From genes to brain to new therapeutics

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Schizophrenia: The essentials
(ca. end of the 20th century)

• Diagnosis is based on subjective and nonspecific phenomena

• Genes collectively account for most variance in risk

• Environmental adversity in early development accounts for a small increase in risk

• Subtle deviations in childhood development

• Abnormal function of frontal and temporal cortical circuitry

• Subtle nonspecific abnormalities in neuronal architecture

• Antidopaminergic drugs are therapeutic
Developmental antecedents of schizophrenia are well established.

The later boys stand during the first year of life, the greater the risk of schizophrenia.

Increased frequency of childhood enuresis in adult patients with schizophrenia

Hyde et al. Brain 2008

* P<.0001

Frequency of Enuresis

Patients N=211
Healthy Sibs N=234
Controls N=335

\( \lambda_s = 2.6 \)
Schizophrenia

- Low SES
- Immigration
- Urbanicity
- Substance abuse
- Poor cognitive performance
- Social withdrawal
- Perinatal complications
- Genetic predisposition
- Abnormal development
- Other psychiatric disorder
- Older father

(LIBD)
LIEBER INSTITUTE for BRAIN DEVELOPMENT
Psychiatric disorders are *polygenic* and genetically *heterogeneous*.

The genome wide association study (GWAS) of common sequence variants in the genome.
**PGC1: can you believe 51,695 subjects?**

Ripke et al Nat Gen 2011

<table>
<thead>
<tr>
<th>SNP</th>
<th>Chr.</th>
<th>Mb</th>
<th>Alleles</th>
<th>Frequency</th>
<th>$P$ (GC-adjusted $P$)</th>
<th>OR (95% CI)</th>
<th>Consistency of direction</th>
<th>Gene</th>
<th>Distance (kb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1525579</td>
<td>1p21.3³</td>
<td>98.3</td>
<td>TG</td>
<td>0.80</td>
<td>$5.72 \times 10^{-7}$ ($6.52 \times 10^{-5}$)</td>
<td>1.14 (1.08–1.19)</td>
<td>+++++++</td>
<td>MIR137</td>
<td>Intragenic</td>
</tr>
<tr>
<td>rs17662626</td>
<td>2q32.3³</td>
<td>193.7</td>
<td>AG</td>
<td>0.91</td>
<td>$1.59 \times 10^{-11}$ ($6.87 \times 10^{-10}$)</td>
<td>1.12 (1.09–1.16)</td>
<td>+ +++++</td>
<td>PCGEM1</td>
<td>343</td>
</tr>
<tr>
<td>rs2021722</td>
<td>6p21.3-p22.1</td>
<td>30.3</td>
<td>CT</td>
<td>0.78</td>
<td>$4.30 \times 10^{-11}$ ($2.76 \times 10^{-9}$)</td>
<td>1.18 (1.13–1.23)</td>
<td>+ +++++</td>
<td>TRIM28</td>
<td>Intragenic</td>
</tr>
<tr>
<td>rs10503253</td>
<td>8p23.2³</td>
<td>4.2</td>
<td>AC</td>
<td>0.19</td>
<td>$7.60 \times 10^{-3}$ (n.a.)</td>
<td>1.08 (1.01–1.14)</td>
<td>+ +++</td>
<td>CSMD1</td>
<td>Intragenic</td>
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<tr>
<td>rs7004633</td>
<td>8q21.3³</td>
<td>89.8</td>
<td>GA</td>
<td>0.18</td>
<td>$1.45 \times 10^{-8}$ ($3.22 \times 10^{-7}$)</td>
<td>1.16 (1.11–1.21)</td>
<td>++</td>
<td>MMP16</td>
<td>421</td>
</tr>
<tr>
<td>rs7914558</td>
<td>10q24.32³</td>
<td>104.8</td>
<td>GA</td>
<td>0.59</td>
<td>$1.07 \times 10^{-3}$ (n.a.)</td>
<td>1.08 (1.03–1.13)</td>
<td>+ +++</td>
<td>CNNM2</td>
<td>Intragenic</td>
</tr>
<tr>
<td>rs11191580</td>
<td>10q24.33³</td>
<td>104.9</td>
<td>TC</td>
<td>0.91</td>
<td>$1.82 \times 10^{-8}$ ($3.11 \times 10^{-6}$)</td>
<td>1.10 (1.07–1.13)</td>
<td>+ +++</td>
<td>NT5C2</td>
<td>Intragenic</td>
</tr>
<tr>
<td>rs548181</td>
<td>11q24.2</td>
<td>125.0</td>
<td>GA</td>
<td>0.88</td>
<td>$2.91 \times 10^{-8}$ ($5.69 \times 10^{-7}$)</td>
<td>1.20 (1.13–1.26)</td>
<td>++++++</td>
<td>STT3A</td>
<td>1</td>
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<tr>
<td>rs12966547</td>
<td>18q21.2</td>
<td>50.9</td>
<td>GA</td>
<td>0.58</td>
<td>$2.60 \times 10^{-10}$ ($5.99 \times 10^{-9}$)</td>
<td>1.09 (1.06–1.12)</td>
<td>+++++++</td>
<td>CCDC68</td>
<td>126</td>
</tr>
<tr>
<td>rs17512836</td>
<td>18q21.2</td>
<td>51.3</td>
<td>CT</td>
<td>0.02</td>
<td>$2.35 \times 10^{-8}$ ($4.78 \times 10^{-7}$)</td>
<td>1.40 (1.28–1.52)</td>
<td>+++++++</td>
<td>TCF4</td>
<td>Intragenic</td>
</tr>
</tbody>
</table>
PGC 3 – let’s try 70,000 subjects!
Now over 70 loci are GWAS “significant”
Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis

