Pharmacogenetics

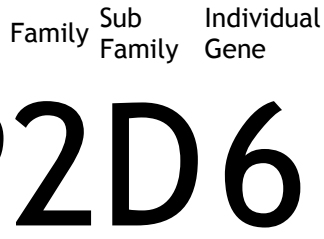
Relevance in the treatment of depression

Imagine: one of your patients is newly diagnosed with depression but before prescribing medication you perform a simple blood test in the surgery to predict which drug will have the best chance of therapeutic effect with minimal adverse effects. Furthermore you can also do this for a whole range of drugs and diseases including hypertension and epilepsy. A dream perhaps, but the first step towards reality has already been made. In January 2005 the FDA approved AmpliChip CYP450 the first widely available pharmacogenetic test.

First it might be helpful to provide an overview of the cytochrome P450 (CYP450) enzyme system which is responsible for metabolising most drugs.

The CYP450 System

Many drugs are metabolised by the CYP450 enzymes in the liver. The end result is either inactive compounds that can be excreted, or active compounds which can be further metabolised leading to eventual removal from the body. The CYP450 system consists of many enzyme subtypes each metabolising a specific range of drugs (substrates).



Some of the enzymes (e.g. CYP2D6 and CYP2C19) exhibit genetic polymorphisms and the frequency of these polymorphisms varies between ethnic groups. These genetic differences mean some people have an enzyme with reduced or no activity. In the case of CYP2D6 there are at least 3 variants giving phenotypes who are poor metabolisers, extensive metabolisers (the majority of people) or ultra fast metabolisers.

People who are poor metabolisers may have an increased risk of adverse reactions to a drug metabolised by the affected enzyme or reduced capability to convert a parent drug in to the active drug. As an example of genetic variation, the frequency of CYP2D6 poor metabolisers is 5 - 10 % in Caucasians and 1% in East Asians.

Some CYPs (CYP3A4) can have their activity increased (induced) by other drugs leading to increased substrate metabolism. Conversely some drugs can block (inhibit) the activity of a CYP enzyme and reduce substrate metabolism.

Examples:

- Fluoxetine is a substrate for CYP2D6 and a potent inhibitor of this enzyme. TCAs such as amitriptyline are also metabolised by CYP2D6. Fluoxetine will inhibit this and increase plasma concentrations of the TCA and increase dose related adverse effects.
- The activity of codeine is mainly due to conversion to morphine by CYP2D6. A poor metaboliser for this enzyme will have poor analgesic response due to lack of conversion. A drug which is an inhibitor of CYP2D6 (e.g. paroxetine) will, in effect, change a normal metaboliser to a poor metaboliser.
- A CYP2D6 poor metaboliser will have reduced capacity to metabolise some antidepressants (e.g. fluoxetine, paroxetine and amitriptyline) and be more sensitive to dose related adverse effects.
- Theophylline is a substrate for CYP3A4. Phenytoin induces CYP3A4 which increases the metabolism of theophylline and reduces plasma concentrations.

Many antidepressant and psychoactive drugs are metabolised by CYP2D6, and to a lesser extent, CYP2C19 which exhibit genetic polymorphism (see Table 1).

Table 1. Main metabolic pathways of commonly prescribed antidepressants

Drug	Main Metabolising enzyme	Notes
Fluoxetine	CYP2D6 Some other CYPS involved	Potent inhibitor of CYP2D6 Active metabolite (norfluoxetine) inhibits CYP3A4
Paroxetine	CYP2D6	Potent inhibitor of CYP2D6
Citalopram	CYP2C19 CYP2D6 only partly involved.	Only inhibits CYP2D6 very weakly
Venlafaxine	CYP2D6	CYP2D6 inhibitors taken at same time will increase plasma concentrations of venlafaxine. Active metabolite is metabolised by CYP3A4
Most TCA's (e.g. amitriptyline)	CYP2D6 Some other CYPs involved	CYP2D6 inhibitors taken at same time will increase plasma concentrations of TCA.

In general CYP2D6 poor metabolisers are likely to have poor tolerance to TCAs, venlafaxine and the SSRIs paroxetine or fluoxetine. A smaller dose may be required for therapeutic effect and to minimize adverse effects. Citalopram may be better tolerated by CYP2D6 poor metabolisers. Conversely, CYP2C19 poor metabolisers are likely to have poor tolerance of some TCAs and possibly citalopram.

The science has a long way to go before we can truly predict response from CYP genotyping but the potential is obvious.

There is also still some way to go before the true clinical relevance and justification for this test are known and there is currently minimal evidence for using it in clinical practice.

Related reading and resources

De Leon J, Armstrong S, Cozza K. Clinical guidelines for psychiatrists for the use of pharmacogenetic testing for CYP4502D6 and CYP4502C19. Psychosomatics 2006;47:75-85.

Drug Interactions; Defining genetic difference on pharmacologic responses. Available from; http://snipurl.com/xckc

Martin J, Fay M. Cytochrome P450 drug interactions: are they clinically relevant? Aust Prescr 2001;24:10-2. Available from; http://snipurl.com/xcka