ALL mortality has been shown to differ by genetic ancestry[107]. For instance, Hispanic/Latino children in general have a 2.27 times higher mortality compared to NHW children [mortality rate ratio (MRR) = 2.27 (95%CI: 1.68-3.06)], with a MRR of 2.56 (95%CI: 1.93-3.40) in continental Hispanic/Latino children (Mexicans, Central Americans, and South Americans) but with a MRR of only 1.23 (95%CI: 0.74-2.03) in Caribbean Hispanic/Latino children (Puerto Ricans, Cubans, and Dominicans)[107], suggesting that higher Indigenous American ancestry is associated with poorer overall survival.

In Black childhood ALL patients, improvement of 5-year survival lags behind compared to in other races/ethnicities[108]. The largest improvements of survival in Blacks occurred at much later diagnosis periods (1995-2001 and 2002-2008) compared to those in NHWs and AI/ANs (1988-1994 and 1995-2001)[84]. Promisingly, SEER data have revealed a decreased inequality in ALL survival between Black and NHW children[83,85,109]. From 1992-1995 to 2003-2007, 5-year relative survival rate improved faster in Black children (APC = 3.01) than in NHW children (APC = 1.37)[85]. In another study, from 1975-1983 to 2000-2010, the difference in 5-year cumulative mortality of ALL between Black and NHW children reduced from 15% to 3%; compared with NHWs, the adjusted hazard ratio (HR) for Blacks dropped from 1.46 (95%CI: 1.09-1.94) to an insignificant 1.21 (95%CI: 0.74-1.96)[83].

API and AI/ANs also have significantly worse survival of childhood ALL compared to NHWs[83,84], with the 5-year cumulative ALL mortality being 10% in APIs, and 19% in AI/ANs versus being 8% in NHWs at 2000-2010[83]. Compared with NHW counterparts, APIs diagnosed at 1-9 years, and AI/ANs diagnosed at 10-19 years had about twice the ALL mortality HR[83]. Further, in a stratified analysis for Asian subgroups, when comparing to NHWs, East Asians in general (i.e., Chinese, Filipino, Korean, Japanese, Vietnamese and other Southeast Asians combined) had significant inferior outcomes, with particularly worse survival for Vietnamese [relative risk (RR) = 2.44 (95%CI: 1.50-3.97)] and Filipino [RR = 1.64 (95%CI: 1.13-2.38)] patients, whereas the inferior outcomes for Koreans, Japanese and other Southeast Asians were non-significant[84].

AYAs

A "survival cliff" has been observed for ALL in AYA patients at age 17 to 20 years, where the survival rate drops considerably during just this 3-year difference in age, and accounts for nearly half of the total survival decrease from childhood to older adults[110]. This substantial drop of survival rate partly results from the high frequency of the high-risk Ph-like B-ALL subtype among AYAs[95-99]. Based on data obtained from the Texas Cancer Registry, among AYA ALL patients, the overall 5-year survival rate was better in females than in males, and it has improved over time across all races/ethnicities in both sex groups[88]. However, improvement in the survival rate of Black AYA patients lags behind other racial/ethnic groups, similar to the pattern seen in Black children. Among AYA patients, survival in Black males diagnosed in 2004-2012 [66.9% (95%CI: 64.0%-69.6%)] was significantly worse than in NHW [78.2% (95%CI: 77.2%-79.1%)] and in

Hispanic/Latino males [71.8% (95%CI: 70.3%-73.3%)] diagnosed back in 1995-2003[88]; Black females diagnosed in 2004-2012 [76.9% (95%CI: 75.2%-78.4%)] had a worse survival rate compared to NHW females diagnosed in 1995-2003 [83.9% (95%CI: 83.2%-84.2%)][88].

Older adults

Older adult ALL patients have the worst survival across all age groups[77-82]. While approximately 22.5% of patients are diagnosed after the age of 55 years, 54.6% of ALL-related deaths occur in patients in this age stratum[111]. This is likely related to the elevated prevalence of multiple high-risk subtypes of ALL in older adults. First, both Ph+ ALL and Ph-like ALL are very common subtypes of B-ALL among older adults aged 60 years or above (Ph+ ALL: approximately 50%; Ph-like ALL: 24%-26%)[96-99,112,113]. In addition, older adults with Ph-negative B-ALL tend to present with high-risk cytogenetics and complex karyotypes[114,115] associated with increased risks of treatment failure and treatment complications[81].

