STANLEY CENTER
FOR PSYCHIATRIC RESEARCH
AT BROAD INSTITUTE

The Long View: Gene Targeting for Complex Circuit Disorders

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Statement of interests

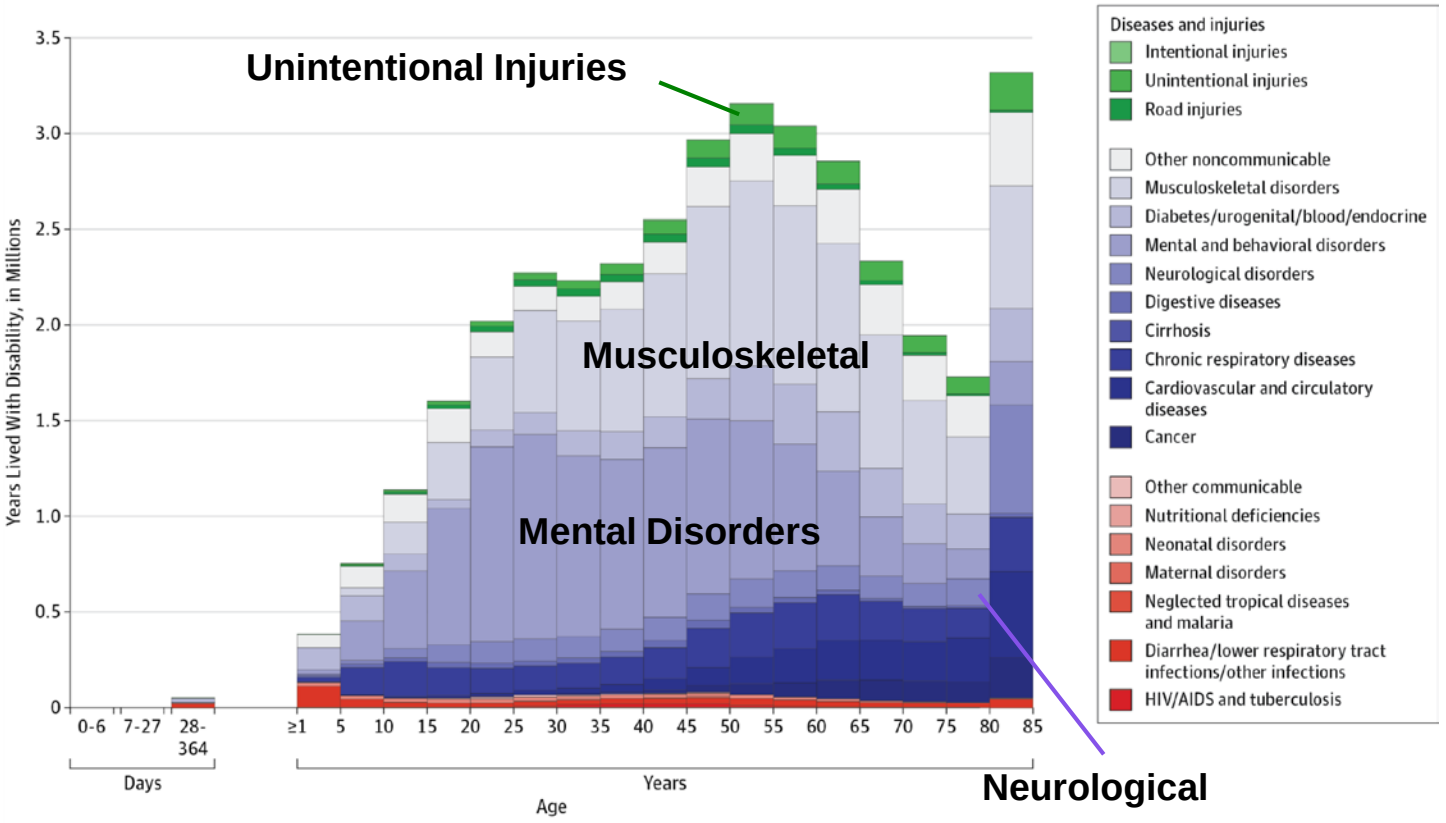
Industry

- Director, Voyager Therapeutics
- Director, Q-State Biosciences
- Scientific Advisory Board, Janssen
- Scientific Advisory Board, BlackThorn
- Scientific Advisory Board, F-Prime Capital

Relevant Nonprofit

- Director (Board Chair) Charles A Dana Foundation
- SAB (Co-chair) One Mind for Research

Neuropsychiatric disorders are the common, chronic, disabling diseases of the young



Burden of Diseases, Injuries, and Risk Factors, U.S.1990-2010:

Years lived with *disability* by age and disease class

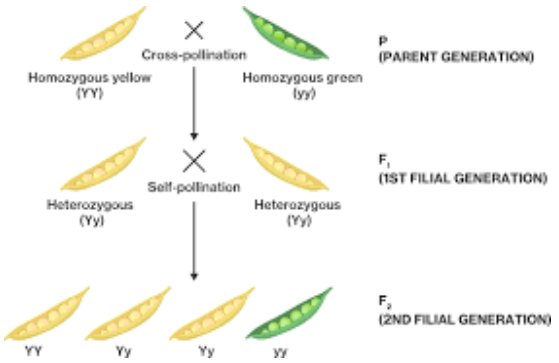
Source: JAMA 2013 doi:10.1001/jama2013.13805

