Genetic Maps of the Brain Reveal the Developmental Origins of ASD and Related Psychiatric Disorders

Meet the Scientist Series
Brain and Behavior Foundation

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Conflict of Interest

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Outline

• Introduction: We are in the midst of a genetics revolution that is transforming our knowledge of disease (“Precision Health” in ASD).

• What we have learned about ASD from genetics to this point.

• Most genetic variation does not impact actual protein coding genes, but regions of the genome that regulate their expression. So, understanding the mechanisms through which genetic risk factors act necessitates having “maps” of gene regulation in developing human brain.

• These maps implicate early cortical development as a substantial period of risk for both early (ASD) and later onset (SCZ, BD, MD) disorders.
A New Revolution in Healthcare

**Medicine Today**
Reactive, population-based, one-size-fits-all model of care

**Precision Health**
Predictive, preventive, patient-centric model of care
The Goal of Precision Medicine

Deliver the right treatment, every time, to the right person...

“Prediction is very difficult, especially if it's about the future.”

Niels Bohr
(Nobel Prize in Physics, 1922)
Major Goals

• Diagnosis

• Prediction: Disease Risk, Outcome

• Prevention

• Optimize Treatment Choice

Understand Disease Pathophysiology
Having Genetic Information Can Help Determine Best Response to Treatments

Most drugs prescribed in the US are effective in less than 60% of treated patients.
Two major drivers:

Dramatically decreasing DNA sequencing costs alter approach to human disease as computing power increases.

Result: Millions of Genomes Sequenced and the Power to Analyze Them....
We are at the beginning of what will be an explosion of genetic discoveries across populations!

Cost of genome sequencing continues to drop rapidly...

...which results in many more human genomes being sequenced...

...and a more accurate understanding of human disease.

New drug targets
Prevention
Diagnosis & prognosis
Optimize treatment (avoid adverse reactions and optimize efficacy)
Rare vs. Common Genetics

Rare mutations: sufficient to be causal (large effect)

Common variants (>1% in population): contribute to disease in an additive (aggregate) fashion

Geschwind 2011

TRENDS in Cognitive Sciences
Genetic (Polygenic) risk score in the population

- **Increased risk:** Carry many risk alleles
- **Decreased risk:** Carry few risk alleles

Baseline risk: 5% and 1% of population at highest risk
Genetic contributions to major psychiatric disorders

Geschwind and Flint Science 2015
Whole Exome Sequencing to Find Rare Causal Mutations in Clinical Practice

Clinical exome sequencing in neurogenetic and neuropsychiatric disorders

Brent L. Fogel,¹ Hane Lee,²,³ Samuel P. Strom,²,³ Joshua L. Deignan,²,³ and Stanley F. Nelson²,³,⁴

Table 3. Rates of diagnosis for neurological disorders using clinical exome sequencing

<table>
<thead>
<tr>
<th>Number of patients or families</th>
<th>Diagnostic genetic result</th>
<th>Rate of neurologic diagnosis</th>
<th>Overall diagnostic rate (all presentations)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>213</td>
<td>55</td>
<td>26%</td>
<td>25% (62/250)</td>
<td>3</td>
</tr>
<tr>
<td>324</td>
<td>99</td>
<td>31%</td>
<td>30% (152/500)</td>
<td>62</td>
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<tr>
<td>673</td>
<td>175</td>
<td>26%</td>
<td>26% (213/814)</td>
<td>4</td>
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<tr>
<td>1756</td>
<td>455</td>
<td>26%</td>
<td>25% (504/2000)</td>
<td>5</td>
</tr>
<tr>
<td>2966</td>
<td>784</td>
<td>26%</td>
<td>26% (931/3564)</td>
<td></td>
</tr>
</tbody>
</table>

These rare Mendelian forms of disease are estimated to account for about 7% of patients.
Implications of Knowing Genetic Causes of Disease

• Knowing the genetic basis of the disorder has significant implications for treatment and recurrence risk.
  – *new* mutations vs. heritable (environment?) - recurrence risk!
  – How is it inherited (Mendelian)? — counseling.

