Whole Genome Association Study of Bipolar Disorder

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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% prevalence
- Male and Female prevalence equal
  - M:F = 1:3 in unipolar disorder
- 60-80% of cases begin with mania
- 4-18% of those with depression later have mania
- Stable features
  - Seasonality (Seasonal Affective Disorder)
  - Psychosis
  - Rapid cycling
- Related syndromes and disorders
  - Mixed states
  - Schizoaffective disorder
  - Substance abuse and alcoholism
Bipolar Phenotypes

- Bipolar I
- Bipolar II
- Cyclothymia
- Unipolar
- Dysthymia
- Unipolar-Hyperthymic
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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<tbody>
<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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<td>Mendlewicz and Rainer, 1974</td>
<td>606</td>
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<td>Goetzl et al., 1974</td>
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<td>Helzer and Winokur, 1974</td>
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<td>Gershon et al., 1975</td>
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<td>James and Chapman, 1975</td>
<td>239</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>
<td>172</td>
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<td>Trzeblatowska-Trzeciak</td>
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<td>Angst, 1980</td>
<td>400</td>
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<td>Dunner, Go, and Fieve, 1980</td>
<td>1199</td>
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<tr>
<td>Taylor, Abrams, and Hayman, 1980</td>
<td>600</td>
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<tr>
<td>Gershon et al., 1982</td>
<td>598</td>
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<td>Tsuang et al., 1985</td>
<td>608</td>
<td>3.9</td>
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<tr>
<td>Rice et al., 1987</td>
<td>557</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>7364</strong></td>
<td><strong>6.8</strong></td>
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Total Morbid Risk (%) BP: 10.4
## 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>
<td>Concordance (%)</td>
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<tr>
<td>Luxenberger, 1930</td>
<td>3/4</td>
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<tr>
<td>Rosanoff et al., 1935</td>
<td>16/23</td>
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<td>Slater, 1953</td>
<td>4/7</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>
<td>66.7</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><strong>95/146</strong></td>
<td><strong>65.0</strong></td>
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<tr>
<td></td>
<td><strong>39/278</strong></td>
<td><strong>14.0</strong></td>
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</table>
Linkage hotspots for bipolar disorder and schizophrenia
Are Bipolar Disorder and Schizophrenia Different?

- Bipolar Genes
- Common Genes
- Schizophrenia Genes
Linkage Peaks for Bipolar Disorder
Wave 1-4 Combined Sample

- Single locus LOD > 1
- Interaction NPL p < 0.0001
NIMH Genetics Initiative for Bipolar Disorder
Consortium Sites

Waves 1 & 2
Waves 3 & 4
Wave 5
## NIMH Genetics Initiative for Bipolar Disorder

<table>
<thead>
<tr>
<th>Wave</th>
<th>Sites</th>
<th>Ascertainment</th>
<th>Families</th>
<th>Subjects</th>
<th>Subjects with DNA</th>
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</thead>
<tbody>
<tr>
<td>Wave 1</td>
<td>4 sites</td>
<td>BPI probands</td>
<td>97</td>
<td>758</td>
<td>571</td>
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<tr>
<td>Wave 2</td>
<td></td>
<td></td>
<td>56</td>
<td>437</td>
<td>358</td>
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<tr>
<td>Wave 3</td>
<td>9 sites</td>
<td>BPI-BPI sib pairs</td>
<td>218</td>
<td>1581</td>
<td>995</td>
</tr>
<tr>
<td>Wave 4</td>
<td></td>
<td></td>
<td>275</td>
<td>1583</td>
<td>1057</td>
</tr>
<tr>
<td>Wave 5</td>
<td>11 sites</td>
<td>BPI unrelated cases</td>
<td>2142 total</td>
<td>1861 EA</td>
<td>2142</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Goal 5,500</td>
<td></td>
<td>281 AA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>388 parents</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>646</td>
<td>6501</td>
<td>5123</td>
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Subject Ascertainment

- 11 sites nationwide
- Project-wide web site
- Site specific web sites
- Hospital based
- Outpatient clinics
- Patient support groups
- Local psychiatrists
Phenotypic Assessment Diagnosis

- Diagnostic Interview for Genetic Studies (DIGS) 3.0
  - Interviewer administered survey
  - Both face-to-face and telephonic
  - Large dataset – 2400 variables
  - Detailed assessment of mood disorder
  - Survey of wide range of psychiatric syndromes
  - Reliability tested

