Psychiatric genomics 2018:
what the clinician needs to know

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Disclosure #2

An estimated 2.6% of your DNA is from Neanderthals.

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?
“New tool: Genotyping makes prescribing safer, more effective.”

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

— Current Psychiatry, September 2004
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></th>
<th>First Degree Relatives</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bipolar</td>
<td>Unipolar</td>
<td></td>
</tr>
<tr>
<td><strong>Probands</strong></td>
<td>MR</td>
<td>OR</td>
<td>MR</td>
</tr>
<tr>
<td>Bipolar</td>
<td>6.7%</td>
<td>10.8*</td>
<td>15.4%</td>
</tr>
<tr>
<td>Unipolar</td>
<td>2.2%</td>
<td>3.4*</td>
<td>18.7%</td>
</tr>
<tr>
<td>Controls</td>
<td>0.7%</td>
<td>1</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

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

Key point

• 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

Courtesy J Smoller
Schizophrenia c. 2009 (~4,000 cases)
Schizophrenia 2011 (~10,000 cases)

PGC, Nature Genetics 2011
Schizophrenia 2012 (~25,000 cases)

Stephan Ripke for PGC (WCPG 2012)
Biological insights from 108 schizophrenia-associated genetic loci

Schizophrenia Working Group of the Psychiatric Genomics Consortium*

Significance of test: 4* < 0.001, 5* < 1.0*10^-04, 6* < 1.0*10^-06, 7* < 1.0*10^-12, 8* < 1.0*10^-50, 9* < 1.0*10^-100
Bipolar disorder: ~7 loci, and counting...

PGC-bipolar, Nat Gen 2011; Green Mol Psych 2013
**CACNA1C**

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 cross disorders

- CACNA1C linked to...
  - Bipolar disorder
  - Schizophrenia
  - ?recurrent major depression
What a difference 75k cases makes: 15 novel loci for major depression
What about rarer variants?

Sebat, Science 2007
Overview: rarer de novo variants

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

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

Searching for disease ‘mimics’.
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
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)
What about the other 20-80% of risk?

Genes are not (necessarily) destiny: environment matters!

Example: Early adversity/stressful life events and mood disorders
Clinical take-home (part 1)

• 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
Pharmacogenetic model

Genetic variation → Drug response

Drug level (warfarin)
Efficacy (lithium)
Adverse effect (statins)
...

www.mghcme.org
Pharmacogenomics in medicine, 2018

- >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
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

**Show results for**

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>Fluorouracil Toxicity</td>
<td>★★★★★</td>
<td>Typical</td>
</tr>
<tr>
<td>Response to Hepatitis C Treatment</td>
<td>★★★★★</td>
<td>Typical</td>
</tr>
<tr>
<td>Pseudocholinesterase 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 Response [new]</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 Dose Toxicity</td>
<td>★★</td>
<td>Typical Odds</td>
</tr>
<tr>
<td>Heroin Addiction</td>
<td>★★</td>
<td>Typical Odds</td>
</tr>
</tbody>
</table>
The prototypical pharmacokinetic gene: 
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
In the State of Massachusetts, hospital discharge on medications metabolized by cytochrome P450 is associated with greater readmission and total cost...

N=124,230 (State of MA claims)
N=79,990 (Boston hospitals)

For individuals with 1+ CYP450 substrate at discharge:
Total healthcare cost increased by $397.65 per month, after adjusting for medication count, comorbidity, age, sex, ...

McCoy et al, Pharmacogenomics Journal 2016
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
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)
Do not memorize cyp450 interactions...

• Good current resource:
  http://medicine.iupui.edu/clinpharm/ddis/main-table/
  Can also go to...
  http://clearer.mghcedd.org

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

• For non-CYP450 assays, extent of support for individual variants varies widely.

• Unfortunately, studies of clinical intervention have looked only at full panel, not individual genes...
  – One small negative randomized single-blind trial
  – Two positive cost-effectiveness studies
  – Larger single-blind studies ongoing
The bad news...

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 weight gain

Discovery cohort n=139; replication cohorts n=205 Malhotra; Arch Gen Psych 2012
Clozapine-induced agranulocytosis is associated with rare HLA-DQB1 and HLA-B alleles

Jacqueline I. Goldstein, L. Fredrik Jarskog […] Patrick F. Sullivan

Nature Communications 5, Received: 02 April 2014
Genetic variants associated with response to lithium treatment in bipolar disorder: a genome-wide association study
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
Where else do we go from here?

• Making better use of clinical data
Predicting risk for treatment resistance using clinical features

http://trdrisk.mghcedd.org; Perlis Biol Psych 2013
Opening the black box!

Individual risk score

This bar graph shows the contribution of each clinical feature, collected in the prior form, to the risk estimate. Features which increase risk, relative to the mean population risk, are colored in red; those which decrease risk are colored in green. One way to see how a given variable impacts risk is to hit the 'back' button on your browser, and experiment with different values in the calculator.

- QIDS insomnia (mid)
- QIDS energy
- Family impact
- QIDS insomnia (late)
- Education
- Recurrent (3+ prior)
- African-American
- Experienced trauma
- Witnessed trauma
- Marital status
- PTSD
- QIDS total score
- Psychosis

http://trdrisk.mghcedd.org; Perlis Biol Psych 2013
Predicting out-of-hospital falls

(Fall-associated injury model presented in Castro BMJ 2014)
Modeling drug response in a dish
Psychiatric genomics: what the clinician needs to know