Pharmacogenetics and Personalized Medicine
A Game Changer

Variability among individuals

Sir William Osler, 1892

“If it were not for the great variability among individuals, medicine might as well be a science and not an art.

Disclosure

Information related to Genetic Markers and Genetic Assay was adapted
For this presentation with permission from
http://genomind.com

How do we know how a patient will respond to a medication?

• DUH – We don’t.
• Factors that affect response – many variabilities
• Result: clinicians use an educated trial and error method
• How will a patient respond to a particular medication?
• Will they experience an adverse response?
• Some patients take months to respond to the right medication cocktail

Treatment Resistance in Psychiatry

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Initial Remission Rate</th>
<th>Treatment Resistant/Relapse</th>
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<tbody>
<tr>
<td>Depression (MDD)</td>
<td>30.37% (STAR-D)</td>
<td>57% treatment intolerant</td>
</tr>
<tr>
<td>Bipolar Disorder (BD)</td>
<td>24.77% (STEP-BD)</td>
<td>52-70% relapse rate</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>16-44% (CATIE)</td>
<td>Up to 70% discontinue</td>
</tr>
<tr>
<td>Anxiety (GAD)</td>
<td>12-60%</td>
<td>Recurrence in up to 50%</td>
</tr>
<tr>
<td>Obsessive Compulsive Disorder (OCD)</td>
<td>25-71%</td>
<td>Up to 80% in 10 year follow up</td>
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40-80% of psychiatric patients have untreated symptoms. Many have abandoned drug therapies due to inefficacy or side effects.
Why Should We Test?

- Improve chances of selecting the right drug the first time
- Reduce medication choices using trial and error method
- Genetic markers "validate" psychiatric disorders as "medical" in origin.
- Understanding genetic markers may
  - Assist management
  - Improve outcomes in a more time efficient manner
  - Reduce stigma

Pharmacogenetics & Implications for Practice

Advantages

- Reducing adverse responses will improve patient safety and compliance
- Reduced experimentation will mean a more rapid therapeutic response
- Reduce unresponsiveness to medications – will better determine what medications to use and which ones to avoid
- Cost effective

What Are Biomarkers?

Gene Based: Single Nucleotide Polymorphisms (SNPs)

Epigenetics: Methylation, Acetylation

Gene Expression and Proteins

Brain Imaging

"Over 25% of ALL common medications have genetic Information that can be tested And used to personalize medical treatment” (Frueh et al, 2008)

Genetics 101
Nature vs. Nurture

GENES + Environment = Phenotype

- In psychiatry we do a good job of determining what environmental factors have contributed to a particular disorder
- Until now, we have not had access to a large component of our phenotype - genetic factors

GENECEPT ASSAY + Patient History = Personalized Treatment

Gene/Environment Interaction

Definitions

Let’s start with some basics.

- DNA synthesis = specific sequences of nucleotides
- DNA → Protein synthesis
- Protein synthesis → Directs metabolism

What is DNA?

- Chromosomes are long strands of DNA (23 pairs)
- DNA (deoxyribonucleic acid) is composed of four nucleotide base pairs: adenine (A), thymine (T), guanine (G), and cytosine (C)
- Genes are sections of DNA that code for proteins
- Each person has approximately 23,000 different genes, which are 99.9% identical between all individuals

Genes Code for Proteins – “Recipe”

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Definitions – 2 Significant Players

- Allele
  - One member of a pair of genes, at a specific location on a specific chromosome.
  - One allele from each parent
- Substrate
  - Drug that binds to and is metabolized by an enzyme
Genotype – Genetic Identity

- A combination of alleles located on chromosome pairs which determine a specific trait.
- Homozygous or heterozygous
- Genotype is an individual's Genetic identity

Phenotype

- The observable physical or biochemical characteristics of an organism
- determined by both genetic and environmental factors.
- Physical and biochemical characteristics
- Height, weight, skin color - examples

Recipe Errors - Oops

- As DNA is transcribed and translated, errors occur that can:
  - Alter the proper structure and function of proteins
  - Affect response to medications which target these proteins or associated pathways.

