Psychiatric Genetics in the Direct-to-Consumer Era

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Disclosures

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

Equities (<1%) in Pfizer, Merck, Abbvie
Learning objectives

• To review genetic measures that have been introduced into clinical psychiatry, or may be in the near-term

• To understand implications of direct-to-consumer genetic testing on routine care

• To anticipate patient questions on genetic testing, and be able to answer them based on the latest scientific evidence
Case study

Your new patient is a 23 year old man with a diagnosis of schizophrenia, and who has persistent negative symptoms. He is accompanied by his parents, who have brought with them a report on their son’s genetic profile from 23andMe®.

His parents are concerned that he is an “MTHFR double heterozygote” and want to know what this means for his long-term prognosis and treatment options.

They have gone online and found several “MTHFR support groups,” and based on what they have found are wondering if he should take a special form of folic acid called methylfolate.
Why are genetics important?

Heritability of various conditions:

- Autism: High heritability
- Schizophrenia: Very high heritability
- Bipolar: High heritability
- ADHD: High heritability
- Depression: Medium heritability
- Anxiety: Moderate heritability
- Breast Cancer: Low heritability
Some basic terminology...

Copy Number Variant (CNV)

Possible consequences of CNV change:

- Genes duplicated, deleted, or disrupted
- Amount and/or function of protein changes
Some basic terminology...

Single Nucleotide Polymorphism (SNP)

...A G C G T A A G A T C G T G A A C G T A G A C C...

...A G C G T A A C A T C G T G A A C G T A G A C C...

Possible consequences of G to C change:

- Silent or unknown
- Change in protein structure
- Change in amount of protein that is made
Some basic terminology...

Genome Wide Association Study (GWAS)

x 1000’s of healthy individuals

x 1000’s of individuals with schizophrenia
Schizophrenia GWAS

Psychiatric Genomics Consortium (PGC)

2011

21,856 participants
5 loci
Schizophrenia GWAS

Psychiatric Genomics Consortium (PGC)

Major Histocompatibility Complex (MHC)
rs115329265 (A/G)

2011
13.6% A
86.4% G
21,856 participants
5 loci

2014
15.0% A
85.0% G
150,064 participants
108 loci

Individuals with Schizophrenia

Healthy Individuals

85.0%
86.4%
15.0%
13.6%
A
G
A
G

Conditional analysis of schizophrenia risk and the MHC SNP rs115329265 revealed a significant association with the risk of schizophrenia. The results were consistent across multiple datasets and replicated across different populations. The association was also observed in both individuals with schizophrenia and healthy controls, suggesting a potential role in the susceptibility to the disorder. This finding highlights the importance of the MHC region in the genetic predisposition to schizophrenia and opens up new avenues for further research into the molecular mechanisms underlying the disease.
Schizophrenia GWAS

Psychiatric Genomics Consortium (PGC)

>18% of genetic risk explained by common genetic variants
Polygenic risk

Brainstorm Consortium, Science 2018

The diagram shows genetic correlation and p-value significance between different mental health disorders, including ADHD, Anorexia nervosa, Anxiety disorders, ASD, Bipolar disorder, MDD, OCD, PTSD, Schizophrenia, and Tourette Syndrome. The colors and symbols represent the strength and significance of the genetic correlation between these disorders.
MTHFR

Common variants:
- rs1801133 677C>T
- 222Ala>Val
- rs1801131 1298A>C
- 429Glu>Ala
MTHFR

van Meurs et al., Am J Med Nutr 2013
MTHFR “double heterozygote”

rs1801133
Copy 1: 677C
Copy 2: 677T

rs1801131
Copy 1: 1298A
Copy 2: 1298C

...~40% of the U.S. population are double heterozygotes
MTHFR genotype: clinical value

• Does being a double heterozygote increase risk for schizophrenia?  
  ...No

• Does being a double heterozygote increase risk for negative symptoms of schizophrenia?  
  ...Maybe
Folate and negative symptoms

Cao et al., Psychiatry Res 2016

Goff et al, Am J Psychiatry 2004
MTHFR and negative symptoms

Roffman et al., Schiz Bull 2013
MTHFR genotype: clinical value

- Does being a double heterozygote increase risk for schizophrenia?  
  ...No

- Does being a double heterozygote increase risk for negative symptoms of schizophrenia?  
  ...Maybe

- Does taking folic acid help?  
  ...Maybe
Folic acid for negative symptoms

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>n</th>
<th>r² (%)</th>
<th>SMD</th>
<th>WMD</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total symptoms</td>
<td>7</td>
<td>340</td>
<td>0</td>
<td>-0.20</td>
<td>-0.41 to 0.02</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>5</td>
<td>281</td>
<td>0</td>
<td>-0.25</td>
<td>-0.49 to -0.01</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>PANSS positive subscale score</td>
<td>4</td>
<td>260</td>
<td>21</td>
<td>-0.07</td>
<td>-0.69 to 0.55</td>
<td>0.83</td>
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</tr>
<tr>
<td>PANSS general subscale score</td>
<td>2</td>
<td>97</td>
<td>0</td>
<td>-1.57</td>
<td>-3.62 to 0.48</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>CDSS score</td>
<td>5</td>
<td>281</td>
<td>28</td>
<td>0.18</td>
<td>-0.45 to 0.81</td>
<td>0.58</td>
<td></td>
</tr>
</tbody>
</table>