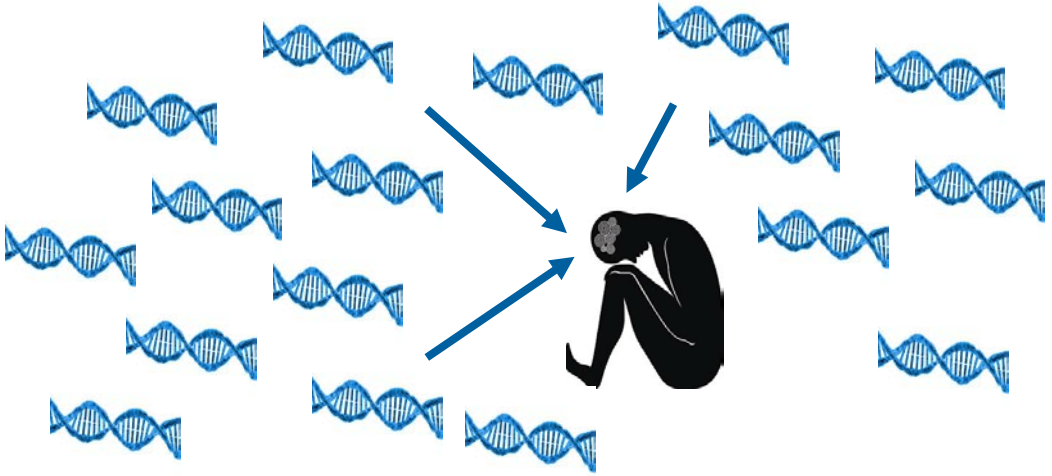
What genes shall we target?

Despite the high heritabilities of common neuropsychiatric disorders, therapeutic targets are not easy to identify

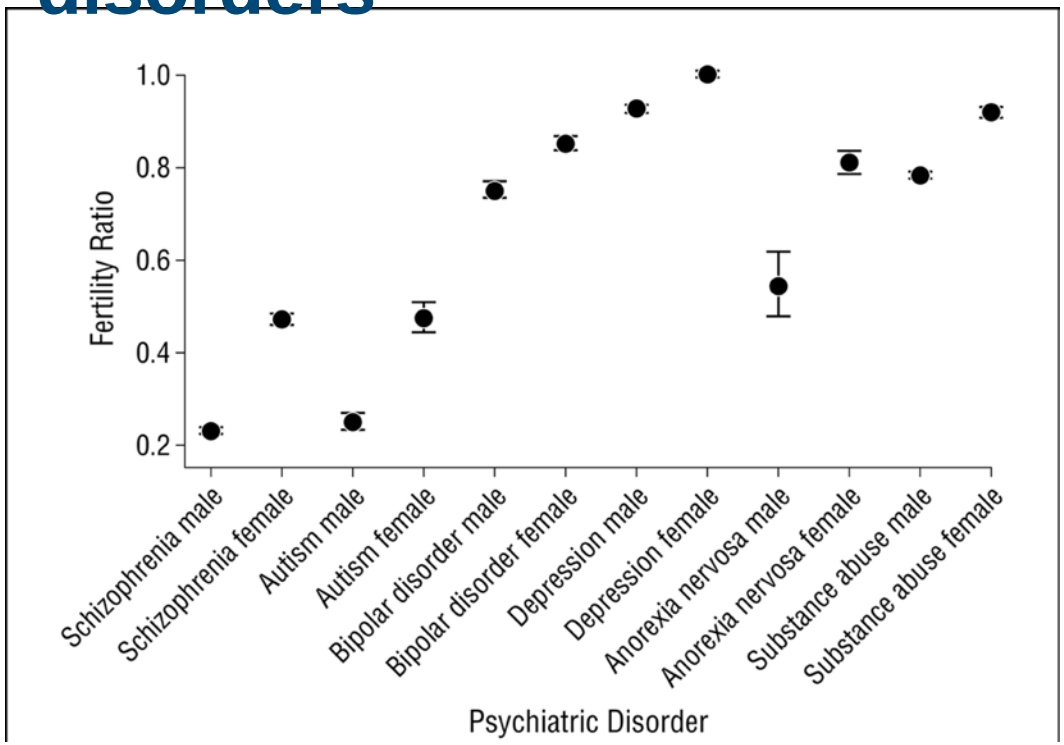
Disorder	λ	Heritability (h^2)
Autism Spectrum	25	0.8
Schizophrenia	9	0.8
Bipolar Disorder	8	0.7-0.8
Major Depression	2-5	0.35

Our brains are not like Mendel's peas; most relevant phenotypes result from myriad small genetic nudges rather than a large genetic shove





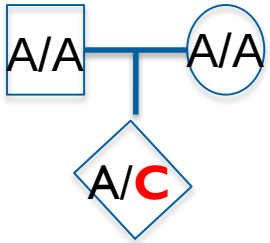
Reproductive fitness gives insight into low penetrance of risk alleles for early onset disorders



Fertility ratios by disorder and gender.
A fertility ratio of 1 = that of the general population.