• Knowing the genetic basis of the disorder has potentially significant implications for treatment and prevention.
  – Identify mechanism of disease and target therapy
  – Gene - environment interactions.
  – Mechanism of mutation may be preventable.
  – Early Diagnosis and Intervention!!
ASD is a heterogeneous neurodevelopmental syndrome and overlaps with other neurodevelopmental disorders.

“Social Cognition and Mental Flexibility

General: Abnormal circuit development and function ("Canalization"; Waddington)

Geschwind Cell 2007
Alarcon et al. AJHG 2001, 2008
Vernes et al. NEJM 2008
Lowe et al. AJP 2015
Cantor et al. Mol Psych 2018
Rapid Growth in ASD Genetics: Many Genes

Bourgeron T, 2017
10.1016/j.crvi.2016.05.004

Abrahams and Geschwind, Nature Reviews Genetics, 2008
Many forms of genetic variation and modes of inheritance of ASD

22q11-13 del, CHD8, DYRK1A, SCN2A, ARID1B, ANK2, GRIN2B, SYNGAP1, ADNP, TBR1, POGZ, KATNAL2... Smith Lemli Opitz CNTNAP2...

Timothy syndrome, (del)16p11, (dup)15q11-13 Tuberous Sclerosis, Fragile X, DMD

Common Variation (MET? CNTNAP2?, SEMA5a?)

Genetic testing can currently identify approximately 20% of mutations contributing to ASD:

Clinical Microarray, Fragile X, Exome sequencing.
Genetics has transformed the clinical landscape in Autism Spectrum Disorder (ASD)

Circa 2008

- Many Genes (1000+?)
- None account for >1% of cases
- Highly additive effects
- Strong pleiotropy

Circa 2016

- More than 200 candidate genes
- Clearer mechanistic models
- Many advances…evidence for convergence and cross disorder overlap
- Major drug development efforts in autism ongoing…

De La Torre-Ubieta *Nat Med* 2016
Comorbidity: rare variants $\rightarrow$ DD, ID, epilepsy


# Comorbidities
Racial and Ethnic Diversity are Critical to Improving Accuracy of Genomic Testing

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Genetic Misdiagnoses and the Potential for Health Disparities

Arjun K. Manrai, Ph.D., Birgit H. Funke, Ph.D., Heidi L. Rehm, Ph.D., Morten S. Olesen, Ph.D., Bradley A. Maron, M.D., Peter Szolovits, Ph.D., David M. Margulies, M.D., Joseph Loscalzo, M.D., Ph.D., and Isaac S. Kohane, M.D., Ph.D.

UCLA, WashU, JHU, Emory, AEU
Genes act through many levels of function to impact behavior

AUTISM GENES: WHEN AND WHERE DO DISEASE RISK GENES ACT? (DO THEY CONVERGE?)
Heterogeneous genetic risk converges in biological networks

When and where do autism genes act?

When:
Early cortical development

Where:
Cortical connectivity

Fig. 1. The stages of brain development (top) and different windows of vulnerability (bottom). Developmental processes occur in phases, setting the stage for potential periods of vulnerability. Insults early in life (bottom) will be assimilated into innervation patterns, whereas a later pre-pubertal insult will cause functional changes that are more adaptive.
Heritable variation is identified with genome wide association studies (GWAS)

Most genetic risk for autism resides with common variation

Trent Gaugler1, Lambertus Klei2, Stephan J Sanders3,4, Corneliu A Bodea1, Arthur P Goldberg5-7, Ann B Lee1, Milind Mahajan4, Dina Manaa1, Yudi Pawitan5, Jennifer Reichert5,6, Stephan Ripke10, Sven Sandin8, Pamela Sklar6,8,11,12, Oscar Svantesson9, Abraham Reichenberg5,6,13, Christina M Hultman9, Bernie Devlin2, Kathryn Roeder1,14 & Joseph D Buxbaum5,6,8,11,15,16

Genome-Wide Association Study
But figuring out the meaning or mechanisms of actions for GWAS "hits" can be difficult

- Most GWAS variants lie in poorly annotated non-coding genomic regions.
- These genetic variants reside within regulatory elements and exert effects through long-range regulation of gene expression.
- Which are functional and what their targets are is unclear.
- This underscores the need for functional maps of non-coding regions.

