Psychiatric genomics 2016: what the clinician needs to know

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Disclosures

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

• Dr. Perlis has consulted to or served on scientific advisory boards from Genomind, Healthrageous, Pamlab, Perfect Health, Pfizer, Proteus Biomedical, and RID Ventures

• Dr. Perlis receives royalties/patent fees from Concordant Rater Systems (now Bracket, a Medco subsidiary)
Disclosure #2

An estimated 2.6% of your DNA is from Neanderthals.

(You) 2.6% 54th percentile

Average Northern European user 2.6%

MODERN HUMANS
- Higher brow
- Narrower shoulders
- Slightly taller

NEANDERTHALS
- Heavy eyebrow ridge
- Long, low, bigger skull
- Prominent nose with developed nasal chambers for cold-air protection

23andme, accessed July 2015
Overview

• Update on genetics of psychiatric and neurodevelopmental disorders
• When to talk to a medical geneticist
• What is pharmacogenomics
• When to consider testing
• Where do we go from here?
Case #1: All in the Family

• Mr. Z. is a 51 y.o. accountant with bipolar 1 disorder, stable on lithium for >10 years.

• He refers his 18 y.o. son, a college student who ‘seems down’.

• Without knowing anything else, son’s most likely diagnosis is...?
Weighted Summary Risks of Mood Disorders From Family Studies of Bipolar Disorder

<table>
<thead>
<tr>
<th>Probands</th>
<th>Bipolar</th>
<th>Unipolar</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MR</td>
<td>OR</td>
</tr>
<tr>
<td>Bipolar</td>
<td>6.7%</td>
<td>10.8*</td>
</tr>
<tr>
<td>Unipolar</td>
<td>2.2%</td>
<td>3.4*</td>
</tr>
<tr>
<td>Controls</td>
<td>0.7%</td>
<td>1</td>
</tr>
</tbody>
</table>

MR = Morbid Risk; OR = Odds Ratio (vs. controls) * p < 0.001

• Psychiatric disorders do run in families...
• BUT not everyone will manifest the same disorder – or even any disorder!

• SO beware diagnosis-by-family-history
The DISC1 family

St. Clair Lancet 1990
### Estimates of Heritability

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Approx. $h^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism</td>
<td>90%</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>80%</td>
</tr>
<tr>
<td>Type II DM</td>
<td>80%</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>60%</td>
</tr>
<tr>
<td>Alcohol Dependence</td>
<td>55%</td>
</tr>
<tr>
<td>Asthma</td>
<td>48%</td>
</tr>
<tr>
<td>Major Depression</td>
<td>42%</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>27%</td>
</tr>
</tbody>
</table>

*Smoller, Sheidley, Tsuang 2007*  
*Psychiatric Genetics: Application in Clinical Practice*
Estimating overlap between disorders

PGC Nature Genetics 2013
The Usual Suspects: why candidate gene studies were hard

- Serotonin Genes
- Dopamine Genes
- Norepinephrine Genes
- GABA Genes
- Neuropeptide Genes

Courtesy J Smoller
Schizophrenia c. 2009 (~4,000 cases)
Schizophrenia 2011 (~10,000 cases)
Schizophrenia 2012 (~25,000 cases)
Biological insights from 108 schizophrenia-associated genetic loci

Schizophrenia Working Group of the Psychiatric Genomics Consortium*
Bipolar disorder: ~6 loci, and counting...

PGC-bipolar, Nat Gen 2011; Green Mol Psych 2013
Calcium ion channels

Calcium channel blockers have been used to treat bipolar disorder

PGC-bipolar, Nat Gen 2011

Courtesy Pamela Sklar  www.mghcme.org
These variants don’t just affect risk for bipolar disorder…

The bipolar disorder risk allele at CACNA1C also confers risk of recurrent major depression and of schizophrenia

EK Green¹, D Grozeva¹, I Jones¹, L Jones², G Kirov¹, S Caesa², K Gordon-Smith¹,², C Fraser¹, L Forty¹, E Russell¹, ML Hamshere¹,³, V Moskva¹,³, I Nikolov¹,³, A Farmer¹, P McGuffin⁴, Wellcome Trust Case Control Consortium⁵, PA Holmans¹,³, MJ Owen¹, MC O’Donovan¹ and N Craddock¹

Phenotypic Effects of a Bipolar Liability Gene Among Individuals With Major Depressive Disorder

Francesco Casamassima¹,², Jie Huang³,⁴, Maurizio Fava²,⁴, Gary S. Sachs²,⁴, Jordan W. Smoller³,⁴, Giovanni B. Cassano¹, Lorenzo Lattanzi¹, Jøs Fagerness³, Jonathan P. Stange⁶ and Roy H. Perlis⁶,³,⁴,*

Diagnostic Products Corp, Los Angeles, CA, USA (control levels = 1.9 ± 1.3 nm). Chromogranin A was measured using a two-site immunoassay kit (ALPCO Diagnostics, Salem, NH, USA) (control levels = 29.6 ± 21.3 ng ml⁻¹). Fold change (FC) was calculated as the disease:control ratio of analyte levels. Statistical significance (P-value) was determined by two-tailed t-tests. Significant FC values are indicated in bold font.

disorder patients (Table 1), suggesting that these molecules are not altered in all neuropsychiatric disorders.

