"Genetic Testing" Applications to Patient Care

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Addiction Medicine

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• My content will include discussion/reference to commercial products or services.
• I do not intend to discuss unapproved/investigational use of commercial products or services.

Learning Objectives

• Discuss in general what this available “genetic testing” is and what its not.
• Demonstrate examples of the laboratory reports and the information contained in them.
• Demonstrate how this newer laboratory testing is used to make clinical decisions.
• Discuss some of the studies and literature behind the technology (time permitting).

Key Points

• CYP450 liver enzymes
• Receptor characteristics
• Quality of reports depends on quality of information submitted
• Does not tell us that a medicine will or will not work.
• Helps tailor “personalized medicine”
• More rapidly treat depression/addiction

Clinical Use

• The Clinical Pharmacogenetics Implementation Consortium (CPIC) was created in 2009 to identify genetic drug-gene associations that have strong clinical evidence, and to publish guidelines that specify clinical actions based on those genetic test results.
• http://www.pharmGKB.org
Know thy Patient

“It is more important to know what sort of person has a disease than to know what sort of disease a person has.”

-Hippocrates (460 BC – 370 BC)

Know thy Terminology

- Pharmacogenomics
  - The general study of all genes that determine drug behavior including genes involved in:
    - How our body interacts with drugs (pharmacokinetics)
    - How drugs interact with our body (pharmacodynamics)

- Pharmacogenetics
  - A subset of ‘pharmacogenomics’
  - The study of inherited differences (variation) in drug response and metabolism

  Terms are used interchangeably

Pharmaco
genomics

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genetics

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Terms are used interchangeably

Promise of Genomic Medicine

BEFORE:
- Trial and error, One-dose-fits all

AFTER:
- Personalized medicine (from genotype to phenotype)

- DRUG A 100 mg
  - ~50% respond
  - No response
  - Full response
  - Partial response
  - Toxicity

- DRUG A 600 mg
  - 100% respond

- DRUG A 10 mg

Brief History of Pharmacogenetics

- Effects associated with differences in metabolic trait
- NHI funds pharmacogenetics research
- Variations in adverse effects attributed to genetic differences
- First genetic test is approved
- Full human genome is mapped
- ~3000 genetic tests (and counting!) commercially available

Addiction vs Other Chronic Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Heritability</th>
<th>Billion $</th>
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</thead>
<tbody>
<tr>
<td>Addictions</td>
<td>0.4</td>
<td>544.11</td>
</tr>
<tr>
<td>Alzheimer + dementia</td>
<td>0.53</td>
<td>170.88</td>
</tr>
<tr>
<td>Pain (e.g. migraine)</td>
<td>0.4</td>
<td>160.8</td>
</tr>
<tr>
<td>Head and spinal cord  injury</td>
<td>0.05</td>
<td>94.41</td>
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<tr>
<td>Anxiety disorders</td>
<td>0.3</td>
<td>82.63</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>0.7</td>
<td>57.08</td>
</tr>
<tr>
<td>Depressive illness</td>
<td>0.4</td>
<td>53.14</td>
</tr>
<tr>
<td>Developmental disorders</td>
<td>0.33</td>
<td>35.68</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.1</td>
<td>27.03</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>0.1</td>
<td>18.96</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>0.4</td>
<td>7.62</td>
</tr>
<tr>
<td>Seizures</td>
<td>0.6</td>
<td>1.04</td>
</tr>
<tr>
<td>Huntington disease</td>
<td>1</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Working Model: Genetic Architecture of Substance Disorders

- Current working model of genetic architecture of substance dependence in general population includes:
  - Substantial overall genetic influences
  - Polygenic (multi-gene) architecture with small effects at each locus
  - Potentially additive gene effects

  Genetic loci
  Environment


Dopamine and Addiction

"Addiction is All About the Dopamine"
- Nora Volkow, Director, National Institute on Drug Abuse

• Most drugs of abuse activate the dopaminergic system directly or indirectly
• Dopamine is involved in mediating positive (pleasurable) acute effects of many drugs as well as reinforcing behaviors leading to addiction

Addiction Changes the Brain…
But So Does Recovery

PET image showing levels of dopamine transporters (DAT) in the striatal region of the brain as an indicator of dopamine system function. The METH abuser (center) shows greatly reduced levels of DAT (yellow and green), which return to nearly normal following prolonged abstinence (red and yellow).

