Genetics of Schizophrenia:  
On the Road to Precision Medicine

Ayman H. Fanous, MD

Professor and Chair, Department of Psychiatry  
University of Arizona College of Medicine-Phoenix

Psychiatrist, Phoenix VA Medical Center
Disclosures

• Nothing to disclose
Main Collaborators

SUNY Downstate Medical Center
  Tim Bigdeli, Ph.D.
  Roseann Peterson, Ph.D.

Virginia Commonwealth University
  PI: Kenneth S. Kendler, M.D.
  Michael Neale, Ph.D.
  Edwin van den Oord, Ph.D.
  Brien Riley, Ph.D.
  Xiangning (Sam) Chen, Ph.D.
  Todd Webb, Ph.D.
  Silviu-Alin Bacanu, Ph.D.
  Alexis Edwards, Ph.D.

Broad Institute of Harvard and MIT
  Steven McCarroll, Ph.D.
  Bob Handseker, Ph.D.
  Colm O’Dushlaine, Ph.D.
  Jennifer Moran
  Kimberly Chambert

Queens University, Belfast, UK
  PI: Anthony O’Neill, M.B.

Health Research Board, Dublin, Ireland
  PI: Dermot Walsh, M.B., F.R.C.P.I.

Johns Hopkins University
  Brion Maher, Ph.D.
  Kelly Benke, Ph.D.

Rutgers University
  PI: Carlos Pato, MD, Ph.D
  PI: Michele Pato, MD
  James Knowles, Ph.D
  Helena Medeiros, MSW
  Janet Sobell, Ph.D.

University of Coimbra, Portugal
  Maria H. Azevedo, MD
  Antonio Macedo, MD

Dept. of Psychiatry, Sao Miguel, Azores
  PI: Carlos Paz Ferreira, MD
  Celia Barreto, Ph.D.
Schizophrenia – Brief Historical Overview

Tandon et al. Schizophr Res. 2009 May;110(1-3):1-23
• One of the top 15 leading causes of disability worldwide
• Individuals with schizophrenia have an increased risk of premature mortality
• The estimated average potential life lost for individuals with schizophrenia in the U.S. is 28.5 years
  – Co-occurring medical conditions, such as heart disease, liver disease, and diabetes, contribute to the higher premature mortality rate
• An estimated 4.9% of people with schizophrenia die by suicide
• Annual cost in US (direct + indirect) estimated to be $25-$102 billion
Schizophrenia is highly familial

Figure 1 Life-time MR for schizophrenia in various classes of relatives of a proband, adapted from Gottesman.¹
But is it genetic?

Allelic Association: Single Nucleotide Polymorphisms (SNPs)

- 3 billion nucleotide base-pairs in the human genome (A, C, T, G)
- Changes in the sequence (SNPs) occur naturally every ~1,000 bp
- May be
  - Silent
  - Exonic: synonymous, non-synonymous, truncating
  - Intronic
  - Splice site
  - Affect regulation of gene expression (promoters, enhancers)
- Common (>=1%) or rare
Allelic Association: Single Nucleotide Polymorphisms (SNPs)

- If a SNP allele’s frequency is different in cases compared to controls, it is “associated” with the illness.
- A SNP could be associated by either a) being causally related to the illness, or b) very close to another SNP that is causally related (due to linkage disequilibrium)
Psychiatric Genomics Consortium (PGC)

- Purpose: to conduct mega-analyses of genome-wide SNP data for psychiatric disorders
- Began in 2007, now includes most investigators in the field
- Initially Focused on SCZ, BPD, MDD, Autism, ADHD. Expanded to eating, anxiety, substance use disorders, PTSD, ADHD
- Each disorder group has a phenotype workgroup
- One Cross-Disorder Workgroup
- Is the largest biological experiment ever conducted in psychiatry:
  - 500+ investigators
  - >100 institutions in dozens of countries
  - Currently 100,000’s of subjects currently in analysis and growing rapidly
PGC Schizophrenia Working Group

