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Pharmacogenetics and the Pharmacist

In this article, Dr Monica Strugaru and Associate Professor Martin C Henman from The School of Pharmacy and Pharmaceutical Sciences at Trinity College Dublin provide an overview of pharmacogenetics, including the differing approaches taken internationally and the pharmacist's role in pharmacogenetics.

Since receptors, enzymes, ion channels, pumps and transporters comprise the majority of the types of molecules that may be absent or exhibit as dysfunctional in pathology, they determine our susceptibility to disease, and because they are also central to the actions of drugs and to the processes of pharmacokinetics, they determine our response to drugs.

All of these molecules are proteins and are coded for by a gene. Each person's collection of genes, their genome, is unique. Therefore, analysing the genome and mapping the potential problems at the level of the gene is the basis of personalised, or precision, medicine. Using this information to improve the diagnosis of disease and the likely response to drug treatment of individual patients is, quite obviously, a massive and expensive undertaking. Selecting the patients and diseases which can benefit the most from this comprehensive approach is still being evaluated and is largely confined to hospital practice. Using genetic knowledge to guide the selection of drugs and of the regimen is slightly less complicated and consequently is more advanced, and, can be used in community pharmacy practice.

Pharmacogenetics is the study of "variability in drug response due to heredity". The term was first introduced by Vogel in 1957 and is now used interchangeably with "pharmacogenomics", which is the study of "how an individual's genetic inheritance affects the body's response to drugs", and encompasses all genes in the genome that may determine drug response. Pharmacogenomics is often abbreviated as PGx.

Polymorphism

Polymorphism, i.e. genetic variability, is characterised by differences in gene expression. The medicines' interaction with the human body at pharmacokinetic and/or pharmacodynamic level involves proteins such as enzymes and receptors. Therefore, the genetic profile could determine different responses in how medicines are processed throughout the body (from absorption and interaction with the body to metabolism and elimination).

The CYP450 enzymes have many isoforms, are crucial to drug metabolism and have multiple genetic variants. These genetic variants give rise to four categories of patients: poor metaboliser, intermediate metaboliser, normal metaboliser and ultrarapid metaboliser, with specific clinical consequences (depending on the degree of over- or under-expression and if the medicine is a pro-drug or an active drug). For instance, the CYP2D6 gene, which codes the expression of the CYP2D6 enzyme, is highly polymorphic, with more than 100 known variants. CYP2D6 is responsible for metabolising approximately a quarter of all prescribed medicines, and there are already evidence-based data and guidelines on the gene-drug interactions emerging from different CYP2D6 gene expressions. For example, codeine is metabolised by CYP2D6 and a poor metaboliser will experience little to no effect as the poor gene expression will hinder codeine's conversion into morphine, the active metabolite. On the other hand, an ultrarapid metaboliser might experience supra-therapeutic drug levels, which are further linked to adverse drug reactions and opioid toxicity.

For frequently prescribed drugs that are subject to drug-gene interactions, an undesirable response to the drug is often what alerts the prescriber to the need for a pharmacogenetic test. For example, a Canadian study reported that the most common reasons for pharmacogenetic testing were ineffective therapy (43%), to address an adverse reaction (32.6%), and to guide initiation of therapy (10.4%), while the medications most frequently implicated in triggering pharmacogenetic screening included antidepressants (33.9%), statins (22.1%), clopidogrel (12.6%) and proton pump inhibitors (12.6%). *Table 1* provides a description of clinical implications of drug-gene interactions.

A study undertaken in the Netherlands reported that patients were exposed to more than 50 million pharmacogenetic drugs over a study period of seven years from the total of an annual average population of 11.4 million. It was estimated that a quarter of those exposures were predicted to present a risk, i.e. they were experienced by individuals with actionable genotypes and could influence the response to the drug.