Taken together, these findings show that hyperinsulinemia may have a role in the onset of schizophrenia. This has important implications, as elevated insulin levels can have deleterious effects on brain function.⁸ In addition, this suggests the possibility

CACNA1C (rs1006737) is associated with schizophrenia

In a large collaborative study combining three separate whole-genome association studies, the CACNA1C gene (rs1006737) was recently found to display a genome-wide significant association with bipolar disorder (BPD). Here, we report for the first time the
Genetics of major depression

PGC-MDD, Mol Psych 2012
What about rarer variants?

Sebat, Science 2007
Overview: rarer de novo variants

• In autism and schizophrenia: multiple genes strongly implicated but...
  – No smoking gun

• In bipolar disorder and recurrent depression:
  – Data are mixed/insufficient
‘Phenocopies’

Like neurosyphilis: once a test exists, we can start to look for specific ‘mimics’.
When to think about neurodevelopmental syndromes

• Dysmorphia
• Intellectual Disability
• Epilepsy
• Atypical psychiatry symptoms (eg, visual hallucinations)
Next steps

• NOT medical sequencing

• Pedi neurology (or pediatrics)
• Medical genetics consult

• Why pursue workup?
  – Often helpful to parents to have a name/community
  – May point towards unrecognized systemic features (eg, cardiovascular)
Example:
22q11 (Velocardiofacial Syndrome)

Narrow eye opening, long narrow face with flat cheeks, prominent nasal root, bulbous nose, ...

Known increased risk for psychosis (as well as manic-like symptoms) (up to 30%)

Kobrynski Lancet 2007; Gothelf CAPCNA 2007
What about the other 20-80% of risk?

Genes are not (necessarily) destiny: environment matters!

Example: Early adversity/stressful life events and mood disorders
Brief digression: SSRI exposure and autism

- Efforts persist to link in utero SSRI exposure to autism risk (1)
- Absolute increase in risk <0.5%
- More likely risk travels with disease, not treatment! (2)
  - => greater likelihood of SSRI use during pregnancy
  - => greater risk for autism in offspring

(1) Croen, Arch Gen Psych 2011; Boukhris JAMA Ped 2015)
(2) Clements Mol Psych 2015, Castro Trans Psych in press, others...
Clinical take-home

• Beware diagnosis by family history.

• No validated genetic tests for common psychiatric disorders – yet.

• In patients with intellectual disability, epilepsy or other neurologic findings, dysmorphic appearance – consider pedi neurology or medical genetics consult
The era of precision medicine?

• Efficacy
• Tolerability
• Safety
“New tool: Genotyping makes prescribing safer, more effective.”

— Current Psychiatry
“New tool: Genotyping makes prescribing safer, more effective.”

– Current Psychiatry, September 2004
Pharmacogenetic model

Genetic variation → Drug response

- Drug level (warfarin)
- Efficacy (lithium)
- Adverse effect (statins)
- ...
Pharmacogenomics in medicine, 2015

- >100 labels reflect genetic data
- **Majority relate to safety or dosing**
- Nearly all derived from post-hoc analysis

- **Psychotropic:**
  - CYP450
  - HLA (carbamazepine)

[http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm](http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm)
Example: Carbamazepine

• Testing for carbamazepine toxicity
  – SJS/TEN seen in 1.6/10,000 Caucasians
    • but 5-30x more common in some Asian groups
  – HLA-B*1502:
    • Positive predictive value ~0.1
    • Negative predictive value ~1
  – Labeling: test for variant in Asian patients, use alternative drug if positive

Carbamazepine US package insert
### Drug Response

Data is not yet available. Data for other profiles in your account are still shown.

**Show results for**

[See new and recently updated reports](#)

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#### 23andMe Discoveries were made possible by 23andMe members who took surveys.

<table>
<thead>
<tr>
<th>Name</th>
<th>Confidence</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (Coumadin®) Sensitivity</td>
<td>★★★★★☆☆☆☆</td>
<td>Increased</td>
</tr>
<tr>
<td>Abacavir Hypersensitivity</td>
<td>★★★★★☆☆☆☆</td>
<td>Typical</td>
</tr>
<tr>
<td>Alcohol Consumption, Smoking and Risk of Esophageal Cancer</td>
<td>★★★★★☆☆☆☆</td>
<td>Typical</td>
</tr>
<tr>
<td>Clopidogrel (Plavix®) Efficacy</td>
<td>★★★★★☆☆☆☆</td>
<td>Typical</td>
</tr>
<tr>
<td>Fluouracil Toxicity</td>
<td>★★★★★☆☆☆☆</td>
<td>Typical</td>
</tr>
<tr>
<td>Response to Hepatitis C Treatment</td>
<td>★★★★★☆☆☆☆</td>
<td>Typical</td>
</tr>
<tr>
<td>Pseudochoinesterase Deficiency</td>
<td>★★★★★☆☆☆☆</td>
<td>Typical</td>
</tr>
<tr>
<td>Oral Contraceptives, Hormone Replacement Therapy and Risk of Venous Thromboembolism</td>
<td>★★★★★☆☆☆☆</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Caffeine Metabolism</td>
<td>★★★★★☆☆☆☆</td>
<td>Fast Metabolizer</td>
</tr>
<tr>
<td>Metformin Metabolism</td>
<td>★★★★★☆☆☆☆</td>
<td>Typical Odds of Positive Response</td>
</tr>
<tr>
<td>Antidepressant Response</td>
<td>★★☆☆☆☆☆☆</td>
<td>See Report</td>
</tr>
<tr>
<td>Beta-Blocker Response</td>
<td>★★☆☆☆☆☆☆</td>
<td>See Report</td>
</tr>
<tr>
<td>Floxacin Tolerance</td>
<td>★★☆☆☆☆☆☆</td>
<td>Typical Odds</td>
</tr>
<tr>
<td>Heroin Addiction</td>
<td>★★☆☆☆☆☆☆</td>
<td>Typical Odds</td>
</tr>
</tbody>
</table>

