Cytochrome P450 enzymes and their potential role in antidepressant treatment response

Karen Hodgson

Cytochrome P450 enzymes

• Key role in the metabolism of antidepressants.

**SSRI**
- ESCITALOPRAM
  - Demethylation
  - CYP3A4, CYP2C19 and CYP2D6
  - DESMETHYLCITALOPRAM
    - 25-50% as active as drug

**Tricyclic antidepressant**
- NORTRIPTYLINE
  - Hydroxylation
  - CYP2D6
  - 0H-NORTRIPTYLINE
    - 10% as active as drug

• Common genetic variation in some of these enzymes
Genetic variability in CYP450 enzymes

- CYP2C19 and CYP2D6 are highly polymorphic;
  - many forms of genetic variation from non functional genes to duplications of genes.
- Genetic differences associated with differences in enzyme activity

<table>
<thead>
<tr>
<th>Genetic variation</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 3 copies of “normal” allele</td>
<td>Ultra metaboliser</td>
</tr>
<tr>
<td>At least 1 “normal” allele</td>
<td>Extensive metaboliser</td>
</tr>
<tr>
<td>1 non-functional, 1 decreased / 2 decreased function alleles</td>
<td>Intermediate metaboliser</td>
</tr>
<tr>
<td>2 non-functional alleles</td>
<td>Poor metaboliser</td>
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</tbody>
</table>
CYP450 genotypes and antidepressant response

- Variability between patients in treatment response
  - Trivedi et al. 2006 estimate 30% achieve remission with first treatment
- Do differences in rates of drug metabolism predict the variability seen in antidepressant treatment response?
GENDEP Project

- Large European multicentre pharmacogenetic study
- Moderate/severely depressed patients
- Partially randomised to one of two antidepressants
  - Escitalopram (SSRI) or Nortriptyline (tricyclic)
- Followed for 12 weeks of treatment
  - Weekly measurements on depression symptoms
  - MADRS (Montgomery-Åsberg Depression Rating Scale) was the primary outcome measure used
- Detailed clinical and genetic information available

See Uher et al. 2009, Pharmacogenomics Journal for further study details
Whole GENDEP cohort (n=868)

- Escitalopram
  - N=498
  - Genotyped for CYP2C19
    - N=443
    - 77 drop out of study before week 8
  - Serum measurements at week 8
    - N=266
- Nortriptyline
  - N=368
  - Genotyped for CYP2D6
    - N=334
    - 79 drop out of study before week 8
  - Serum measurements at week 8
    - N=191
Methods

• **Genotyping**
  – Roche AmpliChip CYP450 Test
  – Common polymorphisms in CYP2C19 & CYP2D6

• **Serum concentrations of antidepressant**
  – Samples taken at week 8 of treatment
  – Drug and primary metabolite measured:
    • Escitalopram and desmethylcitalopram
    • Nortriptyline and total 10-hydroxynortriptyline
  – Measured using achiral turbulent flow liquid chromatography

• **Treatment response**
  – Weekly MADRS scores (repeated measures used)
Dosage and serum levels

- Protocol-driven flexible dosage
  - Escitalopram 10-30mg/day, Nortriptyline 50-150mg/day
- Highly significant association between dose and serum concentration of drug and metabolite
- No association between dose and CYP450 genotype

Genotypic Frequencies

![CYP2C19 (escitalopram)](chart)

![CYP2D6 (nortriptyline)](chart)
Analysis

• Separate metabolic pathways: drug-specific analyses
• Linear mixed effects models
  – Repeated measures of treatment response
  – Covariates; age, sex, dose, cytochrome P450-inhibiting comedications, centre of recruitment.
  – Plus baseline depression severity and effects of time when considering treatment response
Is CYP450 genotype associated with serum concentration?

CYP2C19 genotype category

CYP450 genotype

Serum level of escitalopram

Treatment response
Is CYP450 genotype associated with serum concentration?

1. **CYP450 genotype**

   - Drug (p<0.0001)
   - Metabolite (p=0.0026)
   - Metabolite:drug ratio (p<0.0001)

   CYP2D6 genotype category

   - Total 10-Hydroxynortriptyline levels (µg/L)
   - Total 10-Hydroxynortriptyline: nortriptyline ratio

   **Serum level of nortriptyline**

   **Treatment response**
Is CYP450 genotype associated with treatment response?

Escitalopram; \( n=443, \beta =0.165, SE=0.233, p=0.478 \)

Nortriptyline; \( n=334, \beta =0.127, SE=0.524, p=0.807 \)
Is serum level of drug associated with treatment response?

- **Escitalopram;** $n=235$, $\beta = 0.345$, $SE = 0.385$, $p=0.370$
  - CYP450 genotype
  - Serum level of escitalopram
  - Treatment response

- **Nortriptyline;** $n=169$, $\beta = -0.073$, $SE = 0.466$, $p=0.876$
  - CYP450 genotype
  - Serum level of nortriptyline
  - Treatment response

Also, no significant association for metabolite/metabolite:drug ratios
Serum level of drug and response; not covarying for dose

*Escitalopram; n=266, ß=0.870, SE=0.345, p=0.012*

- **CYP450 genotype** → Serum level of escitalopram → Treatment response

*OH-Nortriptyline; n=188, ß=1.403, SE=0.446, p=0.002*

- **CYP450 genotype** → Serum level of nortriptyline → Treatment response

No significant association for other measures of serum concentration
Conclusions

• Variability in treatment response unrelated to either CYP450 genotype or serum levels of drug

• In terms of implications for genetic testing to guide treatment, our results suggest CYP450 genotype doesn’t add information beyond clinical observation
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Everyone else involved in GENDEP


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I have no conflicts of interest

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