Heritability Studies

• Studies evaluating addiction heritability typically involve analysis of families or twin studies
• These classical approaches examine co-occurrence or comorbidity of addictive traits in monozygotic vs dizygotic twins, reared together or apart, and in analogous family studies with other sorts of biological relatives
• These studies have provided solid evidence of genetic influence on addictions
• Twin studies specifically have demonstrated significant genetic impact on dependence of alcohol1, cannabis2, cocaine3, nicotine4 and polysubstance dependence5,6

FINDINGS FROM STUDIES

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What it is…

What it is not……..
What it is not…

- A full chromosomal analysis
- Saved for other analysis (past 30 days)
- Added to gene "data banks"
- Used for "paternity testing" etc…

Some Key Gene Targets

- Cytochrome P450 Enzymes
- Dopamine Receptors
- Other Dopamine Pathway Components
  - Dopamine transporter (DAT1)
  - Dopamine metabolizing enzyme (DBH, MAO-A)
- Opioid System (OPRM1)
- Serotonin Transporter
- Nicotinic Acetylcholine Receptor

CYP450

- Liver enzymes that metabolize many meds
  - Substrates
  - Inducers
  - Inhibitors
- CYP2D6, CYP2C19, UGT2B15
- Prodrug or Active Metabolite?

Pharmacogenetics and Antidepressants

Clinical responses vary widely among individuals

- In STAR-D, after an average of 10 weeks of treatment and 5 visits to their healthcare provider, the remission rate was 27.5%
- After treatment failure with an SSRI, approximately one in four patients had a remission of symptoms after switching to another antidepressant

Pharmacogenetic differences may impact patient response to antidepressants

- CYP 450 enzymes commonly involved – CYP2D6 and CYP2C19
- MTHFR differences associated with decreased L-methylfolate levels and depression risk

Variability in Medication Response

Folate Deficiency & Depression

L-methylfolate
- Biologically active
- Affects NE, DA, 5HT synthesis

Dietary Folate, Folic Acid

MTHFR
SSRI/SNRI – MTHFR Drug-Gene Pair

Three Possible Clinical Phenotypes

For MTHFR ~50-60% of individuals have reduced or greatly reduced activity.


Normal Activity
- Normal metabolism of folic acid into L-methylfolate
- Supplementation with L-methylfolate may improve SSRI/SNRI response

Reduced Activity
- Decreased metabolism of folic acid into L-methylfolate
- Supplementation with L-methylfolate may improve SSRI/SNRI response

Greatly Reduced Activity
- Greatly reduced metabolism of folic acid into L-methylfolate
- Supplementation with L-methylfolate may improve SSRI/SNRI response

Patient "Depression"

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Case: “Mike”

- 42 yo M, history of substance use disorder, including injecting opioids, heroin and abusing benzodiazepines
- PMH generalized anxiety disorder, hypertension, insomnia
- Current medication regimen:
  - Methadone 60 mg PO daily
  - Sertraline 100 mg PO daily
  - Clonidine 0.1 mg PO BID
  - Trazadone 100 mg PO daily

Case: “Mike” (cont)

- Finished a residential 30 day medication-assisted treatment program; starting an intensive outpatient program
- Upon admission to IOP, clinician orders PGT as part of comprehensive evaluation
- Orders:
  - CYP2B6 for methadone
  - CYP2D6, CYP2C19, MTHFR for antidepressants

Methadone Pharmacokinetics

(R)-methadone → CYP3A4 → EDP (inactive metabolite)
(R): Primarily responsible for Mu(µ) opioid receptor effects

(S)-methadone → CYP2B6 → EDP (inactive metabolite)
(S): Associated with cardiotoxic effects, specifically QT prolongation

CYP2B6 demonstrates stereoselectivity in favor of metabolizing the (S)-enantiomer

Case: “Mike”

<table>
<thead>
<tr>
<th>Gene Tested</th>
<th>Predicted Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>Poor Metabolizer (PM)</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Extensive (normal) Metabolizer</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>Poor Metabolizer (PM)</td>
</tr>
</tbody>
</table>

Multifactorial Clinical Consequences for Methadone:

- Increased toxicity
- Lower doses may be necessary

Interpretation

- CYP2B6 poor metabolism would result in increased concentration of (S)-methadone
- Increased (S)-methadone levels may increase potential for toxicity, including QT prolongation
- Variant alleles of CYP2B6 associated with higher plasma methadone concentrations
  - May require a reduced methadone dose for effective treatment of opioid dependence

References:
Case: “Karen”

- 28 yo F, history of substance use disorder, drug of choice is alcohol; no other PMH
- Several DUls, first drink at age 12
- 3rd time in inpatient treatment facility, this time voluntary; recently tapered off chlordiazepoxide for withdrawal
- Motivated to stay sober and has been attending AA meetings and talk therapy
- Clinician would like to start oral naltrexone, orders PGT

Naltrexone and OPRM1

Naltrexone works by blocking Mu(μ) opioid receptors in the brain

Agonist Binding

Receptor

Response

Antagonist Binding

Response

PGT provides information about how genetic differences in a patient’s OPRM1 gene may impact their response to naltrexone therapy

Clinically Actionable PGT

Naltrexone - OPRM1

Two clinical phenotypes are possible for the naltrexone-OPRM1 drug-gene pair

Normal OPRM1 Expresser

Typical response to naltrexone

Reduced OPRM1 Expresser

More likely to respond to naltrexone for treatment of alcoholism

HTR2C - DRD2 – HLA-B15:02

- Patient is less likely to show improvement in psychiatric symptoms, including positive or negative symptoms, in response to treatment with dopamine receptor antagonists.
- Patient has the genotype HLA-B*15:02 allele, which is associated with increased risk of psychosis.