Table 1: **Medicines which can be involved in drug-gene interactions ("pharmacogenetic drugs")**
*(*Please note that the list is not exhaustive and there are different levels of evidence for these drug-gene interactions presented here.)*

Medicine	Gene	Drug-Gene Interaction
Abacavir	HLA-B	*57:01 allele positive: Results in higher adverse reaction risk (hypersensitivity reactions). In individuals with the HLA-B*57:01 variant allele, abacavir is not recommended and should be considered only under exceptional circumstances.
Amitriptyline	CYP2D6	Affected subgroups: ultrarapid, intermediate, or poor metabolisers. May alter systemic concentrations.
Atomoxetine	CYP2D6	Affected subgroups: poor metabolisers. Results in higher systemic concentrations and higher adverse reaction risk. Adjust titration interval and increase dosage if tolerated. CYP2D6 poor metabolisers are not associated with clinically significant change in QT(c) when exposed to atomoxetine in healthy individuals.
Azathioprine	TPMT and/or NUDT15	Affected subgroups: intermediate or poor metabolisers: Alters systemic active metabolite concentration and dosage requirements. Results in higher adverse reaction risk (myelosuppression). Consider alternative therapy in poor metabolisers. Dosage reduction is recommended in intermediate metabolisers for NUDT15 or TPMT. Intermediate metabolisers for both genes may require more substantial dosage reductions. For poor metabolisers for both genes: For non-malignant conditions, consider alternative non-thiopurine immunosuppressant therapy. For malignancy, start with drastically reduced doses (reduce daily dose by 10-fold and dose thrice weekly instead of daily) and adjust doses of azathioprine based on degree of myelosuppression and disease-specific guidelines. Allow 4 – 6 weeks to reach steady state after each dose adjustment.
Carbamazepine	HLA-B	*15:02 allele positive: Results in higher adverse reaction risk (severe skin reactions). Avoid use unless potential benefits outweigh risks and consider risks of alternative therapies. Patients positive for HLA-B*15:02 may be at increased risk of severe skin reactions with other drugs that are associated with a risk of Stevens Johnson Syndrome/Toxic Epidermal necrolysis (SJS/TEN).
Celecoxib	CYP2C9	For poor metabolisers: Results in higher systemic concentrations. Reduce starting dose to half of the lowest recommended dose in poor metabolisers. Consider alternative therapy in patients with juvenile rheumatoid arthritis. Allele C is associated with increased AUC of celecoxib when treated with celecoxib as compared to allele A.

Medicine	Gene	Drug-Gene Interaction
Citalopram	CYP2C19	For poor metabolisers: Results in higher systemic concentrations and adverse reaction risk (QT prolongation). Patients with the CYP2C19*2 allele who are treated with citalopram may have a decreased drug clearance/metabolism and decreased tolerance, especially in combination with another no function allele (*2, *3, *4, *6, *8) (poor metaboliser phenotype) as compared to patients with the CYP2C19*1/*1 genotype. Contradictory findings reported no association of CYP2C19 genotype with tolerance, also no association with response or remission are reported. One study reported an association of poor metabolisers with increased remission if tolerant to citalopram.
Clopidogrel	CYP2C19	For intermediate or poor metabolisers: Results in lower systemic active metabolite concentrations, lower antiplatelet response, and may result in higher cardiovascular risk. Alternative antiplatelet therapy is recommended (if no contraindication), e.g., prasugrel, ticagrelor. Ultrarapid metabolisers: Increased platelet inhibition; decreased residual platelet aggregation.
Codeine	CYP2D6	For ultrarapid metabolisers: Results in higher systemic active metabolite concentrations and higher adverse reaction risk (life-threatening respiratory depression and death). Alternatives that are not affected by this CYP2D6 phenotype include morphine and non-opioid analgesics. Tramadol, and to a lesser extent hydrocodone and oxycodone, are not good alternatives because their metabolism is affected by CYP2D6 activity.
Escitalopram	CYP2C19	For poor metabolisers: May result in higher systemic concentrations. Consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolised by CYP2C19. Ultrarapid metabolisers: Increased metabolism when compared to extensive metabolisers. Lower plasma concentrations will increase probability of pharmacotherapy failure. Consider an alternative drug not predominantly metabolised by CYP2C19.
Ibuprofen	CYP2C9	For poor metabolisers: Significantly reduced metabolism and prolonged half life; higher plasma concentrations may increase probability and/or severity of toxicities. Initiate therapy with 25 – 50% of the lowest recommended starting dose. Titrate dose upward to clinical effect or 25 – 50% of the maximum recommended dose with caution. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals. Upward dose titration should not occur until after steady state is reached (at least 5 days). Carefully monitor adverse events such as blood pressure and kidney function during course of therapy. Alternatively, consider an alternate therapy not metabolised by CYP2C9 or not significantly impacted by CYP2C9 genetic variants in vivo.
Mercaptopurine	TPMT and/or NUDT15	For intermediate or poor metabolisers: Alters systemic active metabolite concentration and dosage requirements. Results in higher adverse reaction risk (myelosuppression). Initial dosages should be reduced in poor metabolisers; poor metabolisers generally tolerate 10% or less of the recommended dosage. Intermediate metabolisers may require dosage reductions based on tolerability. Intermediate metabolisers for both genes may require more substantial dosage reductions.
Nortriptyline	CYP2D6	Affected subgroups: ultrarapid, intermediate, or poor metaboliser: May alter systemic concentrations. For poor metabolisers: Greatly reduced metabolism of tricyclic antidepressants (TCAs) to less active compounds compared to normal metabolisers. Higher plasma concentrations of active drug will increase the probability of side-effects. Avoid tricyclic use due to potential for side-effects. Consider alternative drug not metabolised by CYP2D6. If a TCA is warranted, consider 50% reduction of recommended starting dose. Utilise therapeutic drug monitoring to guide dose adjustments.
Ondansetron	CYP2D6	For ultrarapid metabolisers: Increased metabolism to less active compounds when compared to normal metabolisers and is associated with decreased response to ondansetron and tropisetron (i.e. vomiting). Select and alternative drug not predominantly metabolised by CYP2D6 (i.e. granisetron).
Oxcarbazepine	HLA-B	*15:02 allele positive: Results in higher adverse reaction risk (severe skin reactions). Patients positive for HLA-B*15:02 may be at increased risk of severe skin reactions with other drugs that are associated with a risk of Stevens Johnson Syndrome/Toxic Epidermal necrolysis (SJS/TEN). If patient is oxcarbazepine-naive, do not use oxcarbazepine.
Paroxetine	CYP2D6	Affected subgroups: ultrarapid, intermediate, or poor metabolisers: May alter systemic concentrations. For poor metabolisers: Greatly reduced metabolism when compared to extensive metabolisers. Higher plasma concentrations may increase the probability of side-effects. Select alternative drug not predominantly metabolised by CYP2D6 or if paroxetine use warranted, consider a 50% reduction of recommended starting dose and titrate to response.
Rasburicase	G6PD	Deficient: At risk of acute hemolytic anemia. Rasburicase is contraindicated; alternatives include allopurinol.