Cross-Disorder Group of the Psychiatric Genomics Consortium*

Four “loci” identified in 61,220 subjects

*Lancet 2013*
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>
</tr>
</thead>
<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>2.54x10^-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>1.39x10^-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>1.87x10^-8</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>4.29x10^-8</td>
<td>1.08 (1.05–1.12)</td>
</tr>
</tbody>
</table>

Lancet 2013

Compare with: Sklar et al Nature Genetics 2011, N=11,974 cases

Table 3 Association results for the primary GWAS, replication and combined samples

<table>
<thead>
<tr>
<th>SNP</th>
<th>Chr.</th>
<th>Position</th>
<th>A1</th>
<th>A2</th>
<th>Primary GWAS</th>
<th>Replication</th>
<th>Combined GWAS and replication</th>
<th>Genes in the LD region</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs4765913</td>
<td>12</td>
<td>2,290,157</td>
<td>A</td>
<td>T</td>
<td>6.50 x 10^-6</td>
<td>1.15</td>
<td>1.52 x 10^-8</td>
<td>CACNA1C</td>
</tr>
</tbody>
</table>
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
A clinician’s perspective:  
Three key points in this talk

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

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

3. Genes impact on outcome and treatment response and will lead to new therapies.
Schizophrenia: genes and associated neurobiology

Genes:
- multiple susceptibility alleles each of small effect

Cells:
- subtle molecular abnormalities

Systems:
- abnormal information processing

Behavior:
- complex functional interactions and emergent phenomena
“The path from changes in the score (DNA code) to changes in the music (behavior)”

**Genes:**
- multiple susceptibility alleles each of small effect

**Cells:**
- subtle synaptic molecular abnormalities

**Distributed Neural Systems:**
- abnormal information processing

**Perturbed Cognition:**
- as an emergent phenomena
Schizophrenia: genes and associated neurobiology

Genes:
- multiple susceptibility alleles each of small effect

Cells:
- subtle molecular abnormalities

Systems:
- abnormal information processing

Behavior:
- complex functional interactions and emergent phenomena

psychosis
temperament
Executive cognition in MZ twins *discordant* for schizophrenia

Wisconsin Card Sort Categories

Goldberg et al *Arch Gen Psych* 1990
Abnormal behavior reflects abnormal brain function

**Genes:** risk associated genotypes

**Cells:** molecular biology

**Systems:** abnormal information processing

**Psychiatric Disorder**

**Behavior:** complex functional interactions and emergent phenomena
Abnormal prefrontal “efficiency“: A schizophrenia intermediate phenotype

The “N Back” working memory task

fMRI

Patients > Controls
(N=13) (N=18)

Healthy Siblings > Controls
(N=48) (N=33)

Callicott et al. Cereb Cortex 2000
Bipolar/schizophrenia risk associated gene **CACNA1C** modulates cortical efficiency during working memory in normal subjects

rs1006737: AA > GG + GA

N=316, p=.01 FDR corrected

Extrapolated to N=10,000, p<4.87e-109

Bigos et al Arch Gen Psychiatry 2010
A clinician’s perspective:

