Nature vs. and Nurture: Epigenetics and Personalized Medicine
Learning Objectives

• Explain the molecular principles underlying personalized medicine

• Assess the potential use of pharmacogenetics for optimal patient care

• Identify the genetic polymorphisms associated with various mental health disorders and treatment responses

• Interpret pharmacogenomic test results and communicate the findings to patients and families
A 46-year-old man has not responded to 3 sequential antidepressant monotherapies. Genetic testing reveals that he is heterozygous for the -141C insertion/deletion allele (Ins/Del) for the dopamine D2 receptor gene (DRD2). Based solely on this genetic result, would an atypical antipsychotic be preferred as an augmenting agent for this patient?

1. Yes
2. No
Pretest Question 2

A 34-year-old patient with depression has the S/S genotype for the serotonin transporter gene (SLC6A4). Based solely on this genetic result, which treatment might be preferred for this patient?

1. Selective serotonin reuptake inhibitor
2. Serotonin-norepinephrine reuptake inhibitor
3. Noradrenergic tricyclic antidepressant
A 24-year-old woman with depression has just had genetic testing, including testing of the genes for catechol-O-methyltransferase (COMT) and methylenetetrahydrofolate reductase (MTHFR). Her symptoms are theoretically consistent with severe dopamine deficiency with apathy, anhedonia, psychomotor retardation, and cognitive slowing. Based on the current literature, which genetic testing results might be most likely?

1. COMT Val/Val and MTHFR (T/T) or (C/T)
2. COMT Val/Val and MTHFR (C/C)
3. COMT Met/Met and MTHFR (T/T) or (C/T)
4. COMT Met/Met and MTHFR (C/C)
Psychiatric Disorders

- Psychiatric disorders are categorical collections of symptoms chosen by a committee of experts
- Psychiatric disorders are revised periodically by the DSM (Diagnostic and Statistical Manual of the American Psychiatric Association)
- Psychiatric disorders are descriptive and reliable but not predictive of treatment response or linked to neurobiology
- Psychiatric disorders are not diseases
Each psychiatric disorder is likely to represent many diseases (perhaps hundreds)

Psychiatric symptoms correlate somewhat with malfunctioning brain circuits

Psychiatric disorders do not correlate well with genotypes, biosignatures, or brain circuits

Thus, the current diagnostic strategy is to attempt to link symptom domains that cut across psychiatric disorders to inefficient information processing in specific brain circuits
Genetics and Epigenetics

**GENETICS**
The sequence of DNA that is inherited

**EPIGENETICS**
The process of determining if a given gene is expressed

Can One Inherit a Behavior or a Psychiatric Disorder?

- genotype
- subtle molecular abnormality
- abnormal information processing (biological endophenotype)
- behavior with complex functional interactions and emergent phenomena (symptom endophenotype)
• There is no known gene for any psychiatric disorder, nor is one ever likely to be found
• Genes do not code for psychiatric disorders
• Genes do not code for psychiatric symptoms
• Genes code for proteins and epigenetic regulators, many of which regulate the efficiency of information processing in brain circuits, which can be visualized with neuroimaging techniques
• Thus, psychiatric research is attempting to link circuits upstream to treatment response and downstream to regulatory genes
Hypothetical Path Linking Circuits to Symptom Domains and Biomarkers

DSM syndrome

symptom domain

abnormal information processing (neuroimaging)

molecular abnormality (biomarker signature)

gene expression

epigenetic

gene

clinical subtype/treatment response
Hypothetical Path From Genes via Molecules, Circuits, and Information Processing to Symptoms, Syndromes, and Mental Illnesses

- Risk gene 1: Altered enzyme for monoamine degradation
- Risk gene 2: Altered synaptic plasticity machinery
- Risk gene 3: Altered development in prefrontal cortex

- Biological endophenotype
- Symptom endophenotype
- Executive dysfunction
- Phenotype
- Schizophrenia
- Delusions

A: Overactivation, normal, baseline, hypoactivation
B: Biological endophenotype

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Stress-Diathesis Model, Part 1:

*no risk gene, normal function*
Stress-Diathesis Model, Part 2:
1 risk gene, normal function