Ramifications:

- Common and Rare Variants can readily be transmitter at very low effect sizes (OR < 1.1)
- Large effect alleles occur *de novo* (i.e., no opportunity yet for natural selection to act), but very rarely transmitted

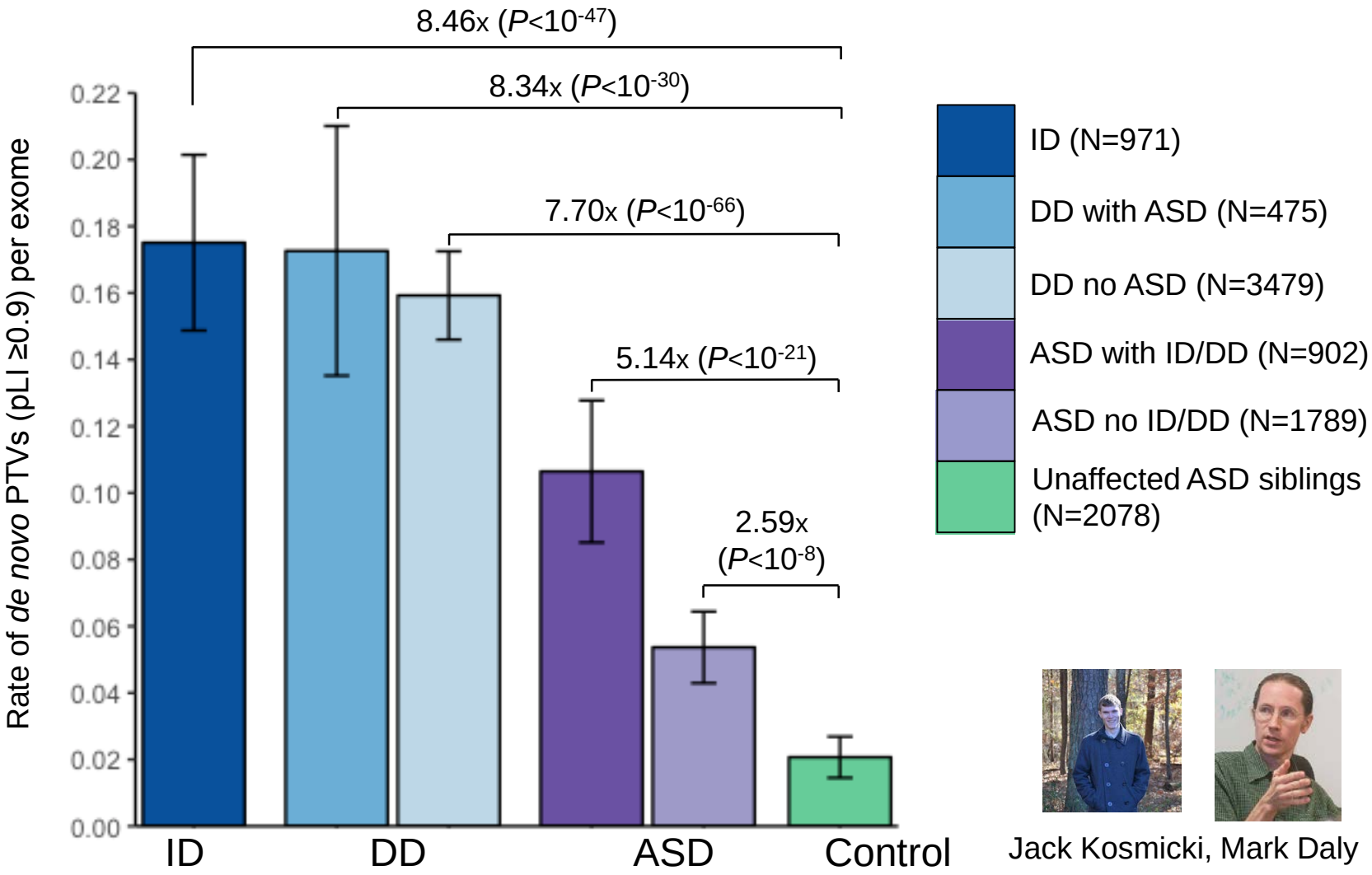


Power et al. JAMA Psychiatry. 2013;70(1):22-30.