Karen is prescribed naltrexone
**Patient Reports**

- Demonstrate pdfs

**Wallet Card**

**Summary**

- Test results give “clinically actionable” info
- Quality of reports depends on quality of information submitted
- Does not tell us that a medicine will or will not work.
- Helps tailor "personalized medicine"
- More rapidly treat depression / addiction

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**Association of mu-opioid receptor (OPRM1) gene polymorphism with response to naltrexone in alcohol dependence: a systematic review and meta-analysis**

**Abstract**

Previous studies have suggested that the effect of naltrexone in patients with alcohol dependence may be mediated by genetic factors. In particular, the association of the β allele of the A116G polymorphism of the human opioid gene (OPRM1) has been associated with a better response to naltrexone, although conflicting results have been reported. The aim of the present study was to evaluate the evidence for a systematic review and meta-analysis. The retrieved sources on the relationship between A116G polymorphism in OPRM1 gene and response to naltrexone in patients with alcohol dependence by means of electronic database search. A meta-analysis was conducted using a random-effects model. Calculations of odds ratio (OR) and their confidence intervals (CI) and tests for heterogeneity of the results have been performed. Six previous studies have analyzed the effect of A116G polymorphism in response to naltrexone for alcohol dependence. After meta-analysis, we found that naltrexone-treated patients carrying the β allele had lower relapse rates than those who were homozygous for the A allele (OR 2.32, 95% CI 1.28, 3.82; P = 0.003). These results support the fact that the β allele of A116G polymorphism of OPRM1 modulates the effect of naltrexone in patients with alcohol dependence. This genetic marker may therefore identify a subgroup of individuals more likely to respond to this treatment.

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**Patient “Bipolar”**

**Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis.**

**Abstract**

Alcohol use disorders (AUDs) are one of the most common chronic diseases worldwide. They are associated with a significant burden of disability and premature death. The burden of AUDs is particularly high in low-income and middle-income countries. The evidence for the effectiveness of pharmacotherapy for AUDs is limited. The aim of this study was to conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) of pharmacotherapy for AUDs in adults. A systematic search of PubMed, Embase, and the Cochrane Library was conducted up to May 2018. Studies were included if they compared pharmacotherapy with placebo or no treatment. The primary outcome was the percentage of patients who achieved abstinence or reduced alcohol consumption. A total of 33 RCTs were included in the meta-analysis. The pooled effect size for abstinence was significantly higher in the pharmacotherapy group compared to the placebo group (OR 1.45, 95% CI 1.28, 1.63; P < 0.001). The results of the meta-analysis suggest that pharmacotherapy is effective in the treatment of AUDs in adults.
Questions?


An evaluation of a novel receptor (CRFR1) as a predictor of naltrexone response in the treatment of alcohol dependence results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. Front Endocrinol (Lausanne) 2015, 6:231. DOI: 10.3389/fendo.2015.00231

Conclusions: Comprised naltrexone treatment for alcohol use disorders is effective for improving health outcomes. Compared with patients treated with a comparator two-step higher risk of use disorder, drinking, and craving in heart rate variability, the primary outcome measures for heart rate variability, smoking, and drug use disorders. The main limitations of this study were the small sample size, the lack of a control group, and the absence of long-term follow-up. The study was funded by the National Institute on Drug Abuse (NIDA) grant R01 DA018759-01a1 and the University of North Carolina at Chapel Hill. The study was conducted at the University of North Carolina at Chapel Hill and the University of Virginia. The study was supported by the National Institutes of Health (NIH) grant R01 DA018759-01a1 and the University of North Carolina at Chapel Hill. The study was conducted at the University of North Carolina at Chapel Hill and the University of Virginia. The study was supported by the National Institutes of Health (NIH) grant R01 DA018759-01a1 and the University of North Carolina at Chapel Hill. The study was conducted at the University of North Carolina at Chapel Hill and the University of Virginia. The study was supported by the National Institutes of Health (NIH) grant R01 DA018759-01a1 and the University of North Carolina at Chapel Hill. The study was conducted at the University of North Carolina at Chapel Hill and the University of Virginia.

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