Transdiagnostic Genomics for Precision Medicine in Psychiatry

Stephan Ripke, May 8th 2018

Psychiatric Genomics Consortium
Classic tools for medical diagnoses/research
Schizophrenia

• Symptoms typically come on gradually, begin in young adulthood,
• 0.3–1.0% of people are affected by schizophrenia during their lifetimes, males > females
• Wide range of “positive” and “negative” Symptoms:
  – elusions, disordered thoughts and speech, and tactile, auditory, visual, olfactory and gustatory hallucinations
  – little emotion, poverty of speech, inability to experience pleasure, lack of desire to form relationships, and lack of motivation.
• Wide range of cognitive dysfunction: working memory, long-term memory, verbal declarative memory, semantic processing, episodic memory, attention, learning
• Additionally: anxiety disorders, major depressive illness, substance-use disorders
Chlorpromazine

- It’s drug characteristic (blocking DRD2 receptor) is still the central pharmacologic mechanism for treating psychotic diseases (schizophrenia).
- **Common side effects** include movement problems, sleepiness, dry mouth, low blood pressure upon standing, and increased weight.
- **Serious side effects** may include the potentially permanent movement disorder tardive dyskinesia, neuroleptic malignant syndrome, and low white blood cell levels.
Chlorpromazine cont.

• World Health Organization's List of Essential Medicines
  – “one of the great advances in the history of psychiatry”

• found 1950 in France in anaesthetic research
  -> incidental finding
The molecular targets of all of today’s approved psychiatric drugs are the same as the targets of their pre-1960 prototypes (Table 2), and their mechanisms of action are not understood beyond a few initial molecular events\textsuperscript{13}.

![Table 2. Major classes of drugs developed to treat psychiatric disorders. NE, norepinephrine; 5-HT, 5-hydroxytryptamine (serotonin); GABA, \(\gamma\)-aminobutyric acid.](image)

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Prototype compound</th>
<th>Molecular target(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood stabilizer</td>
<td>Lithium ((\text{Li}^+))</td>
<td>GSK3(\beta), inositol 1-phosphatase*</td>
</tr>
<tr>
<td><strong>Antipsychotic drugs</strong></td>
<td>Chlorpromazine</td>
<td>Dopamine (D_2) receptor</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Iproniazid, Imipramine</td>
<td>Monoamine oxidase, NE, and 5-HT transporters</td>
</tr>
<tr>
<td>Benzodiazepine receptor agonists</td>
<td>Chlordiazepoxide</td>
<td>GABA(_A) receptor, benzodiazepine site</td>
</tr>
</tbody>
</table>

*Although much research favors GSK3\(\beta\) (glycogen synthase kinase \(\beta\)) as the relevant target of \(\text{Li}^+\), the drug’s mechanism of action remains uncertain.
Heritability consistent and indisputable...

Sullivan, Daly, O’Donovan 2012
Genetics:

1. Predict if/when someone will develop a specific disorder, how severe it will be, and what treatment could work best.

2. Understand the biology of the disease so we can design better treatments, possible prevention strategies and early diagnostics.
Recessive Trait – blue eyes
Huntington’s Disease

- Symptoms:
  - subtle problems with mood or mental abilities
  - general lack of coordination and an unsteady gait
  - uncoordinated, jerky body movements
  - Mental abilities generally decline into dementia
  - Symptoms usually begin between 30 and 50 years of age
Huntington’s Disease

• HD affects about 4 to 15 in 100,000 people of European descent.
• HD is typically inherited from a person's parents.
• Diagnosis is by genetic testing, which can be carried out at any time, regardless of whether or not symptoms are present.
• The disease is caused by an autosomal dominant mutation in either of an individual's two copies of a gene called Huntingtin.
• There is no cure for HD.
Genetic Testing – PKU (Phenylketonuria)

- Inherited (autosomal recessive) disorder that increases the levels of phenylalanine in the blood
- If PKU is **not treated**, phenylalanine can build up to harmful levels in the body, causing **intellectual disability and other serious health problems**
- PKU occurs in **1 in 10,000 to 15,000** newborns
- Most cases of PKU are detected shortly after birth by **newborn screening**, and treatment is started promptly
- People who are diagnosed early and maintain **a strict diet** can have **normal health and a normal life span**
Success of research in mendelian traits vs. complex traits