Source: Mark Daly, Ben Neale

De novo protein truncating variants (PTV) burden by ascertainment

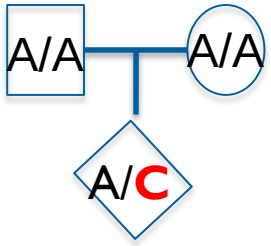
ID/DD strongest irrespective of ASD status
ASD with ID/DD more PTVs than without ID/DD
ASD without ID/DD significant, but at same rate as ADHD and other diagnoses



Jack Kosmicki, Mark Daly

Possible playbook for *de novo* mutations—not suspected prenatally

- Somatic cell (brain) repair of severe neurodevelopmental disorders due to penetrant *de novo* mutations: possible strategy
  - Disease models such as Rett (mouse and macaque) and Shank3 (macaque) can be evaluated for translational relevance
  - **Key experiments: timing and efficacy of postnatal rescue**
  - Then consider development of brain gene therapy (e.g., replacement, editing)

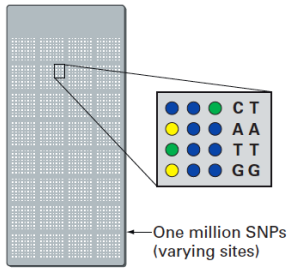


Rett mouse

Schizophrenia is a polygenic trait: PGC wave 3 schizophrenia GWAS

65,205 cases and 87,919 controls

256 genome wide significant loci



Average OR=1.08


Stephan Ripke


Mick O'Donovan


Mark Daly

Source Stephan Ripke; unpublishe

Schema Consortium: Rare transmitted exome variants associated with schizophrenia have modest effect sizes

25,033 cases / 51,507 controls yield only two genes with exome-wide levels of significance

TJ Singh

Mark Daly

TRIO

Affects dendritic branching

Component of histone methyltransferase

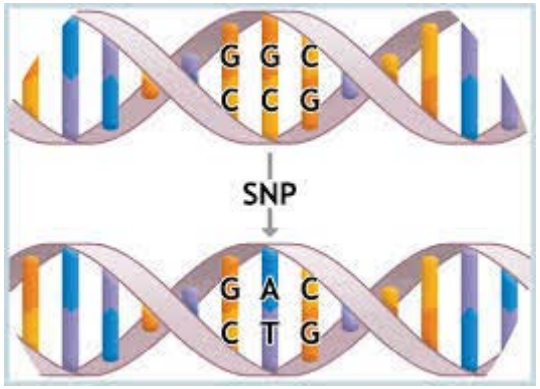
SETD1A

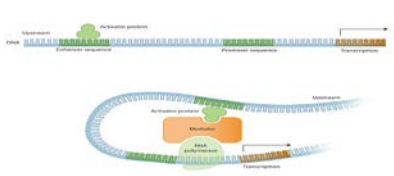
GRIN2A

NMDA receptor subunit 2A

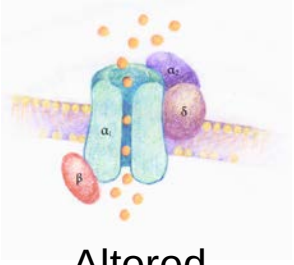
The challenges for gene targeting in common neuropsychiatric and cognitive phenotypes

- Extreme polygenicity, phenotypic heterogeneity
- For common early-onset disorders, risk alleles are of low penetrance.
  - Later onset (e.g., AD) have a few more penetrant alleles (e.g., APOE ε4)
- Pleiotropy
- Limitations of preclinical models
- *Timing*: Does development 'lock in' some neural phenotypes?





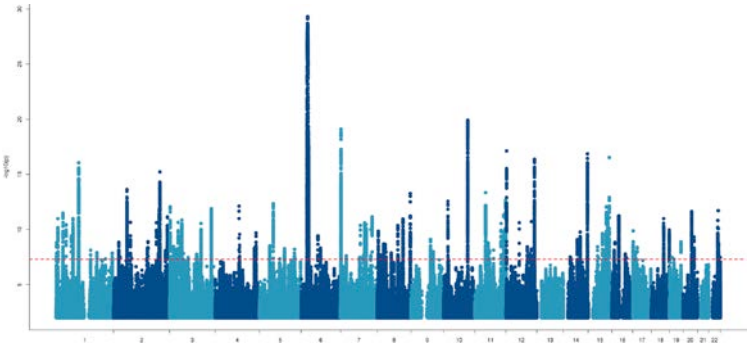
Altered gene expression



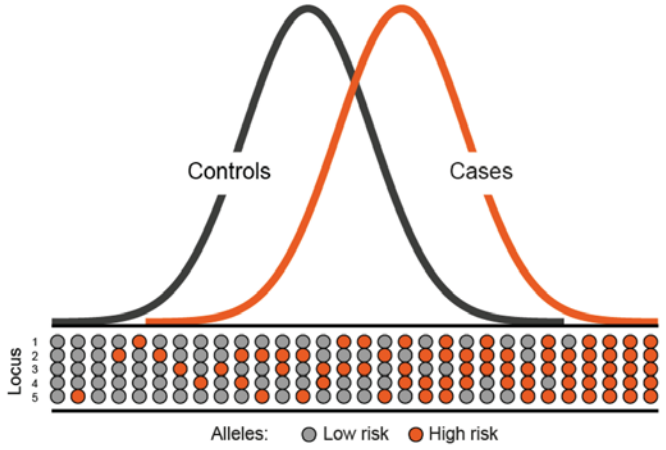
Altered RNA/protein

Aggregate signals: Polygenic Risk Scores (PRS)

