Pharmacogenetics of childhood acute lymphoblastic leukemia

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Despite improvements in combination drug therapy and risk stratification, approximately 20% of pediatric patients with acute lymphoblastic leukemia (ALL) still experience drug resistance and treatment failure due to drug toxicities. In European populations, about 50% of thiopurine-induced cytotoxic adverse reactions, such as severe neutropenia and leukopenia, are explained by *NUDT15* and *TPMT* genetic variants. According to the established guideline from the Clinical Pharmacogenetics Implementation Consortium (CPIC), the thiopurine dose is pharmacogenetically titrated based on the known risk variants of *NUDT15* and *TPMT*. However, a substantial proportion of patients with leukemia presenting no genetic variation in *NUDT15* or *TPMT* still experience life-threatening toxicities, which may result in dose reduction and/or discontinuation of thiopurine, resulting in therapeutic failure and relapse of leukemia.

Throughout the multicenter study, we have investigated a novel pharmacogenetic (PGx) markers and interactions associated with thiopurine intolerance from hematological toxicities using whole-exome sequencing in childhood patients with ALL. We used the gene-wise variant burden (GVB) method, which quantitates the cumulative variant burden of one or more genes into a single score with dimensionality reduction, thus providing a reliable frame for multiple gene-interaction analysis. The categorical nature of the traditional star allele haplotype-based method can complement the quantitative nature of the GVB method for evaluating the complex interplay of multiple genes/variants. For instance, designating three categories [i.e., poor (PM), intermediate (IM), and normal (NM) metabolizers] per gene creates an exponentially increasing complexity of 3^N for a drug with *N*-gene PGx interactions. *NUDT15* and *TPMT* have been assigned nine PGx subgroups for thiopurine, which will increase exponentially following new PGx discoveries across different ethnic groups.

We identified and evaluated the deterministic effect and their interaction of novel candidate PGx variants on the last-cycle 6-mercaptopurine (6-MP) dose intensity percentage (DIP) tolerated by pediatric patients with ALL. We identified *CRIM1* rs3821169 homozygote in East Asians as a novel risk variant of thiopurine-induced hematological toxicities. Heterozygotes of the variant have revealed only mild effects on thiopurine toxicity, with an unknown clinical impact. The traditional two-gene model (*NUDT15* and *TPMT*) for predicting the tolerated 6-MP DIP < 25% was outperformed by the three-gene model that included *CRIM1*, in terms of the area under the receiver operating characteristic curve (0.734 vs. 0.665), prediction accuracy (0.759 vs. 0.756), sensitivity (0.636 vs. 0.523), positive predictive value (0.315 vs. 0.288), and negative predictive value (0.931 vs. 0.913). Furthermore, four-gene-interplay models including *NUDT15*, *TPMT*, *CRIM1*, and *IL6* revealed the best odds ratio (8.06) and potential population impact [relative risk (5.73), population attributable fraction (58%), number needed to treat (3.67), and number needed to genotype (12.50)]. Interplay between *IL6* rs13306435 and *CRIM1* rs3821169 was suggested as an independent and/or additive genetic determinant of thiopurine intolerance beyond *NUDT15* and *TPMT* in pediatric ALL.