Promisingly, the 1973-2008 SEER data revealed a significant improvement for patients aged over 45 years in survival among the overall population, NHWs, and in particular APIs (19.8%), and a large but marginally significant improvement for Blacks (11.3%)[89]. However, these improvements were not seen in Hispanic/Latino patients. For instance, in 2003 to 2008, the 5-year survival rate of older adult Hispanic/Latino ALL patients was only 13.9% compared with 23.6% in NHWs and 17.1% in Blacks[89], perhaps due to the high frequency of Ph-like ALL in Hispanic/Latino ALL patients[99]. Similarly, in the 1980-2011 SEER data, there was a modest improvement of median overall survival rate of ALL among adults aged 60 years or above[116], partly attributable to advances in novel therapies for Ph+ ALL[117].

FACTORS ASSOCIATED WITH DISPARITIES IN ALL RISK AND OUTCOMES

Differences in ALL tumor biology

Immunophenotype

The World Health Organization (WHO) classifies ALL based first on immunophenotype, and categorizes patients into either B-ALL or T-ALL[118], with both comprising multiple subtypes defined by structural chromosomal alterations[119]. B-ALL prevalence is higher than T-ALL, accounting for approximately 80% of ALL cases in children and 75% in adults in the United States[120]. In childhood ALL, the B-cell immunophenotype confers more favorable survival than T-ALL, whereas in adults survival is substantially higher for T-ALL than B-ALL[5,114,121,122], likely due to differences in molecular subtypes across age groups. In both children and adults, B-ALL appears to have a higher incidence in Hispanics/Latinos compared to other races/ethnicities[5]. On the other hand, T-ALL occurs more frequently in Black children, in whom a T-ALL-related genetic variant in *USP7* is overrepresented[30]. Thus, the contribution of immunophenotype to disparities in the survival of ALL patients may vary across population groups.

Cytogenetic subtypes

The most common chromosomal alterations in childhood B-ALL are high hyperdiploidy (chromosomal number 51-67) and t(12;21)(p13;q22) translocation encoding the *ETV6-RUNX1* fusion gene[115,123]. Each presents in 25%-30% of children with ALL[119], and is associated with a favorable prognosis[115,124]. However, both subtypes are less common in adolescent ALL patients and very rare in adult ALL patients[119]. Among ALL cases in the California Childhood Leukemia Study, the prevalence of high hyperdiploidy was similar in Hispanics/Latinos and NHWs, at 28.3% and 27.6%, respectively[125], whereas there was a significantly lower frequency of ETV6-RUNX1 translocation in Hispanics/Latinos (13%) than in NHWs (24%)[126]. To our knowledge, the frequencies of these two subtypes have not been compared across race/ethnicity in AYAs or older adults, perhaps due to small numbers.

The Ph chromosome translocation [t(9;22), i.e., Ph+], which results in the *BCR-ABL1* fusion gene[127], is infrequent among childhood B-ALL patients (< 5%) but presents in up to half of adult B-ALL cases and becomes more prevalent with increased age (22% in patients < 40 years of age, 41% in patients ≥ 40 years and nearly 50% in patients aged 60 years or older)[97,112,113]. A higher percent of Ph+ B-ALL has been reported in Black AYA/adult patients compared with in NHW and Hispanic/Latino patients[99,128]. A similar pattern has been identified in children - compared with Ph-negative ALL patients, Ph+ ALL patients were more likely to be Black[129]. Although Ph chromosome has been historically recognized as an adverse prognostic factor for ALL, Ph+ ALL now has noninferior or even superior outcomes compared to Ph-negative ALL in older adult ALL patients[113,130,131], due to recent advances in novel therapies such as CAR-T cell therapy and tyrosine kinase inhibitor therapy[117].