The Genecept Assay

- The Genecept Assay was introduced commercially in 2010:
  - Patented gene-based assay informs treatment decisions for patients with mental health conditions, such as:
    - depression, anxiety, obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), bipolar disorder, post traumatic stress disorder (PTSD), autism, schizophrenia, chronic pain and substance abuse
- There are other companies: GeneSight

Single Nucleotide Polymorphism (SNPs)

- Most common variant among people
- Each SNP represents a difference in a single nucleotide building block
- Example: SNP may replace the nucleotide cytosine (C) with the nucleotide thymine (T) in a certain stretch of DNA
- AATTCC → AATTTC
- AATTCC
- AATTTC

Contributes to Phenotype

- MTHFR: C/T
- DRD2: C/Del
- SLC6A4: L/S
- COMT: Val/Val

Alleles are different variants of a gene. Humans are diploid organisms and receive one allele from each parent.
Why Pharmacogenetics?

- Individual genotype is invariable from birth to death.
- Based on our raw DNA
- Genotype is NOT affected by treatments/drugs
- Importance - CYP450 enzymes are essential for drug metabolism
  - Approximately 35% of psychotropics are metabolized by
    - CYP2D6 or CYP2C19
  - Influences both therapeutic and adverse responses to medications

CYP450’s Important to Drug Metabolism

- CYP2D6
  - Most important (50%)
  - Inducible
- CYP2C19
  - Next in line (20%)
  - Not inducible
- CYP 2C9 and 2C19
  - 15%
  - Inducible

Pharmacogenetics

2. Study of how genetic variations influence response to medication.

Pharmacodynamics/Pharmacokinetics?

- Pharmacodynamics – What the drug does to the body
  - Interactions with receptors, transporters, & neurotransmitters
- Pharmacokinetics - What the body does to the drug
  - Including absorption, metabolism, elimination

Genetic Testing

- Variations in DNA can alter
  - gene functions
  - individual responses to psychotropic medications
- These differences can be partially explained by analyzing genetic functioning
- Help the clinician develop informed and personalized therapeutic decisions
Genecept Assay Genes in Detail: Kinetic Variants

Kinetic Variants Mediate Drug Response

- Gene variants associated with altered liver enzyme metabolism activity may lead to side effects and toxicity

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<tr>
<th>Variant</th>
<th>Description</th>
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<td>PM</td>
<td>Poor metabolizers or inhibitors of P450 may have increased drug serum levels and adverse events.</td>
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<td>IM</td>
<td>Intermediate metabolizers or inhibitors of P450 may have elevated drug serum levels and adverse events.</td>
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<tr>
<td>EM</td>
<td>Extensive metabolizers metabolize substrates normally.</td>
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<td>UM</td>
<td>Ultra-rapid metabolizers or inducers of P450 may have reduced drug serum levels and poor efficacy.</td>
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Gene variants associated with altered liver enzyme metabolism activity may lead to side effects and toxicity.

IM PM Poor metabolizers or inhibitors of P450 may have increased drug serum levels and adverse events.

IM Intermediate metabolizers or inhibitors of P450 may have increased drug serum levels and adverse events.

EM Extensive metabolizers metabolize substrates normally.

UM Ultra-rapid metabolizers or inducers of P450 may have reduced drug serum levels and poor efficacy.

Genecept Assay Genes in Detail: Dynamic Variants

18 Genes Analyzed

Specific Genes

What are they and what are the implications of genetic variations?

CYP1A2 Environmental Inducers

- CYP1A2 is highly induced by certain environmental factors
- Tobacco smoke: CYP1A2 levels will be increased with smokers
- Cruciferous vegetables: broccoli, cauliflower, cabbage consumption will increase CYP1A2 levels
- Char-grilled meats: consumption of char-grilled meats will increase CYP1A2 levels

Swen et al 2011; http://www.fda.gov/
Serotonin Transporter (SLC6A4)

- SLC6A4 is reported as L(A) (normal) or L(G) or S (risk)
- Patients carrying the S or L(G) allele are at higher risk for side effects and lack of response to SSRIs

Clinical Impact:
- Caution with SSRIs
- Therapeutic Options: SNRIs and Atypical Antidepressants

Serotonin Transporter Gene SLC6A4

- Reported as L(A)(normal), L(G), or S (risk)
- Patients with L/G or S are at higher risk for poor response or side effects

Clinical Impact:
- Use caution with SSRIs
- Therapeutic Options: May substitute SNRIs or atypical antidepressants, if clinically indicated

2 Ion Channels in the Brain and Psychiatric Disorders

- Homozygotes of the ANK3 T allele or CACNA1C A allele are at higher risk of altered neuronal signaling. Mediate excitatory signaling. Mood instability.
- Clinical Impact: therapeutic options include agents that reduce neuronal signaling such as mood stabilizers, atypical antipsychotics, omega 3 fatty acids

