Update on the Genetics of Schizophrenia: The Road to Precision Psychiatry

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FINANCIAL DISCLOSURE

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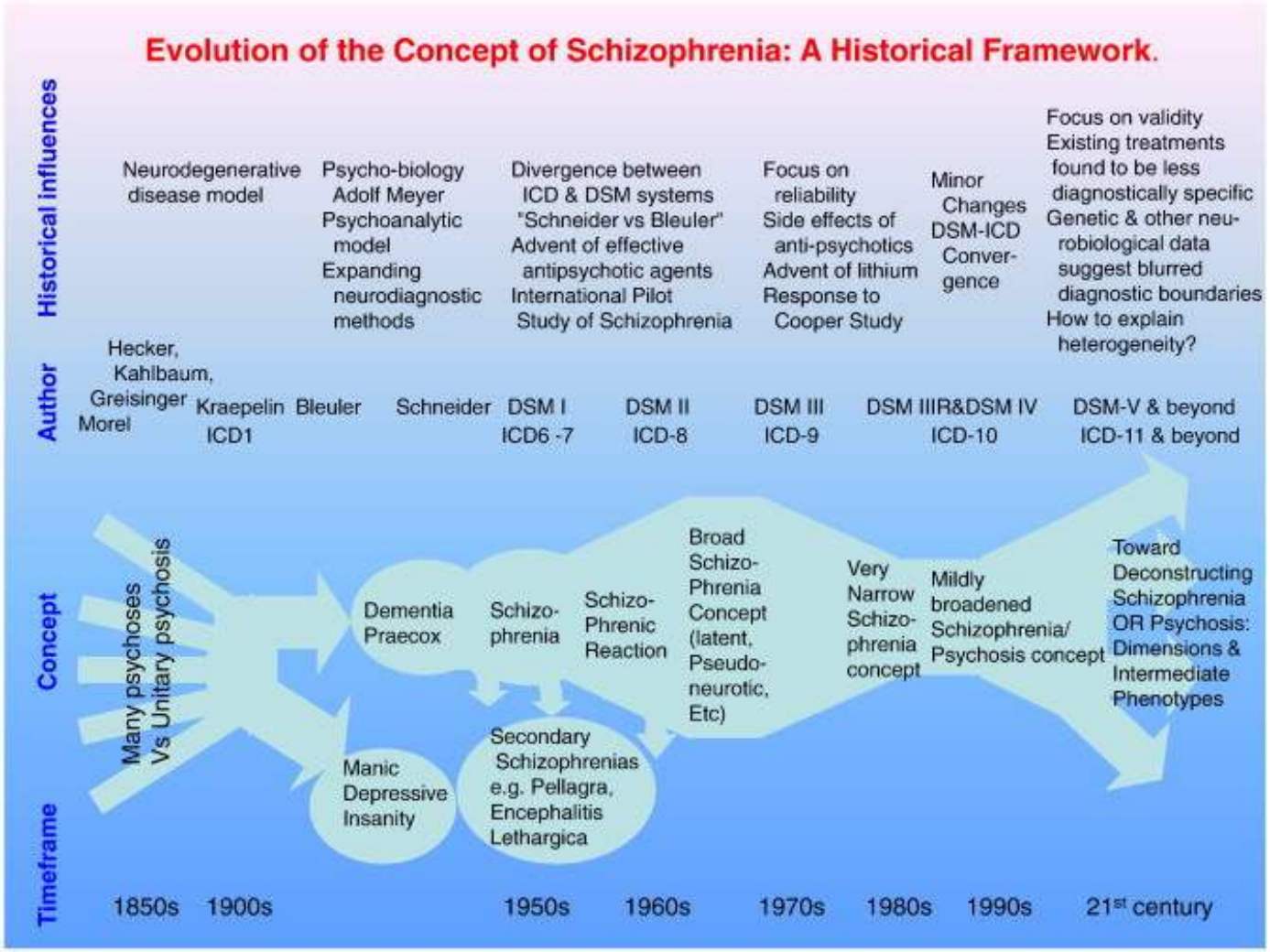
Schizophrenia – Brief Historical Overview



Tandon et al. Schizophr Res. 2009 May;110(1-3):1-23

Schizophrenia – Public Health Impact

- One of the top 12 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 familial AND genetic

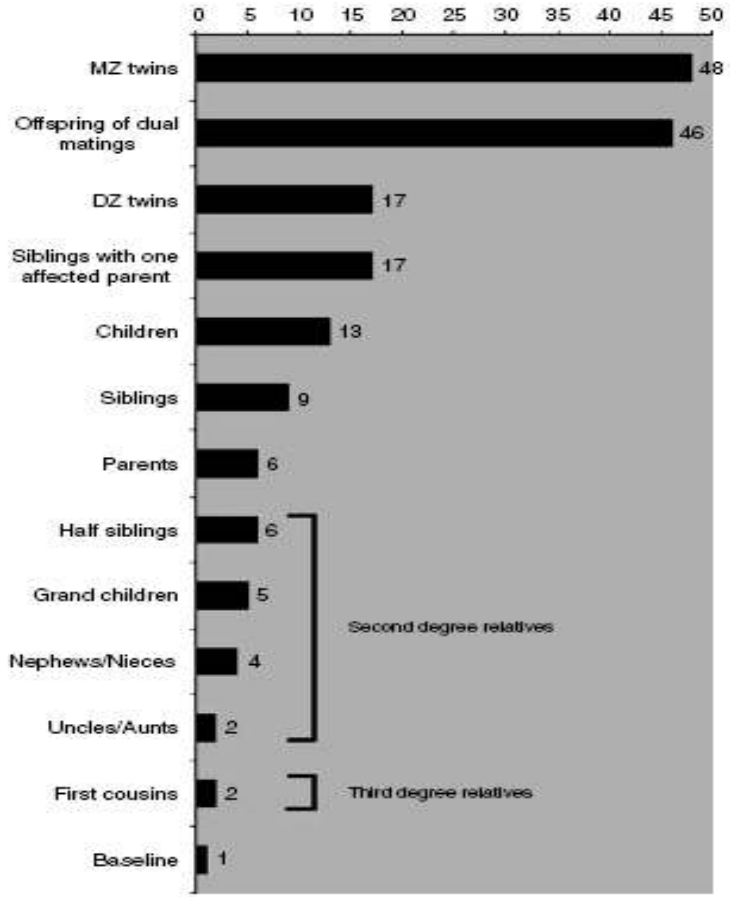
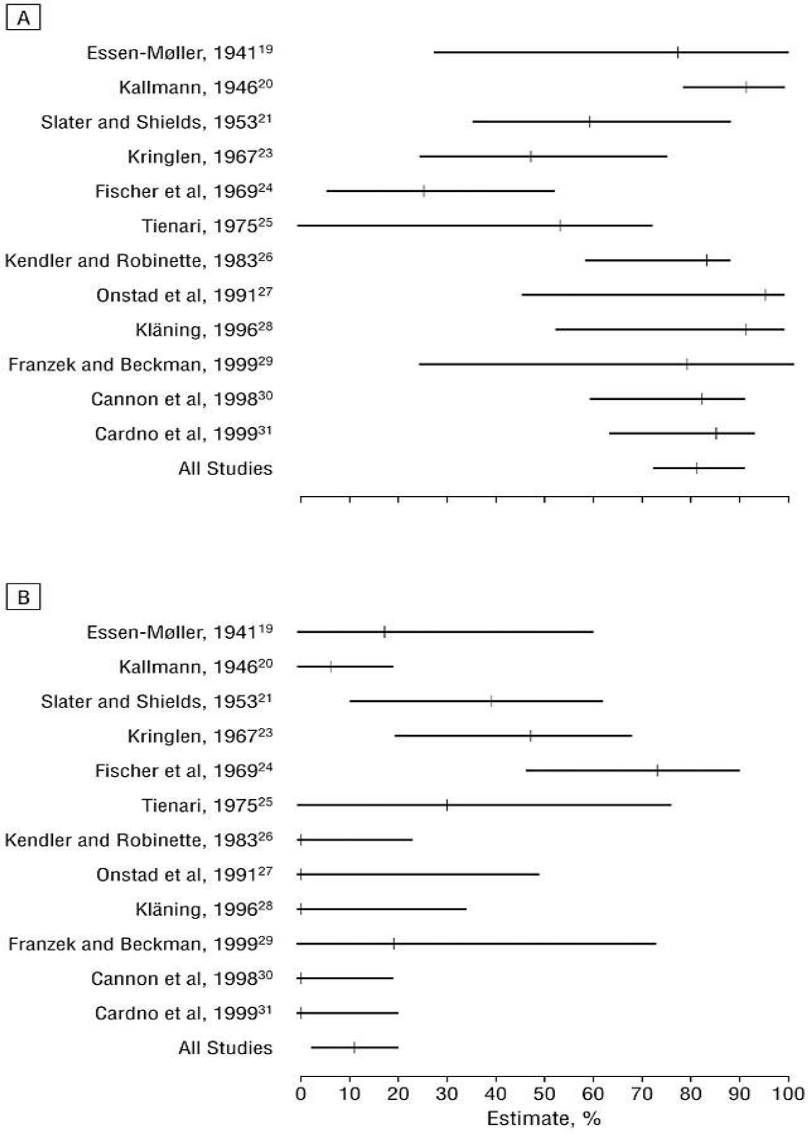


Figure 1 Lifetime MR for schizophrenia in various classes of relatives of a proband, adapted from Gottesman.[1]



Sullivan, P. F., Neale, M.C., and Kendler, K.S. Arch Gen Psychiatry 2003;60:1187-1192.

