The State of Psychiatric Genetics Research

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Virginia Institute of Psychiatric and Behavioral Genetics
NAMI State Convention
6/8/14
Outline of Talk

• Illustrate current approaches in psychiatric genetics. I will illustrate these across a wide array of psychiatric and drug abuse disorders.

• 3 major current paradigms

• 1. “Classical methods” – family, twin and adoption studies. No DNA involved.

• 2. New “polygene” approaches – will explain.

• 3. Gene finding molecular methods – major one is now Genome Wide Association Studies or GWAS. Also, will use “snp” for single nucleotide polymorphism.

• Will go slow! Lots of time for questions.
Introduce Terminology of Genetic Epidemiology

• We know that all major psychiatric and substance use disorders run in families.
• We know that part of the reason they run in families is the role of genetic factors.
• How important are genetic factors across the major psychiatric disorders?
## Heritability Of Psychiatric Disorders

<table>
<thead>
<tr>
<th>Heritability</th>
<th>Psychiatric Disorders</th>
<th>Other Important Familial Traits</th>
</tr>
</thead>
<tbody>
<tr>
<td>~zero</td>
<td></td>
<td>Language, Religion</td>
</tr>
<tr>
<td>20-40%</td>
<td>Anxiety disorders,</td>
<td>Myocardial Infarction,</td>
</tr>
<tr>
<td></td>
<td>Depression, Bulimia,</td>
<td>Normative Personality, Breast</td>
</tr>
<tr>
<td></td>
<td>Personality Disorders</td>
<td>Cancer, Hip Fracture</td>
</tr>
<tr>
<td>40-60%</td>
<td>Alcohol and drug</td>
<td>Blood Pressure, Asthma</td>
</tr>
<tr>
<td></td>
<td>dependence</td>
<td>Plasma cholesterol, Prostate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cancer, Adult-onset diabetes</td>
</tr>
<tr>
<td>60-80%</td>
<td>Schizophrenia</td>
<td>Weight, Bone Mineral Density</td>
</tr>
<tr>
<td></td>
<td>Bipolar Illness</td>
<td></td>
</tr>
<tr>
<td>80-100%</td>
<td>Autism</td>
<td>Height, Total Brain Volume</td>
</tr>
</tbody>
</table>
Psychiatric Diagnosis and Genetics

- Bulk of prior genetic epidemiology of psychiatric disorders have been at level of the individual disorder.
- I want to ask a question about the structure of genetic risk factors.
- Is there only one dimension?
- Does each DSM category have its own set of risk genes?
- A Norwegian collaboration allowed us to address this question for the common psychiatric disorders.
The Structure of Genetic and Environmental Risk Factors for Axis I and Axis II Disorders

• Collaborative attempt to replicate and extend earlier findings in our Virginia Twin Study with a range of Norwegian colleagues led by Dr. Ted Reichborn-Kjennerud.

• 2,801 young adult twin pairs from the population based Norwegian Institute of Public Health Twin sample.

• 1,386 complete pairs – mean age 28.2

• All 10 axis II PDs

• 12 common axis I disorders

• Very challenging model fitting.
Points to Ponder

• Middle ground between a single “g” factor for psychopathology and “DSM” got it right that each disorder is etiologically unique.

• Differences between what genes do and what the environment does.

• Passes the “clinical intuition/common sense” test.
Genetic Epidemiology of Drug Abuse from a Nationwide Sample in Sweden

- A focus on adoption studies – both conventional and “expanded” designs.
- A focus on cross-generational transmission
- Drug abuse as a classic complex phenotype with important genetic and environmental risk factors.
Genetic and Familial Environmental Influences on the Risk for Drug Abuse

A National Swedish Adoption Study

Kenneth S. Kendler, MD; Kristina Sundquist, MD, PhD; Henrik Ohlsson, PhD; Karolina Palmér, MS; Hermine Maes, PhD; Marilyn A. Winkleby, PhD, MPH; Jan Sundquist, MD, PhD

Context: Prior research suggests that drug abuse (DA) is strongly influenced by both genetic and familial environmental factors. No large-scale adoption study has previously attempted to verify and integrate these findings.

Objective: To determine how genetic and environmental factors contribute to the risk for DA.


Setting: Sweden.

Participants: The study included 18 115 adopted children born between 1950 and 1993; 78 079 biological parents and siblings; and 51 208 adoptive parents and siblings.

