



NORMENT

Norwegian Centre for
Mental Disorders Research



Analysis of genome-wide association studies uncovers genetic loci shared between schizophrenia and cognitive traits

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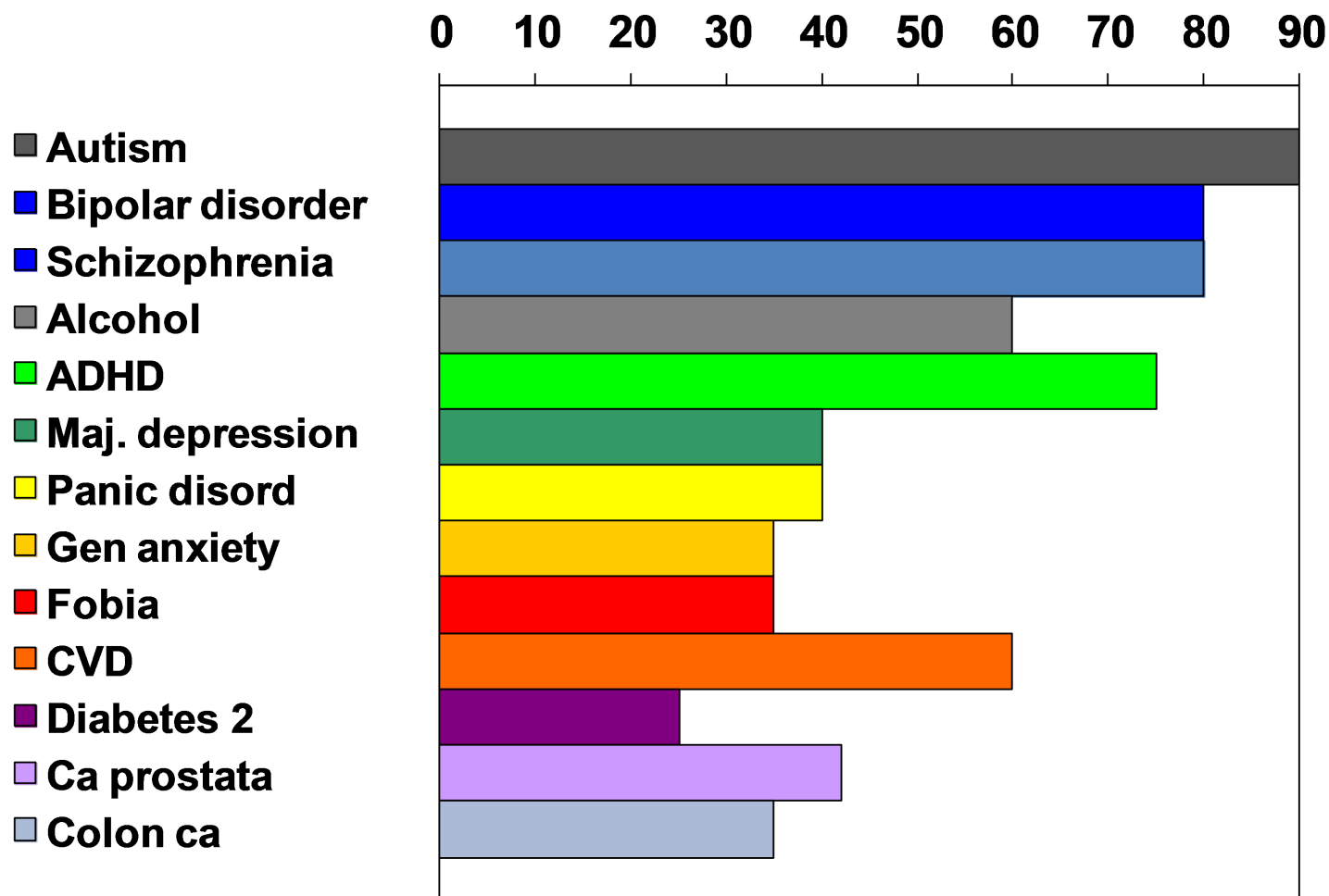
No conflicts of interests to declare

