Pharmacogenomic Testing in Psychiatry: A New Connection Point

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THREE PATIENTS

Patient 1
Venlafaxine XR 75 mg qd
No SE
Full remission

Patient 2
Venlafaxine XR 150 mg qd
Severe SE:
GI, fatigue, sexual
No response

Patient 3
Venlafaxine XR 300 mg qd
No SE
No response
ANTIDEPRESSANT EFFICACY

Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial

<table>
<thead>
<tr>
<th>Step</th>
<th>QIDS-SR16 Response</th>
<th>Treatment Intolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47%</td>
<td>16%</td>
</tr>
<tr>
<td>2</td>
<td>27%</td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td>15%</td>
<td>26%</td>
</tr>
<tr>
<td>4</td>
<td>18%</td>
<td>34%</td>
</tr>
</tbody>
</table>

*Interpretive graphic of STAR*D trial

The study of how inherited genetic variation affects an individual’s response to medications.

“I can’t tolerate that medication”
CENTRAL DOGMA OF GENETICS

DNA creates RNA creates amino acids (building blocks of proteins)
DNA changes can have profound effects on protein production and function
DNA

Four nucleotide base molecules (A, G, T, C) comprise the information in DNA.

- Adenine
- Guanine
- Cytosine
- Thymine

The two bases on the DNA duplex molecule are called base pairs.
THE HUMAN GENOME

Your genome contains 3 billion base pairs, of which 3 million (0.1%) vary between individuals (polymorphisms).

Even a single nucleotide polymorphism (SNP) in a gene can modify:

- the function of the protein
- the amount of protein produced
GENES AND ALLELES

An “allele” is the term that refers to the different versions of a gene.

In most cases, we randomly inherit one copy of each gene from each parent.

The combination of alleles (genotype) creates a certain physical presentation (phenotype).

Figure 2.6b
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IMPLICATIONS FOR FAMILY HISTORY

CYP2C19 alleles
*1 normal activity
*3 no activity
*17 increased activity
Polymorphisms in pharmacodynamic genes can affect drug action at its target (e.g. receptor binding).

Polymorphisms in pharmacokinetic genes (e.g. CYP450) can affect drug blood levels.
KEY PHARMACOGENOMIC GENES

GeneSight Psychotropic
Pharmacokinetic (PK)
CYP2D6
CYP2C19
CYP2C9
CYP1A2
Pharmacodynamic (PD)
SLC6A4 (serotonin transporter)
5HTR2A (serotonin 2A receptor)

GeneSight ADHD
Pharmacokinetic (PK)
CYP2D6
Pharmacodynamic (PD)
ADRA2A ($\alpha_2$A adrenergic receptor)
COMT (catechol-o-methyltransferase)

GeneSight Analgesic
Pharmacokinetic (PK)
CYP2D6
Pharmacodynamic (PD)
OPRM1 (μ opioid receptor 1)
The CYP450 system is a family of about 57 enzymes responsible for drug metabolism, primarily in the liver.

Multiple enzymes may be involved in the metabolism of a given drug.

The CYP450 family contains several highly polymorphic genes.

Genes and enzymes share names, e.g. CYP1A2 gene creates CYP1A2 protein.
PK: CYP2D6

- A critical enzyme for metabolizing multiple antidepressants and antipsychotics.
- A highly variable gene with 17 common, clinically relevant polymorphisms.
- Located at a site on chromosome 22.
- Duplications can occur.
CYP2D6 ALLELES

*1 Normal “wild-type” CYP2D6 Gene

Functional CYP2D6 enzyme
CYP2D6 ALLELES

*4 Mutated CYP2D6 Gene

Non-functional CYP2D6 enzyme
CYP2D6 ALLELES

*5 Deleted CYP2D6 Gene

DNA

No mRNA produced

No CYP2D6 enzyme (*5)
CYP2D6 ALLELES

Duplication of *1 “wild-type” CYP2D6 Gene

Functional CYP2D6 enzyme
CYP450 METABOLIZER PHENOTYPES

**Ultrarapid (UM)**: Rapid rate of metabolism

**Extensive (EM)**: Normal metabolism

**Intermediate (IM)**: Reduced rate of metabolism

**Poor (PM)**: Slow rate of metabolism

CYP2D6 Phenotype Frequency
CYP2D6 AND NORTRIPTYLINE

Nortriptyline

Hydroxylation
CYP2D6
1-3, 5, 6

Z-10-hydroxynortriptyline

Hydroxylation
CYP2D6
1-8

E-10-hydroxynortriptyline
CYP2D6 AND NORTRIPTYLINE

PRODRUG: CODEINE AND CYP2D6

Codeine is a prodrug that is converted to morphine by CYP2D6.

PMs are likely to receive no analgesic benefit from codeine.

UMs are likely to have abnormally high doses of morphine from a standard dose.

Case report of morphine poisoning in a breastfed newborn whose mother was taking codeine

“Some people have genetic variations that make [CYP2D6] over-active, causing codeine to be converted to morphine faster and more completely than in other people. These ultra-rapid metabolizers are more likely to have higher than normal amounts of morphine in their blood after taking codeine. High levels of morphine can result in breathing difficulty, which may be fatal.”