• Has proceeded in 3 stages:
  – PGC1: 9,400 cases 23,000 controls
  – PGC2: 37,000 cases 113,000 controls
  – PGC3: 77,000 cases 244,000 controls

• Sample currently includes
  – >90 study samples from sites in the US and Europe
  • 74.3% EUR, 17.5% ASN, 5.7% AA and 2.5% LAT
    – Future work will increasingly focus on non-EUR populations
Genome-wide Association Studies (GWAS): Testing for Allelic Association at Millions of *common* SNPs Across the Genome

PGC1 9,400 cases 23,000 controls – 13 loci

Genome-wide Association Studies (GWAS):
Testing for Allelic Association at Millions of SNPs Across the Genome
PGC2: 37,000 cases 113,000 controls – 108 loci

Genome-wide Association Studies (GWAS):
Testing for Allelic Association at Millions of SNPs Across the Genome
PGC3: 77,000 cases 244,000 controls – 278 loci

PGC SCZ Working Group, Nature. 2022 Apr;604(7906):502-508
Largest SCZ GWAS to date: Primary Findings

- 287 loci were statistically significant
  - 120 (106 coding) genes prioritized based on gene expression and fine-mapping
- Separate analyses for males and females resulted in genetic correlation of 1.
- Overall SNP-based heritability .24
  - “Missing heritability”
- PRS explained more of the variance in EUR and more severely affected samples (hospitalized and CLOZ-treated)
  - Compared to the lowest centile of PRS, the highest centile of PRS has an odds ratio for schizophrenia of 39
  - Median area under the receiver operating characteristic curve (AUROC) is only 0.72
    - This is insufficient to predict diagnosis in the general population
Genes with relatively high specificity for expression in every tested region of human brain were significantly enriched for associations.

Brain-expressed genes in neurons, but not non-neuronal cells, were enriched for associations.
• Gene ontologies associated with SCZ
  • 24 of >7,000 tested were significantly over-represented
    • Processes: development, differentiation and synaptic transmission
    • Cellular components: ion channels, synapses and both axon and dendritic annotations
    • In particular, post-synaptic genes were over-represented
Feasibility of identifying genetic variants by risk allele frequency and strength of genetic effect (odds ratio)

Evidence of rare variant effects: Copy Number Variants (CNV’s)

Moore's law: the number of transistors in a dense integrated circuit doubles about every two years.
Rare Variant Effects:
Schizophrenia Exome Sequencing Meta-Analysis (SCHEMA) consortium

• In addition to strong evidence for common variant effects in SCZ (via GWAS), rare CNV’s have strong effects
  – This suggests that rare gene-disrupting variants might also strongly increase risk

• SCHEMA global collaborative effort to analyze sequence data from many studies
  – 24,248 individuals with schizophrenia and 97,322 controls from seven continental populations
  – Tested for an excess of disruptive variants per gene
  – Analysis limited to variants with allele count of 5 or less
    • a) Protein truncating variants (PTV’s), defined as stop-gained, frameshift, or essential splice donor or acceptor variants, or
    • b) Damaging missense variants
Results from meta-analysis of Ultra Rare Variants (URVs) in 3,402 trios, 24,248 cases and 97,322 controls.
Results: implicated genes

- Ion transport
  - CACNA1G, GRIN2A (NMDA subunit) and GRIA3 (AMPA subunit)
  - In particular, dysregulation of glutamatergic system is supported
- Neuronal migration and growth
  - TRIO
- Transcriptional regulation
  - SP4, RB1CC1 and SETD1A
- Nuclear transport
  - XPO7
- Ubiquitin ligation
  - CUL1 and HERC1
- Many more genes are thought to have excesses of URVs
- Of 300 DD/ID- and 100 ASD-related genes, there was an excess of URVs in SCZ cases
Shared genetic signal with schizophrenia GWAS

Enrichment of URVs in genes prioritized from fine-mapping of the PGC schizophrenia GWAS
From Genomics to Pathophysiology

- PGC2 GWAS results combined with sequencing families identified a haplotype in complement C4
- Complement C4 found to be overexpressed in post-mortem brain of ind. with SCZ
- Overexpression of C4 in mice resulted in excessive synapse elimination and behavioral changes
  - Less social
  - More anxiety-related behaviors

Yilmaz et al., Nat Neurosci. 2021 Feb;24(2):214-224
Can genetics help explain phenotypic complexity?

