The Genetics of Mood Disorders

How Genetics Will Improve Diagnosis and Treatment

John R Kelsoe, MD
Professor of Psychiatry
Director, Laboratory of Psychiatric Genomics
University of California, San Diego
Thanks DBSA!
Bipolar Disorder
Manic Depressive Illness

- Mania
  - Elevated or irritable mood
  - Grandiosity
  - Decreased need for sleep
  - Increased or pressured speech
  - Flight of ideas or racing thoughts
  - Increased goal directed activity
  - Risk taking
  - Functional impairment

- Depression
  - Low mood
  - Loss of interest or pleasure
  - Change in appetite or weight
  - Insomnia or hypersomnia
  - Fatigue
  - Feelings of worthlessness
  - Impaired memory or concentration
  - Suicidality
  - Clinically significant distress or impairment

1-2% population prevalence worldwide
Clinical Features of Bipolar Disorder

- Age of onset early twenties
- 1-2% of the population worldwide
- Unipolar depression is about 5 times more common
- Male and Female rates equal
- 60-80% of cases begin with mania
- 4-18% of those with depression later have mania
- Alcohol and substance abuse
Classification of Mood Disorders

Unipolar
- Unipolar single episode
- Unipolar recurrent
- Dysthymia

Bipolar
- Bipolar I
- Bipolar II
- Cyclothymia
- Unipolar-Hyperthymic
Mood Disorder Treatment Wish List

- **Diagnosis**
  - More accurate
  - Earlier
  - Better prediction of medication response

- **Medications**
  - Greater efficacy
  - Currently 1/2 - 2/3 receive only partial or limited benefit
  - Fewer side effects
  - More rapid action
# Bipolar Disorder — A Diagnostic Challenge

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
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<tbody>
<tr>
<td>Base (n)</td>
<td>600</td>
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<tr>
<td>Misdiagnosis (%)</td>
<td>69%</td>
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<tr>
<td>Times misdiagnosed</td>
<td>3.5</td>
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<tr>
<td>MDs consulted before Dx</td>
<td>4</td>
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<tr>
<td>Misdiagnosed as (%)</td>
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<tr>
<td>Depression</td>
<td>60</td>
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<tr>
<td>Anxiety disorder</td>
<td>26</td>
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<tr>
<td>Schizophrenia</td>
<td>18</td>
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<tr>
<td>Borderline personality or antisocial personality disorder</td>
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The Drug Pipeline

Drugs discovered by chance

>8 years
>$500 M

Clones of drugs discovered by chance
The Drug Discovery Problem

- Little is understood about the brain biology of mood disorders
- Our theories are primarily based on the mechanism of action of drugs discovered by chance
The Genetics Solution

• Fundamental understanding of disease pathways
• New medications
  • New mechanisms of action
  • More effective
  • Rapid
  • Fewer side effects
• DNA tests for diagnosis
• DNA tests to predict medication response – pharmacogenetics
• Personalized pharmacology
The Future of Gene Based Treatment

DNA Based Diagnosis

- Best current medication
- Novel gene specific targeted medication
- Gene therapy
# Affective Illness In First Degree Relatives

## Bipolar Probands

<table>
<thead>
<tr>
<th>Study</th>
<th>Relatives at Risk</th>
<th>Morbid Risk (%)</th>
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<tr>
<td>Perris, 1966</td>
<td>627</td>
<td>10.2</td>
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<tr>
<td>Winokur and Clayton, 1967</td>
<td>167</td>
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<tr>
<td>Mendlewicz and Rainer, 1974</td>
<td>606</td>
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<td>Goetzl et al., 1974</td>
<td>212</td>
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<td>Helzer and Winokur, 1974</td>
<td>151</td>
<td>4.6</td>
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<td>Gershon et al., 1975</td>
<td>341</td>
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<td>James and Chapman, 1975</td>
<td>239</td>
<td>6.4</td>
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<td>Johnson and Leeman, 1977</td>
<td>126</td>
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<td>Petterson, 1977</td>
<td>472</td>
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<td>Smeraldi et al., 1977</td>
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<td>Trzeblatowska-Trzeciak</td>
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<td>Angst, 1980</td>
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<td>Dunner, Go, and Fieve, 1980</td>
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<td>Taylor, Abrams, and Hayman, 1980</td>
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<td>Rice et al., 1987</td>
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# Twin Studies of Affective Illness