Main Outcome Measures: Drug abuse recorded in medical, legal, or pharmacy registry records.

Results: Risk for DA was significantly elevated in the adopted offspring of biological parents with DA (odds ratio, 2.09; 95% CI, 1.66-2.62), in biological full and half siblings of adopted children with DA (odds ratio, 1.95; 95% CI, 1.43-2.65). A genetic risk index (including biological parental or sibling history of DA, criminal activity, and psychiatric or alcohol problems) and an environmental risk index (including adoptive parental history of divorce, death, criminal activity, and alcohol problems, as well as an adoptive sibling history of DA and psychiatric or alcohol problems) both strongly predicted the risk for DA. Including both indices along with sex and age at adoption in a predictive model revealed a significant positive interaction between the genetic and environmental risk indices.

Conclusions: Drug abuse is an etiologically complex syndrome strongly influenced by a diverse set of genetic risk factors reflecting a specific liability to DA, by a vulnerability to other externalizing disorders, and by a range of environmental factors reflecting marital instability, as well as psychopathology and criminal behavior in the adoptive home. Adverse environmental effects on DA are more pathogenic in individuals with high levels of genetic risk. These results should be interpreted in the context of limitations of the diagnosis of DA from registries.

Arch Gen Psychiatry.
Published online March 5, 2012.
Sample

• Follow-up in 9 public data bases (1961-2009) in Sweden of adoptees and their biological and adoptive relatives.

• Identified 18,115 adoptees born 1950-1993; 78,079 biological parents and siblings; 51,208 adoptive parents and siblings.

• DA recorded in medical, legal or pharmacy registry records.
• Design # 1 – Start with biological parents
  – Risk for DA was significantly elevated in adopted away offspring of biological parents with DA ($\text{OR}=2.09$).

• Design # 2 – Start with affected adoptee
  Risk for DA was significantly elevated in biological full and half-siblings of adoptees with DA ($\text{OR}=1.84$ and $\text{OR}=1.41$, respectively).
  – Risk for DA was significantly elevated in adoptive siblings of adoptees with DA ($\text{OR}=1.95$).
Table 4. Creation of Genetic and Environmental Risk Scores for Adopted Children

<table>
<thead>
<tr>
<th></th>
<th>Adoptive Relations (Environmental Risk Score)</th>
<th>Biological Relations (Genetic Risk Score)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate Analyses</td>
<td>Multivariate Analysis</td>
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<tr>
<td><strong>Parents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug abuse</td>
<td>1.55 (0.86-2.80)</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disease</td>
<td>1.25 (0.86-1.80)</td>
<td></td>
</tr>
<tr>
<td>Alcoholism</td>
<td>1.89 (1.09-3.29)</td>
<td>1.33 (0.76-2.36)</td>
</tr>
<tr>
<td>Convictions</td>
<td>1.42 (1.15-1.76)</td>
<td>1.25 (1.00-1.56)</td>
</tr>
<tr>
<td>Maternal age</td>
<td>0.97 (0.96-0.98)</td>
<td>0.98 (0.97-0.99)</td>
</tr>
<tr>
<td>Maternal divorce</td>
<td>1.51 (1.19-1.92)</td>
<td>1.31 (1.03-1.68)</td>
</tr>
<tr>
<td>Education (low vs high)</td>
<td>0.92 (0.80-1.06)</td>
<td></td>
</tr>
<tr>
<td>Medical hospitalization</td>
<td>1.30 (1.13-1.50)</td>
<td>1.17 (1.01-1.35)</td>
</tr>
<tr>
<td>Death</td>
<td>1.29 (1.02-1.63)</td>
<td>1.37 (1.08-1.73)</td>
</tr>
<tr>
<td><strong>Siblings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug abuse</td>
<td>2.29 (1.61-3.27)</td>
<td>1.76 (1.16-2.67)</td>
</tr>
<tr>
<td>Psychiatric disease</td>
<td>1.57 (1.16-2.11)</td>
<td>1.16 (0.83-1.62)</td>
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<tr>
<td>Alcoholism</td>
<td>1.89 (1.26-2.84)</td>
<td>1.27 (0.80-2.01)</td>
</tr>
<tr>
<td>Convictions</td>
<td>0.99 (0.85-1.14)</td>
<td></td>
</tr>
<tr>
<td>Medical hospitalization</td>
<td>1.25 (1.09-1.44)</td>
<td>1.12 (0.97-1.30)</td>
</tr>
</tbody>
</table>
Extension of Adoption Design

• Two key “vertical” relationships in adoption designs:
  – Biological parent-adoptee – genes only.
  – Adoptive parent–adoptee – environment only

• Adoption is an artificial process. Selection. Role of adoption agencies.