“The only way to know if someone is an ultra-rapid metabolizer is to do a genetic test.”

http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm315497.htm
The Food and Drug Administration (FDA) includes pharmacogenomic language in the package inserts of many of the medications in the GeneSight Psychotropic test:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Recommendation</th>
<th>CYP2D6 PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>“Dosing recommendation in patients who are classified as CYP2D6 poor metabolizers (PM): The aripiprazole dose in PM patients should initially be reduced to one-half (50%) of the usual dose.”</td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>“The maximum dose should be limited to 20 mg/day in patients who are CYP2C19 poor metabolizers.”</td>
<td>CYP2C19 PM</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>“The coadministration of drugs that inhibit P450 2D6 with thioridazine and the use of thioridazine in patients known to have reduced activity of P450 2D6 are contraindicated.”</td>
<td>CYP2D6 IM or PM</td>
</tr>
</tbody>
</table>

The contents of this page have not been endorsed by the FDA and are the sole responsibility of Assurex Health.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Treatment</th>
<th>Dosage</th>
<th>Side Effects</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Venlafaxine XR</td>
<td>75 mg qd</td>
<td>No SE</td>
<td>Full remission</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Venlafaxine XR</td>
<td>150 mg qd</td>
<td>Severe SE: GI, fatigue, sexual</td>
<td>No response</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Venlafaxine XR</td>
<td>300 mg qd</td>
<td>No SE</td>
<td>No response</td>
</tr>
</tbody>
</table>

CYP2D6: 
- **EM**
- **PM**
- **UM**
Serotonin Transporter (SLC6A4)

The serotonin transporter is involved in reuptake of serotonin into the presynaptic neuron.

Selective serotonin reuptake inhibitors (SSRIs) inhibit this process, allowing for more serotonin in the synaptic cleft.
**SEROTONIN TRANSPORTER**

**Serotonin Transporter (SLC6A4)**

The SLC6A4 promoter has two main variants: short (S) and long (L)

The two variants are differentiated by a 44 base pair insertion/deletion

The short allele results in lower transcription rates, providing less active sites for SSRIs.

The short allele is associated with lower rates of remission following SSRI treatment

![SLC6A4 Phenotype Frequency](image)

- High Activity (L/L) 34%
- Moderate Activity (L/S) 48%
- Low Activity (S/S) 18%
PHARMACODYNAMIC PHARMACOGENOMICS

Clinical Application of SLC6A4

Meta-analysis of published literature of the association of 5-HTTLPR with SSRI efficacy in depression – 1435 patients and 15 studies

- Patients with s/s variant had significantly lower remission rates ($p < 0.0001$)

- Patients with s/s and s/l variants had significantly lower response rates ($p = 0.0002$)$^1$

- Two other meta-analyses confirmed similar significant associations$^2,^3$

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CLINICAL OUTCOMES

The Hamm Clinic Study was a prospective, cohort study of 44 adults with a primary diagnosis of a major depressive disorder.* The study compared 8 weeks of treatment guided by pharmacogenomics with unguided treatment as usual (TAU).

**MEAN SYMPTOM IMPROVEMENT AT WEEK 8**

<table>
<thead>
<tr>
<th>Scale</th>
<th>GeneSight</th>
<th>TAU</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QIDS-C16</td>
<td>31.2% (n=22)</td>
<td>7.2% (n=22)</td>
<td>0.002</td>
</tr>
<tr>
<td>HAM-D17</td>
<td>30.8% (n=22)</td>
<td>18.2% (n=22)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Reduction in Score From Baseline (%)

*Minimum score of 14 on the 17-item Hamilton Rating Scale for Depression (HAM-D17).

QIDS-C16=Quick Inventory of Depressive Symptomatology, Clinician Rated;
PHQ-9=Patient Health Questionnaire.

*Treatment guided by pharmacogenomics resulted in up to a **4-fold** greater improvement in symptoms.
Treatment guided by pharmacogenomics resulted in ~70% greater improvement in symptoms.
The Pine Rest Study was a blinded, randomized controlled trial of 49 subjects with a primary diagnosis of a major depressive disorder. The study compared 8 weeks of treatment guided by pharmacogenomics with unguided TAU.

**CLINICAL OUTCOMES**

30% of patients were treated with red-category medications, which resulted in almost no improvement when clinicians were not guided by GeneSight.
CLINICAL OUTCOMES

The UHS Study was a retrospective chart review of 96 adults with a primary diagnosis of a depressive or anxiety disorder. All of the subjects were treated with one or more of the 32 medications based on the GeneSight Psychotropic product. Each subject’s medical record was analyzed for healthcare utilization during a one year period from April 1, 2010 to April 1, 2011.
A meta-analysis of all the clinical studies demonstrated a statistically significant ($p = 0.004$) improvement in the odds of clinical response in favor of pharmacogenomics vs. TAU.

Patients are 2.3 times more likely to respond when treatment is guided by pharmacogenomics compared with TAU.
THANK YOU