Pharmacogenomic and clinical data link non-pharmacokinetic metabolic dysregulation to drug side effect pathogenesis

Drug side effects cause a significant clinical and economic burden. However, mechanisms of drug action underlying side effect pathogenesis remain largely unknown. Here, we integrate pharmacogenomic and clinical data with a human metabolic network and find that non-pharmacokinetic metabolic pathways dysregulated by drugs are linked to the development of side effects. We show such dysregulated metabolic pathways contain genes with sequence variants affecting side effect incidence, play established roles in pathophysiology, have significantly altered activity in corresponding diseases, are susceptible to metabolic inhibitors and are effective targets for therapeutic nutrient supplementation. Our results indicate that metabolic dysregulation represents a common mechanism underlying side effect pathogenesis that is distinct from the role of metabolism in drug clearance. We suggest that elucidating the relationships between the cellular response to drugs, genetic variation of patients and cell metabolism may help managing side effects by personalizing drug prescriptions and nutritional intervention strategies.