• These sorts of relationships also arise much more commonly in a general population.

• Could we identify them? What would we see?
Extension of Adoption Design

• “Not-lived-with” NLW –

• The database was created by entering all individuals in the Swedish population born in Sweden between 1960 and 1990 (N=3,257,987). The database included the number of years, during ages 0-15, that individuals resided in the same household and the same SAMS as their mother, father, possible step-mother and possible step-father.

• NLW - parent-offspring pair where the parent never resided with the offspring or in the same SAMS as the offspring thru age 15.
Extension of Adoption Design

• n=165,315 (versus ~ 27,241 biological parents of adoptees ~ 6:1 ratio).

• 94% fathers, 6% mothers – very different from biological parents of adoptees.

• The not-lived-with status arose in only a small minority of cases (1.5% of fathers and 4.7% of mothers) through death of the parent in the year of the child’s birth.
Extension of Adoption Design

• Step-parent-step child

• Definition - The offspring did not reside the entire time from ages 0-15 with the relevant “missing” biological parent (father or mother) and from age 0-15, resided for at least 10 years with an adult who was i) of the same sex as the missing parent, ii) 18-50 years older than the offspring and iii) with whom they were not biologically related.

• Sample size - 124,800 offspring, 86% step-fathers, 14% step-mothers.
Extension of Adoption Design

• So, three main family types with different parent-offspring relationships
• Intact – genes + environment
• NLW – genes only
• Step – environment only
## Extension of Adoption Design

Results as Hazard Ratios for Risk for Drug Abuse in Three Key Family Types (95% Confidence Intervals) and Three High Risk Co-Relative Designs (90% Confidence Intervals)

<table>
<thead>
<tr>
<th>Nature of Sample/Design</th>
<th>Family Type/Co-relative design</th>
<th>Sources of Parent-Offspring Resemblance</th>
<th>Nature of Hazard Ratio</th>
<th>Results for Father</th>
<th>Results for Mother</th>
<th>Combined Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact Families</td>
<td>Family Type</td>
<td>Genes + rearing environment</td>
<td>DA in Parent Predicting DA in Offspring</td>
<td>3.77 (3.51; 4.06)</td>
<td>3.28 (3.05; 3.52)</td>
<td><strong>3.52</strong> (3.33; 3.72)</td>
</tr>
<tr>
<td>“Never-Lived-With” Parent</td>
<td>Family Type</td>
<td>Genes only</td>
<td>DA in Parent Predicting DA in Offspring</td>
<td>2.73 (2.60; 2.87)</td>
<td>2.70 (2.23; 3.26)</td>
<td><strong>2.73</strong> (2.60; 2.86)</td>
</tr>
<tr>
<td>Step-Parent</td>
<td>Family Type</td>
<td>Rearing Environment only</td>
<td>DA in Parent Predicting DA in Offspring</td>
<td>1.81 (1.55; 2.12)</td>
<td>1.68 (1.12; 2.53)</td>
<td><strong>1.79</strong> (1.55; 2.08)</td>
</tr>
</tbody>
</table>
Extension of Adoption Design

• The general population contains informative family constellations that can complement more traditional adoption designs in clarifying the sources of parent-offspring resemblance.
• A lot of further work to do with these designs.
• We have applied this data to crime. Broadly similar findings.
• Hazard ratios versus correlations of liability – scale issues.
• DA is an etiologically complex syndrome strongly influenced by a diverse set of genetic risk factors reflecting a specific liability to DA and a vulnerability to other externalizing disorders and by a range of environmental factors reflecting marital instability, and psychopathology and criminal behavior in the adoptive home. Adverse environmental effects on DA are more pathogenic in individuals with high levels of genetic risk.
A Quick Detour into Animal Behavior Genetics

- We will explore 2 examples:
  
  Selective breeding for alcohol sleep time in mice
  
  Single gene effects on response to ethanol in fruitflies
Animal Behavior Genetics