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<th>Study</th>
<th>Monozygotic</th>
<th>Dizygotic</th>
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<tr>
<td></td>
<td>Concordance</td>
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<td>Luxenberger, 1930</td>
<td>3/4</td>
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<td>Rosanoff et al., 1935</td>
<td>16/23</td>
<td>69.6</td>
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<td>Slater, 1953</td>
<td>4/7</td>
<td>57.1</td>
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<td>Kallman, 1954</td>
<td>25/27</td>
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<td>Harvald and Hauge, 1965</td>
<td>10/15</td>
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<td>Allen et al., 1974</td>
<td>5/15</td>
<td>33.3</td>
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<td>Bertelsen, 1979</td>
<td>32/55</td>
<td>58.3</td>
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<td><strong>TOTAL</strong></td>
<td>95/146</td>
<td>65.0</td>
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</table>
The Universe of Bipolar Genes

Spectrum temperaments

Bipolar 1

Bipolar 2

Bipolar 3

Unipolar
The Human Genome Project

• Goal
  • Sequence all 3 billion base pairs in the human genome
  • Identify all human genes
• The largest and most important scientific project in the history of biology

• Results
  • Only ~35,000 human genes
  • Function known of ~7000 genes
  • Tools – over 3 Million DNA markers
Genetic Mapping

Collect Families

Study the inheritance of 400 markers on all the chromosomes

Find the chromosomal location of a disease gene

What genes are in that region?

Identify the disease gene

Find the mutation in the gene

Understand the function of the gene
And the mechanism of disease

Human Genome Project
Genome Survey of 20 Bipolar Families

Maximum LOD Score

Bipolar Gene on Chromosome 22

Genetic Distance (cM)
Chromosome 22

Summary of results in Bipolar Disorder and Schizophrenia

Locus

D22S420
D22S264
D22S427
D22S425
D22S539
D22S303
D22S257
D22S1174
D22S315
D22S1164
D22S926
D22S925
D22S421
D22S419
D22S429
D22S1144
D22S689
D22S684
D22S693
D22S691
D22S1ju
D22S5ju
D22S277
D22S683
D22S278
D22S1142
D22S283
D22S692
D22S1045
D22S445
D22S307
D22S270
ata5f505
D22S274

Bipolar Disorder
Schizophrenia

VCFS

13
11.2
11.1
11.22
12.1
12.3
13.2
13.32

UCSD genome scan, LOD 2.2
GRK3
NIMH GIBP consortium, LOD 2.5
Myles Worsley et al., LOD 3.5
Detera-Wadleigh et al., NIMH intramural, LOD 2.5
UCSD genome scan, LOD 3.8
Moises et al., linkage, p<0.01
Sz Collaborative Linkage Group, LD, p<0.0009
Vallada et al., LD p<0.001
Pulver et al., LOD 2.8
Coon et al., LOD 2.1
Are Bipolar Disorder and Schizophrenia Different?

- Bipolar Genes
- Common Genes
- Schizophrenia Genes
Common Genes for Bipolar Disorder and Schizophrenia

1 2 3 4 5 6 7 8 9 10 11

12 13 14 15 16 17 18 19 20 21 22

X Y

★ Bipolar

♦ Schizophrenia
GRK3 regulates sensitivity to neurotransmitters

- Decreases the sensitivity of neurons to neurotransmitters
- Acts as a brake to stress
- Maintains balance in the brain
Acute amphetamine treatment models mania

• Acute amphetamine mimics mania in man
  • Increased energy
  • Rapid thoughts and speech
  • Decreased need for sleep
  • Euphoria

• Chronic amphetamine and binging mimics psychosis
  • Auditory and visual hallucinations
  • Paranoid delusions
GRK3 regulates dopamine

- Dopamine is released by amphetamine
- Dopamine is blocked by antipsychotics
- Amphetamine caused a 14 fold increase in GRK3 in the brain
GRK3 is a Gene For Bipolar Disorder

- GRK3 is inherited with bipolar disorder
- GRK3 is turned on by amphetamine
- A mutation in GRK3 increases risk to bipolar disorder 3 fold
- But this mutation occurs in only 5% of patients
Genes and environment

Gene subset A
Pathophysiology A

Gene subset B
Pathophysiology B

Gene subset C
Pathophysiology C

Environment

Final Common pathway

Disease
Summary

- Current treatments are limited by our lack of understanding of the biology of mood disorders
- Genetics may help us better understand the biological causes of mood disorders
Summary

• Genes explain about 60% of the cause of mood disorders
• Family members are about 7 times more likely to also have bipolar disorder
• Many genes are involved
Summary

- In the near future doctors may use DNA tests to help make diagnoses
- DNA tests may help select the right medication
- Medications will be developed that are used in combination with DNA tests