Glazier, Nadeau and Aitman, Science 2002

*Dark Ages of complex trait genetics*
Study design for gene-finding studies in complex disorders
GWAS = current gold standard

- Hypothesis-generating
- Tests > 7,000,000 single nucleotide polymorphisms (SNP) distributed over the genome → need strong evidence → need big sample size
- Able to identify genetic factors of small effect size
Association Studies

Cases

Controls

Test allele 1 frequency

allele 1

allele 2

Slide from Ben Neale
Genome Wide Association Studies

Repeat 7+ million times for all of your markers -> need big sample sizes for strong evidence

Test allele 1 frequency

Slide from Ben Neale
How to achieve big sample sizes?

1) Genome Resources
2) Technology
3) Collaboration
Concept of Imputation via Linkage Disequilibrium

• GWAS chip, e.g. Illumina OmniExpress chip
  ➢ ~700k SNPs

• Increase SNP density by imputation using reference data

• Result: million of variants

1000 Genomes
A Deep Catalog of Human Genetic Variation

The Haplotype Reference Consortium
PGC SCZ: PCA plot
Crohn’s Disease gene discovery
121 GWS regions

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

Affiliations | Contributions | Corresponding author
Nature 491, 119–124 (01 November 2012) | doi:10.1038/nature11582
Received 17 May 2012 | Accepted 12 September 2012 | Published online 30 October 2012

Genome-wide association defines more than 30 distinct susceptibility loci for Crohn’s disease

Validating therapeutic targets through human genetics

Robert M. Plenge\textsuperscript{1,2}, Edward M. Scolnick\textsuperscript{2,3} and David Altshuler\textsuperscript{2,4,5}

<table>
<thead>
<tr>
<th>Retrospective examples</th>
<th>HMGCR</th>
<th>rs3846663</th>
<th>Statins</th>
<th>Hyperlipidaemia</th>
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<tbody>
<tr>
<td>PPARG</td>
<td>rs1801282</td>
<td>Thiazolidinediones</td>
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<tr>
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<td>Abatacept</td>
<td>Rheumatoid arthritis</td>
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<tr>
<td>IL12B</td>
<td>rs12188300</td>
<td>Ustekinumab</td>
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<tr>
<td>RANKL</td>
<td>rs9533090</td>
<td>Denosumab</td>
<td>Osteoporosis</td>
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</table>
GWAS in Psychiatry

• Given the success in other medical fields, hopes were understandably high
SCZ – 2009 (ISC)

2601 cases, 3345 controls

0 genome wide significant sites
Basic figures:
- >800 members
- >100 institutions
- 36 countries

Data:
- Raw genomic data from ~400,000 individuals today
- 9 psychiatric disorders (more are coming)
  - BIP, SCZ, MDD, AUT, ADD, AN, PTSD, OCD, SUA
35,476 cases and 46,839 controls

97 genome wide significant sites
(108 with replication)
The glutamatergic hypothesis

GRM3 (chr. 7): metabotropic glutamate receptor 3

GRIN2A (chr. 16): NMDA glutamatergic receptor subunit

SRR (chr. 17): serine racemase
Dopamin receptor (DRD2) is amongst the associated hits
Calcium Channels (e.g. CACNA1C, chr. 12) are amongst the associated hits
Findings / sample size

N Hits ($p < 5.0 \times 10^{-08}$)

Crohn's: $\sim 10 / 1,000$
Schizophrenia: $\sim 4 / 1,000$
Adult Height: $\sim 3 / 1,000$
(Bipolar Disorder: $\sim 3-4 / 1,000$)

N cases
Discoveries over samplesize

N Hits ($p < 5.0 \times 10^{-08}$)

- Crohn’s: $\sim 10 / 1,000$
- Schizophrenia: $\sim 4 / 1,000$
- Adult Height: $\sim 3 / 1,000$
- (Bipolar Disorder: $\sim 3-4 / 1,000$)