Psychiatric Genomics Consortium (PGC)

- Purpose: to conduct mega-analyses of genome-wide Single Nucleotide Polymorphism (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

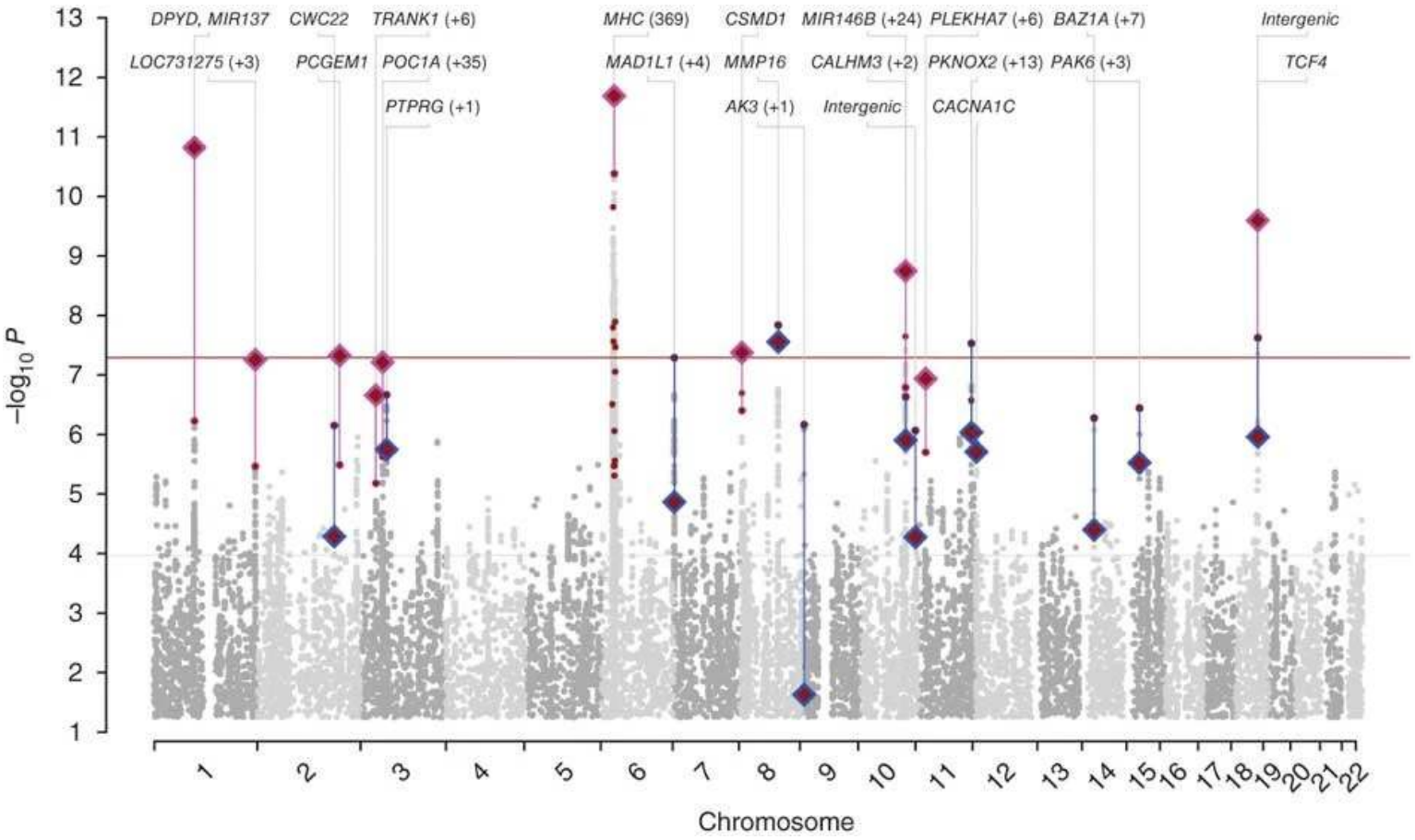
PGC Schizophrenia Working Group

- **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



PGC SCZ Working Group, Nat Genet. 2013 Oct;45(10):1150-9.

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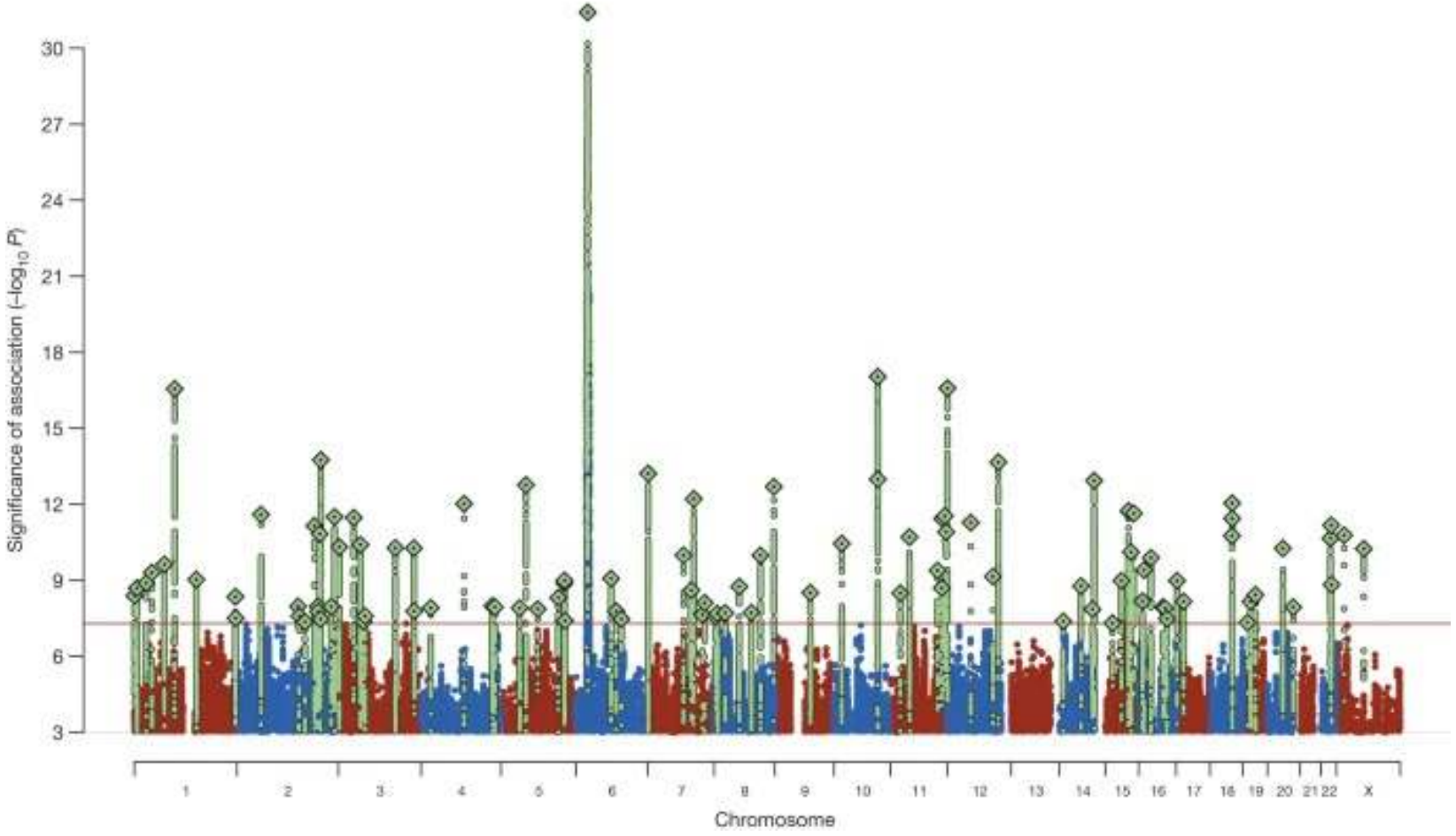
Genome-wide Association Studies (GWAS):