Sakuma et al., Psychopharmacology, 2018
### Folic acid for negative symptoms

**Treatment x genotype interactions**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Negative symptoms, change from baseline</th>
<th>Folate</th>
<th>Placebo</th>
<th>Difference:</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FOLH1</strong></td>
<td>T/T (n=64)</td>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Graph" /></td>
<td>-0.55 per wk</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>T carrier (n=56)</td>
<td><img src="image3.png" alt="Graph" /></td>
<td><img src="image4.png" alt="Graph" /></td>
<td>-0.49 per wk</td>
<td>0.020</td>
</tr>
<tr>
<td><strong>MTHFR</strong></td>
<td>T/T (n=64)</td>
<td><img src="image5.png" alt="Graph" /></td>
<td><img src="image6.png" alt="Graph" /></td>
<td>-0.02 per wk</td>
<td>0.936</td>
</tr>
<tr>
<td></td>
<td>T carrier (n=56)</td>
<td><img src="image7.png" alt="Graph" /></td>
<td><img src="image8.png" alt="Graph" /></td>
<td>-0.16 per wk</td>
<td>0.360</td>
</tr>
</tbody>
</table>

Roffman et al., JAMA Psychiatry, 2013

Allelic risk score:

\[
FOLH1^T (0,1,2) + MTHFR^T (0,1,2) + MTR^A (0,1,2) = 0.68
\]
MTHFR genotype: clinical value

- Does being a double heterozygote increase risk for schizophrenia? ...No

- Does being a double heterozygote increase risk for negative symptoms of schizophrenia? ...Maybe

- Does taking folic acid help? ...Maybe

- Should methylfolate be taken instead of folic acid? ...Maybe
Methylfolate for negative symptoms

**PANSS Negative**

- **L-methylfolate**
- **Placebo**
- **Difference**

Results not dependent on genotype

Roffman et al., Mol Psychiatry, 2017
Does MTHFR genotype add value?

- Worried about low serum folate?
  ...Check it. No need to genotype, at 10x the cost, and questionable utility.

- Does your patient have negative symptoms?
  ...No good reason not to treat empirically with folic acid first.

- But could MTHFR genotype help get to methylfolate more quickly?
  ...Insufficient evidence to say, either from cost effectiveness or efficacy perspective.
Even 23andMe® agrees...

Our Take On The MTHFR Gene

January 5, 2017 By 23andMe under Health and Traits

The *methylene tetrahydrofolate reductase gene*, more commonly known as MTHFR, is the most asked-about gene by 23andMe customers.

Some websites and products have made bold claims that common genetic variants in MTHFR can cause a wide array of health conditions, ranging from blood clots and cancer to autism and migraines. So we decided to dig deeper into the published scientific literature to evaluate the evidence.

Our conclusion?

Despite lots of research - and lots of buzz - the existing scientific data doesn’t support the vast majority of claims that common MTHFR variants impact human health.
...but the genie is out of the bottle

First came the home DNA kits. Now come the support groups

Genetics company 23andMe is rolling out a huge initiative for people with ADHD and depression — but psychologists are worried

23andMe Is Terrifying, but Not for the Reasons the FDA Thinks

The genetic-testing company's real goal is to hoard your personal data

By Charles Seife on November 21, 2013
When is genetic testing indicated?

- FDA guidance:
  HLA-B*1502 prior to carbamazepine in patients of Asian descent (boxed warning)
  Other pharmacogenomic panels (PGx):

<table>
<thead>
<tr>
<th>CYP2D6</th>
<th>Clomipramine</th>
<th>Imipramine</th>
<th>Thioridazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Clozapine</td>
<td>Modafinil</td>
<td>Trimipramine</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>Desipramine</td>
<td>Nefazodone</td>
<td>Venlafaxine</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Desvenlafaxine</td>
<td>Nortriptyline</td>
<td>Vortioxetine</td>
</tr>
<tr>
<td>Arapiprazole</td>
<td>Doxepin</td>
<td>Paliperidone</td>
<td></td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>Duloxetine</td>
<td>Paroxetine</td>
<td></td>
</tr>
<tr>
<td>Brexipiprazole</td>
<td>Escitalopram</td>
<td>Perphenazine</td>
<td></td>
</tr>
<tr>
<td>Carprazine</td>
<td>Fluoxetine</td>
<td>Pimozone</td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>Fluvoxamine</td>
<td>Protriptyline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Iloperidone</td>
<td>Risperidone</td>
<td></td>
</tr>
</tbody>
</table>

Consensus is that they are of limited value in routine clinical use – e.g., among Caucasians, 7-10% are poor metabolizers and <1% are ultrarapid metabolizers

- Autism spectrum disorder with intellectual disability (Copy number variants)
Conclusions and recommendations

• At present, there is no high-quality evidence to support use of direct-to-consumer genetic testing to guide clinical decision-making

• More broadly, despite significant research advances on genetic origins of psychiatric illness, genetic testing is unlikely to be of benefit in the clinic in the near term

• Watch this space though…
Proof-of-concept...

**Table 4.** Coronary Artery Calcification Burden, by Polygenic Risk Score Quintile in CARDIA (Coronary Artery Risk Development in Young Adults)

<table>
<thead>
<tr>
<th>Polygenic Risk Score Quintile</th>
<th>CAC&gt;1%, %</th>
<th>CAC &gt;0* OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>12.1</td>
<td>2.08 (0.89–4.83)</td>
<td>0.09</td>
</tr>
<tr>
<td>3</td>
<td>10.9</td>
<td>2.08 (0.87–4.98)</td>
<td>0.10</td>
</tr>
<tr>
<td>4</td>
<td>14.3</td>
<td>3.02 (1.31–7.00)</td>
<td>0.01</td>
</tr>
<tr>
<td>5 (High)</td>
<td>15.6</td>
<td>2.51 (1.08–5.85)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Natarajan et al., Circulation 2017

**Figure 1.** Incident coronary heart disease events by statin therapy and genetic risk group in WOSCOPS (West of Scotland Coronary Prevention Study).

Thank you!