*Three key points in this talk*

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

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

3. Genes will impact on outcome and treatment response and lead to new therapies.
Genes also interact with the environment to modify the expression of their individual effects. This can lead to exaggerated, compensated, or novel effects.
Increased Risk of Schizophrenia From Additive Interaction Between Infant Motor Developmental Delay and Obstetric Complications: Evidence From a Population-Based Longitudinal Study

Mary C. Clarke, Ph.D.
Antti Tanskanen, Ph.Lic.
Matti Huttunen, M.D., Ph.D.
David A. Leon, Ph.D.
Robin M. Murray, M.D., D.Sc.
Peter B. Jones, M.D., Ph.D.
Mary Cannon, M.D., Ph.D.

Objective: Obstetric complications and developmental delay are well-established risk factors for schizophrenia. The authors investigated whether these risk factors interact in an additive manner to further increase risk for schizophrenia.

Method: The study population encompassed all individuals born in Helsinki between 1962 and 1969 who had developmental records archived in the Helsinki City Archives. Through linkage between the Finnish Population Register, the Finnish Hospital Discharge Register, and the Child Health Archives, child health cards were traced for 189 individuals who had received a diagnosis of schizophrenia and 189 healthy comparison subjects, individually matched for date of birth and sex. Detailed developmental data from the first year of life were extracted.

Results: Delayed attainment of milestones in infancy significantly increased the risk of later development of schizophrenia in a dose-response manner. There was no significant main effect of obstetric complications on risk for schizophrenia and no significant association between obstetric complications and subsequent developmental delay. However, the additive effect of obstetric complications and delayed attainment of developmental milestones significantly increased the risk of schizophrenia beyond that associated with each factor independently (odds ratio=4.6, 95% confidence interval=1.3–17.2).


Interaction of serious OC’s with SNPs in genes associated with anoxia-ischemia

<table>
<thead>
<tr>
<th>SNP</th>
<th>Gene</th>
<th>OC status</th>
<th>OR</th>
<th>95% CI</th>
<th>OR P-value</th>
<th>N families</th>
<th>N minor allele transmissions (%)</th>
<th>LRT P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2494735</td>
<td>AKT1</td>
<td>Absent</td>
<td>1.0</td>
<td></td>
<td></td>
<td>59</td>
<td>36 (61.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Present</td>
<td>7.18</td>
<td>(0.91, 56.75)</td>
<td>0.062</td>
<td>17</td>
<td>15 (88.2)</td>
<td>0.037</td>
</tr>
<tr>
<td>rs3803300</td>
<td>AKT1</td>
<td>Absent</td>
<td>1.0</td>
<td></td>
<td></td>
<td>78</td>
<td>11 (14.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Present</td>
<td>3.89</td>
<td>(0.83, 18.20)</td>
<td>0.085</td>
<td>24</td>
<td>14 (58.3)</td>
<td>0.012</td>
</tr>
<tr>
<td>rs1130233</td>
<td>AKT1</td>
<td>Absent</td>
<td>1.0</td>
<td></td>
<td></td>
<td>71</td>
<td>31 (43.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Present</td>
<td>3.97</td>
<td>(1.13, 13.92)</td>
<td>0.031</td>
<td>24</td>
<td>16 (66.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>rs2049046</td>
<td>BDNF</td>
<td>Absent</td>
<td>1.0</td>
<td></td>
<td></td>
<td>73</td>
<td>23 (31.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Present</td>
<td>0.15</td>
<td>(0.032, 0.73)</td>
<td>0.019</td>
<td>21</td>
<td>3 (14.3)</td>
<td>0.011</td>
</tr>
<tr>
<td>ss76882600</td>
<td>BDNF</td>
<td>Absent</td>
<td>1.0</td>
<td></td>
<td></td>
<td>74</td>
<td>39 (52.7)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Present</td>
<td>12.45</td>
<td>(1.63, 94.60)</td>
<td>0.015</td>
<td>23</td>
<td>17 (73.9)</td>
<td>0.028</td>
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<tr>
<td>rs875462</td>
<td>DTNBP1</td>
<td>Absent</td>
<td>1.0</td>
<td></td>
<td></td>
<td>61</td>
<td>39 (63.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Present</td>
<td>9.49</td>
<td>(1.23, 73.30)</td>
<td>0.031</td>
<td>18</td>
<td>14 (77.8)</td>
<td>0.025</td>
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<tr>
<td>rs7808623</td>
<td>GRM3</td>
<td>Absent</td>
<td>1.0</td>
<td></td>
<td></td>
<td>72</td>
<td>22 (30.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Present</td>
<td>3.39</td>
<td>(0.95, 12.17)</td>
<td>0.061</td>
<td>23</td>
<td>12 (52.2)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

*aNumber of families differs for each SNP because only fully genotyped families were used in analysis.
Large structural variations in the DNA molecule ("CNVs") occur during DNA replication.
22q11 Hemideletion Syndrome: Velo-Cardio-Facial Syndrome (VCFS)
Specific recurrent CNVs are found in 2-5% of patients with the diagnosis of schizophrenia.