Testing for Allelic Association at Millions of SNPs Across the Genome

PGC2: 37,000 cases 113,000 controls – 108 loci



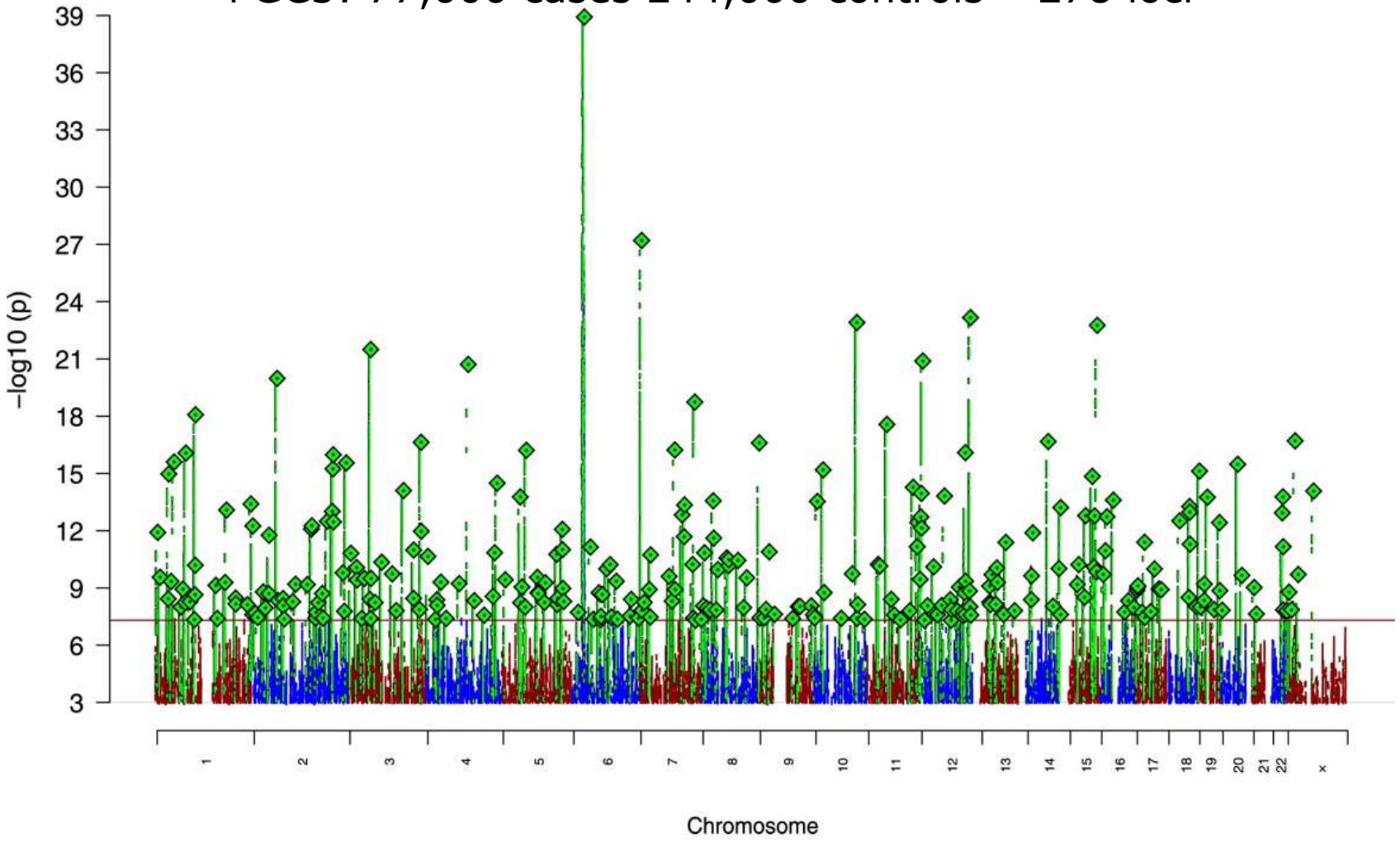
PGC SCZ Working Group, Nature. 2014 Jul 24;511(7510):421-7

nature

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

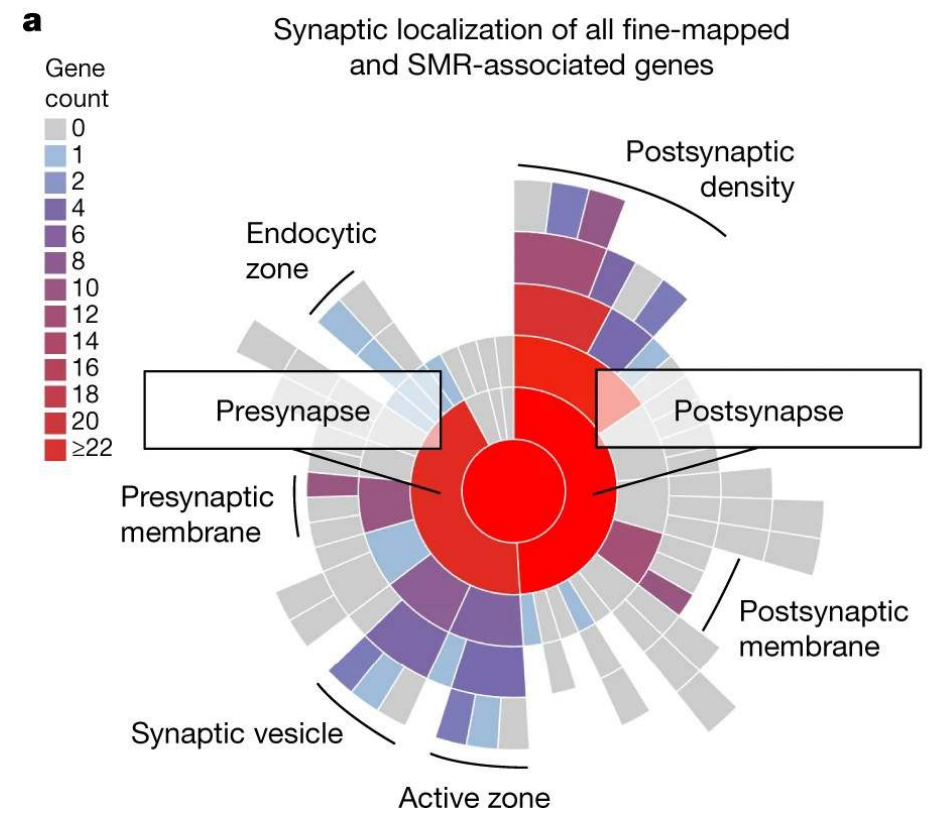


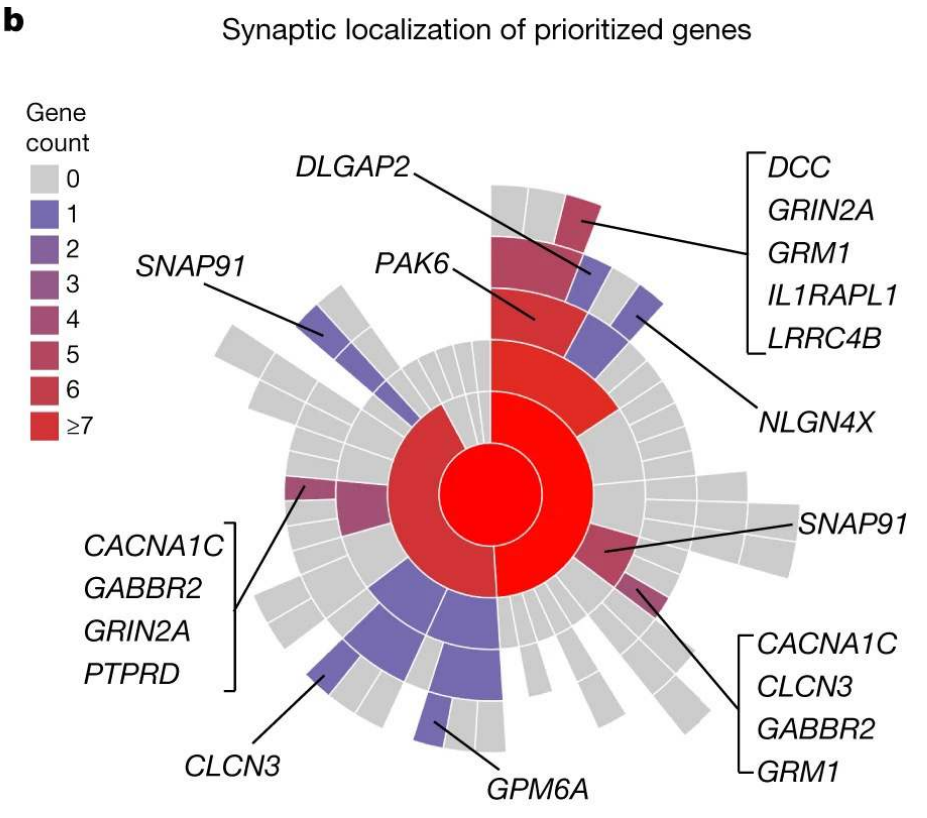
PGC SCZ Working Group, Nature. 2022 Apr;604(7906):502-508

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

- **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**





GWAS in non-European populations

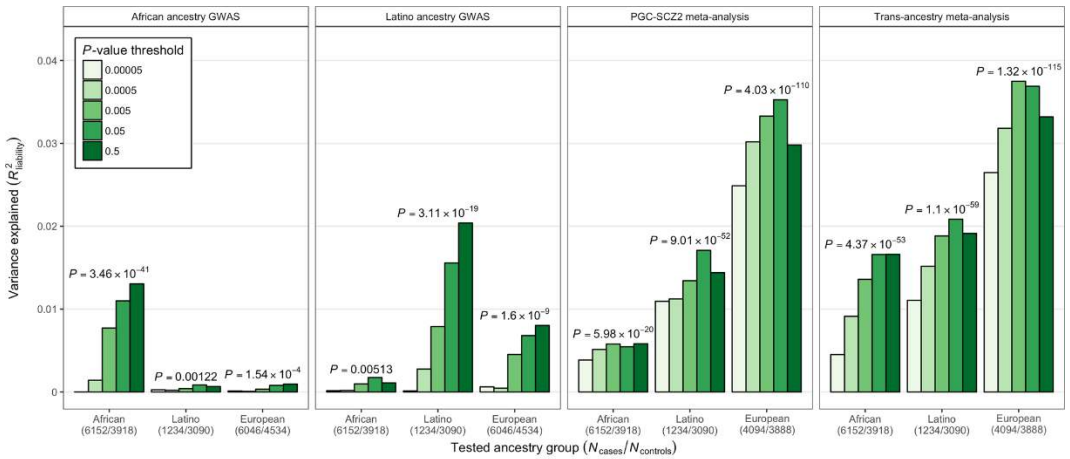
- The vast majority of previous genetic studies of SCZ have been done in EA populations
  - However, results cannot be fully generalizable across ethnic groups due to allele freq. differences and LD
- The Genomic Psychiatry Cohort (GPC) is the largest study to date of AA individuals:
  - Represents new and repository samples of AA/LA/EA cases and controls
  - 6152 AA schizophrenia and schizoaffective disorder cases and 3918 screened controls
    - Now on a par with the earlier large-scale EA studies (PGC1)