- risk gene
- mild stressor
- severe stressor

no stressor normal function normal function
Stress-Diathesis Model, Part 3: 2 risk genes, slowing of function, but compensation and no breakdown

- No stressor: Normal function
- Mild stressor: Normal function
- Severe stressor: Normal function
Stress-Diathesis Model, Part 4:

multiple risk genes, slowing of function with mild stressor, but decompensation and breakdown with severe stressor.
Genes and Psychiatric Treatments

• Markers for psychototropic drug metabolism are well established (pharmacokinetics)
  - Low drug levels and lack of efficacy
  - High drug levels and side effects

• Pharmacodynamics
  - Unmet need for predictors of responses to specific psychototropic drugs
Genes and Side Effects of Psychotropic Drugs

• Most psychotropic drug labels already contain references to genetic markers that recommend dose adjustments to mitigate side effects or drug interactions

• However, these are not commonly used
  - Expensive/reimbursement
  - Availability/delay
  - No current standard of care/best practices
  - If anything, phenotyping with therapeutic drug levels is more common than genotyping
No current psychototropic drug is labeled with reference to genetic markers that are linked to whether an individual is more likely to respond or not respond.

Trial and error is the current practice.

However, there is a premium on early response (eg, in depression), as the longer it takes to find an effective treatment, the less likely the treatment is to work and keep working.
<table>
<thead>
<tr>
<th>Pathway</th>
<th>Gene</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin</td>
<td>SLC6A4</td>
<td>Serotonin transporter (SERT); also called serotonin reuptake pump; responsible for termination of serotonin action</td>
</tr>
<tr>
<td>Dopamine</td>
<td>DRD2</td>
<td>Dopamine D2 receptor; target of antipsychotic drugs; theoretically overactive in psychosis and underactive in Parkinson's disease</td>
</tr>
<tr>
<td>Glutamate</td>
<td>CACNA1C</td>
<td>Voltage-gated channel for calcium</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP450</td>
<td>Hepatic enzyme system that metabolizes many psychotropic drugs</td>
</tr>
<tr>
<td>Dopamine</td>
<td>COMT</td>
<td>Enzyme responsible for the degradation of dopamine and norepinephrine</td>
</tr>
<tr>
<td>Metabolism</td>
<td>MTHFR</td>
<td>Predominant enzyme that converts inactive folic acid to active folate</td>
</tr>
</tbody>
</table>
SLC6A4
(Serotonin Transporter)
SLC6A4
(Serotonin Transporter)
SLC6A4 Polymorphisms and Serotonergic Activity

IF

SLC6A4 activity is: SERT expression is: 5HT reuptake is: Synaptic 5HT is:

↑ High[\text{L}(A)/\text{L}(A)]

↓ Low[presence of S or \text{L}(G)]
SLC6A4, Stress, and Depression

• Caspi et al: 5HTTLPR S allele associated with greater sensitivity to stress

• 55 follow-up studies assessing whether 5HTTLPR moderates relationship between stress and depression

• 2 meta-analyses of a subset of those studies found no association

• More recent meta-analysis included all relevant studies exploring the relationship (54)

SLC6A4, Stress, and Depression: Karg et al. Meta-analysis

- Included 54 studies

- 5HTTLPR S allele associated with increased risk of developing depression under stress (P=0.00002)

- By type of stressor, there was an association between S allele and increased stress sensitivity in:
  - Childhood maltreatment group (P=0.00007)
  - Specific medical condition group (P=0.0004)
  - Stressful life events group (P=0.03)

- Using only the studies from the previous meta-analysis, there was no evidence of association