The WHO 2017 revision introduced Ph-like ALL as an additional subgroup for B-ALL[118]. Ph-like B-ALL shares a similar gene-expression profile with Ph+ B-ALL, but does not harbor the *BCR-ABL1* fusion protein expressed from the t(9;22)[118]. Unlike Ph+ ALL that occurs more frequently with increased age, Ph-like ALL has the highest incidence in AYAs (19%-28%), a lower frequency in childhood (10%), and is relatively common among adults aged 40 or above (20%)[96-99]. Ph-like ALL partly contributes to the AYA "survival cliff"[110], and the continuing poor outcomes in older age groups[77-82]. Patients with Ph-like ALL had a significantly inferior event-free and disease-free survival, a lower complete remission rate, and an elevated level of minimal residual disease at the end of the induction therapy compared to non-Ph-like patients[95]. Furthermore, Ph-like ALL likely plays a role in both the high incidence and the inferior survival of ALL in Hispanics/Latinos. Ph-like ALL occurs more frequently in Hispanics/Latinos in particular in AYA/adults[99]. Indeed, Hispanics/Latinos have been shown to account for up to two-thirds of Ph-like ALL in AYA/adult patients[99]. Notably, nearly half of the patients with Ph-like ALL had *CRLF2* rearrangements[96]. Both Ph-like ALL and its subtype with *CRLF2* rearrangements have significantly worse outcomes compared to other subtypes[96,98,99,132-134], and are more prevalent among Hispanics/Latinos compared to other racial/ethnic groups[132]. In sum, the Ph-like subtype contributes significantly to the poor survival of Hispanic/Latino AYA ALL patients.

Genetic variation

Genetic variants contribute to racial/ethnic disparities in ALL incidence

Several ALL risk loci identified by GWAS have been associated with genetic ancestry, and have demonstrated differences in risk allele frequency and/or differences in effect size across population groups[15-32,135,136] [Figure 2]. For example, an increased number of risk alleles at 5 ALL risk single nucleotide polymorphisms (SNPs) rs3731217 (*CDKN2A*), rs7088318 (*PIP4K2A*), rs2239633 (*CEBPE*), rs7089424 (*ARID5B*), and rs3824662 (*GATA3*) was correlated with increased genome-wide Indigenous American ancestry in Hispanic/Latino children[137,138]. *ARID5B* SNP risk allele frequency has also been associated with increased *local* Indigenous American ancestry in Hispanics/Latinos[139]. At the *GATA3* risk locus, SNP rs3824662 has a markedly higher risk allele frequency in Hispanic/Latino than in European ancestry populations, with 39% compared with only 17% frequency in the Genome Aggregation Database (gnomAD) v2.1.1. [Table 1 and Figure 3][57]. Further, the *GATA3* SNP rs3824662 risk allele has been shown to confer a remarkably high risk for Ph-like ALL in both children and AYAs, with an almost 4-fold risk of this subtype[21,135], supporting that this risk locus likely contributes significantly to the increased prevalence of Ph-like ALL in Hispanic/Latino ALL patients.

In two recent GWAS of ALL conducted in Hispanic/Latino-only discovery studies, a novel ALL risk locus was identified at the chromosome 21 gene *ERG*[29,31]. The effect of this locus on ALL risk was larger in Hispanics/Latinos than in NHWs and, in addition, this locus was associated with an increased risk of ALL in Hispanic/Latino individuals both with higher genome-wide and higher local Indigenous American