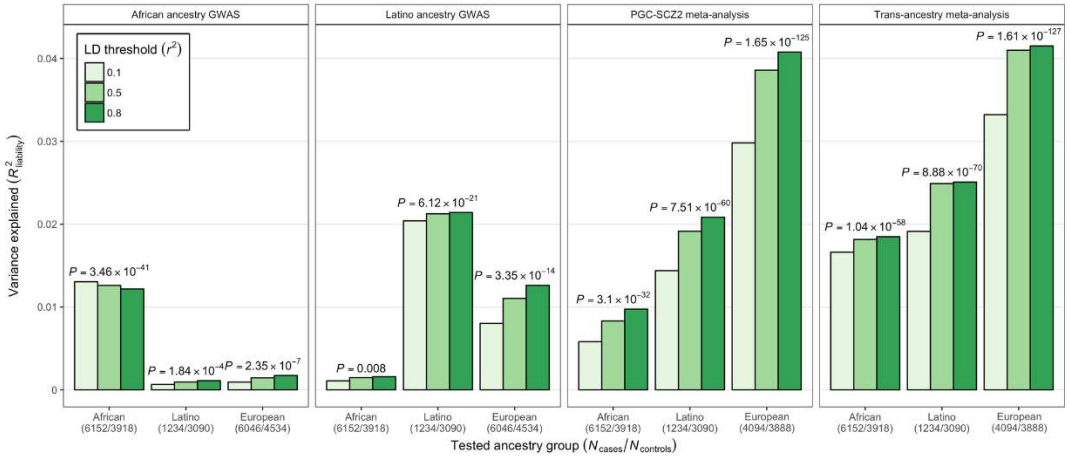
Bigdeli et al., Mol Psychiatry. 2020 Oct;25(10):2455-2467.

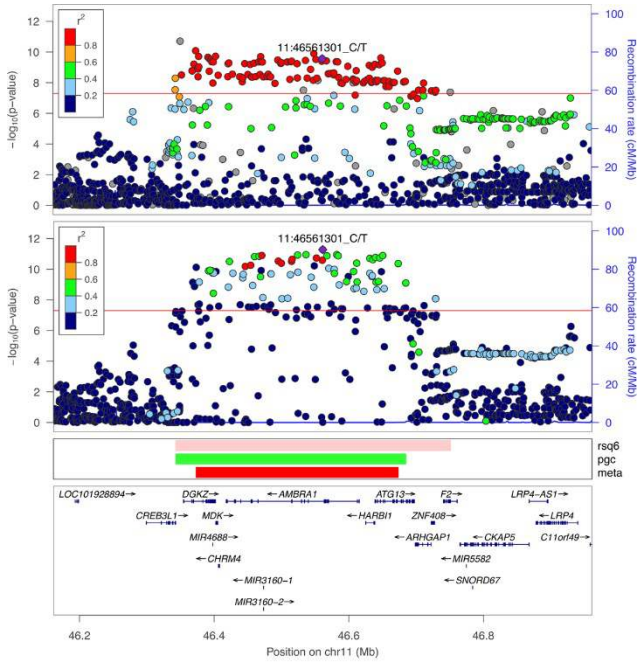
GPC: Primary Results

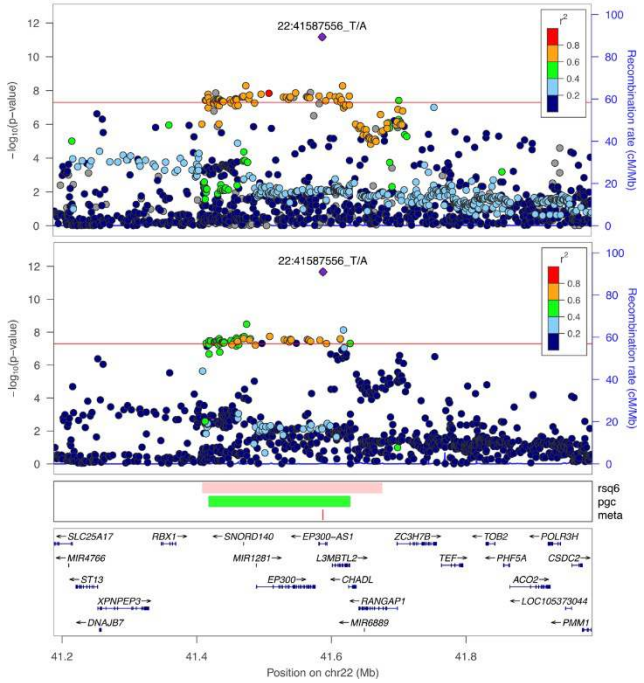
- Consistency of effect:
  - Directions of effect were more consistent genome-wide than would be expected by chance; between AA and BOTH EA and LA groups
- AA:
  - No GWS SNPs in AA alone
  - In meta-analysis with EA: 107 loci were GWS, 10 new
- LA:
  - SNPs in GALNT13 were GWS in LA alone
  - In meta-analysis with EA: 101 loci were GWS, 8 new

Bigdeli et al., Mol Psychiatry. 2020 Oct;25(10):2455-2467.

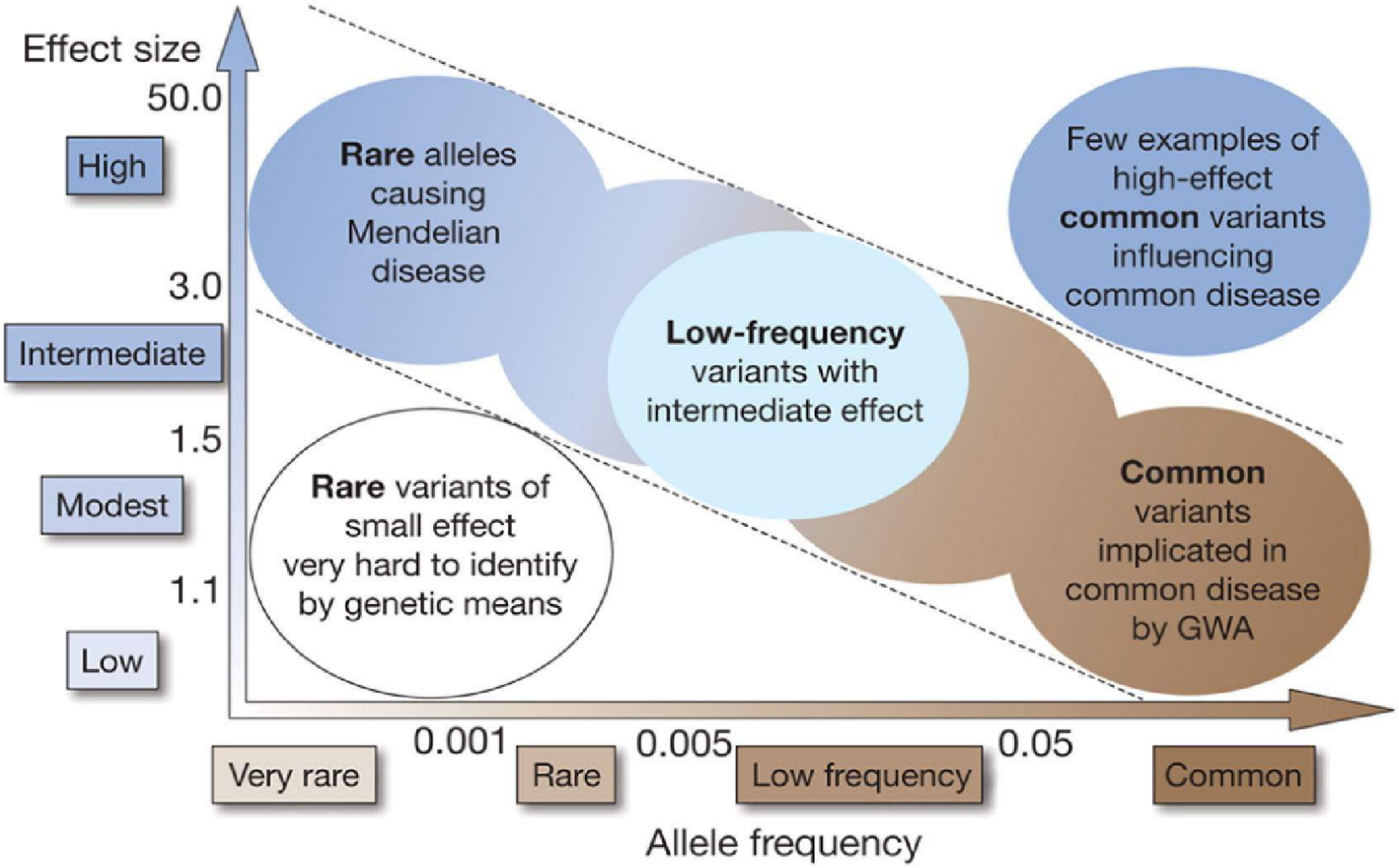

African ancestry GWAS
Latino ancestry GWAS
PGC-SCZ2 meta-analysis
Trans-ancestry meta-analysis
P-value threshold
0.00005
0.0005
0.005
0.05
0.5
Variance explained ($R^2_{liability}$)
$P = 3.46 \times 10^{-41}$
$P = 0.00122$
$P = 1.54 \times 10^{-4}$
$P = 0.00513$
$P = 3.11 \times 10^{-19}$
$P = 1.6 \times 10^{-9}$
$P = 5.98 \times 10^{-20}$
$P = 9.01 \times 10^{-52}$
$P = 4.03 \times 10^{-110}$
$P = 4.37 \times 10^{-53}$
$P = 1.1 \times 10^{-59}$
$P = 1.32 \times 10^{-115}$
African (6152/3918)
Latino (1234/3090)
European (6046/4534)
European (4094/3888)
Tested ancestry group ($N_{cases}/N_{controls}$)


