Psychiatric Genetics: A Clinician's Perspective

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Learning Objective

Explore the role of genetics in psychiatric disorders and evaluate the role of genetic research in evaluating treatment directions.
Dr. Weinberger has no disclosures to report.
Psychiatric Genetics: A Clinician’s Perspective

Three Key Points

1. The genes for psychiatric disorders are not for psychiatric disorders

2. Genetic risk is critically dependent on context (both genetic and environmental)

3. Genetic overlap does not necessarily mean that the mechanisms of risk overlap
Genes and Mental Illness

Why Do We Study Them?

- Most risk for psychiatric illness is related to inheritance
- Genes transcend phenomenological diagnosis
- Genes represent mechanisms of disease
- Genes clarify the environment
- Genes identify individuals who are at risk
- Genes identify biological pathways for the development of new treatments
How are genes “found”?
The Genome Sequence Contains Many Variations

single nucleotide polymorphism (SNP)

AATCC → AAGCC

Susceptibility Genes Are Found by “Association”

A gene is said to be associated with a trait (e.g., an illness) when a variant in the gene is found with increased frequency in a population that is enriched with that trait.

A population of “BLUE” folks – “cases”

- AA
- aA
- Aa
- AA
- AA
- Aa
- AA
- Aa
- CC
- Cc
- Ce
- CC
- Ce
- CC
- Ce
- CC
- Ce

The A gene is associated with the BLUE trait.
The “A” allele is the risk allele.

# Schizophrenia Susceptibility Genes: Strength of the Evidence

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Association with schizophrenia</th>
<th>Linkage to gene locus</th>
<th>Biological plausibility</th>
<th>Altered expression in schizophrenia</th>
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<tbody>
<tr>
<td>COMT</td>
<td>22q11</td>
<td>+ +</td>
<td>+ + + +</td>
<td>+ + +</td>
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<tr>
<td>DTNBP1</td>
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<tr>
<td>NRG1</td>
<td>8p12–21</td>
<td>+ + + . .</td>
<td>+ + +</td>
<td>+</td>
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<tr>
<td>RGS4</td>
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<td>+ + +</td>
<td>+</td>
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<tr>
<td>GRM3</td>
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<td>No, + +</td>
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<tr>
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<td>+</td>
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<tr>
<td>G72</td>
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<td>+</td>
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<tr>
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<td>+ .</td>
<td>+</td>
<td>+ + + +</td>
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<td></td>
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</tbody>
</table>

Virtually every chromosome is involved!

PGC 2 – 80,000 Subjects, Over 100 GWAS “Significant” Loci

PGC = Psychiatric GWAS Consortium; GWAS = Genome-Wide Association Study.
Some Lessons Learned From GWAS Studies of Schizophrenia

- There is no schizophrenia gene, per se
- There is no royal road to risk
- There are many roads to the same syndrome and the same diagnosis

How important is the clinical diagnosis?

Four “loci” identified in 61,220 subjects
Identification of Risk Loci With Shared Effects on Five Major Psychiatric Disorders: A Genome-Wide Analysis

Cross-Disorder Group of the Psychiatric Genomics Consortium

*N = 61,220 subjects (33,332 cases)*

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Base-pair position</th>
<th>Nearest gene</th>
<th>Alleles</th>
<th>Frequency†</th>
<th>Imputation quality score (INFO)</th>
<th>p value</th>
<th>OR (95% CI)‡</th>
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<tbody>
<tr>
<td>rs2535629</td>
<td>3</td>
<td>ITIH3 (+ many)</td>
<td>G/A</td>
<td>0.651</td>
<td>0.942</td>
<td>2.54×10⁻¹²</td>
<td>1.10 (1.07-1.12)</td>
</tr>
<tr>
<td>rs11191454</td>
<td>10</td>
<td>AS3MT (+ many)</td>
<td>A/G</td>
<td>0.910</td>
<td>1.01</td>
<td>1.39×10⁻⁸</td>
<td>1.13 (1.08-1.18)</td>
</tr>
<tr>
<td>rs1024582</td>
<td>12</td>
<td>CACNA1C</td>
<td>A/G</td>
<td>0.337</td>
<td>0.98</td>
<td>1.87×10⁻⁴</td>
<td>1.07 (1.05-1.10)</td>
</tr>
<tr>
<td>rs2799573</td>
<td>10</td>
<td>CACNB2</td>
<td>T/C</td>
<td>0.715</td>
<td>0.825</td>
<td>4.29×10⁻⁴</td>
<td>1.08 (1.05-1.12)</td>
</tr>
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How diagnostically nonspecific are these associations, actually?

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The schizophrenia signal alone is nonsignificant in N = 80,000!

Some Lessons Learned and Some Questions Asked from GWAS Studies of Psychiatric Illness

- There is no schizophrenia or bipolar gene, per se
- There is no royal road to risk
- There are many roads to a psychiatric syndrome
- Are there general psychopathology genes?
  → Probably, yes
- Do shared genetic loci reflect shared mechanisms of illness?
  → Not necessarily
- Is psychiatric diagnosis according to DSM-5 a useful concept?
  → Yes and No

*DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition.*
An Inconvenient Question: Why Are the Clinical Associations So Weak?

Some answers:

- Heterogeneity
- Environmental modification
- Rare variants
- Epigenetics
- Epistasis

GENES DO NOT ENCODE FOR PSYCHIATRIC SYNDROMES
Noncoding Variations Affect Gene Function via Diverse Mechanisms, But They All Read Out in the Transcriptome

**mechanisms**
- splicing
- miRNA
- 5’ UTR variations
- noncoding RNA
- promotor effects
- enhancer effects
- looping
- chromatin state
- DNA methylation

**RNA sequencing in brain**
- splicing, novel exons, TSS’s, UTR’s, abundance

miRNA = MicroRNA; UTR = untranslated regions; TSS = transcription start site.
Epigenetic Control of Expression

CpG (CG) dinucleotides

↓ Methylation &
↑ H acetylation
= ↑ Expression

↓ Methylation &
↑ H acetylation
= ↓ Expression

There is no schizophrenia or bipolar gene, per se

Genes do not encode for psychiatric syndromes

It is unclear whether shared genetic associations reflect shared mechanisms of illness

Evidence suggests susceptibility genes in schizophrenia
Questions & Answers