- Basis: largest GWAS meta-analysis *appropriate for person's ethnicity*
- For each individual, calculate weighted sum (based on effect size) of risk alleles across the whole genome.
- PRS can stratify subjects by severity of genetic loading
- PRS permits identification of shared common variant risk across phenotypes

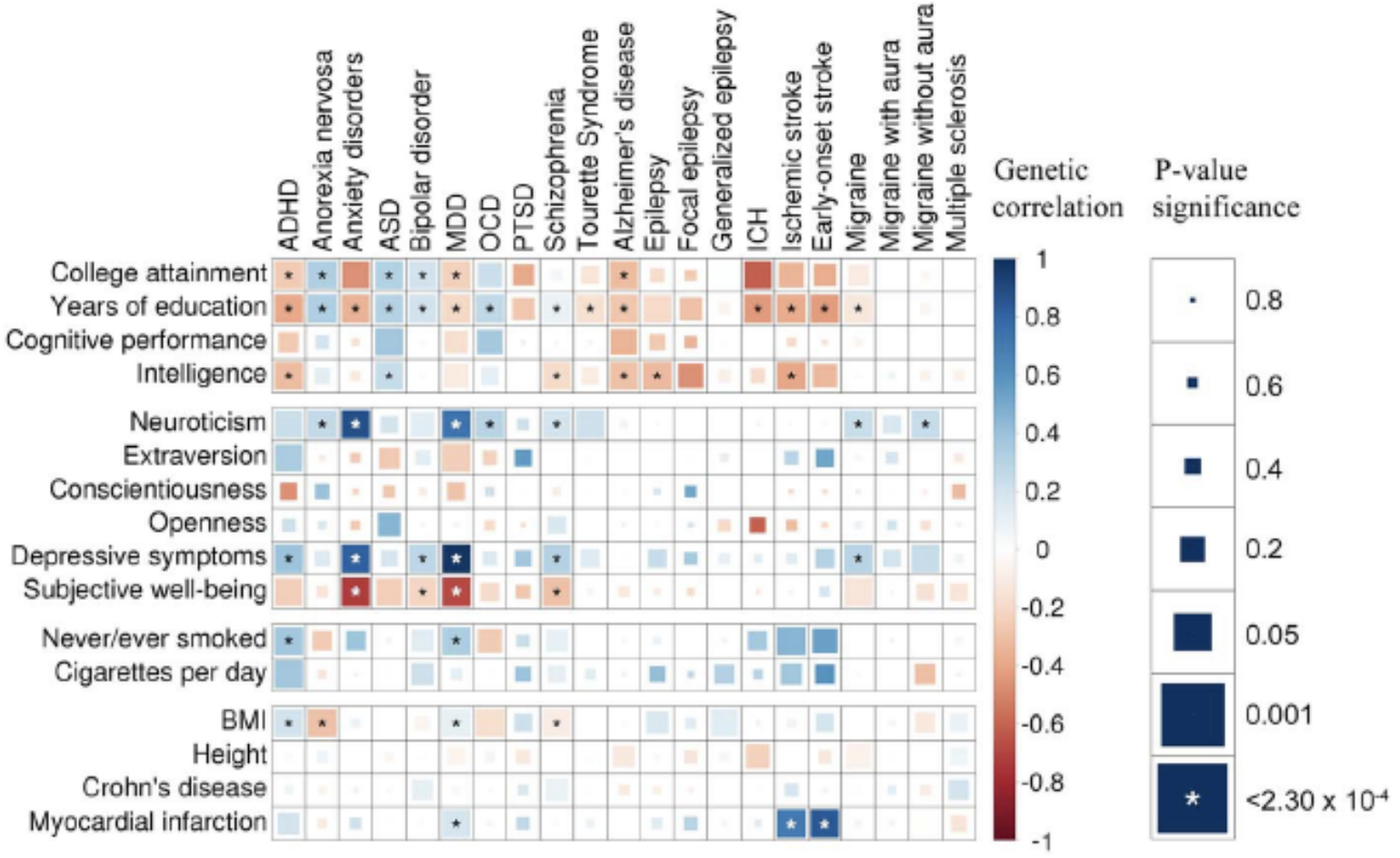


PRS: $\Sigma\beta_i * g_i$



Pleiotropy: Common variant genetic correlations across neural phenotypes:

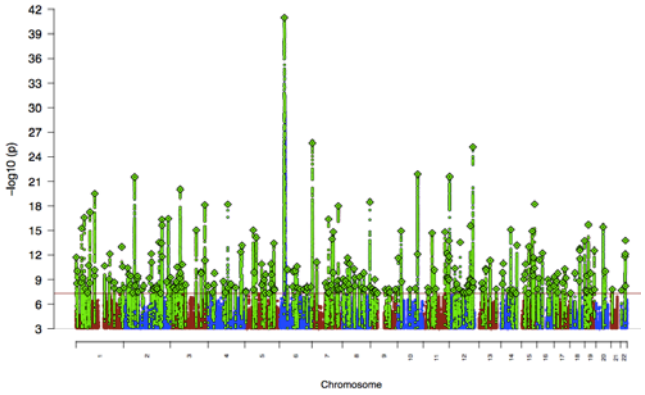
ASD risk is associated with higher IQ and EA