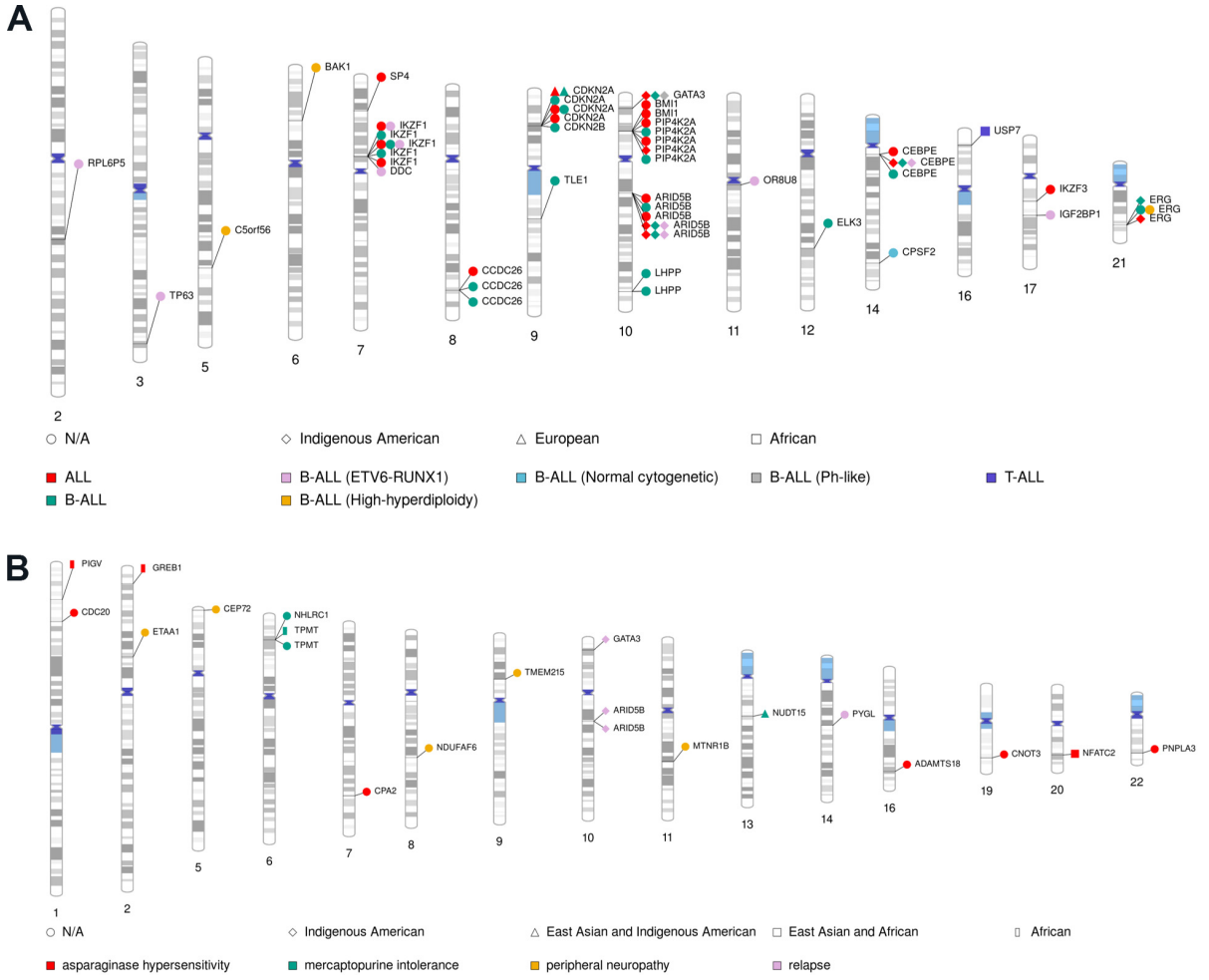

Figure 2. Genetic variants associated with ALL risk and outcomes across the genome. PhenoGram plots[140] were constructed for genetic variants associated with (A) ALL susceptibility, and/or (B) ALL patient outcomes (i.e., relapse and response to therapy). Genetic variants included in the PhenoGrams were identified in the NHGRI-EBI catalog of human genome-wide association studies (GWAS Catalog)[141] and included in published GWAS for acute lymphoblastic leukemia (ALL)[15,16,18-20,24-27,32,135,136] or for outcomes of ALL[142-150]. We also included some variants described in additional papers included in this review for ALL susceptibility[17,21-23,28-31] and ALL patient outcomes[21,139]. For ALL susceptibility (A) we only included variants that passed genome-wide significance levels of $P < 5 \times 10^{-8}$. For patient outcomes (B), we included variants that passed genome-wide significance levels of $P < 5 \times 10^{-8}$ plus variants in *GATA3* and *ARID5B* from gene-specific analyses. Lines are plotted on each chromosome corresponding to the base-pair position of each single nucleotide polymorphism (SNP). Variants are colored by related phenotypes that have been detected in GWAS (from the "Reported trait" column in the GWAS Catalog). Shapes of variants correspond to the genetic ancestry (if any) that has been associated with the SNP risk allele. N/A represents no related ancestry has been reported so far.

ancestry[29,31]. Together, risk loci in *ARID5B*, *GATA3*, *PIP4K2A*, *CEBPE*, and *ERG* likely account for some of the observed differences in ALL incidence between Hispanics/Latinos and non-Hispanic/Latino races/ethnicities, which may be partly explained by the Indigenous American ancestry in Hispanics/Latinos. Indeed, it has been suggested that the *CEBPE*, *ARID5B*, and *GATA3* risk SNPs may account for approximately 3%, 11%, and 11% increased risk of B-ALL in Hispanics/Latinos *vs.* NHWs, respectively[137,138]. Intriguingly, a recent study found that Indigenous American ancestry increased by ~20% on average in Mexican Americans in the United States during the 1940s-1990s, partly attributable to assortative mating, shifts in migration pattern and changes in population size[151]. Given the association between ALL risk alleles and Indigenous American ancestry, this perhaps suggests that this shift in genetic ancestry may contribute to the rising ALL incidence among Hispanics/Latinos, although this warrants