• Selective breeding for alcohol sleep time - Provide a standard ethanol dose and observe time to "righting reflex."
Selective breeding for alcohol sleep time - Began with genetically variable stock of mice with an average sleep time of 2,800 sec (~ 47 minutes). Only allowed those with the longest and shortest sleep time to reproduce. Rapid response to selection - within 4 generations, short-sleep mice had an average sleep time of ~17 minutes while long-sleep mice had an average sleep time of ~75 minutes.
Selecting breeding for alcohol sleep time - Studies suggest that little of the difference is due to differential metabolism of ethanol (pharmacokinetic factors). Rather, most is due to differences in the brain's sensitivity to the sedative effect of ethanol (pharmacodynamic factors). That is, these animals have been selectively breed for high and low brain sensitivity to the sedative effect of ethanol.
Genetics of Ethanol Response in Drosophila

- On-going work in the lab of Mike Grotewiel funded by our Alcohol Research Center
ethanol Rapid Iterative Negative Geotaxis (eRING)
Fly Pilot: Results Summary

- Implicated Clic (chloride intracellular channel gene) family in ethanol sensitivity
On to DNA

Toto, I’ve got a feeling we’re not in Kansas anymore
• Enter the **Genome Wide Association Study**
• GWAS
• On to polygene scores
• Think of this as adding up all the relevant snps across the genome.
• Some true positive findings, some false positives – an aggregate molecular signal.
• Do they work?
• You need a training sample and a test sample.
Figure 2 | Replication of the ISC-derived polygenic component in independent schizophrenia and bipolar disorder samples. Variance explained (R²) for different samples and conditions.
Molecular Validation of the Schizophrenia Spectrum

• Lets see if these methods can validate an important concept in psychiatric genetics: of a schizophrenia spectrum.

• In 270 high density pedigrees, over 1,000 individuals, from Ireland with GWAS.
• Another kind of polygene score.
Whole genome multi-SNP methods: SNP-heritability

- Take individuals “unrelated” in the classical sense
- Estimate genetic relationships between all pairs of individuals
- Relationships very small, but precision comes from large number of relationships
- SNP heritability > 0 when individuals that are genetically more similar are phenotypically more similar
- Eliminates most concerns about shared environment as only relatives less close than second cousins are used and most are far more distant.
Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs

Cross-Disorder Group of the Psychiatric Genomics Consortium

S Hong Lee, Kenneth Kendler and Naomi R Wray

Uses CGTA - GCTA (Genome-wide Complex Trait Analysis)
Psychiatric Genomics Consortium
Cross-disorder Group
PGC-CDG: 320 scientists from 19 countries

PGC-Wave 1, except for ADHD

Stephan Ripke
Ben Neale
Shaun Purcell
Steve Faraone
Jordan Smoller
Roy Perlis
Bryan Mowry
Pat Sullivan
Snp-Heritability

- The is the snp-heritability for the 5 disorders estimated from the PGC-CDG data. Considerably lower than those estimated from twin studies – so clearly not indexing all the genetic variance.
SNP-Genetic Correlations

- SCZ/BPD $r_g = 0.68$ (s.e. 0.04)
- SCZ/MDD $r_g = 0.43$ (s.e. 0.06)
- BPD/MDD $r_g = 0.47$ (s.e. 0.06)
- SCZ/ASD $r_g = 0.16$ (s.e. 0.06)
Molecular Genetics and Diagnosis—single snp variants

- Cross Diagnostic Group from the Psychiatric Genomics Consortium
- Jordan Smoller, Nick Craddock and Kenneth Kendler
Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis

Cross-Disorder Group of the Psychiatric Genomics Consortium

Summary

Background Findings from family and twin studies suggest that genetic contributions to psychiatric disorders do not in all cases map to present diagnostic categories. We aimed to identify specific variants underlying genetic effects shared between the five disorders in the Psychiatric Genomics Consortium: autism spectrum disorder, attention deficit-hyperactivity disorder, bipolar disorder, major depressive disorder, and schizophrenia.

Methods We analysed genome-wide single-nucleotide polymorphism (SNP) data for the five disorders in 33,332 cases and 27,888 controls of European ancestry. To characterise allelic effects on each disorder, we applied a multinomial logistic regression procedure with model selection to identify the best-fitting model of relations between genotype and phenotype. We examined cross-disorder effects of genome-wide significant loci previously identified for bipolar disorder and schizophrenia, and used polygenic risk-score analysis to examine such effects from a broader set of common variants. We undertook pathway analyses to establish the biological associations underlying genetic overlap for the five disorders. We used enrichment analysis of expression quantitative trait loci (eQTL) data to assess whether SNPs with cross-disorder association were enriched for regulatory SNPs in post-mortem brain-tissue samples.

