

CYP450 genotyping in psychiatry - from research to clinical application, focussing on CYP2D6 and CYP2C19

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Dr Aitchison outlined research into SNPs within the CYP2D6 and CYP2C19 genes that are implicated in differential patient response to the TCA class of antidepressants. Individuals were genotyped using traditional methods and the high throughput AmpliChip CYP450 Array. A TCA pilot study was described which concluded that CYP2D6 genotypic category can be used to predict plasma TCA levels. A large scale study called GENDEP has been established to substantiate and extend results obtained from the pilot study.

A significant minority of patients taking antidepressants show an unsatisfactory response and experience adverse effects. Current pharmacogenetic research aims to provide tools that allow individuals to be prescribed drugs that produce the optimum response with minimal side effects.

Dr Aitchison and colleagues have genotyped a number of CYP450 SNPs. This talk focussed upon CYP2D6 and CYP2C19. Both CYP2D6 and CYP2C19 are involved in the metabolism of tricyclic antidepressants (TCAs).

CYP2D6 has four different phenotypes, dependent upon the number of active copies of the gene present: ultrarapid metaboliser (UM), extensive metaboliser (EM), intermediate metaboliser (IM) and poor metaboliser (PM). CYP2C19 is part of a cluster of genes on 10q24. It has three phenotypes, EM, PM and UM (in press).

In order to genotype the SNPs the AmpliChip CYP450 array was designed in collaboration with Roche and Affymetrix. Each array contains 10,000 probes for CYP450 genomic DNA. This assay can be used to detect gene duplication and deletion allele variants in addition to SNPs.

The three main research applications of CYP2D6 and CYP2C19 genotyping in Dr. Aitchison's lab are a) TCA pilot study, b) GENDEP and c) other ongoing work, including studies in ecstasy users.

In the TCA pilot study 47 patients were recruited with ICD-10 depressive disorder or bipolar disorder who had been prescribed a variety of TCAs. In addition to CYP450 genotyping a number of variables were measured: phenotype (debrisoquine), depression rating pre- and post-6 weeks of treatment (HAM-D scale), plasma levels of TCA and N-demethylated metabolite, and drug adverse effects.

CYP2D6 and CYP2C19 genotyping was carried out via standard methods and then 15 of the 47 samples were re-genotyped using the AmpliChip CYP450 test to allow comparison of results. There were no inconsistencies between alleles typed by both methods therefore it was concluded that the array results are reliable. **Additional useful information was also gained from the array** including clarification of genotypes and subclassification of alleles.

The study concluded there are associations between a) plasma TCA levels and *CYP2D6* genotypic category, controlling for *CYP2D6* inhibition (see below) b) patient phenotype (UM, EM, IM and PM) and *CYP2D6* genotypic category, controlling for *CYP2D6* inhibition c) demethylation index (rate of TCA metabolism) and *CYP2C19* gene dosage and d) percentage change in depression rating and *CYP2C19* gene dosage. The former three results would be predicted from the TCA metabolic pathway but not the latter.

Antidepressants can be co-administered with a known inhibitor of enzymes involved in their metabolism to reduce breakdown and therefore increase blood levels of antidepressant. The effects of *CYP2D6* inhibition on TCA plasma concentration was studied:

- In the poor metaboliser category (PM/PM) there was no significant difference with or without inhibitors. This is the expected result since these individuals have no active enzyme therefore no additional inhibition can occur.
- In the PM/IM group only patients who had taken inhibitors were present. These individuals had a very high TCA level (higher than the PM/PM group). This may be because the IM genotype is particularly susceptible to *CYP2D6* inhibition.
- In the IM/EM group a larger effect of inhibition is witnessed than in the PM/EM and EM/EM groups.

In summary, *CYP2D6* genotypic category is strongly predictive of dose-corrected combined TCA level in this pilot study. Therefore *CYP2D6* genotyping could be used to assist clinicians in dosing.

CYP2C19 genotypic category is predictive of demethylation ratio as anticipated from the TCA metabolic pathway (*CYP2C19* is involved in the demethylation step). In addition, *CYP2C19* genotype is associated with an increased percentage change in the HAM-D response: a lower demethylation ratio (i.e. less TCA demethylated to a secondary amine) correlated with increased response to treatment (i.e. reduction of depression symptoms as classified by the HAM-D scale) implying that the tertiary amine is more effective than the secondary.

Adverse effects to TCA treatment were linked to combined TCA level and demethylated metabolite level but not to genotypic categories.

The GENDEP study has been established to substantiate and extend these results. In outline, this is an 18-centre 3-year project funded by the European commission on pharmacogenomics of antidepressant treatment. 1000 patients (400 currently recruited) are being randomised to nortriptyline or escitalopram and rated prospectively over 6 months with samples taken for many different

factors: RNA, DNA, protein etc. For more information please visit <http://gendep.iop.kcl.ac.uk/>.

Finally, Dr Aitchison described two individuals excluded from the TCA study who have interesting CYP2D6 profiles. The first had sub-therapeutic levels of antidepressant in the blood and compliance was queried. They were genotyped as PM/PM. This genotype may lead to early intolerance and therefore no benefit from medication.

The second had a history of multiple drug intolerances and was not on TCA treatment for long enough to measure on the HAM-D scale or monitor plasma concentrations. The individual was genotyped as PM/IM. This genotype may lead to extremely high levels of TCA in the blood and therefore susceptibility to the adverse effects of drugs which are both substrates and inhibitors of TCAs.

A hypothesis resulting from these two case studies is that there may be a high level of early drop-outs from the CYP2D6 PM/PM and PM/IM groups due to adverse reactions to TCAs. This is consistent with early data from the GENDEP study.