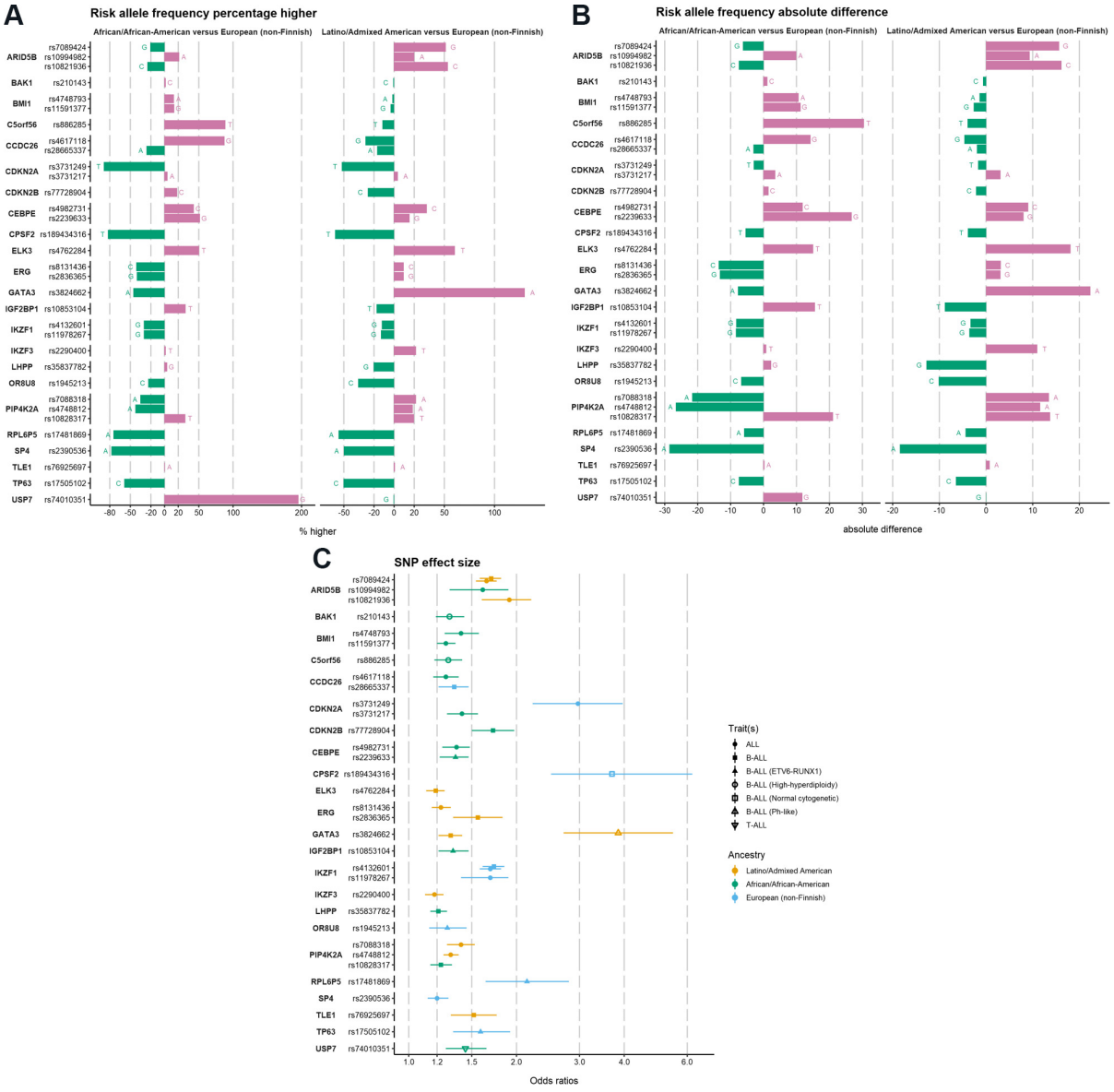

Figure 3. Risk allele frequency and effect size of selected single nucleotide polymorphisms (SNPs) associated with acute lymphoblastic leukemia (ALL) risk. SNPs (*n* = 33, Table 1) are grouped by nearest genes in each panel. (A) Percentage higher of risk allele frequency in Africans/African-Americans and Latinos/Admixed Americans as compared to in Europeans (non-Finnish). Percentage change equation: {{[(Risk allele frequency of Africans/African-Americans or of Latinos/Admixed Americans) / [Risk allele frequency of Europeans (non-Finnish)]] - 1} × 100. Horizontal bars are annotated by risk allele and colored by the direction of percentage difference. (B) Difference of risk allele frequency in Africans/African-Americans and Latinos/Admixed Americans as compared to in Europeans (non-Finnish). (C) Effect size of selected GWAS-identified SNPs associated with ALL risk. Centers of points and horizontal bars indicate point estimates and 95% confidence intervals. Points are shaped by study-reported traits. Points and horizontal bars are colored by ancestry with the highest risk allele frequency. X axis is on a log-10 scale in order to better present those relatively small effect sizes.

further investigation. Further research is needed to determine whether the ancestry-dependent effects from these SNPs are confounded by other genetic or environmental factors, and to discover additional ancestry-associated risk loci via admixture mapping and larger GWAS of ALL with a more diverse population across all age groups.

Apart from the risk loci described above that are associated with Indigenous American ancestry, a novel risk locus for T-ALL was recently identified at the *USP7* gene and was found to be overrepresented in children of African ancestry. This locus may, therefore, contribute to the higher incidence of T-ALL in Black children compared to their counterparts of other races/ethnicities[30].

Finally, we summarized established GWAS-identified SNPs for ALL[15-32] in Table 1, and we observed disparities in risk allele frequency and in effect size of these SNPs. In gnomAD (v2.1.1.)[57], the risk allele frequency of the Ph-like ALL-related SNP rs3824662 (*GATA3*) is 130% higher in Latinos/Admixed Americans compared to in Europeans; further, SNPs in *ARID5B* have a 20%-50% higher risk allele frequency in Latinos/Admixed Americans compared to Europeans [Figure 3A]. Many of the established ALL GWAS SNPs have a higher absolute risk allele frequency in Latinos/Admixed Americans than in Europeans [Figure 3B]. In Blacks, risk allele frequency of the T-ALL-related SNP at rs74010351 (*USP7*) is strikingly high, nearly 200% higher than in Europeans, but the absolute difference is only ~10% because of the low frequency of this risk allele across all populations [Table 1]; other GWAS SNPs did not show consistent differences in risk allele frequency between African and European populations [Figure 3]. The strongest risk effect is seen for the *GATA3* SNP rs3824662 association with Ph-like ALL, with an effect size of nearly 4.0 [Figure 3C].