Findings SNPs at four loci surpassed the cutoff for genome-wide significance (p<5×10^-8) in the primary analysis: regions on chromosomes 3p21 and 10q24, and SNPs within two L-type voltage-gated calcium channel subunits,\( \text{CACNA1C} \) and \( \text{CACNB2} \). Model selection analysis supported effects of these loci for several disorders. Loci previously associated with bipolar disorder or schizophrenia had variable diagnostic specificity. Polygenic risk scores showed cross-disorder associations, notably between adult-onset disorders. Pathway analysis supported a role for calcium channel signalling genes for all five disorders. Finally, SNPs with evidence of cross-disorder association were enriched for brain eQTL markers.

Interpretation Our findings show that specific SNPs are associated with a range of psychiatric disorders of childhood onset or adult onset. In particular, variation in calcium-channel activity genes seems to have pleiotropic effects on psychopathology. These results provide evidence relevant to the goal of moving beyond descriptive syndromes in psychiatry, and towards a nosology informed by disease cause.
• Looked first at most strongly associated SNP in the 4 GW associated regions after clumping. Selected for being significant across all disorders.

<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>
<th>Heterogeneity p value</th>
<th>Best-fit model (BIC)§</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2535629</td>
<td>3</td>
<td>FTH1 (+ many)</td>
<td>G/A</td>
<td>0.651</td>
<td>0.942</td>
<td>2.54×10⁻¹⁴</td>
<td>1.10 (1.07-1.12)</td>
<td>0.27</td>
<td>Five disorder‡</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>
<td>0.32</td>
<td>Five disorder‡</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>1.87×10⁻⁸</td>
<td>1.07 (1.05-1.10)</td>
<td>0.0057</td>
<td>BPD, schizophrenia</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>4.29×10⁻⁹</td>
<td>1.08 (1.05-1.12)</td>
<td>0.57</td>
<td>Five disorder‡</td>
</tr>
</tbody>
</table>
Selected snps

- To be genome wide significant across all 5 disorders.
Unselected snps

- To be genome wide significant for only 1 disorder – in this case either BPD or SCZ
### Rs12576775 – Prior association with BPD

<table>
<thead>
<tr>
<th>Gene</th>
<th>ngt</th>
<th>info</th>
<th>p_value</th>
<th>f_ca(n)</th>
<th>f_co(n)</th>
<th>ln(OR)</th>
<th>STDerr</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>1</td>
<td>0.99</td>
<td>0.347</td>
<td>0.828(2787)</td>
<td>0.822(2635)</td>
<td>0.0478</td>
<td>0.0508</td>
</tr>
<tr>
<td>ASD</td>
<td>5</td>
<td>1.01</td>
<td>0.828</td>
<td>0.828(4949)</td>
<td>0.828(5314)</td>
<td>0.00813</td>
<td>0.0372</td>
</tr>
<tr>
<td>BPD</td>
<td>3</td>
<td>0.98</td>
<td>6.16e-06</td>
<td>0.803(6990)</td>
<td>0.824(4820)</td>
<td>0.164</td>
<td>0.0362</td>
</tr>
<tr>
<td>MDD</td>
<td>3</td>
<td>1.00</td>
<td>0.951</td>
<td>0.823(9227)</td>
<td>0.824(7383)</td>
<td>0.0019</td>
<td>0.0301</td>
</tr>
<tr>
<td>SCZ</td>
<td>3</td>
<td>1.01</td>
<td>0.0695</td>
<td>0.819(9379)</td>
<td>0.826(7736)</td>
<td>0.0545</td>
<td>0.03</td>
</tr>
<tr>
<td>ALL</td>
<td>15</td>
<td>1.00</td>
<td>0.00627</td>
<td>0.819(33332)</td>
<td>0.825(27888)</td>
<td>0.0428</td>
<td>0.0156</td>
</tr>
</tbody>
</table>

**Figure:** The figure shows a forest plot with the ln(OR) and 95% CI for each gene associated with BPD, along with the p_value and STDerr. The plot is overlaid with a histogram showing the distribution of ln(OR) values.
Prior Association With Schizophrenia