Karg K. Arch Gen Psychiatry 2011;68(5):444-54.
SS versus SL/LL; Remission

<table>
<thead>
<tr>
<th>Study</th>
<th>SS Rem. Total</th>
<th>SS or LL Rem. Total</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smeraldi (11)</td>
<td>4</td>
<td>24</td>
<td>0.42</td>
<td>[0.18; 1.01]</td>
</tr>
<tr>
<td>Zanardi 2000 (24)</td>
<td>5</td>
<td>24</td>
<td>0.55</td>
<td>[0.25; 1.18]</td>
</tr>
<tr>
<td>Zanardi 2001 (25)</td>
<td>10</td>
<td>55</td>
<td>0.88</td>
<td>[0.62; 1.35]</td>
</tr>
<tr>
<td>Yu (28)</td>
<td>2</td>
<td>3</td>
<td>0.45</td>
<td>[0.08; 2.62]</td>
</tr>
<tr>
<td>Arias (29)</td>
<td>13</td>
<td>78</td>
<td>0.64</td>
<td>[0.43; 0.96]</td>
</tr>
<tr>
<td>Kato (35)</td>
<td>28</td>
<td>21</td>
<td>0.84</td>
<td>[0.60; 1.19]</td>
</tr>
<tr>
<td>STAR*D (39)</td>
<td>130</td>
<td>560</td>
<td>1.02</td>
<td>[0.89; 1.16]</td>
</tr>
<tr>
<td>Hong (40)</td>
<td>2</td>
<td>5</td>
<td>0.35</td>
<td>[0.07; 1.75]</td>
</tr>
<tr>
<td>Dogan (44)</td>
<td>10</td>
<td>22</td>
<td>0.88</td>
<td>[0.58; 1.33]</td>
</tr>
<tr>
<td>Maron (47)</td>
<td>5</td>
<td>75</td>
<td>0.87</td>
<td>[0.48; 1.58]</td>
</tr>
<tr>
<td>GENDEP (escitalopram) (48)</td>
<td>32</td>
<td>168</td>
<td>0.92</td>
<td>[0.69; 1.23]</td>
</tr>
</tbody>
</table>

Fixed effect model: 241 / 667 = 0.36

<table>
<thead>
<tr>
<th>Study</th>
<th>SS Rem. Total</th>
<th>SS or LL Rem. Total</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serretti (33)</td>
<td>24</td>
<td>99</td>
<td>0.76</td>
<td>[0.55; 1.05]</td>
</tr>
<tr>
<td>Kirchheiner (41)</td>
<td>8</td>
<td>30</td>
<td>1.41</td>
<td>[0.72; 2.78]</td>
</tr>
<tr>
<td>Wilkie (45)</td>
<td>10</td>
<td>29</td>
<td>1.17</td>
<td>[0.63; 2.18]</td>
</tr>
<tr>
<td>GENDEP (nortriptyline) (48)</td>
<td>16</td>
<td>111</td>
<td>0.79</td>
<td>[0.51; 1.23]</td>
</tr>
<tr>
<td>Fixed effect model</td>
<td>58</td>
<td>269</td>
<td>0.88</td>
<td>[0.71; 1.11]</td>
</tr>
</tbody>
</table>

Random effects model: 299 / 840 = 0.36

2007 Meta-analysis:
- Worse remission rate with SS
- Worse response rate with SS and SL
- Slower response with SS

2010 Meta-analysis:
- No significant effect on antidepressant response
- For remission, significant effect only for SS vs. SL/LL

### SLC6A4 and Antidepressant Side Effects

<table>
<thead>
<tr>
<th>Study</th>
<th>l/l and l/s n/N</th>
<th>s/s n/N</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takahasi 2002</td>
<td>5/24</td>
<td>11/30</td>
<td>5.41</td>
<td>0.45</td>
<td>[0.13, 1.56]</td>
</tr>
<tr>
<td>Perlis 2003</td>
<td>7/27</td>
<td>8/9</td>
<td>6.21</td>
<td>0.04</td>
<td>[0.00, 0.42]</td>
</tr>
<tr>
<td>Murphy 2004</td>
<td>34/189</td>
<td>14/55</td>
<td>12.42</td>
<td>0.64</td>
<td>[0.32, 1.31]</td>
</tr>
<tr>
<td>Kato 2006</td>
<td>18/40</td>
<td>21/60</td>
<td>6.45</td>
<td>1.52</td>
<td>[0.67, 3.44]</td>
</tr>
<tr>
<td>Popp 2006</td>
<td>19/92</td>
<td>6/17</td>
<td>5.61</td>
<td>0.48</td>
<td>[0.16, 1.46]</td>
</tr>
<tr>
<td>Hu 2007</td>
<td>124/1352</td>
<td>45/303</td>
<td>46.64</td>
<td>0.58</td>
<td>[0.40, 0.84]</td>
</tr>
<tr>
<td>Smits 2007</td>
<td>137/158</td>
<td>43/51</td>
<td>6.04</td>
<td>1.21</td>
<td>[0.50, 2.94]</td>
</tr>
<tr>
<td>Tanaka 2008</td>
<td>6/31</td>
<td>15/41</td>
<td>7.28</td>
<td>0.42</td>
<td>[0.14, 1.24]</td>
</tr>
<tr>
<td>Wilkie 2008</td>
<td>11/126</td>
<td>4/37</td>
<td>3.94</td>
<td>0.79</td>
<td>[0.24, 2.64]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>361/2039</strong></td>
<td><strong>167/603</strong></td>
<td><strong>100.00</strong></td>
<td><strong>0.64</strong></td>
<td><strong>[0.49, 0.82]</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: \( \chi^2 = 13.34, df=8 \) (\( P=0.10 \)) \( I^2 = 40.0\%

