Genetics and Variable Drug Response

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ANNUAL HEALTH CARE EXPENDITURES CURRENTLY EXceed $2.5 trillion in the United States, a cost burden equivalent to more than $8000 per person per year. Treatment strategies designed to optimize efficacy, ie, avoiding therapeutic failure while minimizing toxicity, hold the potential to reduce this cost burden. For many drugs, variability in outcome is influenced by 1 or more genetic factors. Because many of these genetic factors have only recently been challenged with modern pharmaceuticals, variants of strong clinical relevance are often found at fairly high frequency within the general population.

Individualized drug therapy is especially desirable when the therapeutic index is narrow and the consequences of drug toxicity are life-threatening (eg, antineoplastics, anticoagulants, immune modulators). Many such drugs are administered at maximally tolerated doses. Because these doses are often chosen from population averages, as many as one-third of patients exposed may develop unacceptable toxicity, and a significant proportion of patients will not respond. This increases the risk-benefit ratio for individual patients and imposes a sizeable economic strain on the health care system. An important unanswered question is whether genetics will solve this problem or add further cost to health care with relatively little benefit on outcome.

Early Successes

Initial progress in pharmacogenetics came from small candidate gene studies characterizing a limited number of single-nucleotide polymorphisms (SNPs) in genes encoding drug metabolizing enzymes. One well-established example is thiopurine methyltransferase (*TPMT*). Thiopurine substrates (eg, 6-mercaptopurine) are used for immune modulation and the management of acute lymphoblastic leukemia. Lower *TPMT* enzyme activity leads to increased concentration of active metabolites after administration of thiopurines. Rare individuals with 2 abnormal copies of the *TPMT* gene can develop extreme myelosuppression, which can be fatal in the context of usual doses of thiopurines, necessitating a 10-fold dosage decrease to prevent such toxicity.[1]

Drugs modulating hemostasis, such as clopidogrel[2] and warfarin,[3] also have narrow therapeutic indexes, and clinical outcomes related to the use of these drugs can be strongly influenced by genetic variability in the cytochromes p450 (CYPs). For example, the biologically active form of warfarin is metabolized primarily by CYP2C9, and common variants in this enzyme alter warfarin dosing requirements. Further variance in warfarin dose can be explained by inheritable changes in the vitamin K oxidoreductase complex-1 (VKORC1), an enzyme involved in the drug's mechanism of action. When combined with clinical covariates (age, race, and sex), gene-based drug dosing models explain more than 50% of the overall variability in warfarin requirement,[3] and genetic testing has been shown to reduce the risk of hospitalization by as much as 30% during the first 6 months of therapy.[4]

Ancestry and Effect Size

The development of gene-based warfarin dosing models illustrates another important principle in this field, that variant distribution reflects population structure. For example, the human leukocyte antigen variant HLA-B*15:02 places patients at increased risk for the development of severe adverse skin reactions to carbamazepine, including Stevens-Johnson syndrome, and this variant occurs far more frequently in individuals of Asian ancestry (frequency, 5%-10%) than individuals of European or African ancestry (near 0%).[5] Conversely, the HLA-A*31:01 allele has recently been associated with severe adverse skin reactions to carbamazepine within persons of European ancestry.[6]

Major histocompatibility gene variants contribute to other life-threatening drug reactions as well. The HLA-B*57:01 allele is associated with drug-induced liver injury in the context of flucloxacillin, a relationship initially identified in a genome-wide association study (GWAS) limited to only 51 cases.[7] This allele is also a strong predictor of abacavir hypersensitivity, a relationship for which pharmacogenetic testing is required in many countries. Thus, another emerging principle is that effect sizes are often larger than those observed for complex disease phenotypes. Genome-wide association studies using relatively small sample sizes have linked the IL28B locus to the efficacy of anti–hepatitis C virus therapy,[8] and the SLC01B1 locus to the toxicity of simvastatin.[9] Following each of these GWAS,

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confirmatory studies yielded causal variants with odds ratios greater than 20.

Expanding the Model

For drugs with a narrow therapeutic index, pharmacogenetic studies may hold the potential to resurrect treatments previously withdrawn from the market, particularly for agents designed to fill underserved clinical niches (eg, CB_1 receptor blockers for the treatment of obesity). For drugs with a wider therapeutic index (eg, β antagonists for hypertension), predictive models may need to include combinations of variants with relatively small main effects. For others (eg, β agonists for asthma), predictive models of response improve with the inclusion of genetic loci contributing to disease progression. Many examples are emerging (eg, metformin for type 2 diabetes mellitus) for which additional pharmacokinetic candidate genes (organic cation transporters and multidrug and toxin extrusion proteins) provide insights into absorption, distribution, and elimination beyond information already known about the drug's metabolism.

For many of these drugs, the rarity of serious adverse reactions may require that genetic studies focus on surrogate markers of toxicity. For instance, much work has been done to identify gene variants influencing serum creatine kinase level as a measure of statin intolerance and hepatic transaminases for drug-induced liver injury. However, the degree to which genetic determinants of intermediate toxicity will predict the more extreme phenotypes remains unknown. Although studies of drug-induced QT interval prolongation have provided some insight into predictors of life-threatening ventricular arrhythmias, these investigations have primarily underscored the clinical importance of extremely rare variants.

Moving Forward

The clinical and scientific communities continue to make impressive strides toward characterizing genetic determinants of variability in drug outcome, and gene-based treatment trials provide evidence in support of the claim that this type of information can be leveraged to improve health care. When the HLA-B*15:02 genotype was quantified in approximately 5000 Asian patients, to determine who should not receive carbamazepine for seizure control, the frequency of Stevens-Johnson syndrome and toxic epidermal necrolysis decreased to 0%.[5] The US Food and Drug Administration now provides similar guidance, through the modification of package inserts, for nearly 100 drugs.[10] These drugs include (but are not limited to) analgesics, anesthetics, other psychotropics, neuroleptics, antiarrhythmics, antianginals, antihypertensives, lipid modifying agents, anti-inflammatory agents, antiviral agents, antibacterial agents, immune modulators, antineoplastics, anticoagulants, and acid suppressants.

What makes such an association actionable? The Pharmacogenomics Research Network routinely publishes a dynamic series of gene-based drug dosing guidelines through the Clinical Pharmacogenetics Implementation Consortium.[1] For these guidelines to improve care, full clinical implementation will require widespread clinician education, acceptance, and automated decision support. The current expansion of electronic medical records (EMRs) represents an opportunity to meet these challenges. Most EMRs already contain the basic decision-support tools necessary to warn clinicians about potential drug-drug interactions within the flow of a busy clinical practice. However, clinician acceptance of drug-drug interaction alerts currently remains suboptimal.

Additional work is needed to optimize decision support across a wide variety of clinical settings. As clinicians adopt increasingly sophisticated EMRs, they are presented with a unique opportunity to move gene-based drug dosing into practice. By promoting the meaningful use of EMRs, the Patient Protection and Affordable Care Act of 2010 encourages clinicians to document the maintenance of active medication lists and consider decision-support software capable of identifying drug interactions. Extension of these decision-support strategies to gene-drug interactions will be the key to implementing genetic discoveries that will allow physicians to individualize drug therapy, maximize the likelihood of response, and minimize risk for adverse reactions.

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