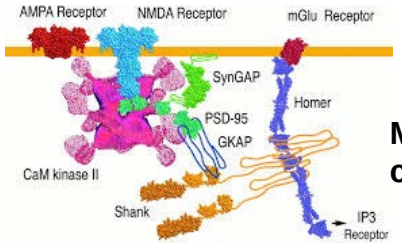


Source: Brainstorm Consortium Science **360**, 2018

Biological interpretation of polygenic risk:

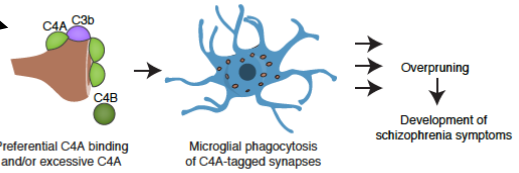
Hypothesis of convergence on a smaller number of cell types, molecular pathways, biological mechanisms





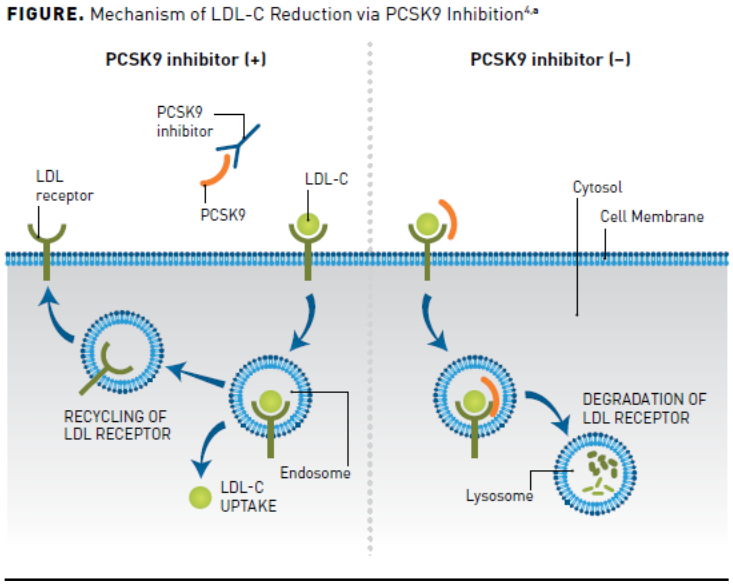
Molecular complexes

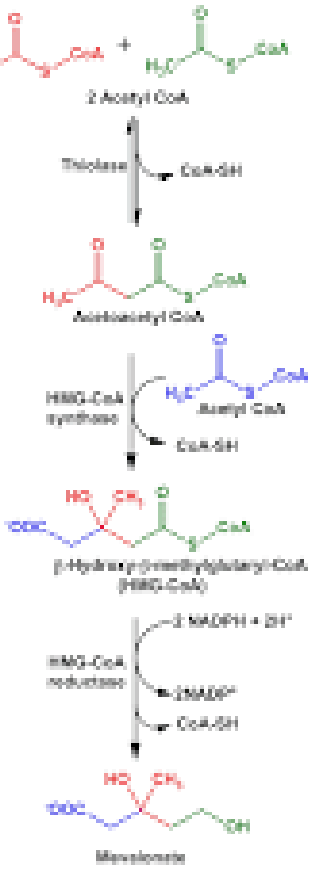
Biological processes



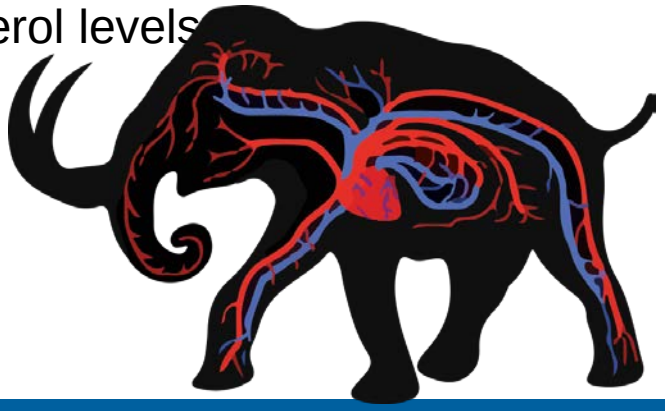
Cell types

We can be lucky—or we will have to get better at multiplexing





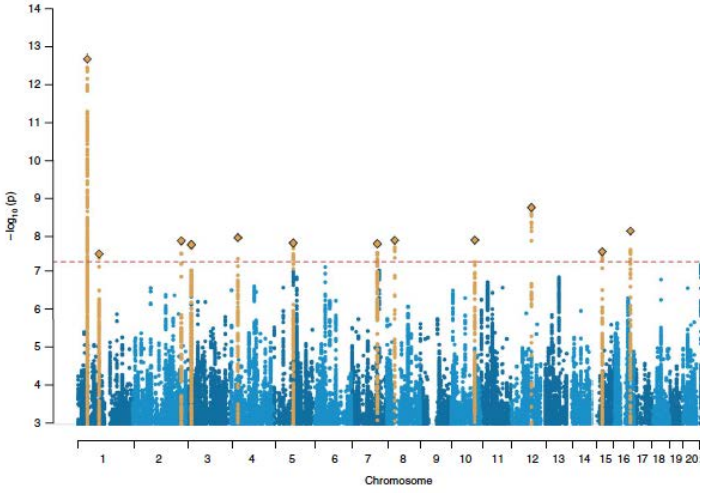
Single targets can emerge from analysis of pathways: HMG-CoA and PCSK9 for LDL cholesterol levels



