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ORAL ABSTRACTS

618.ACUTE LYMPHOBLASTIC LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

The Impact of Age and Genomics on Drug Sensitivity in 1,076 Children and Adults with B-Cell Acute Lymphoblastic Leukemia

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While the cure rate of pediatric acute lymphoblastic leukemia (ALL) now exceeds ~90% with contemporary combination chemotherapy, the prognosis for adults with ALL remains significantly inferior with long-term overall survival ranging from 50% to 70%. Recent studies have uncovered marked differences in ALL genomics between children and adults, with some high-risk subtypes becoming more prevalent with age. However, the underlying biology of age-related disparities in ALL is not fully understood, especially with regard to differences in leukemia sensitivity to chemotherapy.

To address this knowledge gap, we performed *ex vivo* drug sensitivity profiling (i.e., pharmacotyping) of 21 anti-leukemia agents on primary B-ALL diagnostic samples from 767 pediatric (age, 0-18 years) and 309 adult (19-84 years) patients. Drug sensitivity was measured as LC_{50}: the concentration of drug required to kill 50% of the leukemia cells (PMID: 36604538). A total of 7,975 unique LC_{50} values were experimentally determined. RNA-seq was used for subtype classification and gene expression analysis.

Among 21 drugs, seven showed significant differences in overall LC_{50} between children and adults ($P<0.05$ after Bonferroni correction): children displayed higher sensitivity to asparaginase, prednisolone, mercaptopurine, daunorubicin, and inotuzumab, while adults showed higher sensitivity to dasatinib and nelarabine. In multivariate models adjusting for 23 ALL molecular subtypes, only mercaptopurine remained significantly associated with age ($P=1.5\times10^{-5}$), suggesting that age-related differences in drug sensitivity can be primarily attributed to the variation in ALL subtypes between children and adults. For mercaptopurine, within *KMT2A*, *CRLF2*, and *DUX4* subtypes, pediatric samples consistently showed a lower LC_{50} than adults carrying the same genomic abnormality ($P=0.032$, 0.0045, and 0.02, respectively). To explore intra-subtype heterogeneity, we performed unsupervised clustering using gene expression data for each of these three subtypes. Remarkably, within each of these subtypes, we identified two clusters with distinct transcriptomic profiles that were also largely segregated by age group, i.e., an adult-dominated cluster (C-a) and a pediatric-dominated cluster (C-p). In the *KMT2A* subtype, cases in C-a exhibited an over-representation of the *KMT2A*:: *AFF1* fusion, and resistance to mercaptopurine ($P=0.029$), prednisolone ($P=0.0039$), vincristine ($P=0.046$) and cytarabine ($P=0.0037$). Within *CRLF2* ALL, cases in C-a were associated with the pres-

ence of *BCR*:: *ABL1*-like signature and *IGH*:: *CRLF2* rearrangements, and were more resistant to mercaptopurine (*P*=0.0073) and prednisolone (*P*=0.00036) compared to those in C-p. For *DUX4* ALL, C-a was characterized by an under-representation of *ERG* deletions and resistance to mercaptopurine (*P*=0.0056) and prednisolone (*P*=0.0031), compared to C-p within *DUX4*. To explore the clinical relevance of this heterogeneity, we analyzed the *in vivo* treatment response of *KMT2A* (N=35), *CRLF2* (N=59) and *DUX4* (N=118) B-ALL enrolled in six frontline ALL trials. Compared to cases in C-p (usually drug-sensitive), those in C-a (usually drug-resistant) consistently had significantly poorer initial treatment responses as measured by persistent end-of-induction minimal residual disease (≥0.01%) in *KMT2A* (58% vs 9%; *P*=0.0063), *CRLF2* (74% vs 41%; *P*=0.030), and *DUX4* (66% vs 40%; *P*=0.0058) ALL.

In conclusion, these studies have revealed important new insights into the pharmacogenomic basis of age-related differences in B-ALL treatment response. These results indicate that both inter- and intra-subtype heterogeneity contribute to inferior prognosis in adults with ALL, but also point to therapeutic opportunities to improve their outcomes.

