How genomic scans can help predict altered drug response or disease

Genomic scans are now available to identify genetic variants associated with disease and drug response. Alain Li Wan Po, Peter Fardon, Candy Cooley, Sarah Warburton and Colin Barker illustrate the potential usefulness of genomic scans in informing prescribing, using a hypothetical scenario in a community pharmacy as an example.

Whole genome sequencing is now possible and several personal genomic profiles, including those of scientists James Watson (one of the co-discoverers of DNA) and Craig Venter, have been posted on the internet for research purposes. More limited scans to identify genetic variants associated with disease and drug response can be purchased for less than $1,000, and this has generated considerable public interest. Some pharmacogenetic testing are already in routine use in hospital practice (see Panel, p538), notably in oncology and serious infections clinics.

Background

Analytically reliable genomic scans can now be obtained and various health correspondents of the press have already commented on their own experience of having their genome scanned fully or scanned for a panel of genetic variants associated with disease and altered drug response. Although the cost, at the equivalent of less than a year’s season ticket for a premiership football team, is still regarded as expensive, there is little doubt that prices will keep dropping as the technology develops.

Some claim that soon a 10-minute genome scan will be commercially available.1

Closer to practice is the availability of scans to identify specific polymorphisms, reported to be associated with risk of disease or drug response. Specifically, any doctor can now order a cytochrome p450 (CYP) profile, including CYP2D6, for a patient, and a recent survey indicates that over 80 health-related genetic tests are available direct to the consumer in the US.2 Twelve of these were for pharmacogenomic testing, the most common category.

The US company 23andMe (named after the 23 pairs of human chromosomes) provides genetic profiles with single nucleotide polymorphisms (SNPs), which is reported to be associated with, albeit often poorly quantified, disease risk. Sergey Brin, co-founder of Google, has had his scan done by 23andMe, which was founded by his wife Anne Wojcick. It revealed that he had the G2019S mutation, which is associated with an increased risk of Parkinson’s disease, as well as a family history of Parkinson’s disease on his mother’s side.3

23andMe is embarking on a study of genetic associations with parkinsonism and participants are asked to pay $25 instead of the usual price $399 if they are willing to participate in the study.4 With a target of 10,000 subjects, the power of the study will be far...
The Watson genomic code
James Watson’s genetic code is in the public domain. Software tools are also available to allow searching for relevant genetic variants, most notably SNPs, which are known to be associated with altered drug response. Part analysis of Professor Watson’s genetic code is also available on the internet, which highlights some genetic variants associated with drug response. In this article, we will concentrate on the specifics of the scenario (Panel, right), but highlight other relevant issues as well.

Metabolic enzyme polymorphism
Watson’s genetic code shows the presence of an SNP of the CYP2D6 gene, which is associated with poor metabolism of a range of CYP2D6 drug substrates, including codeine.

Codeine Codeine needs to be metabolised to morphine for analgesic efficacy. Therefore, given the impaired metabolic pathway, less morphine would be formed. Moreover, given the small amounts of codeine present in OTC analgesic tablets, it is unlikely that there are products more effective for him than single-ingredient tablets, such as paracetamol.

Dihydrocodeine Dihydrocodeine is another opiate analgesic available OTC in combination with other analgesics (eg, paracetamol). The only structural difference from morphine is the presence of an additional double-bond in the structure.

Biotransformation of dihydrocodeine to dihydromorphine is also mediated by CYP2D6. Although in extensive metabolisers, the pharmacokinetics of both dihydrocodeine and dihydromorphine following ingestion of dihydrocodeine are linear (ie, a doubling of dose leads to a doubling of drug exposure), this may not be the case in poor metabolisers. Therefore, in extensive metabolisers, a higher dose may be required to lead to proportionately larger effects (both positive and adverse). In poor metabolisers, this may not be the case and overdosing may lead to non-linear effects.

The implication of the recent work on the pharmacogenetics of dihydrocodeine is that one would probably expect less pharmacogenetic variability in response to dihydrocodeine than codeine. However, this has not yet been adequately validated by pharmacodynamic and clinical studies. Any greater benefit from dihydrocodeine than codeine because of the former derivative’s analgesic activity in experimental pain models has yet to be proven. Therefore, if a dihydrocodeine analgesic combination is recommended, it may well be more for the placebo additive effect than for anything else. This raises many ethical issues, although many clinicians are happy about prescribing poorly validated medicines believing them to be potentially beneficial.

Lactose intolerance Since Professor Watson has informed you that he is lactose intolerant, there is no need to pursue this further in the genetic code because a patient may still develop an undesirable phenotype in the absence of known causative polymorphisms. Therefore, for Professor Watson, formulations containing lactose as tablet excipient should be avoided.

Wider considerations
Receptor polymorphism In addition to polymorphisms affecting metabolic pathways, drug receptors or targets involved in the pharmacological effect (also called pharmacodynamic effect) may also show functional mutations. The vitamin K epoxide reductase complex subunit 1 (VKORC1), a target for the anticoagulant warfarin, is an example. Professor Watson’s genetic code also shows an SNP in the VKORC1 gene with reference sequence rs8050894. This polymorphism is in strong linkage disequilibrium (tends to be inherited together) with an SNP in the promoter region, which is strongly associated with warfarin sensitivity, leading to a lower dose requirement.

So, if Professor Watson is on warfarin, then there is a need to consider carefully any use of analogues that contain aspirin, which may independently increase the risk of bleeding and possibly complicate therapy. This emphasises the importance of a thorough drug history.