https://reviverestore.org/projects/woolly-mammoth/progress-to-date/

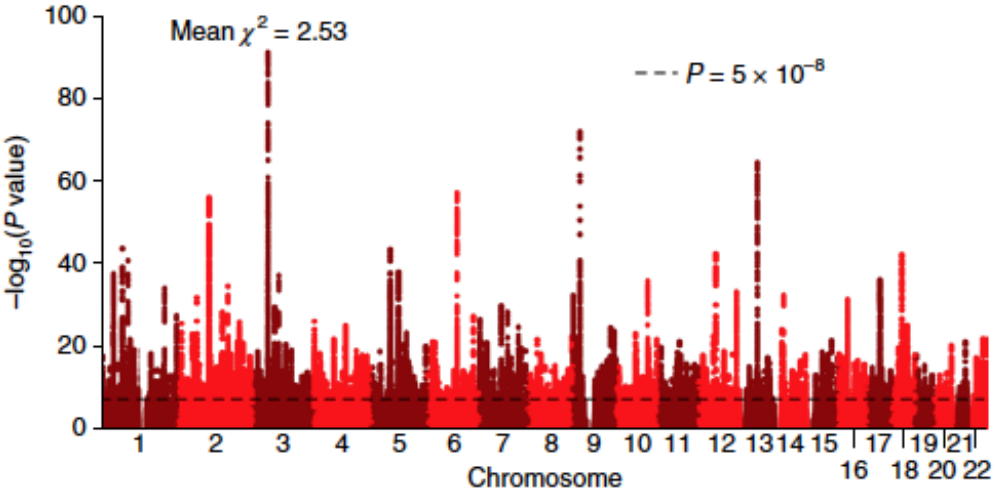
GWAS results for cognitive and behavioral phenotypes

Manhattan plot: meta-analysis of GWAS for ADHD



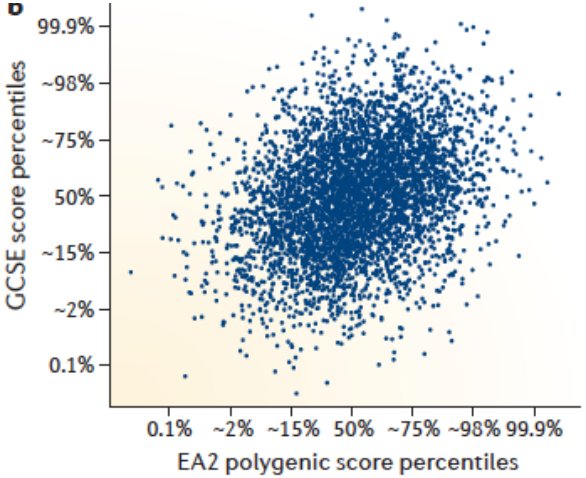
Source: Demontis et al. *Nat. Genet*. 2019

Manhattan plot: GWAS for Educational attainment (1.1 million subjects)

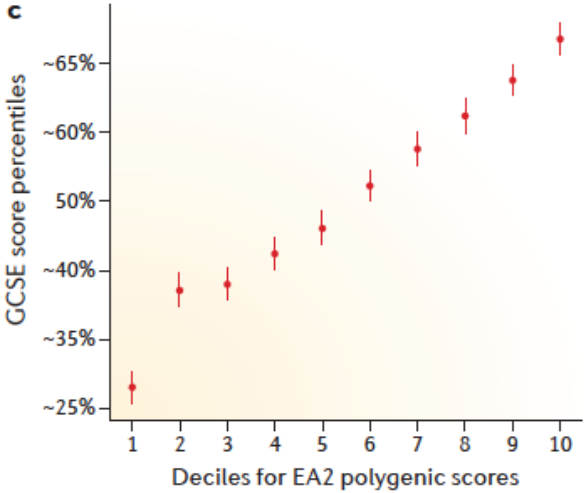


Lee et al. *Nature Genetics* 50:229-237, 2018

Educational attainment (EA2) polygenic scores Vs. UK-wide General Certificate of Secondary Education scores (Age 16)