- Final Best Estimate Diagnostic Procedure
  - DIGS
  - Medical records
  - Other family informants
  - DSM-IV and other systems
Phenotypic Assessment
Rating Scales

- Rating scales
  - TEMPS-A: Affective Temperament
  - TCI-125: Temperament
  - BALM: Circadian rhythmicity
  - Childhood Life Events Scale
  - Lifetime History of Aggression
  - Visual Analog Scale: State rating of mood
  - Wender Questionnaire: Childhood ADHD
  - Zuckerman-Kuhlman: Personality questionnaire
  - Questionnaire about Genetic Risk: Knowledge of genetic risks
Case Selection

- BPI
- Family history
- Primarily EA cases from wave 1-4
- Supplement with wave 5
- Matching Criteria
  - Ethnicity
  - Gender
Control Selection

- Collected by Schizophrenia Consortium (Gejman)
  - Random digit dialing
- Shared samples and genotyping
- Exclude subjects with histories of
  - Major Depression
  - Psychosis
  - Bipolar disorder or schizophrenia
- Matching Criteria
  - Ethnicity
  - Gender
## Case Control Matching

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
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<tbody>
<tr>
<td><strong>N</strong></td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td><strong>Ethnicity (%)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Northern Europe</td>
<td>52</td>
<td>59</td>
</tr>
<tr>
<td>Western Europe</td>
<td>37</td>
<td>32</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Southern Europe</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>42.3</td>
<td>53.6</td>
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<tr>
<td><strong>Gender (% male)</strong></td>
<td>51.8</td>
<td>52.3</td>
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<tr>
<td><strong>Marital Status (% married)</strong></td>
<td>44</td>
<td>69</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td>15 yrs</td>
<td>44% college degree</td>
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# Site Distribution of Cases

<table>
<thead>
<tr>
<th>Site</th>
<th>Count</th>
<th>Percent</th>
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<tbody>
<tr>
<td>Indiana U</td>
<td>150</td>
<td>15</td>
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<tr>
<td>Wash U</td>
<td>184</td>
<td>18.4</td>
</tr>
<tr>
<td>Hopkins</td>
<td>201</td>
<td>20.1</td>
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<tr>
<td>NIMH</td>
<td>162</td>
<td>16.2</td>
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<tr>
<td>U Penn</td>
<td>77</td>
<td>7.7</td>
</tr>
<tr>
<td>UC Irvine</td>
<td>32</td>
<td>3.2</td>
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<tr>
<td>Iowa</td>
<td>46</td>
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<tr>
<td>U Chicago</td>
<td>71</td>
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<td>UC San Diego</td>
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<td>Rush</td>
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<td>UC San Francisco</td>
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<td>Howard</td>
<td>1</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>1000</strong></td>
<td><strong>100</strong></td>
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Two Stage Design

GAIN
Affy 500K or 1M SNP Chip
Cases: 1000 BPI EA, 300 AA BPI
Controls: 1000 EA, 300 AA

Selection of positive regions for followup
Significance
Clustering
Genes, regions or pathways w prior evidence

Additional genotyping in second sample
25,000 SNPs old and new
1000 BPI cases / 1000 controls
MIP – TGEN
Sequenom – U Indiana
SNPlex – UCSD
Illumina - NIMH
Putative Genetic Subphenotypes

- Psychosis (64%)
- Age of onset (19yo)
- Dysphoric / Irritable mania
- Co-morbid anxiety disorders (24% PD)
- Co-morbid substance abuse (~40%)
- Circadian abnormalities
- Suicidality
- Episode frequency
- Polarity at onset
Collaborators

- Indiana U.
  - John Nurnberger
  - Howard Edenberg
  - Tatiana Foroud
  - Eric Meyer

- Johns Hopkins
  - Raymond DePaulo
  - James Potash
  - Dean McKinnon
  - David Cutler

- NIMH
  - Francis McMahon

- Washington U.
  - Ted Reich
  - John Rice

- U Chicago
  - Elliot Gershon
  - Judy Badner

- UCSD
  - John Kelsoe
  - Nik Schork

- UCI -> UCSF
  - William Byerley

- U Iowa
  - William Coryell

- Rush Presbyterian
  - William Schefter

- Howard U
  - William Lawson

- U Pennsylvania
  - Wade Berrettini

- U Michigan
  - Melvin McInnis

- TGEN
  - David Craig
  - Dietrich Stephan