Pharmacogenetics for the prescriber

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Abstract

Pharmacogenetics is the study of how genetic factors affect the response to drugs (efficacy, adverse effects). Variation in genes can affect either a drug's pharmacokinetics (how the drug is handled in the body) or its pharmacodynamics (how it interacts with proteins in the body to produce its effects). Such variation needs to be evaluated in combination with clinical and environmental factors in order to personalize either drug choice or drug dose in individual patients. There are some well-characterized examples of pharmacogenetic variation in clinical practice. As our knowledge of the human genome increases, the challenge will be to translate these findings on genetic variation into clinical practice by generating evidence that shows that genotype-guided prescribing leads to better clinical outcomes than current standard practice.

Keywords Drug efficacy; drug safety; individual variability; personalized medicine; pharmacodynamics; pharmacogenetics; pharmacogenomics; pharmacokinetics; precision medicine; stratified medicine

Key points

- Variability in the response to drug treatment, in terms of both efficacy and safety, is the norm rather than the exception, and is related to both environmental and genetic factors
- Genetic variation might influence either the choice of drug to be prescribed and/or the optimal dosage
- A number of drugs are now prescribed on the basis of a genetic test (e.g. trastuzumab for breast cancer), and this number will increase over the coming years
- Genetic variation is an important cause of increased susceptibility to adverse reactions to drugs (e.g. abacavir, carbamazepine)
- Prescribers must be aware of (1) the drugs for which there is evidence that genetic factors determine response, (2) where they can get the relevant test carried out, and (3) how to interpret the result

Introduction

Drugs are currently licensed on the basis that they show efficacy that is either equivalent or superior to a comparator, or they are superior to placebo, without adverse effects that compromise the overall benefit–risk profile of the drug. However, averaged data from populations disguise the fact that there is great interindividual variability in the response to a standard dose of most drugs. This variability is due not only to patient-related factors (non-adherence, smoking, alcohol, co-morbidities), but also, to an extent that varies from drug to drug, to genetic factors.[1] The study of these genetic factors is known as pharmacogenetics. A more recently introduced term is 'pharmacogenomics', which refers to the effect of the whole genome, rather than individual genes, on the response to drugs.

What are the sources of variability?

Variability in drug response can result from pharmacokinetic and/or pharmacodynamic factors (Table 1). Drug metabolism is the most important pharmacokinetic source of variation and can be caused by genetic variation in both phase I and phase II enzymes. An example of a phase I enzyme for which genetic variability can lead to profound clinical consequences is butyrylcholinesterase (pseudocholinesterase): patients deficient in this enzyme suffer prolonged paralysis after the use of suxamethonium, a depolarizing neuromuscular blocking agent that normally has a duration of action of 10 minutes.

Variability in the expression of the cytochrome P450 enzymes can lead to interindividual variability in metabolism of many drugs.[2] For example, cytochrome P450 2D6 (CYP2D6), which is responsible for the metabolism of 25% of drugs, is absent in approximately 8% of the UK population (who are called poor metabolizers). Eliglustat, an inhibitor of glucosylceramide synthetase used in Gaucher's disease, is metabolized by CYP2D6. Poor metabolizers should be prescribed 50% of the dose required for extensive metabolizers. Variability in phase II enzymes can also be important: for instance, mutations in the *UGT1A1* gene, a member of the glucuronyltransferase family, are responsible for Gilbert's syndrome, because of reduced glucuronidation of bilirubin.

Less work has been done on pharmacodynamic factors causing variation in drug response. Because drugs affect almost every protein in the body, either directly or indirectly, many genes have the potential to affect pharmacodynamic responses. A well-established example is glucose 6-phosphate dehydrogenase (G6PD) deficiency, which renders red blood cells liable to oxidative stress-induced haemolysis on exposure to drugs such as sulphonamides, dapsone and primaquine. G6PD deficiency is now recognized to be the most common enzyme deficiency worldwide and is a cause of drug withdrawal (e.g. the antimalarial chlorproguanil–dapsone). Adverse reactions to newer drugs have also been linked to G6PD deficiency (e.g. rasburicase used to treat gout) and have caused amendments of prescribing guidance.[1]

Some key examples relevant to prescribers

The most significant genetic predictors of efficacy and adverse effects are listed in Table 2. If a patient has an adverse genetic

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Pharmacokinetic and pharmacodynamic factors determining variability in drug response

Pharmacokinetic
- Absorption
- Distribution
- Metabolism
- Excretion

Pharmacodynamic
- Enzymes
- Receptors
- Ion channels
- Transporters

Table 1

variant, the usual prescribing decision is to avoid the implicated drug, alter the dose or continue with the implicated drug but monitor the patient more closely. A few examples are discussed in more detail below.

Drug efficacy

Cancer therapy

Targeted cancer therapy is becoming increasingly important in the management of malignant disease.[3] This has been made possible by our ability to detect changes in the cancer or somatic genome. Each cancer has between 30 and 80 mutations, some of which affect the response to therapy.

The earliest example of targeted therapy was in breast cancer through the use of anti-oestrogen therapy in patients whose tumours were oestrogen receptor positive. More recently, the use of trastuzumab (Herceptin®) has become standard therapy for the 20% of newly diagnosed breast cancers that have an amplification of the *HER2* gene or over-expression of the protein — this improves disease-free and overall survival. Recent advances have included the development of vemurafenib: this targets the *V600E* mutation in *BRAF*, which promotes cell proliferation through activation of the mitogen-activated kinase pathway. The use of vemurafenib in the 50–60% of cases of metastatic malignant melanoma that carry the *V600E* mutation results in an overall response rate of 53% with a median overall survival of 16 months. Patients usually progress after 7 months

The clinically most significant genetic predictors of drug response

Organ or system involved	Associated gene/allele	Drug/drug response phenotype
Blood		
Red blood cells	*G6PD*	Primaquine-induced haemolysis
Neutrophils	*TPMT*2*	Azathioprine/6-mercaptopurine-induced neutropenia
	*UGT1A1*28*	Irinotecan-induced neutropenia
Platelets	*CYP2C19*2*	Stent thrombosis with clopidogrel
Coagulation	*CYP2C9*2, *3, VKORC1*	Warfarin dose requirement
Brain and peripheral nervous system		
CNS depression	*CYP2D6*N*	Codeine-related sedation and respiratory depression
Anaesthesia	Butyrylcholinesterase	Prolonged apnoea with suxamethonium
Peripheral nerves	*NAT2*	Isoniazid-induced peripheral neuropathy
Drug hypersensitivity		See Figure 1
Drug-induced liver injury		See Figure 1
Infection		
HIV-1 infection	*CCR5*	Maraviroc efficacy
Hepatitis C	*IL28B*	α-Interferon efficacy
Malignancy		
Breast cancer	*CYP2D6*	Response to tamoxifen
Chronic myeloid leukaemia	*BCR-ABL*	Imatinib and other tyrosine kinase inhibitors
Colon cancer	*KRAS*	Cetuximab efficacy
Gastrointestinal stromal tumours	*KIT, c-kit*	Imatinib efficacy
Lung cancer	*EGFR*	Gefitinib efficacy
	EML4-ALK	Crizotinib efficacy
Malignant melanoma	*BRAF V600E*	Vemurafenib efficacy
Muscle		
General anaesthetics	Ryanodine receptor	Malignant hyperthermia with general anaesthetics
Statins	*SLCO1B1*	Myopathy/rhabdomyolysis with simvastatin

CNS, central nervous system; HIV, human immunodeficiency virus.

Adapted from Ref. 1.

Table 2

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