Outline

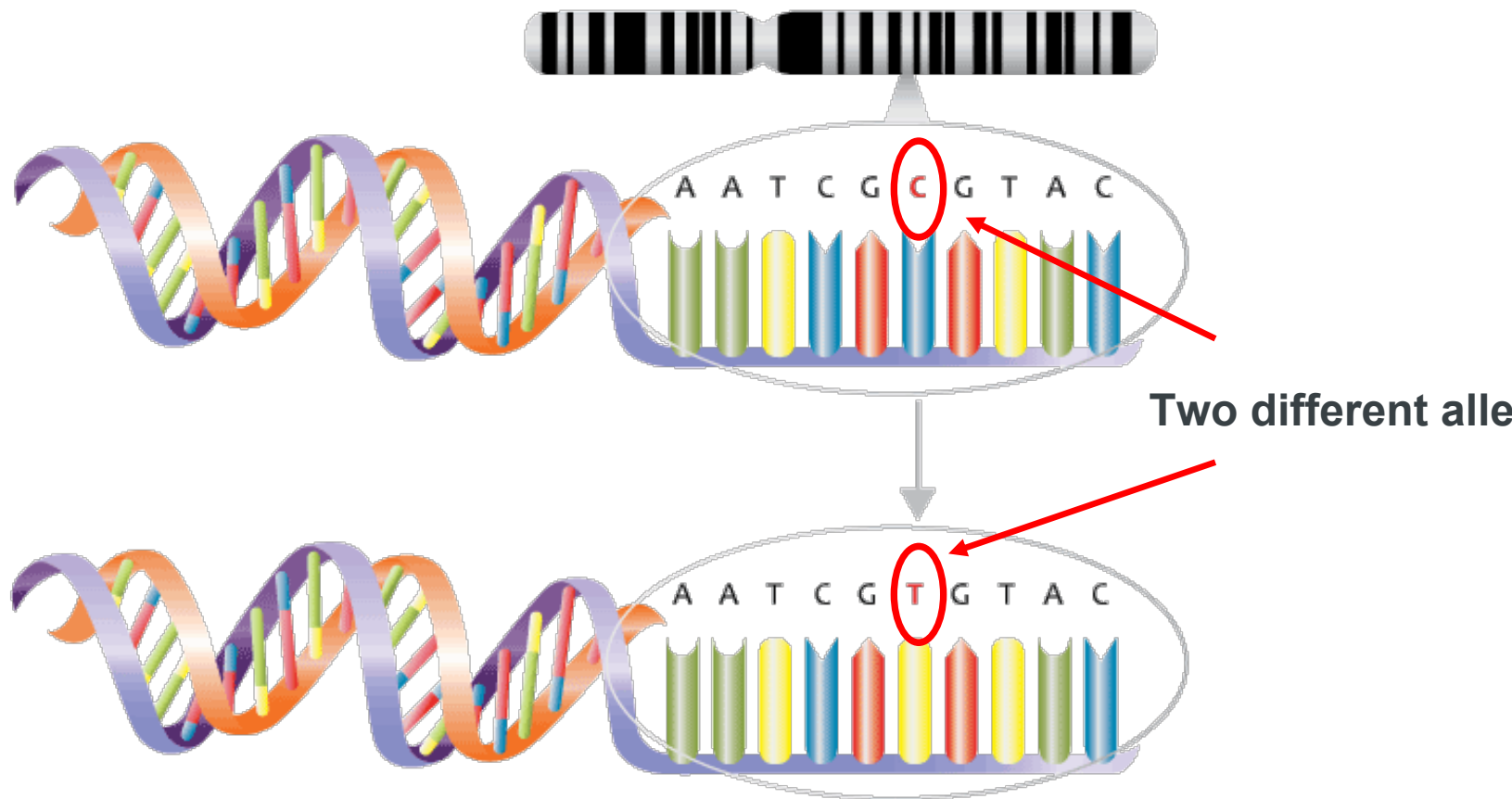
1. Improving GWAS power using Bayesian statistical tools
 1. Standard GWAS statistical approach
 2. All SNPs are not created equal
 3. The conditional false discovery rate (FDR) approach
2. Identification of genetic loci shared between schizophrenia and cognitive traits using conditional FDR