Medicine	Gene	Drug-Gene Interaction
Simvastatin	SLCO1B1	Low function: High myopathy risk. Prescribe a lower dose or consider an alternative statin (e.g. pravastatin or rosuvastatin).
Succinylcholine	BCHE	Affected subgroups: intermediate or poor metabolisers: Results in higher systemic concentrations and higher adverse reaction risk (prolonged neuromuscular blockade). Avoid use in poor metabolisers. May administer test dose to assess sensitivity and administer cautiously via slow infusion.
Voriconazole	CYP2C19	Affected subgroups: intermediate or poor metabolisers: Results in higher systemic concentrations.
Warfarin	CYP2C9 CYP4F2 VKORC1	CYP2C9 intermediate or poor metabolisers: Alters systemic concentrations and dosage requirements. Select initial dosage, taking into account clinical and genetic factors. Monitor and adjust dosages based on INR. CYP4F2 V433M variant carriers: May affect dosage requirements. Monitor and adjust doses based on INR. VKORC1 -1639G> A variant carriers: Alters dosage requirements. Select initial dosage, taking into account clinical and genetic factors. Monitor and adjust dosages based on INR.

Based upon this knowledge, tests to detect pharmacogenetic associations have been developed and marketed. The United States of America's regulatory agency, FDA (Food and Drug Administration), published an announcement recently, arguing the need for evidence-based data to support pharmacogenetic testing – i.e. for trials and studies of practice to be carried out. In addition, they provided lists of approved pharmacogenetic tests, detailing the pharmacogenetic associations (for which the data supports therapeutic management recommendations, for which the data indicates a potential impact on safety or response and for which the data demonstrates a potential impact on pharmacokinetic properties only).

Pharmacogenetics in different countries

PGx and pharmacogenetics research and implementation are at different stages in different countries.

The 100,000 Genomes Projects was completed in the United Kingdom in 2018 and had a broader goal: to sequence 100,000 whole genomes from NHS (United Kingdom National Health Service) patients, focusing at those affected by a rare disease or cancer. Within this, the intention is also to move away from "trial-and-error" prescribing to optimal therapy (based on a "pharmacogenomic" profile that would help identify an optimal treatment). This project is part of the NHS strategy to use genomics in routine care, and the aim is for more whole genomes to be sequenced, in order to support the genomics implementation into practice. Pharmacogenetic testing is available in the United Kingdom through different laboratories, but it is not yet a common practice in community pharmacy.