Test for overall effect: \( Z = 3.49 \) (\( P=0.0005 \))

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SLC6A4
(Serotonin Transporter)

What is the practical implication?

Treatment-resistant depression patients with the S or L(G) alleles may be less likely to respond to and more likely to have side effects on an SSRI/SNRI, so perhaps the next medication should be from another class.
DRD2
(D2 Receptor)
DRD2
(D2 Receptor)
DRD2 Polymorphisms

• –141C Ins/Del (rs1799732) polymorphism represents a deletion (vs. insertion) of cytosine at position –141, located in the 5' promoter region of the DRD2 gene

• Biological explanation for the association of -141C Ins/Del polymorphism with schizophrenia/antipsychotic response is currently unknown
  – In vitro data associate Del with lower expression of D2 receptor
  – In vivo data associate Del with higher density of D2 receptors in striatum

## DRD2 and Antipsychotic Response

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight (%)</th>
<th>Odds Ratio Mantel-Haenszel Fixed-Effects Estimate (95% CI)</th>
<th>Odds Ratio Mantel-Haenszel Fixed-Effects Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lencz et al. (43)</td>
<td>13.5</td>
<td>0.42 (0.12–1.42)</td>
<td></td>
</tr>
<tr>
<td>Malhotra et al. (12)</td>
<td>16.5</td>
<td>0.18 (0.04–0.85)</td>
<td></td>
</tr>
<tr>
<td>Shen et al. (18)</td>
<td>21.9</td>
<td>0.73 (0.32–1.67)</td>
<td></td>
</tr>
<tr>
<td>Wu et al. (46)</td>
<td>27.2</td>
<td>0.38 (0.16–0.94)</td>
<td></td>
</tr>
<tr>
<td>Xing et al. (14)</td>
<td>14.2</td>
<td>1.43 (0.60–3.42)</td>
<td></td>
</tr>
<tr>
<td>Yamanouchi et al. (37)</td>
<td>6.6</td>
<td>1.39 (0.41–4.79)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0</td>
<td>0.65 (0.43–0.97)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2=9.23$, df=5 ($p=0.10$); $I^2=46$

Test for overall effect: $z=2.13$ ($p=0.03$)
DRD2 and Antipsychotic-Induced Weight Gain: Preliminary Data

Weight change (y-axis) is expressed as the log of the ratio of weight at a given time point relative to baseline weight.

N=58 first-episode schizophrenia patients. Average olanzapine dose was higher in Del carriers. Time-by-genotype interaction remained marginally significant in secondary analyses.

What is the practical implication?