Genetics of Atypical Antipsychotic Metabolic Effects

- Satiety signaling: regulation of feeding behavior and energy balance is highly complex and controlled mainly in the hypothalamus
- Serotonin signaling regulates satiety through activation of 5HT2C receptors
  - MC4R is activated by anorectic peptides to induce satiety and inhibited by orectic peptides to inhibit satiety

- Decreased food intake
- Increased energy expenditure
- Increased food intake
- Decreased energy expenditure

5HT2C and MC4R
Genetic Variations Affect Metabolic Risk

- Receptor site on which various neuroleptic medications act
- Regulates appetite and feeling of satiety
- Blocking this pathway (through mutation) leads to increased appetite/food intake
- The C allele – risk for weight gain (80 % of Caucasians)
- The T allele – protective effect against weight gain
- Inositol – helps some people control appetite
Melanocortin 4 Receptor (MC4R)

- Regulates satiety, body weight, and energy balance

**Mutation**
- Melanocortin 4 Receptors (MC4R) A allele may increase risk for weight gain and higher BMI

**Clinical Impact**
- Atypical antipsychotics exacerbate the risk for weight gain for A allele carriers
- Use caution with atypical antipsychotics
- High risk medications: clozapine and olanzapine
- Medium risk medications: aripiprazole; iloperidone; paliperidone; quetiapine; risperidone
- Low risk medications: asenapine; cariprazine; brexpiprazole; lurasidone; ziprasidone

Dopamine Receptor (DRD2)

- Antipsychotic clinical efficacy is highly correlated with the blockade of Dopamine 2 Receptor
- Deletions (DEL) in the dopamine receptor gene can inhibit dopamine signaling
- Indicates that antipsychotics are less likely to be effective and more likely to cause side effects.

**Clinical Impact**
- Use antipsychotics with caution or use an alternative agent

Catechol-o-methyltransferase (COMT)

- COMT is an enzyme found in the prefrontal cortex (PFC)
- Responsible for dopamine degradation
- Normal: Val/Met

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<th>COMT Activity</th>
<th>DNA Locus</th>
<th>Clinical Impact</th>
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<tbody>
<tr>
<td>High (Val/Val)</td>
<td>Low</td>
<td>Improved Executive Function, Superior response with Stimulants</td>
</tr>
<tr>
<td>Low (Met/Met)</td>
<td>High</td>
<td>Superior Executive Function, Cautions with Stimulants</td>
</tr>
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Adrenergic α2A-receptor (ADRA2A)

- ADRA2A
- Receptor involved with neurotransmitter release
- Associated with improved response to stimulant agents
- Stimulant agents may be use if clinically indicated
MTHFR and Folate Metabolism

- Depending on the different combinations of C677T and A1298C alleles
  - total conversion rates of folic acid range from 100% to <30%
  - C677T: T = 35% reduction in conversion rates
  - A1298C: C = 20% reduction in conversion rates

Methylenetetrahydrofolate Reductase

- MTHFR
- Predominant enzyme responsible for converting folic acid to L-methylfolate, active form of folic acid - needed for synthesis of dopamine, neuroepinephrine, dopamine
- Supplementation with L-methylfolate – if clinically indicated
- Deplin

MTHFR Polymorphism

Clinical Utility
- L-methylfolate supplementation may be relevant in patients with the T allele
  - Papakostas et al 2012; Ginsberg et al 2011; Wade et al 2014; Papakostas et al 2014

Brain Derived Neurotrophic Factor

- BDNF - Needed for proper neuronal development and neural plasticity
- Impaired BDNF secretion associated with altered SSRI response – Caucasians
- Met/Met and Val/Met carriers – have poorer response to SSRIs. Impaired cognition and may benefit from increased activity/EXERCISE
- Val/Val carriers may have better response to SSRIs

Brain-derived Neurotrophic Factor (BDNF)

Mutation
- (Val/Met) and Met/Met linked to impaired cellular secretion; At risk for depression, impaired memory, & altered stress response

Clinical Impact:
- Greater levels of physical activity can offset the deleterious effect of Met allele on working memory (Erickson, 2013)
- Exercise has been linked to improved cognition, working memory, and higher BDNF levels
**μ-Opioid Receptor (OPRM1)**

**Mutation**
- The G allele is associated with decreased response to opioids and increased risk for addiction. Decreased sensitization to opioids.