**Rs7004633**

<table>
<thead>
<tr>
<th>rs7004633</th>
<th>G/A</th>
<th>B:99829427</th>
<th>ngt</th>
<th>info</th>
<th>p_value</th>
<th>f_co(n)</th>
<th>f_co(n)</th>
<th>ln(OR)</th>
<th>STDerr</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>2 0.96</td>
<td>0.521</td>
<td>0.807(2787)</td>
<td>0.812(2635)</td>
<td>0.0323</td>
<td>0.0502</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASD</td>
<td>6 0.96</td>
<td>0.917</td>
<td>0.810(4949)</td>
<td>0.813(5314)</td>
<td>0.00391</td>
<td>0.0369</td>
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<tr>
<td>BPD</td>
<td>3 0.92</td>
<td>0.304</td>
<td>0.821(6990)</td>
<td>0.817(4620)</td>
<td>-0.0383</td>
<td>0.0375</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>MDD</td>
<td>6 1.00</td>
<td>0.535</td>
<td>0.812(9227)</td>
<td>0.816(7383)</td>
<td>0.0185</td>
<td>0.0297</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCZ</td>
<td>4 0.91</td>
<td>1.6e-08</td>
<td>0.796(9379)</td>
<td>0.819(7736)</td>
<td>0.173</td>
<td>0.0306</td>
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<tr>
<td><strong>ALL</strong></td>
<td>21 0.95</td>
<td>0.00227</td>
<td>0.809(33332)</td>
<td>0.816(27888)</td>
<td>0.048</td>
<td>0.0157</td>
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**ln(OR), 95% CI**
<table>
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<tr>
<th>rs2021722</th>
<th>C/T</th>
<th>6:30282110</th>
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<tr>
<th></th>
<th>ngt</th>
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<th>p_value</th>
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<th>f_co(n)</th>
<th>ln(OR)</th>
<th>STDerr</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>1</td>
<td>0.98</td>
<td>0.146</td>
<td>0.212(2787)</td>
<td>0.201(2635)</td>
<td>−0.0695</td>
<td>0.048</td>
</tr>
<tr>
<td>ASD</td>
<td>4</td>
<td>1.00</td>
<td>0.86</td>
<td>0.209(949)</td>
<td>0.199(5314)</td>
<td>−0.00598</td>
<td>0.0348</td>
</tr>
<tr>
<td>BPD</td>
<td>0</td>
<td>1.01</td>
<td>0.0429</td>
<td>0.206(6990)</td>
<td>0.218(4820)</td>
<td>0.0684</td>
<td>0.0338</td>
</tr>
<tr>
<td>MDD</td>
<td>0</td>
<td>0.99</td>
<td>0.0261</td>
<td>0.202(9227)</td>
<td>0.217(7383)</td>
<td>0.0853</td>
<td>0.0283</td>
</tr>
<tr>
<td>SCZ</td>
<td>0</td>
<td>0.98</td>
<td>3.94e−08</td>
<td>0.186(9379)</td>
<td>0.212(7736)</td>
<td>0.16</td>
<td>0.0291</td>
</tr>
</tbody>
</table>

| ALL    | 5   | 0.99 | 2.17e−06| 0.200(33332) | 0.211(27888) | 0.0701  | 0.0148 |

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**ln(OR), 95% CI**

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rs17512836
Polygenic dissection of diagnosis and clinical dimensions of bipolar disorder and schizophrenia

Figure 3. Comparison of odds ratios from independent samples of bipolar disorder (BP) (blue) and schizophrenia (SCZ) (red) for genome-wide significant loci previously identified in SCZ.
A Note on Three Levels of Analyses

- **SNPS** – they individually account for trivial proportions of variance in disease risk -- well under 0.5% and more typically ~0.1-0.2%. So to extrapolate from these findings to nosologic relationships is a very long stretch. However, these variants can directly point to possibly shared etiologic mechanisms – e.g. calcium channels.

- **Aggregate polygene signals** – Assess larger %s of variance tapped by the snps.

- **Twin, sibling and adoption designs** - Much more powerful in giving overall picture with good chunks of disease risk. Much more useful for us in thinking about psychiatric diagnoses. But these last two methods don’t give us insight into biology.
Schizophrenia Group

GWAS Meta-Analysis involving more than 25000 cases and 28000 controls.

