Translating genetic and genomic research in neuropsychiatric conditions: lessons from autism research

IOM Genomics Roundtable Workshop

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Daniel H Geschwind, MD PhD

Departments of Neurology, Psychiatry and Human Genetics
David Geffen School of Medicine, UCLA
Approach: Moving from Genes to Pathways to Therapeutics

- Identify Genes.
- Human Patients.
- Mouse models.
- Human post mortem tissue.
- Human neural progenitors – primary neurons.

Identify Pathways

Unidimensional approach

Systems biology approach

Geschwind and Konopka, Nature 2009
Complexity in neuropsychiatric disorders

AUTISM SPECTRUM DISORDER (ASD) is a prototypical example

Phenotypic
- Disorder Overlap
- Endophenotypes

Etiologic
- SNPs, SNVs, CNVs
- Epigenetics
- Environment
- Interactions (GxE, GxG)

Biological pathways
- Molecular
- Cellular
- Circuits
- Behavioral/Cognitive

Devlin and Scherer Curr Opin Genet Dev, 2012

Berg and Geschwind, Genome Biol. 2012
Progress in Understanding ASD Biology

- Genetic variants accounting for about 20% of ASD have been identified (de novo).
- Several variants have been studied in human brain to understand circuit level dysfunction..
- Mouse models have been made to understand synapses, cells, circuits.
- In vitro models in IPSCs have been developed.
- Several new pharmacological treatments are in early trials.
Build it and they will come?
Create a Large, Open Resource

Autism Genetic Resource Exchange

- An open resource shared with the scientific community
- More than 1300 families AND 10,000 DNA samples
  - Greatly accelerated the pace of family collection and research.
  - >330 researchers and 200 publications since 2001!
- Phenotype data:
  - ADI-R, ADOS
  - basic cognitive and language testing
  - physical/neuro exams
  - medical histories
- Biomaterials and Data (Karyotyping/molecular cytogenetics/SNP data).

AGRE provides biomaterials and an unprecedented resource of phenotype and genotype information that is freely available for analysis by members of the scientific community.

Please take the AGRE Researcher Survey

Update:
New Data Available For Download
Pedigrees of 586 Families

AGRE Frequently Asked Questions
Answers to common questions about AGRE.

ISACC User Guide:
A step-by-step guide for downloading phenotype data from ISACC.

GENOTYPE DATA:
Whole Genome Scan and Fine-mapping data on 356 families.
Candidate Gene and Loci Data contributed by Dr. Buxbaum
NEW! Candidate SNP Genotyping data contributed by Dr. Sutcliffe
NEW! Fine-mapping data on Chr.5 and Chr.17 contributed by Dr. Nelson

PHENOTYPE DATA:
ADI-R, ADOS, Raven, and Handedness testing results with all interview data points and computer scored algorithm results are available for download.
Medical histories, Physical Neurological exam data, Peabody scores, and Vineland scores are also available.
What you put in is what will come out


De novo mutations revealed by whole-exome sequencing are strongly associated with autism

Stephan J. Sanders¹, Michael T. Murtha¹, Abha R. Gupta², John D. Murdoch³, Melanie J. Raubeson³, A. Jeremy Willsey¹, A. Gulcan Ercan-Sencicek¹, Nicholas M. DiMuke¹, Neeleop P. Parikh², Jason L. Stein³, Michael F. Walker¹, Gordon T. Ober¹, Nicole A. Terani¹, Younna Song¹, Paul El-Fishawy¹, Ryan C. Murtha¹, Murim Choi¹, John D. Overton¹, Robert D. Bjornson⁴, Nic Kati

Estimate 500-1000 de novo mutations.

Mean effect size = 6
"The Autisms": Many Genetic Syndromes ("the 1%s"), None Specific.

### Table 23.4.2 ASD-related syndromes (modified from [3])

<table>
<thead>
<tr>
<th>ASD-related syndrome</th>
<th>Associated gene(s)</th>
<th>Proportion with ASD</th>
<th>Proportion ASD with syndrome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q21 Duplication</td>
<td>Many</td>
<td>50%</td>
<td>~1%?</td>
<td>[91, 128]</td>
</tr>
<tr>
<td>3p Deletion / duplication</td>
<td>CNTN4</td>
<td>&lt;50%</td>
<td>~1%</td>
<td>[51, 61, 110]</td>
</tr>
<tr>
<td>15q Duplication (maternal)</td>
<td>Many (including UBE3A, GABRB3, SNRPN, and SNURF)</td>
<td>High</td>
<td>~1%</td>
<td>[41]</td>
</tr>
</tbody>
</table>