Genetic variants are associated with racial/ethnic disparities in ALL outcomes

Genetic variation contributes to racial/ethnic disparities not only in ALL susceptibility but also in treatment outcomes[139,152] [Figure 2]. Indigenous American ancestry has been associated with an increased risk of relapse in Hispanic/Latino ALL patients, which may result from the effects of ancestry-related genetic variants on therapy response[153]. For example, in a study conducted in children treated on Children's Oncology Group (COG) clinical trials, *ARID5B* genetic risk alleles that have a higher frequency in Hispanic/Latino populations and are associated with increased Indigenous American ancestry were associated with both ALL susceptibility and relapse risk[139]. In another example, the *GATA3* risk SNP rs3824662, associated with Indigenous American ancestry[138] and Ph-like ALL, has been found additionally to contribute to the increased risk of relapse in both childhood[21,154] and adult ALL patients[155].

Two variants in *TPMT* (rs1142345) and *NUDT15* (rs116855232) have been discovered by GWAS to be strongly associated with thiopurine intolerance during therapy resulting in excessive toxicity in children with ALL[142]. The *TPMT* variant is most prevalent in Blacks and least common in East Asians[142]. The *NUDT15* variant is most prevalent in East Asians, followed by Hispanics/Latinos, and extremely rare in NHWs and Blacks[142]. In a recent sequencing study, 4 additional germline loss-of-function variants were identified in *NUDT15* that confer a major risk for thiopurine intolerance, and appear to be highly prevalent in East Asians, South Asians and Indigenous American populations[156].

Moreover, a study of children with high-risk B-ALL enrolled in COG clinical trials revealed 19 genetic loci associated with increased relapse risk, of which 12 were specific to an ancestry group, including 7 SNPs specific to Hispanics/Latinos and 3 SNPs specific to Black patients[152]. These loci are associated with pharmacokinetic and pharmacodynamic phenotypes (e.g., resistance or rapid clearance of chemotherapy)[152]. Further, including ancestry-specific SNPs in multivariate models of relapse risk significantly attenuated the increased risk of relapse in Hispanic/Latino and Black patients compared to white patients[152].