TRD patients with the Del allele may have a less satisfactory drug response and more weight gain, so perhaps choose something other than augmentation with an atypical antipsychotic.
CACNA1C
(Voltage-Gated Calcium Channel)
CACNA1C
(Voltage-Gated Calcium Channel)
CACNA1C Gene Polymorphisms

• CACNA1C expression: AA>AG>GG
• Polymorphisms may lead to calcium channel disturbances, excess neuronal excitability, and excess glutamate
• This may lead to increased depolarization of selective limbic regions associated with mood and perception
• The CACNA1C rs1006737 A allele has been associated with a risk of:
  – Bipolar disorder
  – Mood disorder recurrence
  – Possibly MDD and schizophrenia

CACNA1C
(Voltage-Gated Calcium Channel)

What is the practical implication?
TRD patients with the A allele may be bipolar spectrum rather than unipolar and may benefit from mood stabilizers, theoretically especially lamotrigine and others that reduce glutamate.
CYP450
Hepatic Enzyme System
CYP450
Hepatic Enzyme System

1A2   2D6   2C9   2C19   3A4

1 = Family
A = Subtype
1 = Gene product

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# CYP450 Polymorphisms

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genetic Basis</th>
<th>Clinical Consequences</th>
<th>Alleles Causing the Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer</td>
<td>More than 2 active gene copies on same allele or increased expression of a single gene</td>
<td>Lack of response to parent drug. Increased adverse drug reaction due to increased metabolite or active drug production</td>
<td>CYP2C19<em>17 CYP2D6</em>1/*2 x N (gene duplication/multiduplication)</td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>2 functional alleles</td>
<td>Ordinary response</td>
<td>CYP2C9<em>1 CYP2C19</em>1 CYP2D6*1</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>1 defective allele or 2 partially defective alleles</td>
<td>Higher parent drug levels. Decreased metabolite formation</td>
<td>CYP2C9<em>2 CYP2D6</em>10 CYP2D6*41</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>2 defective alleles</td>
<td>Higher parent drug levels. Increased risk for adverse drug reactions</td>
<td>CYP2C9<em>3 CYP2C19</em>2 CYP2C19<em>3 CYP2D6</em>4 CYP2D6*5</td>
</tr>
</tbody>
</table>

Ingelman-Sundberg M, Sim SC. Biochem Biophys Res Commun 2010;396:90-4.
The Case: 43-year-old ultra-rapid metabolizer

The Dilemma: How can genetic testing guide the treatment of resistant major depressive disorder?
Patient Intake

- 43-year-old recently divorced man with a history of recurrent depression since high school
- Patient states that he is "more or less normal a quarter of the time and severely depressed the rest of the time"
- He has had several psychiatric hospitalizations and 1 suicide attempt by overdose
- Patient presents with moderate depression and is nearly tearful at times
- He denies suicidal ideation, delusions, hallucinations, and thought disorder
Medication

• Patient has tried a number of antidepressant treatments with very limited success, including:
  – Most SSRIs
  – Most SNRIs
  – Augmentation with atypical antipsychotics
  – 2 MAOIs
  – 7 ECTs

• Current treatments include:
  – The MAOI tranylcypromine, with no apparent benefit
  – Psychotherapy, to which he has shown some response
• Results from a personalized medicine company specializing in mental health indicate that this patient is an ultra-rapid metabolizer for:
  - CYP2D6
  - CYP2C19
  - CYP1A2
  - CYP2C9

• He is also heterozygous for the 5HT transporter and the 5HT2A receptor
• This patient appears to have chronic dysthymia upon which major depressive episodes are superimposed

• He has shown little improvement on numerous antidepressant trials

• Genotyping reveals that this patient is an ultra-rapid metabolizer for several of the cytochrome P450 enzymes; thus, therapeutic levels were likely not reached

• As a heterozygote for the SERT SLC6A4 polymorphism, this patient may respond best to agents with targets outside of the serotonergic system

• Desvenlafaxine is an SNRI that is not metabolized by CYP2D6 and might be least affected by this patient's rapid metabolism

• For a patient such as this, larger than usual antipsychotic doses will likely be required, and therapeutic drug level monitoring is essential
Case Outcome

• Tranylcypromine is discontinued

• Following a 2-week washout period, desvenlafaxine (50 mg/day) is initiated

• At 3-week follow-up, the patient has shown no response

• Therapeutic drug monitoring indicates that the patient has not reached therapeutic levels of desvenlafaxine

• Desvenlafaxine dose is slowly increased to 400 mg/day until therapeutic drug monitoring indicates that a therapeutic drug level has been achieved

• The patient reports improvement in his depressive symptoms
CYP450
Hepatic Enzyme System