Two Canadian projects, PRIME (Pharmacists as Personalized Medicine Experts) and ICANPIC (Innovative Canadian Pharmacogenomic Screening Initiative in Community Pharmacy), focused on personalised medicine in primary care clinical practice. The PRIME project included a multi-component training programme for pharmacists and support for the trained pharmacists during implementation into practice, while the ICANPIC study evaluated the feasibility of implementing pharmacogenetic services into community pharmacy practice and the number of potential drug-gene interactions identified as a result of pharmacogenomic screening. These projects highlight the readiness of community pharmacists to adopt pharmacogenomic screening into practice and their ability to leverage this novel technology to positively affect medication therapy management. These projects also contribute to the optimisation of the pharmacogenetic testing service, which is available in community pharmacies across Canada (test cost estimated between €99 and €330).

Pharmacogenetic testing is available in community pharmacies in Australia, enabling pharmacists to contribute to therapy optimisation. This way, they are at the forefront of personalised medicine and able to provide enhanced care services. The process is advertised and explained by the testing companies as well, detailing about the testing's purpose, reason, cost, organisation and process.

The Netherlands has used testing extensively in hospitals, particularly in areas like psychiatry, and it has some of the most comprehensive guidelines for healthcare professionals, but only around 14.7% of community pharmacists have used PGx testing.

Healthcare professionals can access different resources for evidence-based drug-gene interactions to support their pharmacogenetic clinical recommendations and decisions (Table 2). There are several guidelines available that gather and interpret the pharmacogenetic research findings and provide recommendations on how healthcare professionals can translate the evidence-based phenotype-genotype connection into practice; for instance, CPIC (Clinical Pharmacogenetics Implementation Consortium) guidelines and the Dutch Pharmacogenetics Working Group (DPWG) guidelines.

Table 2: **Web resources for pharmacogenetics**

Name	Link
PharmGKB (developed by DPWG: Dutch Pharmacogenetics Working Group)	https://www.pharmgkb.org/
CPIC (Clinical Pharmacogenetics Implementation Consortium)	https://cpicpgx.org/
Cytochrome P450 Drug Interactions Flockhart Table	https://drug-interactions.medicine.iu.edu/MainTable.aspx
PharmVar	https://www.pharmvar.org/
USFDA (Table of Pharmacogenomic Biomarkers in Drug Labeling)	https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

Pharmacists' role in pharmacogenetics

Pharmacists are an essential link between prescribers, patients and testing facilities when implementing pharmacogenetics into practice. With appropriate training, pharmacists in practice are in a key position to:

- Identify the patients for whom pharmacogenetic testing could be of value;
- Explain the rationale, potential benefits, costs, sample storage and the overall process to the patient;
- Link with the testing facilities;
- Interpret the pharmacogenetic test results in line with the best available evidence;
- Issue reports for the patient and for the prescriber, with adequate recommendations;
- Monitor the implementation; and
- Educate other healthcare professionals or support staff.

Additional pharmacogenetic training will be required for healthcare professionals. There are many initiatives worldwide to foster genomic literacy among healthcare professionals, including pharmacists. The strategic approach targets under- and post-graduate level, is patient-centred and involves experiential education, and covers skill development from basic genetics to patient care decisions within clinical pharmacogenomics. Nevertheless, the multidisciplinary approach and effective communication between different sectors contribute to the optimisation of this new process.

To sum up, the individual genetic characteristics can influence how the body might respond to certain drugs, and in particular situations, this could lead to clinical consequences. Commercial pharmacogenetic tests will become available in Ireland and pharmacists could, as in Australia and Canada, offer this as an additional service. However, development of such a service will require the commitment of significant resources.

How pharmacogenetic testing is implemented in the health sector is important. If it is only available to those with private healthcare, then a small proportion of the population will benefit. How the UK's NHS project develops will be of particular interest. It is worth noting that most of the genomic data entered into databases so far has come from mostly white populations, which is a major limitation for helping other populations. To maximise patient and societal benefit, a multidisciplinary approach, including trained pharmacists, is the starting point for effective and equitable pharmacogenetic testing in primary care and this is something health services in Ireland have yet to attain.

References available on request

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