In-depth analysis of factors affecting variability in thiopurine methyltransferase activity

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The lack of efficiency and severe adverse reactions of drugs are serious problem in pharmacotherapy. Pharmacogenomics is becoming a part of personalized medicine, the practice of administering treatments based on the individual’s genomic profile and informing treatment decisions and allowing for more accurate and efficient selection of therapies that are best suited for specific patients.

Thiopurine methyltransferase (TPMT) is an enzyme that inactivates thiopurine drugs, which are used to treat acute lymphoblastic leukemia, autoimmune diseases and to prevent rejection of transplanted organs. It has been shown in population studies that TPMT activity is trimodally distributed: approximately 0.3%, 11%, and 89% have deficient/low, intermediate, and normal TPMT activity, respectively, indicating that some 11% of individuals in this population may be prone to adverse drug events.

Aside from identifiable inactivating variants of TPMT, there are additional geno- and phenotype variances (e.g., individuals without known genetic variants, but with intermediate TPMT activity and vice versa), especially among individuals with intermediate TPMT activity. This indicates that there are non-genetic and genetic biomarkers other than TPMT genotype influencing TPMT activity.

The aim was to carry out a genotype-phenotype association study of TPMT activity to analyze the correlation between known TPMT variants and enzyme activity. In addition, new genetic and non-genetic biomarkers influencing variation in TPMT activity were investigated.

As a result, we showed for the first time that SAM is an important modulator of TPMT activity. Therefore prospective studies are necessary to evaluate the clinical usefulness of determining SAM levels as a predictive factor of thiopurine therapy response. Additionally, our results indicate that TPMT genetics have a fundamental impact on TPMT activity in humans and provide little support for the proposal that other genes may significantly contribute to the inter-individual variability of TPMT activity.

Although our data confirm that TPMT genotype is a robust predictor of TPMT activity in most individuals, TPMT genotype alone is insufficient to predict TPMT activity reliably. Despite guidelines of how to use genetic markers and interpret the results from genetic analysis, doctors should follow the course of the therapy of every individual according to the existing regimen.