What is the practical implication?
Combining phenotyping via therapeutic drug levels with genotyping CYP450 enzymes, TRD patients who are fast metabolizers with low drug levels and poor therapeutic effects are probably not noncompliant and may require very high oral dosing or alternate routes of administration. TRD patients who are slow metabolizers with high drug levels and side effects may require low levels to tolerate and respond to medications that are substrates of the affected enzyme.
Catechol-O-methyltransferase (COMT)
Catechol-O-methyltransferase (COMT)

Dopamine transporter (DAT)

MAO-A or B destroys DA

MAO-A or B destroys DA

COMT destroys DA

DA
COMT Genotypes

• The COMT gene contains a highly functional and common variation (position 472, guanine to adenine substitution)

• Causes valine to methionine change in peptide sequence of COMT enzyme at codon 108/158 (Val\textsuperscript{108/158} Met)

• Results in significantly reduced COMT enzyme activity

<table>
<thead>
<tr>
<th>Allele</th>
<th>Met/Met</th>
<th>&lt;</th>
<th>Met/Val</th>
<th>&lt;</th>
<th>Val/Val</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>Low</td>
<td>Intermediate</td>
<td>High</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

COMT and Prefrontal DA

- Prefrontal cortex has few dopamine transporters
- Thus, dopamine inactivation in PFC is more dependent on COMT metabolism

<table>
<thead>
<tr>
<th>If COMT activity is:</th>
<th>Synaptic DA concentrations are:</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ High(_{(\text{Val/Val})})</td>
<td>↓ Low</td>
</tr>
<tr>
<td>↓ Low(_{(\text{Met/Met})})</td>
<td>↑↑ Higher</td>
</tr>
</tbody>
</table>

COMT and Cognition

Val carriers

• Reduced COMT activity
• Higher levels of dopamine
• More efficient information processing

Met/Met carriers

n-back

COMT and Schizophrenia

Patients with schizophrenia (N=181)
Unaffected siblings of patients with schizophrenia (N=218)
Controls (N=58)

WCST perseverative error scores were transformed to t-scores and normalized for age and education based on population means.

COMT and SSRI Response

* Adjusted for age, gender, and family history of psychiatric disorders
**p<0.05 for change from week 1 to week 6

# Adjusted for age, gender, and family history of psychiatric disorders
*p<0.05 compared to Met/Met (for Val/Val compared to either Val/Met or Met/Met)
**p<0.01 (for Val/Val compared to either Val/Met or Met/Met)

Baune BT. Neuropsychopharmacology 2008;33:924-32.
Catechol-O-methyltransferase (COMT)

What is the practical implication?

TRD patients with the Val allele may theoretically have lower dopamine and thus cognitive and working memory problems. They may be less likely to respond to an SSRI, so perhaps choose an antidepressant with a different mechanism, theoretically one that boosts dopamine.
Methylenetetrahydrofolate Reductase (MTHFR)
Formation of L-methylfolate

Folic acid (synthetic)

DHFR (dihydrofolate reductase)

Dihydrofolate (dietary)

Tetrahydrofolate

MTHFR (methylene tetrahydrofolate reductase)

*Genetically regulated*
MTHFR Polymorphisms

IF

MTHFR activity is:

High\textsubscript{(C/C)}

Low\textsubscript{(C/T or T/T)}

THEN

L-methylfolate is:

Homocysteine is:

Methylation is:
MTHFR Polymorphism in Schizophrenia

Up to 70% of patients with schizophrenia have an inborn error of folate metabolism\(^1\)

- **CC**: 29%
- **CT**: 49%
- **TT**: 22%

The MTHFR TT genotype is associated with a significantly higher risk of schizophrenia,\(^1-3\) including greater negative symptoms\(^4\) and cognitive impairment\(^5,6\)

The MTHFR 677C>T polymorphism contributes to impaired executive function (cognitive deficits) in patients with schizophrenia independent of its effects on negative symptoms.

Fig. 2. Percent of subjects in each genotype group able to complete at least one category on the Wisconsin Card Sort Test ($\chi^2 = 10.125$, $df = 2$, $p = .006$).