**Clinical Impact**
- Clinicians may increase dose for G allele carriers, however these patients are at risk for substance abuse.
- Non-opioid analgesics may be recommended for G allele carriers.

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>G Allele</th>
<th>Median (IQR)</th>
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<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G55</td>
<td>N/A</td>
<td>24</td>
<td>3.6 (0.4)</td>
<td>3.6 (0.4)</td>
<td>3.6 (0.4)</td>
<td>3.6 (0.4)</td>
</tr>
</tbody>
</table>

**U-Opioid Receptor**

- Opioid receptor activated by natural and synthetic compounds.
- Varied analgesic response, dosage, and abuse/addiction risk.
- Use caution with opioids.
- Use non opioids if clinically indicated.

**Glutamate Receptor Kainate 1 (GRIK1)**

- An predominant excitatory neurotransmitter receptor in brain.
- C allele may be associated with alcohol dependence.
- Polymorphism associated with increased response to topiramate for alcohol abuse.

**Clinical Impact - Topiramate (Topomax)**
- Topiramate blocks glutamate receptors, notably ones with GRIK1.
- Topiramate is more likely to cause side effects in A allele carriers.
- The C/C genotype is associated with better response to topiramate in the treatment of alcohol abuse/alcoholism.

**Evidence Base of the Genecept Assay**

- Inclusion of genes in the panel is supported by strong peer reviewed literature.
- Genomind's clinical team, working closely with our SAB, assesses the strength of the data.
- Genes were selected based on the critical examination of hundreds of studies showing that variations in these genes can inform treatment decisions.
- Report content is fully cited, with 200 references to date.
- Genomind has developed a full Literature Summary, summarizing each citation related to the genetic variations analyzed.
The Genecept Assay – How it Works

Patients provide cheek swab

Results of the test, combined with expert clinical consultations, enable better patient responses to treatment.

Prepped and mailed to a CLIA-certified lab

Online analytical report delivered to clinician

A patented algorithm results in

Genomind's certified physicians and Pharm.D.'s available to discuss results with treating clinicians via telephonic consult

1. Personalized access to consultations with Genomind certified physicians, available to discuss results with every patient report, in a timely manner

2. Creates a significant connection between the patient, their clinical history, their genetic results, and the treating clinician

3. Enhance education of biomarkers and translation of genetic results into potential treatment strategies

4. Can be leveraged for the clinician's family consultations and program discharge planning

The Value of Genomind's Clinical Consultation

Case Study

32 y/o mom, married, stay at home mom, has two children and had Baby #3 five days ago. SVD, uncomplicated.

Chronic diagnosis of Anxiety Disorder since her early teen years. Brother committed suicide at age 21.

Her OB doctor prescribed Sertraline 25 mg yesterday and today she feels much worse. Mother was with her

Presents with severe anxiety, agitation, and afraid she is going to lose control. Does feel attached to her infant.

What would your treatment choice be?

- Different SSRI
- Tricyclic
- Duloxetine
- Bupropion
- Mood stabilizer
- Methylfolate

Patient Results

Patient Results

Interpretation

• Lack of efficacy for SSRI’s could be related to the SLC6A4 or 2C19 variants
• SNRIs and atypical antidepressants are relevant for this patient; clinician decided to prescribe duloxetine
• Caution with any drugs metabolized by 2C19 or 2D6

• CACNA1C variation in combination with clinical presentation, led clinician to try lurasidone.
• Careful monitoring of weight gain was warranted due to the MC4R variation. An exercise regime was recommended due to the presence of this variant as well as the BDNF variation.

Follow-up

• Patient reported:
  - Stable mood, with decreased anxiety
  - No sexual side effects
  - Reduction of HAM-A from 28 to 16
  - Reduction of anxiety, agitation, and headaches has allowed her to become more able to care for her children
• Compliant with regimen and exercise plan

Prior Treatments

Genotyping Assay Guided Treatment

Relevant Genes

- Fluoxetine
- Duloxetine
- 2D6, SLC6A4, BDNF
- Escitalopram
- Lurasidone
- 3A4, CACNA1C, MC4R
- Exercise
- BDNF
- L-methylfolate
- MTHFR
- Omega-3 fatty acids
- CACNA1C

- L-methylfolate and Omega-3 fatty acids were also added to the patient’s regimen due to the presence of variations in MTHFR and CACNA1C.
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Conclusion

• Thank you for your interest and attention.