UNPUBLISHED REPORT FROM PGC-SCHIZOPHRENIA GROUP, HAMBURG October 2012
results are likely to change since more datasets are currently being integrated
Crohn’s 2006 (NIDDK)

759 cases, 929 controls

3 genome wide significant sites
Crohn’s 2008 (meta of 3)

3146 cases, 4842 controls

15 genome wide significant sites
Crohn’s 2010 (meta of 6)

5956 cases, 14927 controls

51 genome wide significant sites
Crohn’s Disease gene discovery
71 published – another 50 newly confirmed

Genome-wide meta-analysis increases to 71 the number of confirmed Crohn’s disease susceptibility loci

Host–microbe interactions have shaped the genetic architecture of inflammatory bowel disease

Nature 491, 119–124 (01 November 2012) doi:10.1038/nature11582
Received 17 May 2012 | Accepted 12 September 2012 | Published online 31 October 2012

Genome-wide association defines more than 30 distinct susceptibility loci for Crohn’s disease
SCZ - Ancient times – 2009 (ISC)

2601 cases, 3345 controls

0 genome wide significant sites
PGC - The Past - 2011

9394 cases, 12462 controls from 17 substudies

5 genome wide significant sites

Genome-wide association study identifies five new schizophrenia loci

Nature Genetics 43, 969–976 (2011) | doi:10.1038/ng.940
Received 16 February 2011 | Accepted 19 August 2011 | Published online 18 September 2011
PGC1- + Sweden + CLOZUK

19200 cases, 20600 controls

36 genome wide significant sites
PGC SCZ wave 2

25785 cases, 28441 controls

62 genome wide significant sites
Accepted 2 weeks ago:

BIOLOGICAL INSIGHTS FROM 108 SCHIZOPHRENIA-ASSOCIATED GENETIC LOCI

Schizophrenia Working Group of the Psychiatric Genomics Consortium

up to 36,989 cases and 113,075 controls
SCZ gene discovery

Genome-wide association analysis identifies 13 new risk loci for schizophrenia

*NATURE GENETICS | LETTER*

Genome-wide association study identifies five new schizophrenia loci

Letter

*Nature 460*, 748-752 (6 August 2009) | doi:10.1038/nature08185; Received 11 February 2009; Accepted 8 June 2009; Published online 1 July 2009; Corrected 5 August 2009

Common polygenic variation contributes to risk of schizophrenia and bipolar disorder
Odds ratio for schizophrenia by risk score profile (RPS) decile
These results represent ground-breaking advances in schizophrenia genetics.
But what might they mean?
In the last part of my talk, I try to outline how I would think about this critical question.
These thoughts are contained in the following recently published paper.
What psychiatric genetics has taught us about the nature of psychiatric illness and what is left to learn

Kenneth S Kendler

Psychiatric genetics has taught us a great deal about the nature of psychiatric disorders. Traditional family, twin and adoption studies have demonstrated the substantial role of genetic factors in their etiology, clarified the role of genetic factors in comorbidity, elucidated development pathways, and documented the importance of gene–environment correlation and interaction. We have also received some hard lessons when we were unable to detect replicable genes of large effect size and found that our much-valued candidate genes did not live up to their expected promise. With more mature molecular and statistical methods, we are entering now a different era. Statistical analyses of aggregate molecular signals are validating earlier heritability estimates. Replicated findings from genome-wide association studies are beginning to emerge, as are discoveries of large-effect size rare genomic variants. The number of such findings is likely to soon grow dramatically. The most pressing question facing the field is what biological picture these results will reveal. I articulate four possible scenarios that reflect (i) no, (ii) minimal, (iii) moderate and (iv) high biological coherence in the replicated molecular variant findings, which are soon likely to emerge. I discuss the factors that will likely influence these patterns, including the problems of etiological heterogeneity and multiple realizability. These findings could provide critical insights into the underlying biology of our psychiatric syndromes and potentially permit us to perceive, ‘through a glass darkly,’ the levels of the mind–brain system that are disordered.

Molecular Psychiatry advance online publication, 30 April 2013; doi:10.1038/mp.2013.50

Keywords: GWAS; heritability; heterogeneity; levels of explanation; philosophy; psychiatric genetics
What should we expect from GWAS?