African ancestry GWAS
Latino ancestry GWAS
PGC-SCZ2 meta-analysis
Trans-ancestry meta-analysis
LD threshold (r^2)
0.1
0.5
0.8
Variance explained ($R^2_{liability}$)
$P = 3.46 \times 10^{-41}$
$P = 1.84 \times 10^{-4}$
$P = 2.35 \times 10^{-7}$
$P = 0.008$
$P = 6.12 \times 10^{-21}$
$P = 3.35 \times 10^{-14}$
$P = 3.1 \times 10^{-32}$
$P = 7.51 \times 10^{-60}$
$P = 1.65 \times 10^{-125}$
$P = 1.04 \times 10^{-58}$
$P = 8.88 \times 10^{-70}$
$P = 1.61 \times 10^{-127}$
African (6152/3918)
Latino (1234/3090)
European (6046/4534)
European (4094/3888)
Tested ancestry group ($N_{cases}/N_{controls}$)


11:46561301_C/T
r^2
0.8
0.6
0.4
0.2
$-\log_{10}$(p-value)
Recombination rate (cM/Mb)
rsq6
pgc
meta
LOC101928894
DGKZ
AMBRA1
ATG13
F2
LRP4-AS1
CREB3L1
MDK
HARBI1
ZNF408
LRP4
MIR4688
ARHGAP1
CKAP5
C11orf49
CHRM4
MIR5582
MIR3160-1
SNORD67
MIR3160-2
Position on chr11 (Mb)

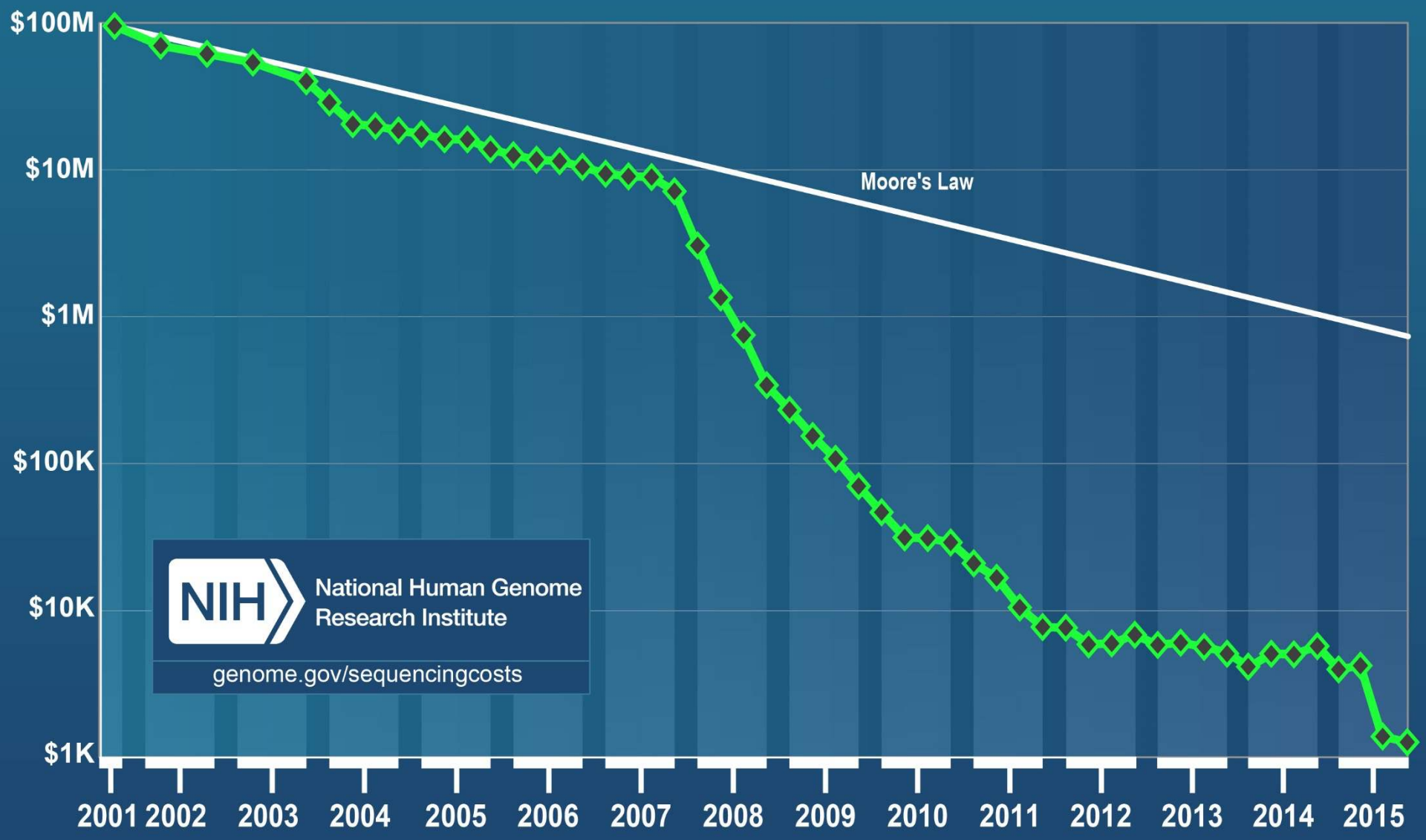

22:41587556_T/A
r^2
0.8
0.6
0.4
0.2
$-\log_{10}$(p-value)
Recombination rate (cM/Mb)
rsq6
pgc
meta
SLC25A17
RBX1
SNORD140
EP300-AS1
ZC3H7B
TOB2
POLR3H
MIR4766
MIR1281
L3MBTL2
TEF
PHF5A
CSDC2
ST13
EP300
CHADL
ACO2
XPNPEP3
RANGAP1
LOC105373044
DNAJB7
MIR6889
PMM1
Position on chr22 (Mb)

Feasibility of identifying genetic variants by risk allele frequency and strength of genetic effect (odds ratio)



Manolio T, et al., Nature 2009;461:747–753

Cost per Genome



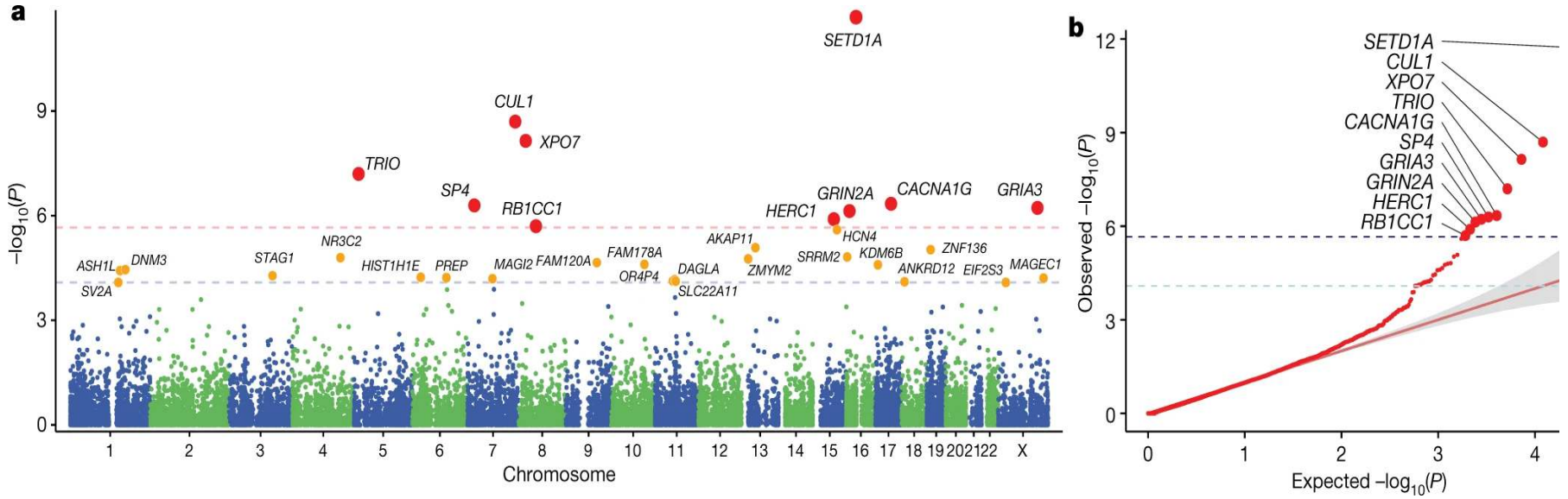
Moore's law: the number of transistors in a dense integrated circuit doubles about every two years.

Rare Variant Effects:

Schizophrenia Exome Sequencing Meta-Analysis (SCHEMA) consortium

- **In addition to strong evidence for common variant effects in SCZ (via GWAS), rare Copy Number Variants (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**
    - **a) Protein truncating variants (PTV's), defined as stop-gain, 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.



