The impact of human genetic variability on ligand-protein interactions and individual drug response

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Biochemical activities of low-molecular compounds and mechanism of action for majority of modern therapeutics are directly related to the interaction of the compound molecule with its target, typically a protein. For instance, adverse drug effects (ADEs), instances when a medication causes an unintended response, contribute substantially to morbidity, the cost of treatment and often appear unpredictably. Genetic variability is thought to account for a substantial fraction of the individual metabolism and drug response in humans - meanwhile our understanding of the contribution of genome individuality remains fragmented. In our project, we combined genome-wide data on human single nucleotide polymorphisms (SNPs) with structural data on drug-protein complexes. Using data from 1000genome project and The Cancer Genome Atlas consortium, at the genome-wide scale, we identify all SNPs potentially affecting the proteins binding affinity for drug-like compounds and metabolites. Our results suggest that SNPs with a serious impact on ADE are present in most individuals; however, most of such polymorphisms are rare requiring a personalized approach to their identification. So, the genetic component for many ADEs may be highly personalized with each individual carrying a unique set of relevant SNPs. The analysis of individual biochemistry and the reduction of ADEs may, therefore, primarily rely on the application of computational genome analysis in the clinic rather than the experimental study of common SNPs.

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