Molecular Psychiatry (2005) 10, 6–13
© 2005 Nature Publishing Group. All rights reserved 1359-4184/05 $30.00
www.nature.com/mp

PERSPECTIVE

Genetic heterogeneity, modifier genes, and quantitative phenotypes in psychiatric illness: searching for a framework

AH Fanous¹,² and KS Kendler²,³

– **Susceptibility gene:**
  • Increases risk of illness, no effect on specific symptom domains

– **Modifier gene:**
  • Affects symptomatic domains once a person becomes ill
  • Does not alter risk by itself
  • Clearly occur in mendelian disorders (e.g. Cystic Fibrosis)

– **Susceptibility-modifier gene:**
  • Increases risk presentations of illness (subtypes) comprising more or less distinct symptomatic domains

– **Overlap gene:**
  • Increases risk of more than one illness
Evidence of Overlap Genes: Heritability and Coheritability of Psychiatric Disorders

Cross-Disorders Group of the PGC. Nat Genet 2013 Sep;45(9):984-94.
Overlap Genes (Pleiotropy): Phe-WAS of SCZ and MDD in VA’s MVP

THE PRECISION MEDICINE INITIATIVE

“Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type—that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?”

- President Obama, January 30, 2015
**Precision Medicine**

- **NIH Definition of Precision Medicine:**
  - ”An emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.”

- **Precision Medicine Initiative:** $216 million to fund research in PM
  - Long-term goal: study a cohort of 1,000,000 people (All of Us program)
  - Genetic data, biospecimens, and Electronic Medical Record (EMR) data

---

**Precision Medicine Ecosystem**

• 20% to 30% of people with schizophrenia do not respond to treatment

• Only widely used therapy for treatment-resistant schizophrenia (TRS) is Clozapine
  – 60% of clozapine patients respond
  – delay in clozapine prescription is associated with resistance even to clozapine

• Biological basis of TRS is unclear
  – One hypothesis is that high SCZ PRS is a risk factor
  – Clozapine’s efficacy might be related to the underlying biology of TRS
  – Genetic studies of TRS have not been done
Traits genetically correlated with treatment resistance

Precision Medicine: Million Veteran Program (MVP)

• MVP aims to create a longitudinal cohort of 2,000,000 veterans at >100 VA sites.
  – >850,000 genotyped to date.
• Participants donate blood, consent to future contact and EMR access, complete survey on lifestyle, military exposure
• Genotyped using customized Affymetrix Axiom Biobank array
  – Pharmacogenomic, Psych chip, HLA, eQTL content added
Precision Medicine: Identifying High-risk Individuals (Extreme Phenotypes) for Genetic Studies in EMR Databases
Developing Precision Medicine Phenotypes from EMR’s: Antipsychotic Metabolic Adverse Effects in VA Nationwide
Conclusions

• Schizophrenia, like many common non-psychiatric disorders, is polygenic
  – Risk is conferred by both common and rare variants
• Its clinical heterogeneity is due in part to genetic heterogeneity
  – Modifier and susceptibility-modifier genes likely to influence the clinical
    phenotype, including symptom dimensions and clinical subtypes
  – Some of these genes influence other disorders
• It shares genetic risk variants, both common and rare, with other psychiatric
  disorders, as well as a number of somatic illnesses
• Contemporary technology allows for unprecedented genomic insight into
  clinical domains comprising the “phenotypic architecture” of psychiatric
  illness
• Genetic dissection of psychiatric phenotypes can inform the development of
  DSM-6 and beyond
• We are now able to identify genetic signatures of drug response (both
  beneficial and adverse effects) using genomics and large-scale EMR data
  – This information can guide the development of Precision Psychiatry modalities to maximize
    benefit and minimize risk to patients