PGC w3 (only CEU)

N cases
PGC SCZ wave3

65,205 cases and 87,919 controls

248 genome wide significant sites (256 with replication from Decode)
Explore results in FUMA

Explore results:

Go to [http://fuma.ctglab.nl](http://fuma.ctglab.nl)

- interactive output (figures and tables)
- all annotations can be viewed and downloaded
- Right now need to be PGC SCZ member

- Of 333 exonic SNPs, 157 were non-synonymous variants.
- There were 7 splicing variants
Replication of the ISC-derived polygenic component in independent schizophrenia and bipolar disorder samples.


Shaun Purcell
Increase in polygenic risk score prediction

Nagelkerke $R^2$

P-value threshold

Significance of test: $4^* < 0.001$, $5^* < 1.0 \times 10^{-04}$, $6^* < 1.0 \times 10^{-08}$, $7^* < 1.0 \times 10^{-12}$, $8^* < 1.0 \times 10^{-50}$, $9^* < 1.0 \times 10^{-100}$
GRS in SCZ

- Case-control difference 0.6 std, $P=4 \times 10^{-175}$

- Predicts family history & severity

![Graph showing AUC=0.7]
• Current Numbers (Apr 19th 2018):
  – 643 schizophrenia cases
  – 931 healthy controls
  – Almost all re-contactable
PRS

558 controls and 294 cases at p < 1

$r^2 = 0.124$, $p = 3.92 \times 10^{-19}$
Collaboration

- Pilot Study already collected: 200 SCZ cases and 200 healthy controls
- Currently Genotyped
- If successful further collection
<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Institution</th>
<th># case</th>
<th># control</th>
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<tbody>
<tr>
<td>Han Chinese</td>
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<td>181</td>
<td>188</td>
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<tr>
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<tr>
<td>Han Chinese</td>
<td>UMC Utrecht (China)</td>
<td>2395</td>
<td>2485</td>
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<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>13941</strong></td>
<td><strong>17071</strong></td>
</tr>
</tbody>
</table>
Genomewide association study identifies 30 loci associated with bipolar disorder

Eli Stahl, Gerome Breen, Andreas Forstner, Andrew McQuillin, Stephan Ripke,
Bipolar Disorder Working Group of the Psychiatric Genomics Consortium, Sven Cichon, Laura Scott,
Roel Ophoff, Ole A Andreassen, John Kelsoe, Pamela Sklar

doi: https://doi.org/10.1101/173062

This article is a preprint and has not been peer-reviewed [what does this mean?].

20,352 cases, 31,358 controls
Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression

Naomi R. Wray, Stephan Ripke, [...] the Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium

130,664 cases
330,470 controls
PGC MDD (2018)
Genetic Testing Complex Trait Prostate Cancer

• Stockholm3 test (STHLM3):
  – Combination of:
    • five protein markers
    • more than a hundred genetic tracers
    • clinical data
  – reduces the number of prostate biopsies
  – www.sthlm3.se
The PGC has made the full results from all published PGC studies available for download. If you download these data, you and your immediate collaborators ("investigators") acknowledge and agree to all of the following conditions:

1. PGC Member
   - PGC member applies for data access via secure PGC data access web-portal
   - Workgroup representatives oversee the approval and access process
   - DAC keeps record of all permissions and approvals
   - Updates yearly

2. PGC Workgroup
   - Scientific Review & Approval
   - Workgroup members review application
   - If no objections, workgroup chair approves proposal

3. Workgroup DAC Representatives
   - Surfsara support staff provide README with symbolic link to data
   - PGC member can work with data on LISA

4. VU University Amsterdam
Summary and conclusion

• Whole genome Common Variant Analysis has shown to be an **utterly successful** tool in psychiatric research.

• Continued **sample size increase** will further enrich our knowledge of the genetic background of psychiatric diseases.

• Much work needs to be done on the research with these new insights.

Broad View: Benjamin Neale - Progress in psychiatric genetics
Biggest thanks to all the researchers, clinicians and probands who have contributed to the PGC effort!!