Environmental exposures and ALL risk

Genetic variation undoubtedly contributes to the racial/ethnic disparities in ALL risk and outcomes, but non-genetic factors also play an important role. In terms of the natural history of the disease, it has been proposed that childhood ALL, in particular B-ALL, follows a "two-hit" model of leukemogenesis[45,157], with *in utero* development of a pre-leukemic clone[158,159] that progresses to overt leukemia following postnatal acquisition of secondary genetic changes[160]. A lack of microbial infectious exposure perinatally or in infancy impacts immune function[161-163], and this in combination with delayed exposure to infections may lead to abnormal immune responses that result in secondary somatic events that drive leukemogenesis[45]. This is supported by epidemiological evidence, including from studies that have assessed the impact of early-life infectious exposure on ALL risk, using proxies such as day-care attendance[164-166], birth order[166-168], and timing of birth[168]. Intriguingly, day-care attendance and higher birth order have been found to have a protective effect on ALL risk among NHWs supporting the "delayed infection" hypothesis[45], but not in Hispanic/Latino children[164-166,168]. On the other hand, Caesarean section and *in utero* CMV infection, found to be risk factors for childhood ALL, conferred a more prominent effect in Hispanics/Latinos compared to NHWs[169-171]. As described above, several genetic variants and high-risk cytogenetic features are more prevalent in Hispanics/Latinos and are correlated with Indigenous American ancestry. More studies are needed to investigate the joint effects of both genetic and environmental risk factors and their potential interactions, particularly in Hispanics/Latinos.

Socioeconomic status and ALL risk and survival

Socioeconomic status (SES) also correlates with the racial/ethnic disparities in ALL risk. For example, in a recent study, when adjusting for percent foreign-born in areas, neighborhood SES was inversely associated with the AAIR of ALL among NHWs and Blacks, but was positively associated with ALL AAIR in Hispanics/Latinos across all age groups[66]. This observed racial/ethnic difference in the relationship between SES and the risk of ALL was reported to be largely driven by data from California[66], where there was an excessive ALL risk in Los Angeles County and a highly diverse population in which Hispanics/Latinos are of an elevated Indigenous American ancestry. This contrasts with another study conducted in children without adjusting for percent foreign-born, in which they found a higher incidence of ALL among lower SES populations for Hispanics/Latinos, but among higher SES populations for other races/ethnicities[172]. One potential reason that leads to this difference is that the former study additionally controlled for percent foreign-born, which is a crucial indicator of the "Hispanic paradox"[100,101], and represents a variety of potential underlying risk factors that may differ by individual and racial/ethnic group.

On the other hand, low SES is consistently associated with poor outcomes in ALL patients. Living in high poverty areas has been associated with high rates of relapse in childhood ALL patients[173]. Children with ALL in the United States residing in neighborhoods with the highest poverty rate have been found to have an almost 2-fold increase in mortality compared with those in neighborhoods with the lowest poverty rate [HR = 1.8 (95%CI: 1.41-2.30)], when adjusting for sex, age at diagnosis, race/ethnicity, and treatment era[174]. Moreover, the difference in 5-year overall survival comparing NHW children with ALL residing in the lowest poverty neighborhoods *vs.* Black patients residing in the highest poverty neighborhoods can be as high as 22%[174]. Furthermore, in SEER data, SES as measured at the neighborhood level significantly mediated the association between race/ethnicity and childhood ALL survival, leading to a 44% reduction from the total to the direct effect of the Black-NHW survival disparity and 31% reduction of the Hispanic/Latino-NHW disparity in survival[175]. The inferior outcomes in high poverty neighborhoods might be attributable to multiple elements, including a poor adherence to therapy (e.g., long-term oral administration of antimetabolites)[176,177], lack of insurance, and the discontinuous coverage of insurance[178-180].