Heritability

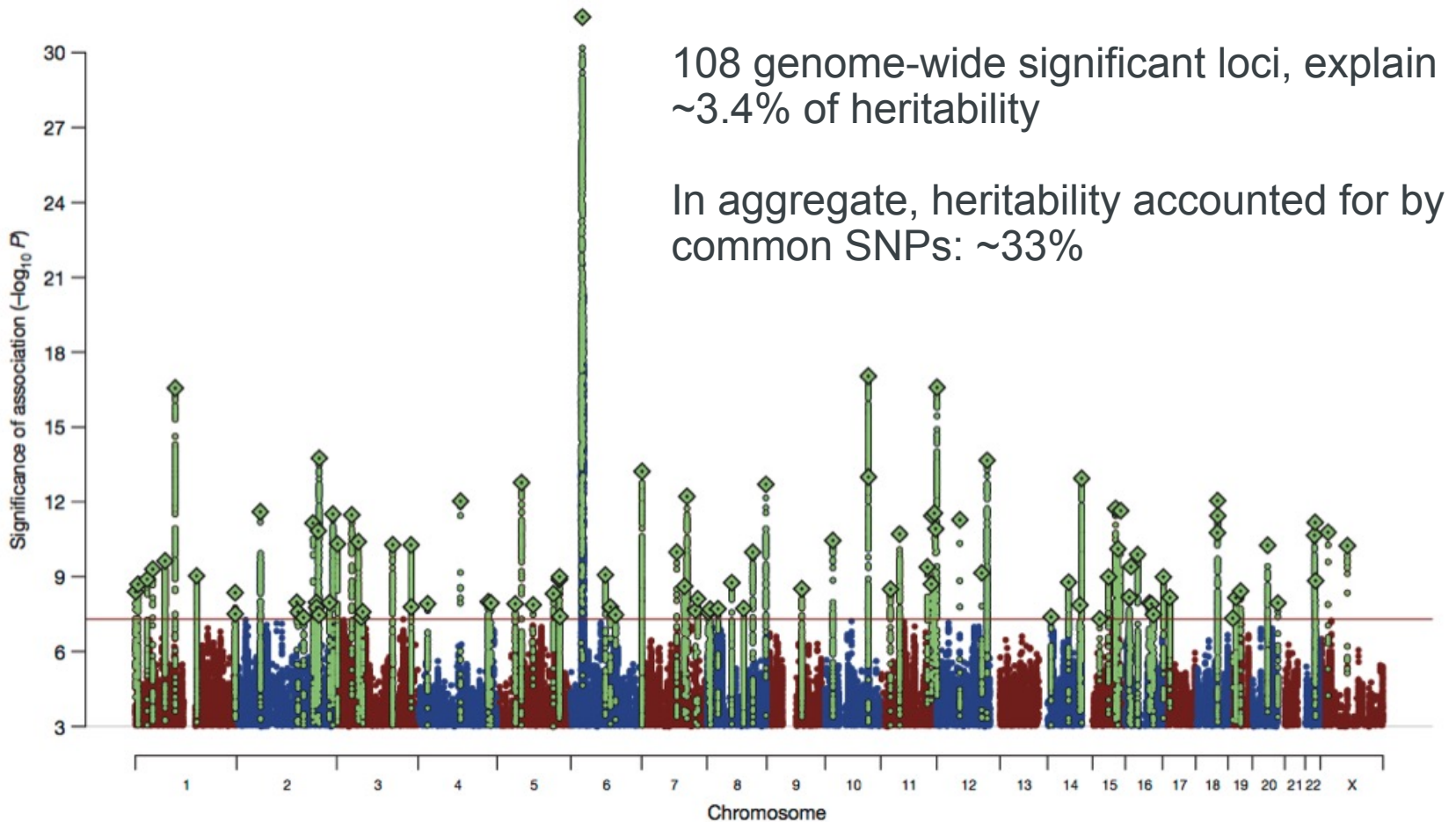
Heritability = Proportion of risk explained by genetic factors (twin/family studies)