Figure 1 Microduplications and microdeletions at 16p11.2

ISC Nat Genetics 2008

McCarthy et al Nat Genetics 2009
A clinician’s perspective: *Three key points in this talk*

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

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

3. Genes impact on outcome and treatment response and will lead to new therapies.
Genes are keys to the biology of cells
Na\(^{+}\)-K\(^{+}\) currents and the action potential

- Represents the inside of the cell
- Depolarization: \(\text{Na}^{+}\) in
- Repolarization: \(\text{K}^{+}\) out
- Few \(\text{Na}^{+}\) open
- Threshold
- Hyperpolarization
- Resting Potential reached and maintained by sodium pump (3 \(\text{Na}^{+}\) out/2 \(\text{K}^{+}\) in)
Genetic Variation in *KCNH2* Associated With Expression in the Brain of a Unique hERG Isoform Modulates Treatment Response in Patients With Schizophrenia

José A. Apud, M.D., Ph.D.
Fengyu Zhang, Ph.D.
Heather Decot, B.S.
Kristin L. Bigos, Ph.D.
Daniel R. Weinberger, M.D.

**Objective:** Antidopaminergic drugs bind to hERG1 potassium channels encoded by the gene *KCNH2*, which accounts for the side effect of QT interval prolongation. *KCNH2* has also been associated with schizophrenia risk, and risk alleles predict increased expression of a brain-selective isoform, *KCNH2* 3.1, that has unique physiological properties. The authors assessed whether genetic variation associated with *KCNH2* 3.1 expression influences the therapeutic effects of antipsychotic drugs.

**Method:** The authors performed a pharmacogenetic analysis of antipsychotic treatment response in patients with schizophrenia using data from two independent studies: a National Institute of Mental Health (NIMH) double-blind, placebo-controlled inpatient crossover trial (N=54) and the multicenter outpatient Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) study (N=364). The *KCNH2* genotype that was previously associated with increased expression of *KCNH2* 3.1 in the brain was treated as a predictor variable. Treatment-associated changes in symptoms were evaluated in both groups with the Positive and Negative Syndrome Scale. The authors also analyzed time to discontinuation in the olanzapine arm of the CATIE study.

**Results:** In the NIMH study, individuals who were homozygous for the *KCNH2* 3.1 increased expression-associated T allele of rs1036145 showed significant improvement in positive symptoms, general psychopathology, and thought disturbance, while patients with other genotypes showed little change. In the CATIE study, analogous significant genotypic effects were observed. Moreover, individuals who were homozygous for the T allele at rs1036145 were one-fifth as likely to discontinue olanzapine.

**Conclusions:** These consistent findings in two markedly different treatment studies support the hypothesis that hERG1-mediated effects of antipsychotics may not be limited to their potential cardiovascular side effects but may also involve therapeutic actions related to the brain-specific 3.1 isoform of *KCNH2*.

*(Am J Psychiatry 2012; 169:725–734)*
A Roadmap for Genes to Drugs

Gene(s) of interest

RNA sequencing in brain → Transcript associated with illness state → Transcript associated with genetic risk

Molecular mechanism of association

Cell models based on molecular mechanisms ↔ Animal models based on molecular mechanisms

CLINICAL STUDIES
Genes, brain and drugs: Conclusions...

• Most complex behaviors are the result of multiple factors that interact biologically.
• Genes are the first objective clues to the causative mechanisms of psychiatric disorders.
• There are many developmental pathways to what we call schizophrenia.
• Genes for schizophrenia likely have their effects on risk by influencing brain development.
• The genetics of psychiatric illness is the game changer both in understanding mechanisms and in finding therapeutic targets based on causation, not phenomenology.

Check out our website: www.libd.org

Learn more about the Brain & Behavior Research Foundation: bbrfoundation.org