**Title:** Fifteen-minute consultation: Pharmacogenomics – a guide for busy clinicians

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***What do we mean by pharmacogenomics?***

Ideally, the right drug is prescribed, for the right person, at the right dose, and the right illness. However, even if we achieve this, some patients do not benefit, or worse suffer adverse drug reactions (ADRs). Estimates for ADRs resulting in hospital admissions amongst paediatric patients range from 0.4 to 10.3%;1 taking this statistic and the average cost of a paediatric inpatient bed in England, the total estimated cost to the National Health Service (NHS) England is in excess of £51 million per annum.2 To improve the chances of a prescription providing benefit rather than harm, individual circumstances (personalisation) are used. This usually consists of age, weight/body surface area, renal and hepatic function, and medical/drug allergy history. Individualised dosing is common in children and is accepted as a method of reducing ADR risk and increasing patient benefit from drugs. It is now increasingly possible to include genetic variability as another factor to personalise drug therapy (Box 1), this is pharmacogenomics.

Pharmacogenomics examines the relationships between genetic variation and drug responses. This can be related to the disease, drug metabolising enzymes, or something else. This technology has the potential to identify those patients whom would respond best to a particular medication, or those who are most likely to suffer an ADR (Figure 1). With the continued progress of global projects aiming to characterize the human genome, such as the Human Genome Project, the HapMap Project and the 100,000 Genomes Project, interest in personalised medicine and pharmacogenomics has continued to rise, and clinical applications in paediatrics are appearing in routine practice.

**Box 1 Definitions**

**Pharmacogenomics:** The study of how genetic variability influences response to medicines, on both an individual and a population level. An umbrella term that captures all possible variations in the transcription and translation of genes, and their effects on medicines.

**Pharmacogenetics:** Often used interchangeably with pharmacogenomics; the more specific of the terms, which describes the study of variability in drug response/harm due to changes in the DNA sequence that directly affects protein structure.

**Single nucleotide polymorphisms (SNPs):** a single base pair substitution, by definition occurring in ≥1% of the population, which can result in a different protein product. However, SNPs do not need to be located in the coding DNA sequence to be clinically relevant and can also be found in structural RNA and regulatory regions.

**Pharmacokinetics (PK):** the time course of **“**what the body does to the drug” in terms of administration, distribution, metabolism and excretion.

**Pharmacodynamics (PD): “**what the drug does to the body” by means of the specific effect(s) of the drug on its target and downstream pathways.

***How do we study pharmacogenomics?***

Pharmacogenomics aims to identify the genes, and gene variants, or the resulting gene products, that are involved in the interaction between a drug and the body.3 Some of the identification methods are described briefly below:

Association methods

**Candidate gene approach:** oldest and simplest approach that examines the variations in a pre-specified gene(s) of interest and how those variations are associated with specific outcomes e.g. drug response. This approach is limited because it relies on existing knowledge of the disease. Whilst these studies require fewer patients, they cannot generate new hypotheses as the gene was selected in advance.

**Genome-wide association study (GWAS):** probes genetic variation by looking at the frequency of SNPs found in case samples and then testing for association in controls. The significance of an association between a SNP and the trait of interest is measured in a chi-squared test in a 2x2 contingency table with adjustment for multiple comparisons. This method does not typically identify the underlying causal variants without further functional studies. In addition, GWAS can require extremely large sample sizes which can make them harder to undertake in paediatrics.

Expression methods

By looking at gene expression profiles, in the form of RNA, in patients with a disease of interest, it is possible to identify genes involved in progression of that disease. This enables the potential identification of drug targets. It is also possible to examine expression or “transcriptomic” profiles for samples that have been treated with a particular drug. One such example is the publicly available connectivity map (CMap) which contains a library of over 1.5 million gene expression profiles generated from approximately 5000 small-molecule compounds tested in multiple cell lines. It is this that enabled Hassane *et al.* to discover two new agents, namely celastrol and 4-hydroxy-2-nonenal, with use in AML.4

Function and Pathway discovery

Once a candidate gene has been identified it is possible to identify further targets by “connecting the dots” in biological pathways.3 For example, if the candidate gene is a kinase enzyme, the downstream phosphorylation targets may also be relevant. Both commercial and public resources are available for pathway analysis including Ingenuity Pathway Analysis and iPathwayGuide.

Exome or Whole Genome sequencing

Many investigators are now turning to the increasingly affordable and high throughput methods of exome or whole genome sequencing as a method of identifying genetic variation. Sequencing has the advantage of being able to identify all variation, both known and unknown, and has the advantage of being able to locate novel variants that would otherwise be missed out using the other approaches described above. However, the large volumes of data generated can be difficult to interpret.

***How is pharmacogenomics currently used in UK clinical practice within paediatrics?***

Clinically relevant discoveries from the methods described are being applied in four key areas within paediatrics: drug development, drug toxicity, risk prediction and disease subclassification.5 Below are four examples of pharmacogenomics being used in routine UK paediatric clinical practice, and patients therefore require genotyping as a part of routine care.