Genetic Risk Factor for Schizophrenia: MTHFR Polymorphism and Homocysteine

- Homozygous (TT) genotype of the MTHFR 677C>T polymorphism plus a 5 µmol/L higher homocysteine level was associated with a 70% higher risk of schizophrenia.

- Homocysteine levels are reported to be 54% higher in patients with schizophrenia than in controls (16.3 µM vs. 10.6 µM) (p<0.0001).
• Methylation is required for:
  – De novo synthesis of biopterin, the cofactor for the rate-limiting enzyme of dopamine formation, so hypomethylation may lead to low dopamine synthesis
  – Silencing of COMT synthesis, so hypomethylation may lead to high COMT levels and high DA destruction (and thus low DA levels)
Genetic Variants for Synthesis of L-methylfolate With Downstream Effects on Monoamines

Folic Acid → Dihydrofolate → Tetrahydrofolate → 10-formyl-THF → 5,10-methylene-THF → 5,10-methenyl-THF → Methionine → S-Adenosylmethionine (SAMe)

DNA → Gene Expression → Monoamine Regulation/Function

Methylene THF → Norepinephrine → Norepinephrine → Serotonin → Serotonin

Methylfolate → Cell Membrane or BBB → L-methylfolate → L-methylfolate

BH4 → BH2 → Tryptophan → Tyrosine → Serotonin → Norepinephrine → Dopamine

MTHFR → Methionine → SAMe → Samadine

Homocysteine → MTR → MTRR → SAH

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So, if L-methylfolate makes biopterin and biopterin makes monoamines, are L-methylfolate responders those with a problem making L-methylfolate?
Treatment Effect by Biomarker: Adjunctive 15 mg L-methylfolate vs. Adjunctive Placebo

Treatment Mean Change Less Placebo Mean Change

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>MTHFR 677 (CC)</th>
<th>MTHFR 677 (CT/TT)</th>
<th>MTR (AA)</th>
<th>MTR (AG/GG)</th>
<th>MTHFR CC + MTRAA</th>
<th>MTHFR T + MTR G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>P=0.017</td>
<td>NS 67%</td>
<td>P=0.087</td>
<td>NS 74%</td>
<td>P&lt;0.001</td>
<td>NS 48%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>P-value</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MTHFR and MTR (L-methylfolate Synthesis)

What is the practical implication?

Treatment-resistant depression patients with inborn errors of L-methylfolate metabolism may be those who respond or respond best to L-methylfolate augmentation of SSRIs/SNRIs; choose another option for those without these metabolic abnormalities.
Exploratory: What Is the Effect of Obesity on the Response to L-methylfolate?

L-methylfolate Magnitude of Effect by Biomarker
(Treatment Mean Change Less Placebo Mean Change)

<table>
<thead>
<tr>
<th></th>
<th>HAM-D 28 Mean Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOTAL</strong></td>
<td>-2.7</td>
</tr>
<tr>
<td><strong>MTHFR CT/TT</strong></td>
<td></td>
</tr>
<tr>
<td><strong>BMI ≥30</strong></td>
<td>-4.7</td>
</tr>
<tr>
<td><strong>MTR AG/GG</strong></td>
<td></td>
</tr>
<tr>
<td><strong>BMI &lt;30 + MTHFR T</strong></td>
<td></td>
</tr>
<tr>
<td><strong>BMI ≥30 + MTR G</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HAMD 28</th>
<th>CGI</th>
</tr>
</thead>
<tbody>
<tr>
<td>P=0.017</td>
<td>P=0.01</td>
</tr>
<tr>
<td>P=0.087</td>
<td>P=0.024</td>
</tr>
<tr>
<td>P=0.001</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>P&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

How Does This Exploratory Marker Interact With Markers for L-methylfolate Synthesis?

L-methylfolate Magnitude of Effect by Biomarker
(Treatment Mean Change Less Placebo Mean Change)


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How Does This Exploratory Marker Interact With Markers for L-methylfolate Synthesis?

