Pharmacogenomics of thiopurine toxicity: make the case for precision medicine

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Elucidation of the genetic basis for inter-patient variability in drug toxicity not only reveals important biology of a drug’s mechanism of action but also provides critical knowledge that enables risk-adapted treatment individualization. Thiopurines are widely used as anti-cancer drugs and as immunosuppressive agents, but also have a narrow therapeutic index due to hematopoietic toxicities. Therefore, there is a compelling rationale for improvements in evidence-based precision medicine approaches to maximize thiopurine efficacy while reducing side effects. By pharmacogenomic profiling, we comprehensively identify genetic factors associated with thiopurine toxicity with the goal to use this information to develop genetics-guided treatment individualization. For example, inherited deficiency in detoxification enzymes TPMT and NUDT15 predisposes children with leukemia to severe thiopurine-induced myelosuppression, and we show that preemptive dose adjustment based on gene genotype effectively minimizes host toxicity without compromising anti-cancer efficacy of this class of drugs. At the forefront of precision medicine, pharmacogenomics holds particularly great promise to transform medical practice with more efficacious and safer therapies across diseases.