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 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 integrating the use of genetic tests into clinical pathways in primary and secondary care.

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

Key points

- Variability in the response to drug treatment, in terms of efficacy and safety, is the norm rather than the exception, and is related to both environmental and genetic factors
- Genetic variation might influence the choice of drug to be prescribed and/or the optimal dosage, and a number of drugs are now prescribed on the basis of a genetic test (e.g. 5-fluorouracil for colon cancer)
- Genetic variation is an important cause of increased susceptibility to serious 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 the response; (2) where they can get the relevant test carried out; and (3) how to interpret the result
- Implementation of pharmacogenetics in clinical practice is in progress in many parts of the world but is mostly limited to the richer nations, with the possibility that this will worsen existing health inequalities

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 caused not only by patient-related factors (non-adherence, smoking, alcohol, co-morbidities), but also, to an extent that varies from drug to drug, by 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 have 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 the metabolism of many drugs.[1] 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 ('poor metabolizers'). Eliglustat, an inhibitor of glucosylceramide synthetase used in Gaucher disease, is metabolized by CYP2D6. Poor metabolizers should be prescribed 50% of the dose required for extensive metabolizers. Another example is that of codeine, a pro-drug metabolized to morphine by CYP2D6. Poor metabolizers do not have pain relief from codeine.

Variability in phase II enzymes can also be important: for instance, mutations in *UGT1A1*, encoding a member of the glucuronyltransferase family, are responsible for Gilbert syndrome because of reduced glucuronidation of bilirubin.

Less work has been done on pharmacodynamic factors causing variations 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 sulfonamides, 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

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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

antimalarial chlorproguanil–dapsone). Adverse reactions to newer drugs (e.g. rasburicase used to treat gout) have also been linked to G6PD deficiency and have caused amendments of prescribing guidance.[1]

Some key examples relevant to prescribers

Table 2 lists the most significant genetic predictors of efficacy and adverse effects. If a person has a genetic variant that either reduces activity (loss of function) or increases activity (gain of function), 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, and are highlighted in a recent report from the Royal College of Physicians and British Pharmacological Society.[2]

Drug efficacy

Cancer therapy

Targeted cancer therapy is becoming increasingly important in the management of malignant disease.[1] 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 by using anti-oestrogen therapy in patients whose tumours were

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, NUDT15*	Azathioprine/6-mercaptopurine-induced neutropenia
	*UGT1A1*28*	Irinotecan-induced neutropenia
Platelets	*CYP2C19*2*	Transient ischaemic attacks/strokes with clopidogrel
Coagulation	*CYP2C9*2, CYP2C9*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 Pirmohamed.[1]

Table 2

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oestrogen receptor positive. Trastuzumab (Herceptin) has become standard therapy for the 20% of newly diagnosed breast cancers showing amplification of the *HER2* gene or overexpression 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 because of secondary mutations, which has led to trials using combination therapy and immune checkpoint inhibitors.

The increasing use of immune checkpoint inhibitors is adding to the complexity of identifying which patients are most likely to respond. There is emerging evidence that patients who have a higher mutational and/or neoantigen load in the tumour are more likely to respond. A new development is tumour-agnostic drugs, which are licensed on the basis of the tumour's molecular signature rather than its location in the body. For example, larotrectinib has been developed for patients with solid tumours who have a neurotrophic tropomyosin kinase receptor gene fusion.

Cystic fibrosis

Cystic fibrosis is an autosomal recessive disease caused by many different mutations in the *CFTR* gene. About 4% of patients have the *G551D* mutation, which results in a protein that is expressed at the cell membrane but is defective. This has led to the development of ivacaftor, which produces marked improvements in lung function in these patients by partially restoring the function of the protein. Indications for the drug have subsequently been extended to >30 mutations (with the same functional effects as the *G551D* mutation) in *CFTR*.

More recent developments include the use of dual (ivacaftor in combination with tezacaftor) and triple (elexacaftor–tezacaftor–ivacaftor) therapies to treat patients with the Phe508del mutation, the most common mutation in cystic fibrosis patients. A major issue that has caused controversy in many countries is the high cost of these therapies.

Drug safety

Warfarin

Individual daily dose requirements of warfarin vary at least 40-fold. A combination of age and body mass index, together with genetic variations in *CYP2C9* (responsible for metabolism of warfarin) and *VKORC1* (the enzyme inhibited by warfarin), accounts for about 60% of the variation in daily dose requirements for warfarin. Dosing algorithms that take into account age, body mass index and variation in the *CYP2C9* and *VKORC1* genes have been developed and were tested in a randomized clinical trial (European Pharmacogenetics of Anticoagulant Therapy (EU-PACT)). This showed that the genotype-guided prescribing of warfarin improved the time in the therapeutic international normalized ratio range by 7% compared with standard care.[3]

Immune-mediated adverse drug reactions

These reactions are characterized by rashes and occasionally by the involvement of other organs such as the liver, kidney, lungs, bone marrow, heart and colon (in combination with the rash or in isolation). The immune response to antigens, including those derived from drugs, is partly under the control of the human leucocyte antigen (HLA) genes on chromosome 6, which is the most polymorphic region of the human genome. Variation in HLA genes is an important determinant of susceptibility to these immune-mediated adverse reactions (Figure 1).[4]

With the anti-HIV drug abacavir, hypersensitivity reactions characterized by rash, fever and gastrointestinal and respiratory manifestations, usually seen in 5% of patients, can be prevented by genotyping for *HLA-B*57:01* before prescription and avoiding abacavir in patients who carry the allele. This is also a cost-effective approach, which has now been mandated through changes in the summary of product characteristics and guidelines from HIV societies.