L-methylfolate Magnitude of Effect by Biomarker
(Treatment Mean Change Less Placebo Mean Change)

BMI and L-methylfolate Response

What is the practical implication?
This is only exploratory, but one might use this in the absence of fancy biomarkers to screen patients for L-methylfolate use (ie, those with obesity and BMI>30).
Methylenetetrahydrofolate Reductase (MTHFR)

What is the practical implication?

TRD patients with the T allele theoretically have lower methylation capacity, higher homocysteine, and lower dopamine. It is not clear whether these patients are more likely to respond to L-methylfolate or SAMe.
MTHFR-COMT Methylation Interaction
Genetic Interactions of MTHFR With COMT: Epistasis

Triple Whammy: MTHFR and Biopterin

<table>
<thead>
<tr>
<th>Gene Allele</th>
<th>COMT Val</th>
<th>MTHFR T</th>
<th>MTHFR T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Downstream Effect</td>
<td>2-4 times higher COMT activity than Met form</td>
<td>More COMT</td>
<td>Reduced biopterin</td>
</tr>
<tr>
<td>Effect on PFC DA</td>
<td>Less DA</td>
<td>Less DA</td>
<td>Less DA</td>
</tr>
</tbody>
</table>

Interactive Effects of MTHFR and COMT on Executive Functioning in Schizophrenia: Epistasis

The Genetics of Antipsychotic-Induced Weight Gain
The MTHFR 677T allele is associated with a 3.6-fold greater risk of developing atypical antipsychotic-associated metabolic syndrome, and the TT genotype may place individuals at a greater risk for insulin resistance with greater central adiposity ($p=0.0001^1$)

HTR2C-759C/T

- Polymorphism in the promoter region of the serotonin 5HT2C receptor gene
- Carriers of the C allele are more susceptible to weight gain

MTHFR and HTR2C

• MTHFR 677 C/T polymorphism
  – CC homozygotes show significantly greater increases in BMI

• HTR2C -759 C/T polymorphism
  – C alleles confer increased risk for antipsychotic-induced weight gain

• Individuals with both the MTHFR CC and HTR2C C are at the greatest risk for increased weight gain and BMI in response to antipsychotic treatment.

### MTHFR and HTR2C

<table>
<thead>
<tr>
<th>HTR2C 759C/T Genotype</th>
<th>MTHFR 677C/T Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>T C or T</td>
<td>T C or T</td>
</tr>
<tr>
<td>C C</td>
<td>C C</td>
</tr>
</tbody>
</table>

MC4R

• The rs489693 locus is located close to the melanocortin 4 receptor gene (MC4R)
  – MC4R is associated with weight gain in the general population
• rs489693 AA homozygotes
  – Greater antipsychotic-induced weight gain and elevated triglycerides, leptin, and insulin compared with AC heterozygotes and CC homozygotes

### MC4R

<table>
<thead>
<tr>
<th>Genotype at SNP rs489693 located on Chromosome 18</th>
<th>12 weeks treatment with quetiapine, risperidone, or aripiprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>[A][A]</td>
<td>[A][C] OR [C][C]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AA (10.03)</th>
<th>AC (4.87)</th>
<th>CC (7.29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean weight gain (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean increase in triglycerides (mg/dL)</td>
<td>51.67</td>
<td>7.29</td>
<td></td>
</tr>
<tr>
<td>Mean increase in leptin (ng/mL)</td>
<td>8.27</td>
<td>3.40</td>
<td></td>
</tr>
<tr>
<td>Mean increase in insulin (µIU/mL)</td>
<td>4.91</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>Mean increase in homeostasis model assessment insulin resistance (HOMA-IR) index</td>
<td>1.23</td>
<td>0.12</td>
<td></td>
</tr>
</tbody>
</table>

Ankyrin-G (ANK3)
ANK3

- Ankyrin-G plays a role in sodium ion channel function
- The ANK3 T allele is associated with increased risk for bipolar disorder
- T allele
  - Associated with dysregulation of sodium channels
  - Reduced white matter integrity
  - Cognitive deficits
  - Mood instability

Summary

- Genetic testing as a clinical tool is still in its infancy, but it has the potential to inform treatment decisions.

- Genotyping may be especially useful for patients who do not respond to or tolerate a drug as expected.

- Caution is essential when bringing genetic testing into the selection of treatment in clinical practice.