### Review

**Table 1. Pleiotropic effects of major genes/mutations associated with ASD and allied neurodevelopmental disorders**

<table>
<thead>
<tr>
<th>Gene/region</th>
<th>Mechanism</th>
<th>Disorders</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRXN1</td>
<td>CNV, PM</td>
<td>ASD, SZ</td>
<td>[36], [50,72,73]</td>
</tr>
<tr>
<td>CNTNAP2</td>
<td>CNV, PM, CP</td>
<td>ASD, ID, epilepsy, LD/SLI, TS</td>
<td>[59,61,74,75]</td>
</tr>
<tr>
<td>16pdel</td>
<td>CNV</td>
<td>ASD, SZ, DD, LD, normal carrier</td>
<td>[33,37,42,76-78]</td>
</tr>
<tr>
<td>16pdup</td>
<td>CNV</td>
<td>SZ, ID, DD, LD, ADHD, normal carrier</td>
<td>[33,39,42,78]</td>
</tr>
<tr>
<td>15q13.3del</td>
<td>CNV</td>
<td>SZ, epilepsy, ASD, normal carrier</td>
<td>[42,73,79]</td>
</tr>
<tr>
<td>17q12del</td>
<td>CNV</td>
<td>SZ, ASD, ID</td>
<td>[80]</td>
</tr>
<tr>
<td>15q11–13dup</td>
<td>CNV</td>
<td>ASD, SZ/psychosis</td>
<td>[33,81]</td>
</tr>
<tr>
<td>22q11</td>
<td>CNV</td>
<td>ASD, ADHD, SZ, ID, epilepsy</td>
<td>[73,82–84]</td>
</tr>
<tr>
<td>1q21</td>
<td>CNV</td>
<td>ASD, SZ, ID, epilepsy</td>
<td>[42,85,86]</td>
</tr>
</tbody>
</table>

Here we list genes, form of genetic risk variant, clinical disorders where the mutation has been observed, and some representative references. This table is not meant to be exhaustive but illustrative of the pleiotropic effects of known ASD genes or loci with relatively large effect sizes (OR > 5–10 for ASD). New abbreviations are as follows: TS, Tourette syndrome and PM, point mutation.
The “endophenotype” concept

- Common neurodevelopmental disorders, such as autism, SLI/dyslexia, ADHD, epilepsy, and MR are not defined based on common etiology.

- The association of genetic factors with specific, measurable components of each disease, called “endophenotypes” will be stronger than the clinical diagnosis alone.

- To be most useful for genetic analysis, endophenotypes should be:
  - Associated with the disease
  - Heritable
  - Relatively stable
  - Identified in first degree relatives more than the general population.
  - Quantifiable
Studying ASD risk variants in humans

CNTNAP2

Non-Risk > Risk

Risk > Non-Risk

increased long-range connectivity with mPFC
increased local frontal connectivity with mPFC

MET

A MET genotype: default mode network connectivity
CC “risk” group

GG “nonrisk” group

GG “nonrisk” > CC “risk”

B Genotype and diagnostic status groups

MET rs1858830 genotype groups

Diagnostic status

TD and ASD MET rs1858830 genotype subgroups

Typically developing

Autism spectrum disorder

1. Heterogeneity of Neuroimaging Phenotypes
2. Stratify Neuroimaging Phenotype (diagnosis independent)
3. Stratify Using Risk Variant(s) That Modulates Phenotypes Across Human Populations
4. Reduce Heterogeneity Using Genotype And Diagnosis

Rudie et al. Neuron 2012
Mice with CNTNAP/.CASPR2 mutations show:
- reduced USV
- reduced sociability
- increased repetitive behaviors
- increase hyperactivity
- increase sensory hypersensitivity

(Penagarikano et al. Cell 2011)
CNTNAP2 mouse knockout
Treatment with Oxytocin

Opportunities:
• Understand mechanism at synapse, cell, circuit level
• Predictive validity – use mouse for in vivo screening

Olga Penagarinkaro, PhD
How do we develop therapeutics?

Using Network Biology to Provide an Integrated View (WGCNA; Zhang and Horvath 2005)


**A gene’s network position is biologically meaningful**

We can identify groups of co-expressed genes called modules that correspond to key elements of biological function (Oldham et al. 2006; Oldham et al. 2008; Winden et al. 2009).

And within modules, we can identify the most central, “hub” genes (Horvath et al. 2006; Oldham et al. 2008, Winden et al. 2009).

**This structure serves as a basis for identification of biological meaningful insights**

- Comparative network analysis – modules
- Comparative network analysis - gene connectivity
- Guilt by association—functional annotation
**Dissect** functional relationships of thousands of genes to a few modules.

Can relate *complex* genetic and phenotypic variables to these modules.

Make specific *experimental predictions*.
Disease complexity and heterogeneity: some lessons

Challenge

• Heterogeneity
  – Genetic
  – Phenotypic

• Etiological overlap
  – Sz, ADHD, ASD, epilepsy

• Multiple levels of dysfunction lead to abnormal behavior and cognition
  – Connecting genetic variation to targetable mechanisms.

Solution

• Large sample sizes needed for power to detect genetic variation.
  – Importance of community resources (not consortia)
  – Data sharing (high quality)

• Cross disorder study
  – Measure appropriate phenotypes
  – Data repositories that work

• Integrative or systems biology approaches are needed
  – Convergent approaches
    • True collaborative research
    • Multidisciplinary
    • Analysis vs. Data Generation
What we have learned from ASD genetics

• Successes
  – Many genetic causes of autism spectrum disorders (ASD) have been identified.
    • This has been fueled by large scale shared patient resources for research that are readily available.
    • True collaboration and multidisciplinary approaches
  – This knowledge greatly facilitates development of multiple model systems and drug development (based on monogenic forms).

• Challenges
  – ASD is an example of extreme genetic/etiologic heterogeneity.
  – Disease etiologies don’t obey diagnostic boundaries
  – Future: EMR based genetics (scale, and cross disorder).
  – Model validity needs to be carefully assessed.
  – Will therapy developed for one form of ASD be relevant to others?
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