108 SCZ-associated genetic loci
(Ripke et al., Nature, 2014)
In only 10 instances was the association signal attributable to a known non-synonymous exonic polymorphism.
What do non-coding regions do?

Alter expression and splicing of target genes

In a cell type, tissue and developmental stage specific manner...

“No maps for these territories”
Generating a reference map of gene regulation during human neurogenesis based on dynamic chromatin accessibility and structure

What genes are expressed?” (RNA-Seq)*

What regions of the genome are active?: Chromatin Accessibility (ATAC-Seq)*

What genes do they regulate?: Chromatin Interaction (Hi-C)*

How do they regulate them?: TF binding site mapping*

*De La Torre Ubieta et al. Cell 2018
*Pouliadakis et al. BioRxiv 2018
*Walker et al. BioRxiv 2018

3 Donors (GW17-19) (3-4 replicates/donor)

Luis de la Torre Ubieta
Hyejung Won
Jason Stein
Regulatory maps help identify genes through which genetic variants are likely acting......

**Chromosome conformation elucidates regulatory relationships in developing human brain**


Gene regulation occurs via chromosome folding that brings regulatory regions into contact with their target gene in a tissue specific manner.

*Only half of the GWAS loci are acting on the closest gene...many are acting more than several hundred thousand base pairs away.*
Comparing active/open regulatory regions in fetal and adult cerebral cortex

- Define a high resolution map of non-coding regulatory elements active during brain development
- Use these data to study human brain evolution and neuropsychiatric disease

De La Torre Ubieta, Stein et al. Cell 2018
Genetic variation within fetal-active genomic regions influences cognition/educational attainment, risk for adult disease and brain size

Partitioned heritability method: Finucane et al., Nat. Genetics, 2015

De La Torre Ubieta et al. Cell 2018
Genetic variation within peaks most active in the cortical germinal zones influences cognition, risk for disease and brain size.
eQTL
Defining eQTL in Fetal Brain

201 Mid-gestation Fetal Brains

- Ribo Zero RNA sequencing
- Genode v19
- 15,925 genes

- High-density genotyping
  - imputed into the 1000G reference panel
  - HG19
  - 6,651,969 SNPs

**eQTL Discovery - FastQTL**
Expression ~ Genotype + Gestation Week + Sex + RIN + 20HCPs + 3 Genotype PCs

- 6,526 eGenes (FDR 0.05)

**spliceQTL Discovery - Leafcutter + FastQTL**
PSI ~ Genotype + Gestation Week + Sex + RIN + 5HCPs + 3 Genotype PCs

- 4,535 sQTLs (FDR 0.05)

**QTL Characterization**
- Functional Enrichment
- Cell Type Specificity
- Age and Tissue Comparison

**Integrative Analysis**
- LD Score Regression
- Partitioned Heritability
- Transcriptome-Wide Association Study
- Co-Expression Networks

Walker et al. BioRxiv 2018
Genetic enrichment in human developmental eQTL

Fetal Splice QTL carry substantial risk

Walker et al. BioRxiv 2018
Cross disorder risk preferentially impacts fetal brain development

PGC CROSS DISORDERS GROUP:
Gene expression of pleiotropic genes (associated with more than one psychiatric disorder) and non-pleiotropic genes differs

Lee et al. 2019, Cell
Conclusions

• Fine grained understanding of gene regulation during human brain development is essential to understanding the functional impact of human genetic variation in the nervous system.

• Integrative genomic and gene-network approaches provide organizing principles for understanding molecular phenotypes in the brain, defining points of potential biological convergence in disease.

• Autism risk genes converge on early fetal brain development during the peak of neurogenesis, involving transcriptional regulation and synaptic development and impacting GLUT neurons (upper layers), but non-exclusively.

• Understanding which genes and cell types are impacted (and when) provides a starting point for developing therapeutics.