The genetic influences on neuropsychiatric disease risk

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Psychiatric disorders: heritable disorders of the brain

**A** Lifetime prevalence

<table>
<thead>
<tr>
<th>Disorder</th>
<th>ANX</th>
<th>AAD</th>
<th>MDD</th>
<th>PHO</th>
<th>CON</th>
<th>ADHD</th>
<th>PTSD</th>
<th>BPD</th>
<th>EAT</th>
<th>OCD</th>
<th>ASD</th>
<th>SCZ</th>
<th>TS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent:</td>
<td>5</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>15</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

**B** Twin/family based heritability

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The Cleveland Clinic Foundation  
(www.clevelandclinicmeded.com)
Aims of molecular genetic research in psychiatry

Identification of disease genes

- Pathophysiology
- Epidemiology
- Pharmacology
- Brain function
- Evolutionary aspects

Understanding

- Classification of disease
- Development of new therapeutics
- Individually tailored medication (precision medicine)
- Specific prevention based on early diagnosis

Application
Research follows genomics knowledge and available technology

Linkage / candidate gene studies

Research follows genomics knowledge and available technology
Strategies to identify genetic risk factors in complex diseases

- Common, low penetrant variants (low risk)
- Rare, highly penetrant "mutations"
- Very difficult to detect
- Unlikely to exist

GWAS

Relative Risk (measure of penetrance) vs. Risk Allele Frequency
Strategies to identify genetic risk factors in complex diseases

Exome / Genome Sequencing

- Rare, highly penetrant "mutations"
- Very difficult to detect
- Low frequency variants with moderate risk
- Unlikely to exist

GWAS

- Common, low penetrant variants (low risk)

Relative Risk (measure of penetrance) vs. Risk Allele Frequency

0,1 to 1,0

10 to 30

GWAS

Exome / Genome Sequencing
GWAS – a new hope for complex genetics

 Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

The Wellcome Trust Case Control Consortium*
GWAS – results not as good as expected....

Figure 4: Genome-wide scan for seven diseases. For each of seven diseases, the log10 of the trend test P value for quality-control-positive SNPs, excluding those in each disease that were excluded for having poor clustering after visual inspection, are plotted against position on each chromosome. Chromosomes are shown in alternating colours for clarity, with P values < 1 × 10^{-5} highlighted in green. All panels are truncated at −log_{10}(P value) = 15, although some markers (for example, in the MHC in T1D and RA) exceed this significance threshold.
Schizophrenia GWAS – 2009 (ISC)
(The International Schizophrenia Consortium, Nature 2009)

2601 cases, 3345 controls
0 genome wide significant sites
GWAS in larger samples will likely identify many more common disease loci

LETTER TO THE EDITOR

Don’t give up on GWAS

Molecular Psychiatry advance online publication, 9 August 2011; doi:10.1038/mp.2011.94

Psychiatric diseases are of major public health importance owing to their enormous morbidity, mortality and personal/societal cost. Little is known for certain about the etiology of these diseases, and treatment, detection and prevention strategies are not directed by knowledge of pathophysiology. As family history is a major risk factor, genetic approaches are critically important for most psychiatric disorders.

The initial set of genome-wide association studies (GWAS) using microarrays to test for the role of common genetic variants for psychiatric disorders did not unambiguously identify risk or protective loci. This ‘disappointing’ pattern of results was also seen in many other diseases to which GWAS was applied. It rapidly became apparent that many ‘failures’ were merely due to low power.

The outcomes of GWAS cannot be declared until intermediate: slightly worse than multiple sclerosis and age-related macular degeneration (0.5), similar to lung cancer (0.4), and slightly better than type 2 diabetes mellitus (0.3), breast cancer (0.2), and body mass (0.1). The pace of gene discovery for schizophrenia is thus typical.

Empirical data from other complex traits can project what might be discovered if we had larger sample sizes for schizophrenia and bipolar disorder. With sample sizes four times larger than those currently available, 30–60 more loci might be identified for schizophrenia and bipolar disorder. This new knowledge would greatly improve pathway analyses to elucidate the fundamental biology of these diseases. With funding, this work could be completed by 2013.