A strong genetic association has been shown in Han Chinese patients between *HLA-B*15:02* and Stevens–Johnson syndrome caused by the anti-seizure drug carbamazepine. In white and Japanese patients, a different HLA allele, *HLA-A*31:01*, acts as the predisposing factor for carbamazepine-induced hypersensitivity reactions (including maculopapular exanthema, hypersensitivity syndrome and Stevens–Johnson syndrome).[5] Other genetic associations between HLA genes and drug-induced toxicities affecting the skin and liver are shown in Figure 1.

Panel genetic testing

Instead of genotyping for one variant whenever a patient needs a drug (a reactive approach), it has been proposed that individuals could be genotyped for a panel of variants so that the genotype results are already available in patient records when a new drug is needed (a pre-emptive approach). In support of this, a recent

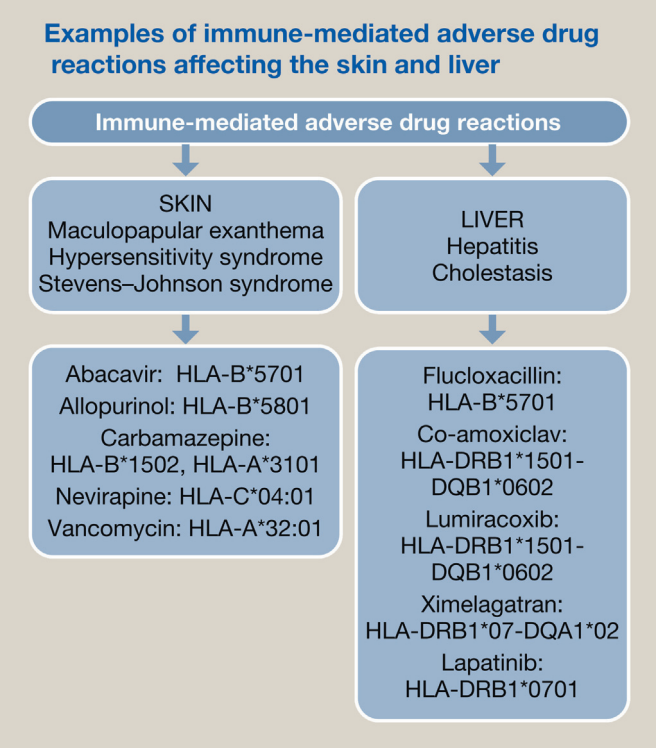

Figure 1

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multicentre, cluster-randomized, crossover implementation study showed that a 12-gene pharmacogenetic panel was able to significantly reduce the incidence of adverse drug reactions.[5]

Future perspectives

At least 0.1% of the human genome is variable, and this accounts for the interindividual differences seen in the human population, including the beneficial and adverse effects of drugs. Many different variants that alter the response to a drug have been identified (Table 2). Our ability to interrogate the human genome is improving all the time, and this will undoubtedly lead to the identification of many other genetic variations affecting the response to drugs. However, it is also important to note that many of these variants will act not in isolation but in combination with environmental factors. Thus, a holistic approach that takes into account both environmental and host factors is needed to ensure the patient is given the right drug, in the right dosage, at the right time to maximize efficacy and minimize harm.[1] ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 25-year-old man presented for review after he was found on routine testing to be HIV positive. He was asymptomatic. Possible future treatment was discussed, including abacavir.

What is the most important test to perform before instituting this therapy?

A. Renal function
B. *HLA-A*31:01 status*
C. Viral load
D. Liver function
E. Acetylator status

Question 2

A 70-year-old man presented with left-sided weakness lasting <12 hours. He had a history of transient ischaemic attacks (TIAs). He was taking atorvastatin (20 mg/day), ramipril and amlodipine (for hypertension both at 10 mg/day) and clopidogrel 75 mg/day, the latter to minimize the risk of future strokes. Adherence was good.
On clinical examination, he was in sinus rhythm (pulse rate 80/minutes) and his blood pressure was 128/88 mmHg.

Investigations

- Total cholesterol 4.8 mmol/litre (<5.2)
- Echocardiogram showed mild left ventricular hypertrophy
- CT scan of the head showed evidence of lacunar strokes

What is likely to be the most important factor in the failure to control his TIAs?

A. Failure of activation of clopidogrel
B. Inadequate dose of clopidogrel
C. Intermittent cardiac arrhythmia
D. Drug interaction
E. Inadequate dose of atorvastatin

Question 3

A 14-year-old boy presented with a respiratory exacerbation of cystic fibrosis caused by *Pseudomonas aeruginosa*. He had a G551D mutation. He had been taking ivacaftor for >12 months, and this had reduced the number of admissions and improved his lung function. However, his parents asked if there was an alternative treatment that would prevent admissions.

What is the most appropriate response?

A. Add tezacaftor
B. Stop the ivacaftor
C. Continue with ivacaftor in an unchanged dose
D. Increase the dose of ivacaftor
E. Offer triple therapy (elexacaftor–tezacaftor–ivacaftor)

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