• Many factors will influence the pattern of results that will emerge. Two are likely to be particularly important: the degree of etiological heterogeneity and the biological level at which the disorders predominantly arises. Heterogeneity is the more straight-forward. At one extreme, there may be dozens of biologically distinct pathways to illness with little or no sharing between them. At the other extreme – etiologic homogeneity – just one pathway to illness awaits discovery.
Scenario 1 – No Coherence

- Completely the wrong question e.g. Eric Turkheimer – “The physics of carpets”
- Jerry Fodor – “the physics of money”
- Or, more likely, perhaps there are too many ways for the human brain to produce the symptoms and signs of psychiatric disorders (e.g., sad mood, auditory hallucinations, grandiosity) for us to have any chance for biologically coherent pathways to emerge from the hundreds or thousands of risk variants that make small contributions to risk.
Scenario 2 – Minimal Coherence

• Predicts that these analyses will reveal minimal coherence with small pockets of connectivity. The genes identified by GWAS, sequencing and CNV analyses would form modest-sized inter-related sets but with no meaningful connections between them. They would not connect up to reveal major pathways to illness.

• Think of a GWAS study of “pleasure of roller coasters” or “risk for divorce.” Bits of coherent neurobiology that contribute but no “there there.”
Scenario 3 – Moderate Coherence

• This scenario predicts that our bioinformatic analysis of the risk genes detected in GWAS, CNV and sequencing analyses would reveal a number of pockets of biological coherence that would reflect relatively discrete and substantial pathways contributing to disease risk. But they would not connect up into one grand pathway.

• The most likely way in which this pattern could arise is classical biochemical genetic heterogeneity. There might be several independent genetically influenced pathways to our major psychiatric syndromes. Each of these pathways would produce “clouds” of associated variants but they will not link up.
Scenario 3 – Moderate Coherence

• A slightly different scenario is possible. Imagine that the disorder arises from dysfunction at a high level thalamo-cortical circuit that is contributed to by abnormalities in any one of multiple neuronal cell types with distinct neurotransmitter systems and key glial support cells. These genetic systems “interact” but their interaction occurs so many steps away from the pathogenic genes that the interaction is muted and highly variable across individuals because of stochastic developmental process and variable environmental exposures. Some connectivity between these pathways is there, but it is patchy and unstable enough to be statistically unreliable.
Scenario 4 – High Coherence

- In this most optimistic scenario, depicted in figure 2d, most or all of the verified risk genes identified through GWAS, sequencing and/or CNV analyses will map to a single coherent inter-connected biological pathway. This will occur only if the genetic underpinnings of the disorder reflect a high degree of etiologic homogeneity. Put in another way, the individual genes would reflect a system with a high degree of equifinality – all pointing to a single disease process.
Scenario 4 – High Coherence

- This could arise because psychiatric disorders are truly biochemical disorders as illustrated in figure 1a. Or, they could result from disorders at a cellular or network level but in such a way as to make their biological connections easily detectable with our current methodology. That is, we might have a robust equifinal model in which we can detect multiple causal routes to a final higher level cause.

- This result would be the gene network equivalent of discovering a Mendelian disorder.
VIPBG

- Virginia Institute for Psychiatric and Behavioral Genetics
- Established at VCU in 1996.
- In the Virginia Biotech Park
- 800 East Leigh St Richmond
- 18 faculty, 22 pre- and post
doctoral training students.
- Two NIH training grants.
- Our own PhD program: Psychiatric, Behavioral and Statistical Genetics.
VIPBG

- We have major research programs in
  - Schizophrenia
  - Major Depression
  - Drug Abuse
  - Alcoholism
  - Anxiety Disorders
  - PTSD
  - Nicotine Dependence

- We have funded collaborative projects with multiple other US centers and in
  - England
  - Ireland
  - Australia
  - Norway
  - Sweden
  - China
  - Finland
VIPBG

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- Hermine Maes PhD
• CDG:

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• Patrick F Sullivan (chair), Patrick Bender, Sven Cichon, Nicholas Craddock, Mark J Daly, Stephen V Faraone, John Kelsoe, Thomas Lehner, Douglas Levinson, Mick O’Donovan, Pablo Gejman, Jonathan Sebat, Pamela Sklar, Jordan W Smoller. See appendix for PGC Collaborators from Analysis Committee (Mark J Daly, chair), ADHD Workgroup (Stephen V Faraone, chair), Autism Workgroup (Mark Daly, Bernie Devlin, cochairs), Bipolar Disorder Workgroup (John Kelsoe, Pamela Sklar, cochairs), Major Depressive Disorder Workgroup (Patrick Sullivan, chair), Schizophrenia Workgroup (Michael O’Donovan, chair).
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