Given the initial successes in the identification of loci for schizophrenia and bipolar disorder, we assert that GWAS will continue to be of great importance in the identification of novel biological candidates for psychiatric illness. GWAS has tremendous potential to advance our understanding of these complex conditions.
GWAS in larger samples will likely identify many more common disease loci

LETTER TO THE EDITOR

Don’t give up on GWAS

Psychiatric Genomics Consortium

Molecular Psychiatry (2011), 1–2
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www.nature.com/mp

A hallmark of applying high-throughput technologies like GWAS is the apparent failure to detect associations in many other diseases to which GWAS was applied. It rapidly became apparent that many ‘failures’ were merely due to low power.

The outcomes of GWAS cannot be declared until given the initial successes in the identification of loci for schizophrenia and bipolar disorder, we assert that GWAS will continue to be of great importance in the identification of novel biological candidates for psychiatric illnesses. GWAS has not provided answers by

PGC Schizophrenia - 2011

9,394 cases, 12,462 controls

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
25’785 cases, 28’441 controls

62 genome wide significant sites
PGC Schizophrenia - 2014

35'476 cases, 46'839 controls

128 genome wide significant sites

PGC SCZ working group, Nature 2014
No Evidence That Schizophrenia Candidate Genes Are More Associated With Schizophrenia Than Noncandidate Genes

Emma C. Johnson, Richard Border, Whitney E. Melroy-Greif, Christiaan A. de Leeuw, Marissa A. Ehringer, and Matthew C. Keller

ABSTRACT

BACKGROUND: A recent analysis of 25 historical candidate gene polymorphisms for schizophrenia in the largest genome-wide association study conducted to date suggested that these commonly studied variants were no more associated with the disorder than would be expected by chance. However, the same study identified other variants within those candidate genes that demonstrated genome-wide significant associations with schizophrenia. As such, it is possible that variants within historic schizophrenia candidate genes are associated with schizophrenia at levels above those expected by chance, even if the most-studied specific polymorphisms are not.

METHODS: The present study used association statistics from the largest schizophrenia genome-wide association study conducted to date as input to a gene set analysis to investigate whether variants within schizophrenia candidate genes are enriched for association with schizophrenia.

RESULTS: As a group, variants in the most-studied candidate genes were no more associated with schizophrenia than were variants in control sets of noncandidate genes. While a small subset of candidate genes did appear to be significantly associated with schizophrenia, these genes were not particularly noteworthy given the large number of more strongly associated noncandidate genes.

CONCLUSIONS: The history of schizophrenia research should serve as a cautionary tale to candidate gene investigators examining other phenotypes: our findings indicate that the most investigated candidate gene hypotheses of schizophrenia are not well supported by genome-wide association studies, and it is likely that this will be the case for other complex traits as well.
Archival Report

No Evidence That Schizophrenia Candidate Genes Are More Associated With Schizophrenia Than Noncandidate Genes

Emma C. Johnson, Richard B., Marissa A. Ehringer, and Mattl

ABSTRACT

BACKGROUND: A recent analysis of genome-wide association study (GWAS) data showed that these candidate genes are associated with the disorder than within non-candidate genes that are selected at random. It is possible that variants within those candidate genes that are enriched above those expected by chance, are driving the association.

METHODS: The present study used publicly available data of GWAS conducted to date as input. Specific GWAS data and the list of candidate genes are enriched for associations with schizophrenia.

RESULTS: As a group, variants in candidate genes are more associated with schizophrenia than were variants in control sets of genes. This association is significantly associated with schizophrenia.

CONCLUSIONS: The history of schizophrenia candidate genes is not well supported by genome-wide association studies, and it is likely that this will be the case for other complex traits as well.
Lesson learned: nature of common variants & sample sizes needed in complex genetics

Lesson learned: nature of common variants & sample sizes needed in complex genetics

- polygenicity is a common feature of psychiatric disorders
- common variants usually have very small effect sizes (OR <1.2)

Quantifying the overall effect of common variation on phenotype: SNP correlation

Quantifying the overall effect of common variation on phenotype: SNP correlation

Astonishing insights into the genetics of these disorders:

• Different degree of heterogeneity (SCZ<BD<MDD)

• Strong genetic overlap (>60%) between SCZ and BD (stronger than BD/MDD and even MDD/MDD!)