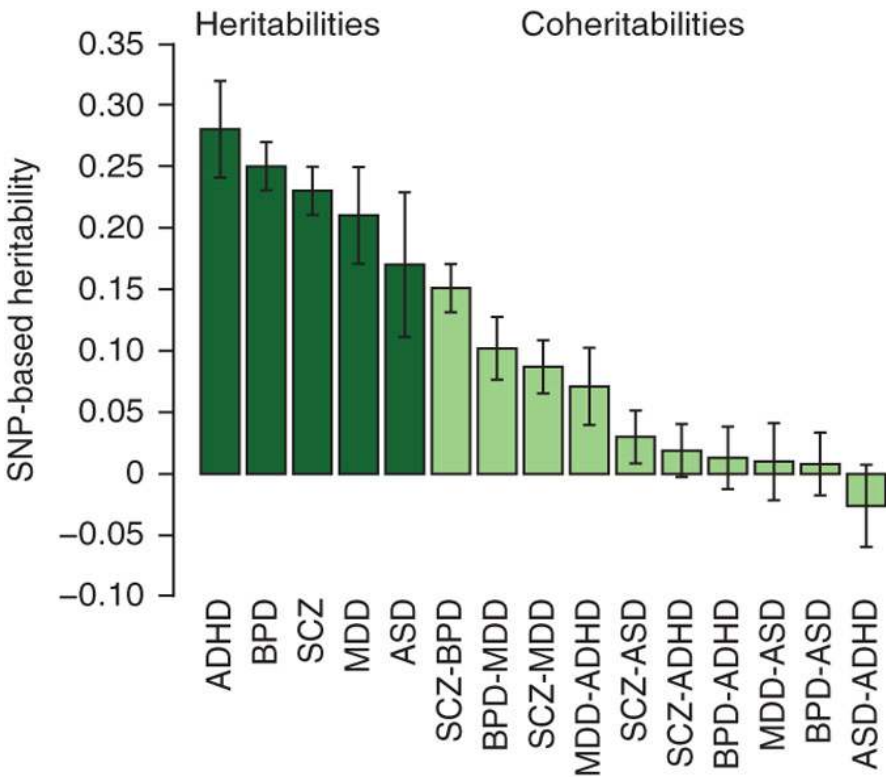
SCHEMA 2022 Apr;604(7906):509-516 nature

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
- Processes and pathways overlap with results of common variant studies

Can genetics help explain phenotypic complexity?

- **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



Molecular Psychiatry (2005) 10, 6–13

www.nature.com/mp

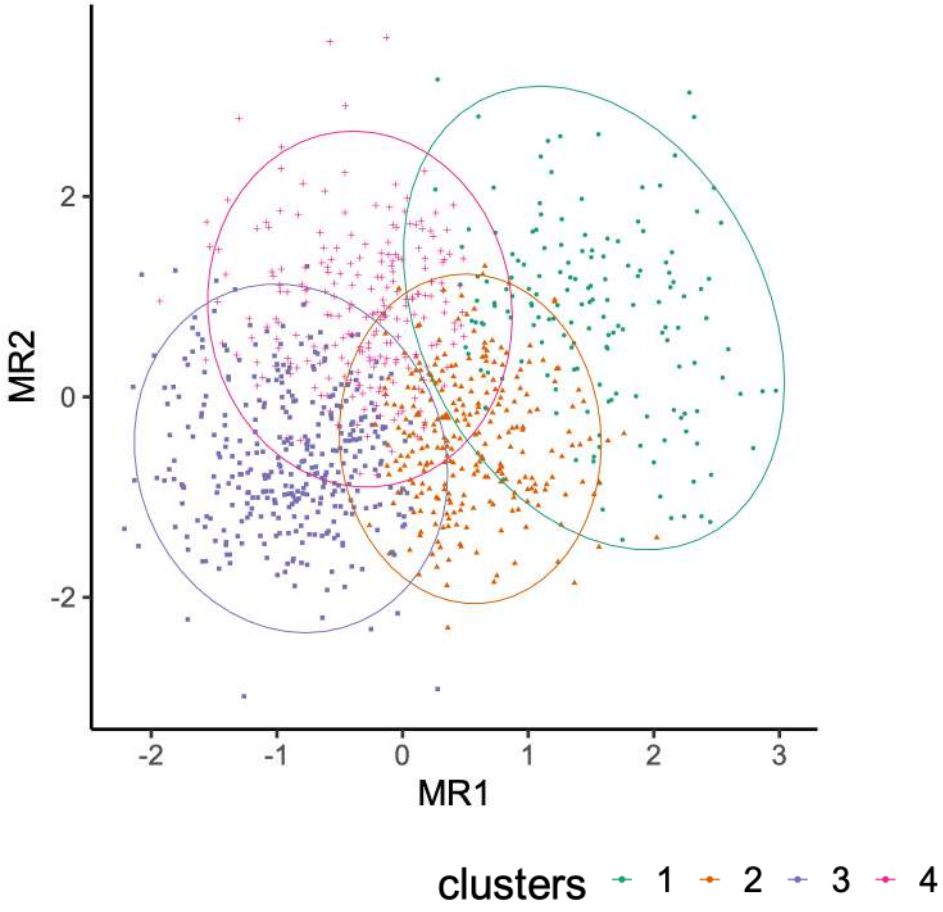
PERSPECTIVE

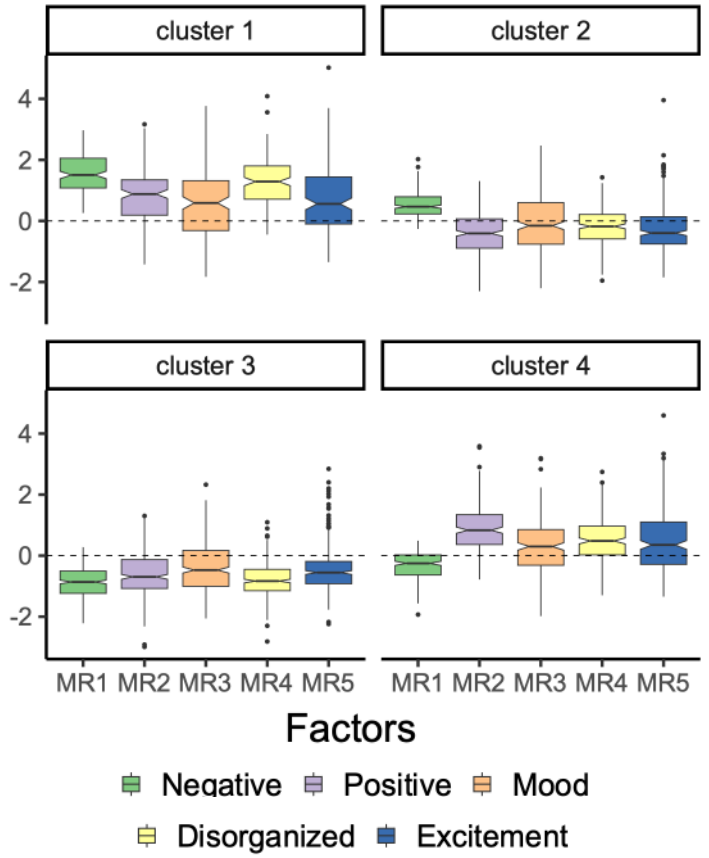
Genetic heterogeneity, modifier genes, and quantitative phenotypes in psychiatric illness: searching for a framework

AH Fanous[1,2] and KS Kendler[2,3]

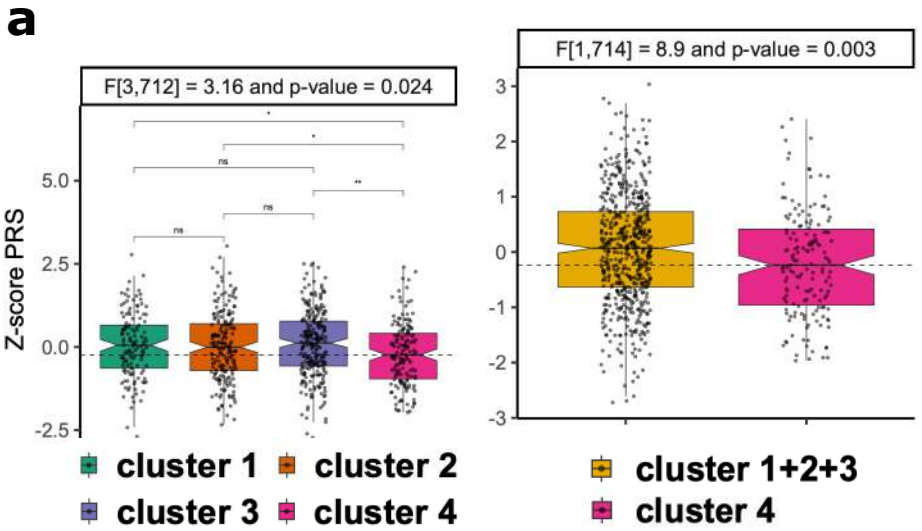
Cross-Disorders Group of the PGC. Nat Genet 2013 Sep;45(9):984-94.