A scenario in a pharmacy
James Watson, a 74-year-old, calls in during one of his trips to London. He is generally healthy but occasionally develops bad headaches, which he ascribes to pressure from the media. He says that the latest episode was brought on by some comments he made at a lecture which, in his view, were misrepresented. He asks for your advice on what tablets he could take. His paracetamol tablets do not seem to have worked and he has tried other over-the-counter analgesics as well.

Being a pioneer in DNA research and genomics research, he presents you with his personal genomic code (jmwatsonsequence.cshl.edu/cgi-perl/gbrowse/jmwsequence) and asks you to give your advice. He volunteers that he is lactose intolerant. What do you do?

1. Run for the door and call the police
2. Ignore his genomic code and proceed normally with a medicines review taking account of relevant clinical information and information held on your drug–drug interaction databases
3. Have a stab at identifying major issues identifiable from his genetic code, including genetic variants which flag drug–drug interactions

Let us assume you decide to be brave and attempt to read his code to give him some informed advice. What are you likely to find in his personal genomic code?

Pharmacogenetic tests in routine use
Chlamydia Nucleic acid amplification test. A positive test result allows pharmacists to supply azithromycin over-the-counter for both the patient tested and his or her sexual partner(s).

Epidermal growth factor receptor The test identifies over-expression of epidermal growth factor receptors (EGFRs) and gene amplification. This is a data-sheet requirement for the prescribing of cetuximab, which is used in the treatment of colorectal cancer.

HER-2 The prescribing of trastuzumab (used to treat breast cancer) requires identification of functional polymorphisms. Therefore, given the small amounts of codeine present in OTC analgesic tablets, it is unlikely that there are products more effective for him than single-ingredient tablets, such as paracetamol.

HLA-B*5701 The test for HLA-B*5701 identifies individuals who are hypersensitive to abacavir, HLA-B*5701.

KRAS mutation test The prescribing of panitumumab for advanced colorectal cancer requires identification of functional KRAS and EGFR over-expression.

Presence of Bcr-Abi translocation (Philadelphia chromosome) The presence of the Bcr-Abi translocation (Philadelphia chromosome) is a diagnostic feature of chronic myelogenous leukaemia.

Tuberculosis The tuberculosis test is used to identify multidrug-resistant TB rapidly in developing countries.

For personal use only. Not to be reproduced without the permission of the editor (permissions@pharm.org.uk)

www.pjonline.com
same way that a potential drug interaction gued that knowing that a patient has a geno- log reverse transcriptase inhibitor used to potentially lethal abacavir (a nucleoside ana- variants. T esting for HLA-B*5701 to predict with low penetrance is still debated. However, genotyping for susceptibility genes polygenic diseases, such as breast cancer. genotyping is now widely accepted not only that technically, reliable scans can, and will, be done at increasingly affordable prices.

The quantification of risk of disease from genotyping is now widely accepted not only for monogenic diseases, but also for some polygenic diseases, such as breast cancer. However, genotyping for susceptibility genes with low penetrance is still debated.

The clinical use of genotyping for drug-response is established for only a few genetic variants. Testing for HLA-B*5701 to predict potentially lethal abacavir (a nucleoside anal- og reverse transcriptase inhibitor used to treat HIV and AIDS) hypersensitivity is prob- ably the best example. For most genetic vari- ants associated with drug response, the clinical use is less established, and genotyping for CYP2D6 is an example. It could be ar- gued that knowing that a patient has a geno- type which predicts a poor metaboliser phenotype should alert the clinician in the same way that a potential drug interaction leading to altered drug pharmacokinetics would. A clinician would not prescribe an in- teracting drug without weighing the harm- benefit balance. An SNP may highlight the same risk as a drug interactor and should be treated accordingly.

One of the major challenges to the appli- cation of pharmacogenetic testing (including CYP2D6 testing) in clinical practice is that, in most cases, the relationship between response and genetic variant is imperfect. Rarely does a genetic variant always predict a particular response. The extent to which a test is useful depends on the accuracy of predictions in routine patient care. Moreover, even for a ge- netic variant strongly associated with a drug response, the latter is often altered by other factors, such as age, organ function, concomi- tant drug ingestion and other variants not only of the same gene but also of other genes involved in the metabolic or response path- ways of the drug concerned.

For example, after codeine ingestion, any morphine formed is conjugated to the 3- and 6-glucuronides through the intermediary of the enzyme uridyl glucuronosyltransferase 2B7 (UGT2B7). Similar metabolic conjuga- tions occur for any dihydrocodeine formed after taking dihydrocodeine. Although mor- phine–3–glucuronide is inactive, the 6–glu- curonide is active. A recent case-control study suggests that breastfed infants of mothers who were treated with codeine for obstetric pain and who were ultra-rapid CYP2D6 metabolisers and were UGT2B7*2 homozy- gotes (individuals with both alleles of this type) had a greater risk of developing poten- tially life-threatening central nervous system depression.11

Conclusion The scenario of a patient coming in with his or her genetic metabolic profile is no longer fictional. Neither is the usefulness of geno- typing for predicting likely drug response in secondary care. The clinical professions in pri- mary care need to be ready for this pharma- cogenetics challenge. If you knew that a patient was taking a drug which interferes with one that you intend to prescribe, would you not take that into account? Knowing that a patient has a genetic variant which nullifies or amplifies the action of a drug should surely be given the same careful consideration dur- ing the drug prescribing process.

The science of medicine requires that the risks and benefit be traded off. The art of medicine is the integration of results of this deliberation with the patient’s preferences to arrive at the best course of action for the patient.

Clinical implication Although we have adopted a light-hearted approach to this dis- cussion, the implications for practice are real and potentially serious. Although personal whole genomic profiling is still costly and technically, reliable scans can, and will, be done at increasingly affordable prices.

References