• Majority of common risk factors shared between ethnicities

SNP-based heritability: contribution of common variation to phenotypic variance

Strategies to identify genetic risk factors in complex diseases

- **Exome / Genome Sequencing**

- **Relative Risk (measure of penetrance)**
  - Very difficult to detect
  - Rare, highly penetrant “mutations”
  - Low frequency variants with moderate risk
  - Common, low penetrant variants (low risk)

- **Risk Allele Frequency**
  - 0.1, 1.0, 10, 30
1q21 Microdeletion associated with schizophrenia (4,200 patients, 39,800 controls: OR=14.83)

Contribution of rare CNVs to schizophrenia

Correlation between population rates and ORs for schizophrenia

George Kirov Hum. Mol. Genet. 2015;24:R45-R49
Contribution of rare CNVs to schizophrenia

Most CNVs are associated with different brain diseases (e.g. SCZ and Developmental Delay) => pleiotropy
Contribution of CNVs to psychiatric disorders

Contribution of rare variation at single nucleotide level to psychiatric disorders

• Preliminary evidence for increased rates of rare inherited mutations in ASD, de novo mutations (in SCZ); not well replicated yet

• Various challenges:
  Statistical power low, in particular for medium effect sizes
  For detection of de novo variants parents are needed
  Relatively large amount of private mutations (100-200 per individual)
  Functional consequences of rare variants largely unclear

• Several international consortia have formed to increase sample sizes, results can be expected soon
Heterogeneous risk factors converge in biological networks

Genetic analysis
- Affected child
- Genetic variant or mutation (Increasing risk)

Hundreds of associated genetic variants across the genome

Genome organized into co-expressed modules with molecular network analysis
- ASD mutations are highly enriched in specific module(s)

Annotated molecular pathways:
- Transcriptional regulation,
- Chromatin modification,
- Neurogenesis

Explore gene/module relationship to development, region and cell type

Further important use of genetic results: clinical re-classification of psychiatric disorders
Clinical diagnosis

ADHD  ASD  SCZ  BPD  MDD  ADD

Population-level genetic characterization

GWAS, analysis of CNV and other structural chromosomal variation (microarray and WGS), identification of rare genetic variants (via WES and WGS)

Define individual genetic risk

Refinement of clinical classification based on genetics and neurobiology

Reverse phenotyping using single associated variants or a cumulative “polygenic risk score” (PRS)

Refinement of clinical classification based on genetics and neurobiology
Genetic studies inform various follow-up studies to get a better biological understanding of brain function and dysfunction

- functional studies (animal models, iPSC, etc.)

- better molecular maps of individual brain cells and brain regions (eQTLs/meQTLs)

- neuroimaging studies to elucidate the impact of associated variants: single rare/common phenotype-associated variants or PRS

Krug et al., Schizophr Bull, 2013
Erk et al., Biol Psychiatry, 2014
Identification of a neurogenetic mechanism for associated SNP in ZNF804A

fMRI in 115 healthy probands with functionally validated working memory test (n-back task); depending on rs1344706 genotype (ZNF804A):

- results suggest alteration of connectivity of dorsolateral-prefrontal cortex [DLPFC]
- fits with previous observations of dysconnectivity of these brain areas in schizophrenia

⇒ ZNF804A influences connectivity, disturbed connectivity: risk factor for SCZ
Understanding genetic effects at multiple levels and scales

- Genome
- Transcriptome
- Methylome
- Cells
- Regional architecture
- Brain networks

(Clinical) phenotype

Interindividual variability

Environment
Lessons learned from genetic studies in neuropsychiatric disorders

- Molecular genetic results most consistent with a polygenic contribution of common and rare variants
- The genetic architecture (i.e. number and genetic effects of involved genetic variants) differs between neuropsychiatric disorders
- Some disorders show significant genetic overlap
- The genetic architecture of many neuroimaging phenotypes will probably be similar

Important terms:
- Heterogeneity, polygenicity, pleiotropy
- SNP correlation, SNP-based heritability
Thank you for your attention