Individual prediction is poor



Correlation of group averages when polygenic scores divided into deciles

Plomin & von Stumm *Nat Reviews Genet* 2018

Cognitive and behavioral phenotypes, including common disorders are quantitative

- Normal and disorder-associated traits and polygenic loading are normally distributed in populations (e.g., IQ, educational attainment, ADHD, ASDs, depression)
- This means that setting thresholds for diagnosis and treatment require a deliberative decision
- This also means that an intervention developed as treatment can be deployed for enhancement: yielding functional outcomes better than reversing pathology or better than species-typical
- For polygenic cognitive and behavioral phenotypes this has already produced suggestions of embryo selection in IVF
- For traits that emerge in childhood, this raises important questions for society as well as for regulators and practitioners about multiplex gene therapy postnatally and genomic engineering of embryos.

The Stanley Center Community

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Funding
Stanley Foundation
Kent and Liz Dauten
Ray Dalio Foundation
NIMH
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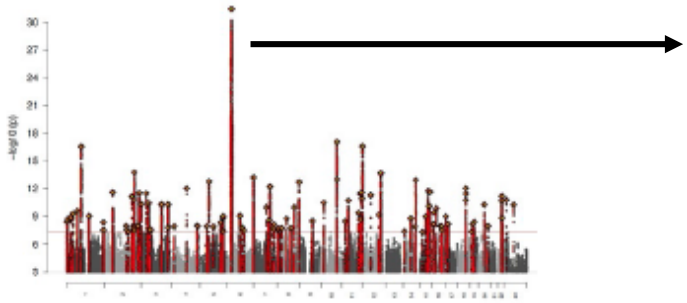
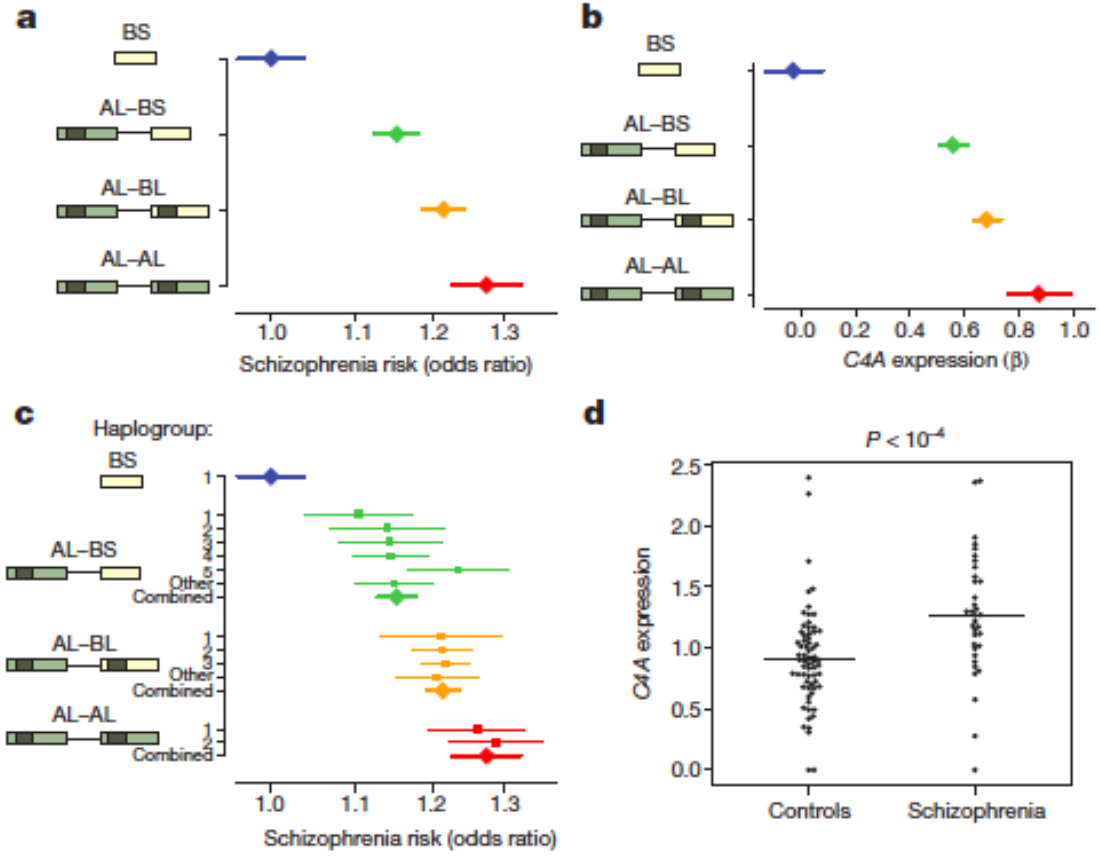
Alleles of *C4* shape schizophrenia risk in proportion to their effects on expression of *C4A protein*



MHC locus; fine mapping implicates Complement Factor 4A (C4A)



Steve McCarroll Beth Stevens

Sekar et al. Nature 2016