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**My Home**

- Inbox (1)

**My Health**

- Disease Risk
- Carrier Status
- Drug Response
- Traits
- Health Labs

**My Ancestry**

- Maternal Line
- Paternal Line
- Relative Finder
- Ancestry Painting
- Global Similarity
- Ancestry Labs

**Sharing & Community**

- Compare Genes
- Family inheritance
- 23andMe Community
- Genome Sharing

**23andMe**

- Research Surveys (28)
- Research Snippets
- Research Initiatives
- Research Discoveries
The prototypical pharmacokinetic gene: \textit{CYP450 2D6}

- Most important member of palette of hepatic drug/toxin-metabolizing enzymes ("phase I")
- Relevant effects on 25%+ of pharmacopeia (for all CYP450, up to 80%)

De Gregori Curr Drug Metab 2010; Ingelman Pharm Ther 2007
The prototypical pharmacokinetic gene: **CYP450 2D6**

- Small deletions/polymorphisms
  - Poor metabolizer
- Deletion of entire locus
  - Poor metabolizer
- One functional copy, one deletion
  - Intermediate metabolizer
- Two functional copies
  - Extensive or wildtype metabolizer
- Duplication
  - Ultrarapid metabolizer

De Gregori Curr Drug Metab 2010; Ingelman Pharm Ther 2007
Impact of CYP2C19 on escitalopram/citalopram blood level

Chang, Clin Pharmacokinet 2014; meta-analysis of 16 studies
Gene Variants in CYP2C19 Are Associated with Altered In Vivo Bupropion Pharmacokinetics but Not Bupropion-Assisted Smoking Cessation Outcomes

Zhu, Drug Metab Dispos. 2014
Example

Drug 1→ poor metabolizer→

= higher than expected blood levels

= ?greater risk for adverse effects
Solution

Drug 1 -> poor metabolizer ->

= higher than expected blood levels

= ?greater risk for adverse effects

So – avoid this drug if there are other good choices, but...

If required, simply start low(er) and go slow(er) –
generally aim for low end of therapeutic range
Example 2

Drug 2 -> ultrarapid metabolizer ->
  = lower than expected blood levels
  = ?greater risk for nonresponse
Solution

Drug 2 -> ultrarapid metabolizer ->
  = lower than expected blood levels
  = ? greater risk for nonresponse

So – avoid this drug if there are other good choices, but...

*If required, titrate cautiously but consistently to response – may require high end of therapeutic range, or even supratherapeutic doses*
Managing non-wildtype patients on CYP450 substrates

- monitor adverse effects
- consider checking a blood level (trough)
Need for continued caution after titration
In MDD, CYP2D6 substrate-inhibitor combinations are associated with poorer adherence

- n = 5,630

Sicras-Mainar, Eur Psychiatry. 2014
Do not memorize cyp450 interactions...

• Good current resource:

http://medicine.iupui.edu/clinpharm/ddis/main-table/

• Consider using software for automated interaction checking
What about other pharmacogenomic tests?

• For non-CYP450 assays, extent of support for individual variants varies widely.
• One small negative RCT, but cautious optimism from open nonrandomized studies
• Larger RCT’s ongoing
The bad news...

Essay

Why Most Published Research Findings Are False
John P.A. Ioannidis

• “It can be proven that most claimed research findings are false.”

• Small samples, small effects, multiple hypotheses, varying definitions, and...

• “chase for statistical significance”

Ioannidis PLOS One 2005
Genetics of antidepressant remission

Remission at 12 weeks by HAM-D; Gendep, MARS, and STAR-D Investigators - AJP 2012
MC4R and antipsychotic-associated weigh gain

Discovery cohort n=139; replication cohorts n=205 Malhotra; Arch Gen Psych 2012
ICE CREAM is GOOD FOR YOU
*NOT based on science.
Do we need a biomarker for depression?

- "During the past month have you felt depressed or down? During the past month have you been bothered by having little interest or pleasure in doing things?"

- 83% sensitivity, 92% specificity for MDD

PHQ-9: Kroenke JGIM 2001
Getting comfortable with probability
Psychiatric genomics: what the clinician needs to know