Genes, Circuits, Behavior: From psychiatry genetics to personalized medicines

Anirvan Ghosh, F. Hoffmann-La Roche
Imagine this…

*Treatment of mental illness based on individual genome sequence*

Risk genes

Co-expression networks

Patient stratification

Personalized treatment
Psychiatric disorders are highly heritable. 

Genes play a major role.

MZ twins: 60-80%  
DZ twins: 10-30%  
Siblings: 10-20%

Recurrence risk: General Population 1%  

Sullivan et al., 2012
NDD and schizophrenia are highly heritable disorders

*Risk genes are widely distributed in the genome*

SNP - single nucleotide polymorphisms

RM - rare mutations

CNV - copy number variations

Geschwind et al.
Genetic architecture of schizophrenia and autism

*Common & rare mutations in hundreds of genes*

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**Polygenic models**

<table>
<thead>
<tr>
<th>Model</th>
<th>Combination of CVs</th>
<th>Major effect RV in background of CVs</th>
<th>Combination of RVs and CVs</th>
<th>‘Two hit’ RV</th>
<th>Single causative RV</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD or SZ</td>
<td><img src="image1" alt="Diagram" /></td>
<td><img src="image2" alt="Diagram" /></td>
<td><img src="image3" alt="Diagram" /></td>
<td><img src="image4" alt="Diagram" /></td>
<td><img src="image5" alt="Diagram" /></td>
</tr>
<tr>
<td>Sub Threshold Parents/relatives</td>
<td><img src="image6" alt="Diagram" /></td>
<td><img src="image7" alt="Diagram" /></td>
<td><img src="image8" alt="Diagram" /></td>
<td><img src="image9" alt="Diagram" /></td>
<td><img src="image10" alt="Diagram" /></td>
</tr>
</tbody>
</table>

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**Evidence in SZ**

**Evidence in ASD**

Berg and Geschwind, 2012 Genome Biology
Schizophrenia: genes implicated by common variants

**Genome-wide association studies (GWAS)**

- 36,989 cases & 113,075 controls
- 108 genome-wide significant loci

- L type calcium channels (4 subunits)
- Gene set: post synaptic density
- Gene set: RNAs bound by FMRP
- Glutamate receptors
- Dopamine D2 receptors
Autism: genes implicated by rare variants

Whole exome sequencing studies

The contribution of \textit{de novo} coding mutations to autism spectrum disorder

Synaptic, transcriptional and chromatin genes disrupted in autism

2517 families
2270 families
1601 ASD
5397 controls

Voltage-gated ion channels
Gene set: Synaptic transmission
Gene set: FMRP targets
Gene set: Chromatin modifiers
Emerging themes from psychiatric genetic studies

**Risk genes are shared across multiple psychiatric disorders**

**Common variants**

**Rare variants**

**Copy number variants**

- Developmental delay
- Autism
- Schizophrenia
- Epilepsy
- 15q13.3 deletion

Nature Genetics, 2014


Iossofov et al, Nature 2014

Malhotra et al, Cell 2012

Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs

Cross-Disease Group of the Psychiatric Genomics Consortium
A framework for drug discovery in psychiatry & NDD

Synapses & circuits as the point of intervention
Next generation of targets in NDD and psychiatry

Synapse and Signaling modulators

• Compelling genetic association and target tractability

• Disease-relevant phenotypes in cellular (iPS) and animal models

• Evidence of circuit dysfunction for key behavioral domains from human imaging and behavioral studies
Cellular phenotype identification using iPSCs

Modeling neurobehavioral disorders

Large-scale whole genome sequencing in psychiatry

*Big science will drive novel discoveries & precision treatment*

Whole genome sequencing of 10,000 autism cases

Whole genome sequencing of 10,000 schizophrenia and bipolar disorder cases

The Genomic Psychiatry Cohort: Partners in Discovery

Risk genes for ASD and SZ

Molecular pathways and endophenotypes

Convergent cellular phenotypes

Circuit and behavior analysis in model systems

Target development

Large-scale whole-genome sequencing

Molecular maps of human brain
- co-expression networks
- protein-protein interaction networks

Imaging maps
- EEG
- MRI

iPSCs

Precision trials

Personalized medicine

Molecular/genetic subtypes of ASD and SZ
Doing now what patients need next
Backup slides
A new era of gene discovery in psychiatric disorders

*Risk and causal genes can be reliably identified*

Key drivers of gene discovery

- **Genome resources**
  - Human Genome, HapMap and 1000 genomes project

- **Genomic technologies**
  - Microarrays
  - Exome sequencing
  - Whole genome sequencing

- **Large scale collaborations**
  - Psychiatric Genomics Consortium (PGC)
  - Autism Genome Project (AGP), Simons Simplex Collection (SSC)
Increase in diagnostic yield by WGS
- 70% of WGS cases have a clinically relevant rare penetrant mutation

Paternal age effect: de novo mutations increase with increasing father’s age
- partially explains increased risk of ASD in older fathers
Autism: Rare de novo mutations contribute significant genetic risk for ASD

**Evidence from exome sequencing and CNV studies**

- denovoCNVs and coding point mutations contribute 30% of ASD risk.
- 30 novel causal ASD genes identified
  - with recurrent(>2) loss of function de novo mutations in the same gene
- New causal genes implicate novel biological pathways such as chromatin modifier genes in ASD risk
Schizophrenia: genes implicated by rare variants

**Whole exome sequencing studies**

A polygenic burden of rare disruptive mutations in schizophrenia

De novo mutations in schizophrenia implicate synaptic networks

2500 SZ  
2500 controls  
623 families

Voltage-gated calcium channels

Gene set: post synaptic density-95

Gene set: ARC complex

Gene set: NMDAR complex

Notably, both common and rare variants implicate convergent gene sets
ASD risk genes cluster into specific cellular and molecular processes.

Emerging themes from psychiatric genetic studies

*Reciprocal mutations associated with psychiatric traits*

Malhotra et al, Cell 2012
Synapses are convergence pathways for risk genes

Relationship of susceptibility genes to synaptic dysfunction

Neuronal synapses harbor many tractable targets including GPCRs and ion channels

NDD & SZ-related genes
- in synapse function
- in neuronal maturation
- in protein translation
Developmental timing and cellular specificity of the molecular pathways disrupted by ASD risk genes

<table>
<thead>
<tr>
<th></th>
<th>ASD</th>
<th>ID</th>
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<tbody>
<tr>
<td>Genes</td>
<td>Rare de novo exome variants</td>
<td>Candidate genes</td>
</tr>
<tr>
<td></td>
<td>Siblings ASD No ASD</td>
<td>Candidate genes</td>
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<tr>
<td>Molecular networks</td>
<td>Gene modules sharing</td>
<td>Transcriptional regulation</td>
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<tr>
<td></td>
<td>function, expression pattern, protein interactions, regulation</td>
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<tr>
<td>Age (prenatal to infancy)</td>
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Anatomical circuits

<table>
<thead>
<tr>
<th>Cortical layers</th>
<th>L2-3</th>
<th>L4</th>
<th>L5</th>
<th>L6</th>
</tr>
</thead>
</table>

ASD genes converge to disrupt neural development and cortical-cortical connectivity

ID genes show less specificity

Parikshak et al, Cell 2013

Willsey et al, Cell 2013

Integrative genomics implicate mid-fetal cortical glutamatergic neurons