Oncology and gastroenterology

*Azathioprine and Mercaptopurine*

Azathioprine inhibits DNA synthesis and is used to treat paediatric leukaemias and inflammatory bowel disease by means of immunosuppression. Azathioprine is a prodrug which is almost exclusively converted into the active drug 6-mercaptopurine (6-MP) by reductive cleavage of the thioether group. Thiopurine S-methyltransferase (TPMT) catalyzes the S-methylation of 6-MP to the inactive metabolite 6-methylmercaptopurine. TPMT polymorphisms that result in decreased or absent TPMT occur with a frequency of approximately 5-10% in the general population, meaning that up to 1 in 300 patients will be homozygous and therefore at increased risk of 6-MP toxicity. TPMT genotyping is therefore recommended to identify these patients prior to commencing therapy in order to achieve optimal therapeutic levels whilst minimising the risk of toxicity.6 11

Respiratory medicine

*Cystic fibrosis and Ivacaftor*

Ivacaftor is relatively new drug, approved for use by NHS England in 2012.8 It acts a potentiator of the cystic fibrosis transmembrane conductance regulator (CFTR), thus increasing the likelihood that the CFTR chloride channel will be open, and restoring chloride ion flow. It is currently licensed for use in children aged 2 years and older with at least one of the following mutations: G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D (NHS England).

Infectious diseases

*HIV and abacavir*

Abacavir is a reverse transcriptase inhibitor that is available in the UK for treatment of HIV in paediatric patients aged 3 months or older. Its use has been limited by severe hypersensitivity reactions, occurring in up to 5% of patients. Susceptibility to these reactions have been strongly associated with HLA-B\*5701 allele carriage, particularly amongst Caucasians and Africans/Afro-Americans.9 Therefore, current recommendations are that prior to initiating therapy with abacavir, or if restarting treatment and HLA-B\*5701 status is not known, patient testing for the HLA-B\*5701 allele should be performed.7 If the patient is positive for this allele, abacavir prescription should be avoided and recorded as an allergy.

Anaesthetics and analgesia

*Codeine*

Codeine belongs to the wider family of opioids which is converted to its active form, morphine, primarily by the hepatic drug metabolising enzyme cytochrome P450 CYP2D6. Over 100 allelic variants have been identified in CYP2D6 of which several result in reduced or no enzyme activity.12 In patients whom are “poor” or “intermediate” metabolisers, the analgesic effects of codeine may be inadequate due to lower levels of the active morphine. At present in the UK there are no consensus guidelines on which patients should be screened for CYP2D6 variants.



**Figure 1.** Diagrammatic illustration of how pharmacogenomics can help explain drugs which have clinical effect (Efficacy) and / or adverse drug reactions (ADR) in human patients.

**What are the areas of active research and potential future applications?**

Tacrolimus is a commonly used immunosuppressant used post solid organ transplant. It is characterized by a narrow therapeutic window and large PK variations. Reaching optimal therapeutic levels post-transplant is critical, yet therapeutic drug monitoring is rarely helpful in the first few days post-transplant due to widely fluctuating blood levels.10 Tacrolimus is metabolised by CYP3A5. Expression of the variant allele CYP3A5\*1 results in high levels of the CYP3A5 mRNA and protein, whereas individuals homozygous for CYP3A5\*3 are known as “non-expressors” and produce little functional enzyme.11 Hendijani *et al.10* were able to show that defining the individual genetic profile for CYP3A5 polymorphisms in transplant patients, can help to predict individual dose requirements, even before initiation of treatment.

Using a GWAS, Hawcutt and colleagues have recently identified a genetic variant in the *PDGFD* gene (rs511198) that resulted in an almost 6-fold increased risk of adrenal suppression in paediatric patients using regular high dose inhaled corticosteroids as part of their asthma control.13 They estimated that 1 in 27 children with asthma would need to be tested to avoid one case of adrenal suppression. If considered to be clinically cost-effective there is the potential to personalise asthma therapy for many paediatric patients.

**What are some of the challenges in paediatric pharmacogenomics?**

It should be noted that the majority of pharmacogenomic data used in therapeutic guidelines, generated by regulatory bodies such as the FDA and NICE, are generated in adult patients. Therefore, extrapolating the results to paediatric populations can be inaccurate, and paediatric specific research is required.

Also, as with any genetic testing, pharmacogenomic testing raises the possibility that family members may also be affected. This is particularly pronounced in paediatric practice when the patient is often accompanied and represented by a parent or other family member(s). If we take the example of TMPT enzyme deficiency, the activity of the enzyme is inherited in an autosomal co-dominant manner. If the patient has two low-activity copies of the TMPT gene they will be at greatest risk of thiopurine induced drug toxicity. This in turn indicates that each parent is either a poor or intermediate metabolizer themselves and therefore so will be the case for other full siblings of the patient of interest.

**Conclusion**

Pharmacogenomics is a promising field, with increasing, but not yet in widespread use, in the paediatric world. We have provided some examples of drugs used in paediatrics where pharmacogenomics is used to personalise treatment, or where impact is likely in the near future. Whilst these and other methods continue to identify links between genetic variations and pharmacotherapy, the clinical usefulness of this research has yet to be fully appreciated enough to make it into clinical practice.

Looking to the future, there is considerable room for expansion as pharmacogenomic data continues to accumulate. Therefore, physicians should aim to familiarize themselves with the key terms used in pharmacogenomics and the contributions to personalised pharmacotherapy.

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