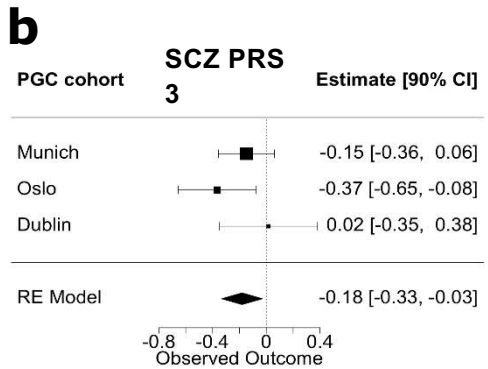
Subtypes of SCZ in the PGC:
Evidence of Etiological Heterogeneity

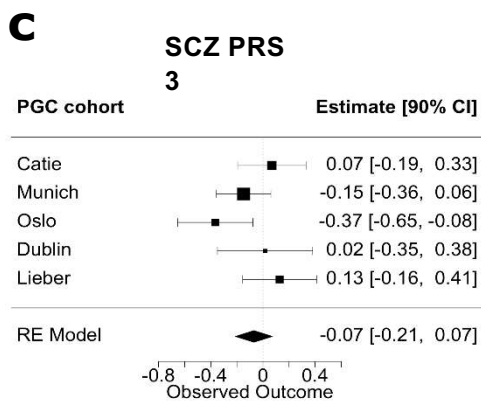


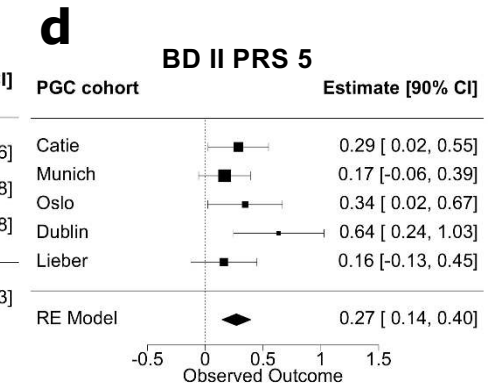


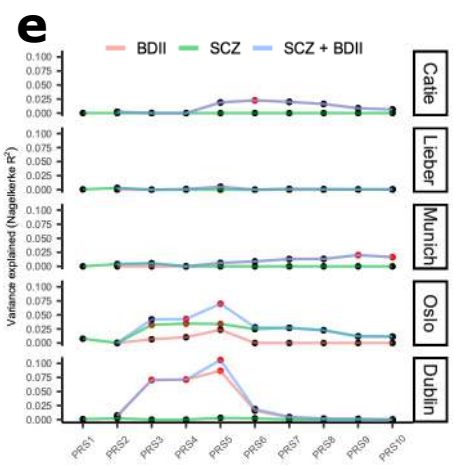
Pergola et al, submitted


a
F[3,712] = 3.16 and p-value = 0.024
Z-score PRS
5.0
2.5
0.0
-2.5
ns
ns
ns
*
*
**
cluster 1
cluster 2
cluster 3
cluster 4
F[1,714] = 8.9 and p-value = 0.003
3
2
1
0
-1
-2
-3
cluster 1+2+3
cluster 4


b
SCZ PRS 3
PGC cohort
Estimate [90% CI]
Munich
-0.15 [-0.36, 0.06]
Oslo
-0.37 [-0.65, -0.08]
Dublin
0.02 [-0.35, 0.38]
RE Model
-0.18 [-0.33, -0.03]
-0.8 -0.4 0 0.4
Observed Outcome


c
SCZ PRS 3
PGC cohort
Estimate [90% CI]
Catie
0.07 [-0.19, 0.33]
Munich
-0.15 [-0.36, 0.06]
Oslo
-0.37 [-0.65, -0.08]
Dublin
0.02 [-0.35, 0.38]
Lieber
0.13 [-0.16, 0.41]
RE Model
-0.07 [-0.21, 0.07]
-0.8 -0.4 0 0.4
Observed Outcome


d
BD II PRS 5
PGC cohort
Estimate [90% CI]
Catie
0.29 [0.02, 0.55]
Munich
0.17 [-0.06, 0.39]
Oslo
0.34 [0.02, 0.67]
Dublin
0.64 [0.24, 1.03]
Lieber
0.16 [-0.13, 0.45]
RE Model
0.27 [0.14, 0.40]
-0.5 0 0.5 1 1.5
Observed Outcome


e
BDII
SCZ
SCZ + BDII
Variance explained (Nagelkerke R²)
Catie
Lieber
Munich
Oslo
Dublin
PRS1
PRS2
PRS3
PRS4
PRS5
PRS6
PRS7
PRS8
PRS9
PRS10

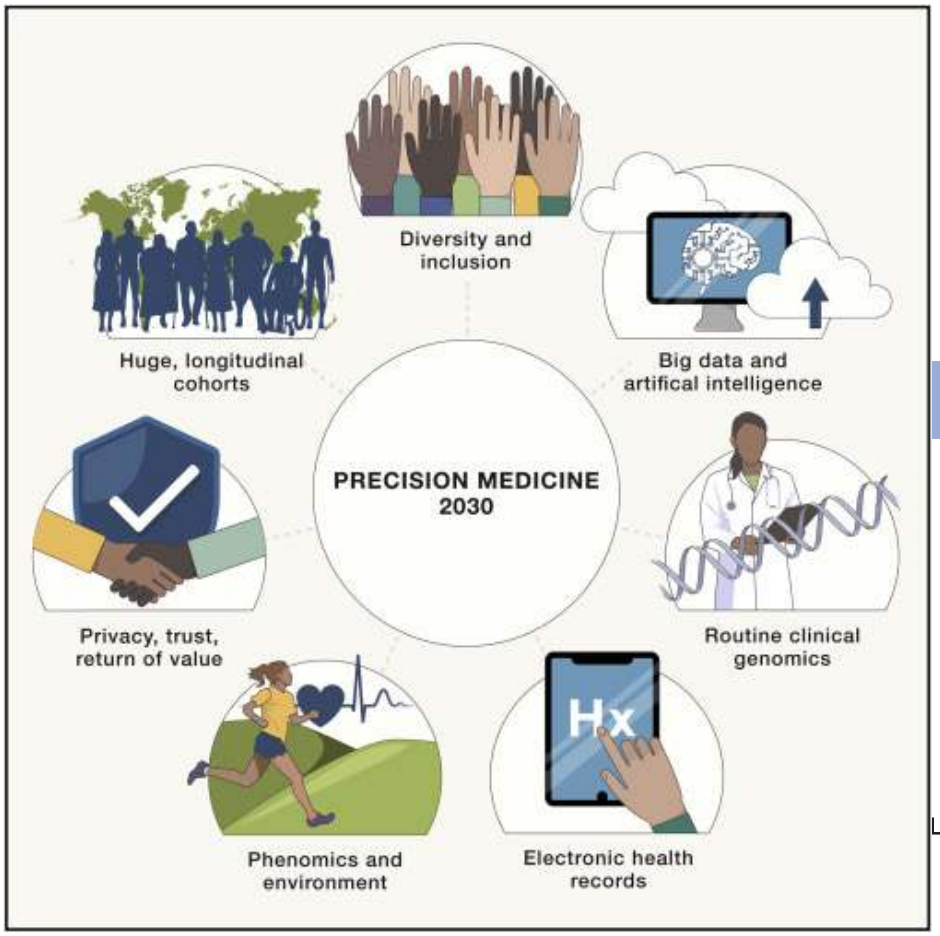
THE PRECISION MEDICINE INITIATIVE

JUMP TO A SECTION (JAVASCRIPT://)

"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?"

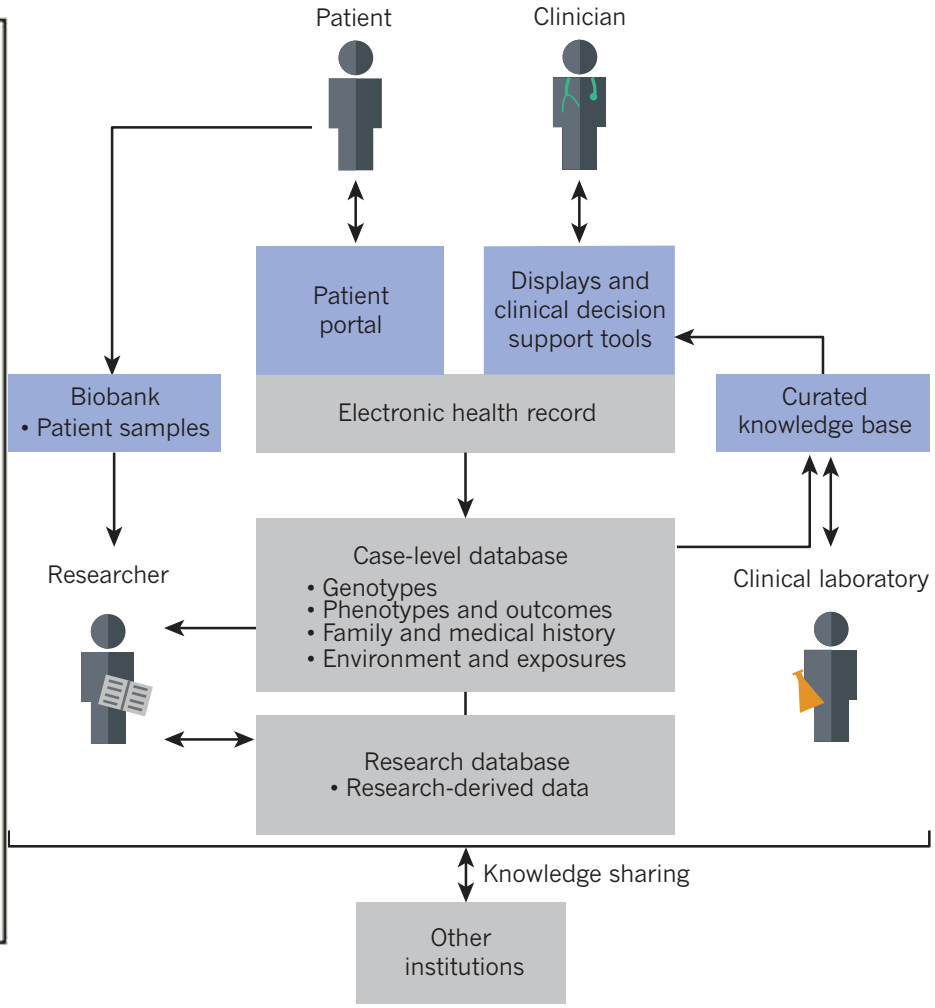
- President Obama, January 30, 2015

Precision Medicine



Precision Medicine 2030-Seven Ways to Transform Healthcare

Denny and Collins: Cell. 2021 Mar 18;184(6):1415-1419.