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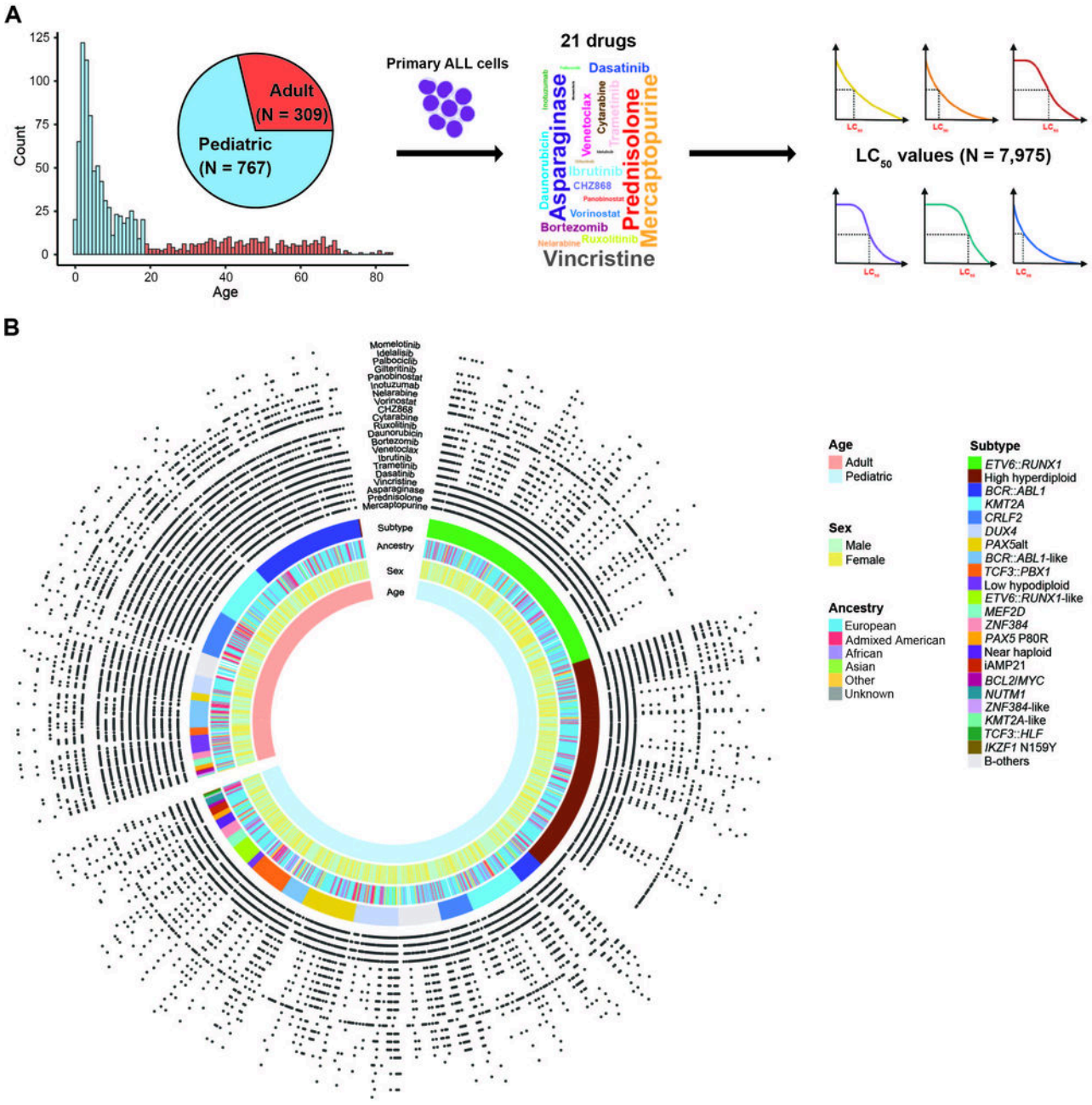

Fig. 1 Overview of this study. (**A**) Drug sensitivity was tested for primary diagnostic samples from 767 pediatric and 309 adult B-ALL patients on 21 drugs. A total of 7,975 LC_{50} measurements were obtained. (**B**) Circos plot of the age, sex, ancestry, subtype and availability of drug sensitivity data of the patients tested in this study.

Figure 1

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