Access to care

Previous studies have shown that older age was associated with less treatment adherence[80], and that compliance with therapy was more problematic for AYAs than for other age groups[181-183]; however, the heterogeneity by race/ethnicity has been investigated mostly in childhood ALL patients. Lower exposure to mercaptopurine increases the risk of relapse in ALL, and thus the increased risk of relapse in Hispanic/Latino children with ALL compared with NHW children with ALL may in part result from a lower compliance to oral mercaptopurine therapy[184]. In a 6-month adherence monitoring program of 327 patients with ALL, Hispanic/Latino children had a significantly lower level of adherence along with lower SES compared to NHW children[177]. In another 5-month follow-up study among children with ALL from COG, adherence rates for oral 6-mercaptopurine were significantly lower in Blacks (87%) and Asian Americans (90%), as compared to NHWs (95%), after adjusting for SES[185]. These suggest that compliance to therapy could be explained by factors other than SES. In addition, the type of insurance payer is a significant predictor of adherence among ALL patients. It has been found that ALL patients with commercial insurance payers had significantly higher levels of adherence compared to those with Medicaid[186]. Compared to other age groups, the AYA group is less likely to have insurance, with around 40% of individuals between 19 and 29 years old being uninsured[187]. Hispanic/Latino and Black adult patients with cancer are more likely to be uninsured or Medicaid-insured than NHW adult patients[180]. A pediatric cancer study has also demonstrated that Hispanic/Latino patients were less likely to have insurance[188]. Notably, despite that Black children with ALL were significantly more likely to have high-risk prognostic profiles compared to NHW children, it has been found that with equal access to effective antileukemic therapy, Blacks and NHWs had the same high rate of cure[189].

Recruitment to clinical trials

In addition to the elevated incidence of Ph-like ALL in AYA ALL patients[96-99], potential factors that contribute to the AYA "survival cliff" also include the transition from pediatric to adult treatment regimens[110] and the low recruitment rate of AYA patients into clinical trials[190]. For instance, a drop off in clinical trial accruals for ALL has been identified during age 16-24, where the estimated treatment trial accrual proportion decreased dramatically from 50% at age 16 to below 10% at age 24 during 2000-2014[190]. This pattern strongly suggests that the AYA survival cliff could be in fact largely due to an "accrual cliff", as survival has been found to strongly correlate with trial accrual[190]. Moreover, there was a lack of improvement in ALL survival in patients aged 20-29 years since 1989 (APC = 0.33, $P = 0.39$), corresponding to the negligible increase of trial accrual in AYAs during 2000-2015[190]. In addition to AYAs, elderly ALL patients are rarely eligible for clinical trials and are underrepresented in trials of new cancer therapy[191,192], and the underrepresentation in clinical trials for cancer therapies has been found to underlie the poor outcomes of elderly patients[192]. In addition to age disparities, Black AYA cancer patients are less likely to be enrolled on a clinical trial compared to NHW AYAs[193], and NHWs continue to comprise the majority of participants in these trials[194].

CONCLUSIONS AND FUTURE DIRECTIONS

In this review, we described racial/ethnic disparities in ALL risk and survival; evaluated how these vary across the age spectrum; and examined the potential causes of these disparities, including genetic and non-genetic risk factors. Genetic risk factors certainly play a significant role in contributing to these disparities, as several ALL risk loci are associated with genetic ancestry, and have demonstrated different risk allele frequencies and/or effect sizes across population groups. In particular, multiple studies have shown that Ph-like ALL is associated with poor survival in both children and adults, and the risk of Ph-like ALL is associated with specific *GATA3* risk alleles that occur more frequently in Hispanics/Latinos with elevated Indigenous American ancestry. A variety of genomic aberrations have been discovered underlying Ph-like ALL and are likely to be drivers of leukemogenesis[195], which offers a great opportunity for precision

medicine approaches to use molecule inhibitors targeted at these lesions. Racial/ethnic categories in epidemiologic studies also capture, albeit imperfectly, the influence from bias, racial discrimination, culture, socioeconomic status, access to care, and environmental factors[60]. In this review, we recognize that these non-genetic factors are associated with the disparities in ALL risk and survival. Improving survival in Hispanic/Latino and Black patients with ALL will require both improved access to care and inclusion of more diverse populations in future clinical trials and genetic studies.

DECLARATIONS

Authors' contributions

Researched the literature and prepared the paper: Xu K, de Smith AJ

Made substantial contributions to the discussion of content and reviewing/editing of the manuscript before submission: Xu K, Feng Q, Wiemels JL, de Smith AJ

Availability of data and materials

NHGRI-EBI GWAS Catalog data are available at https://www.ebi.ac.uk/gwas/docs/file-downloads. Genetic variants associated with ALL risk and outcomes illustrated in the PhenoGram plots [Figure 2] are available at: https://github.com/XUKEREN/jtgg_data.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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