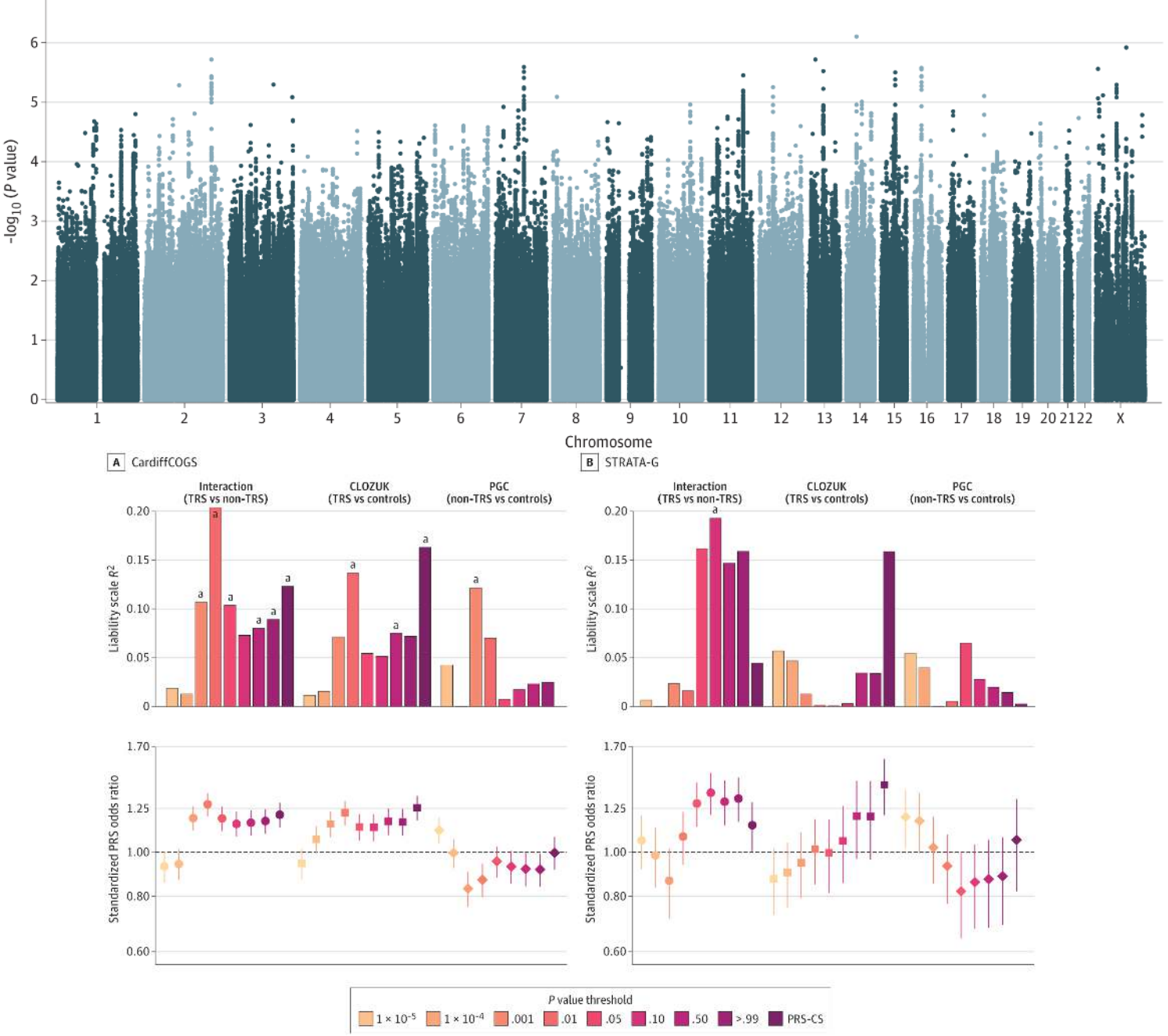
Precision Medicine Ecosystem

Aronson and Rehm 2015. Nature 526 10/15/2015 p.336-342

Precision Psychiatry: Treatment Response

Treatment Resistance in Schizophrenia

- 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



Pardiñas et al., JAMA Psychiatry. 2022;79(3):260-269.

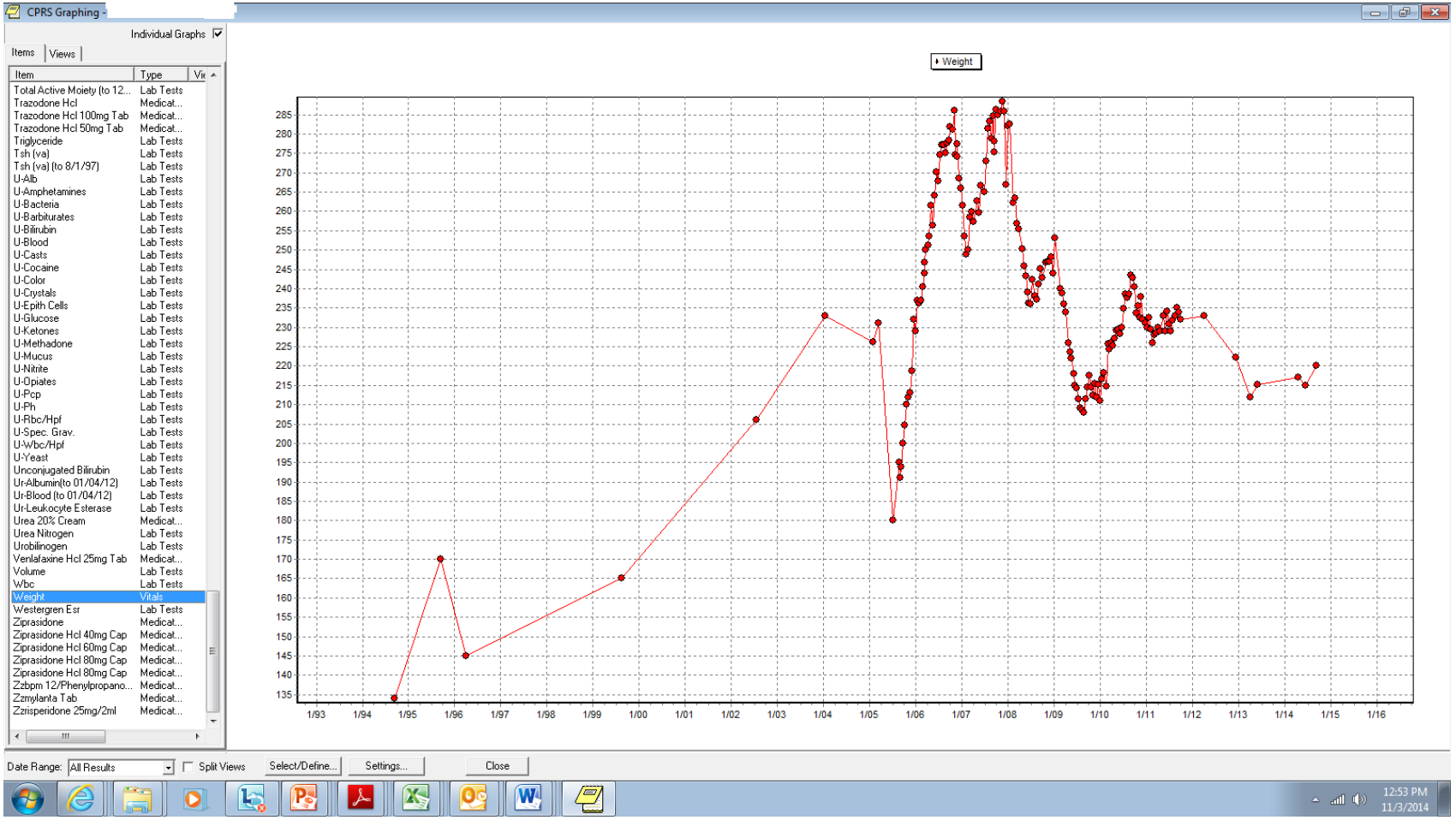
Precision Medicine:
Million Veteran Program (MVP)

- MVP aims to create a longitudinal cohort of 2,000,000 veterans at >100 VA sites.
  - >650,000 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

THE UNIVERSITY OF ARIZONA

Precision Medicine:

Identifying High-risk Individuals (Extreme Phenotypes) for Genetic Studies in EMR Databases



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
- Results from EA populations cannot be fully generalized to non-EA populations. More studies of non-EA needed.
  - Multi-ancestry analyses likely to facilitate gene finding due to their greater variation
- 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