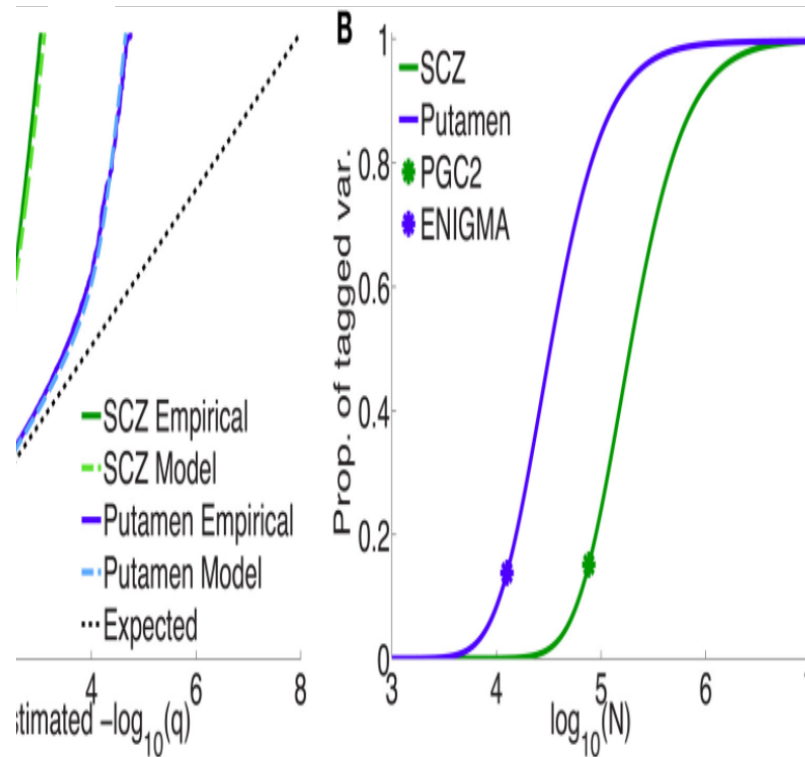
Single-nucleotide polymorphisms (SNPs)



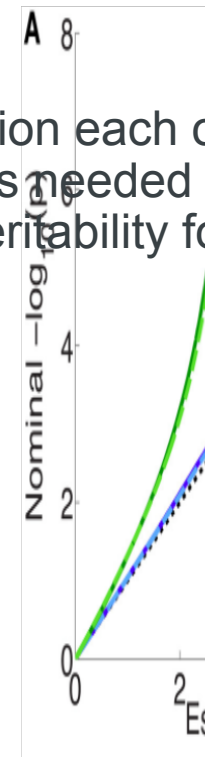
Genome-wide association study (GWAS) of schizophrenia (SCZ)



Large GWAS sample sizes required to uncover small 'polygenic' effects

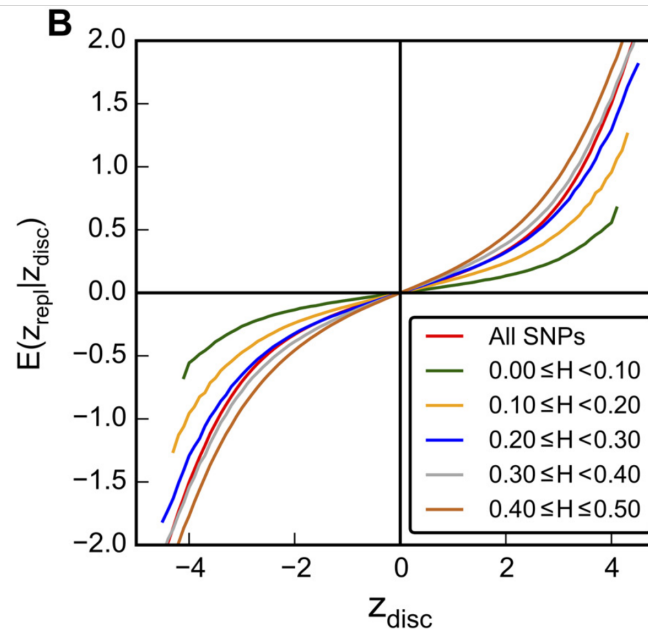
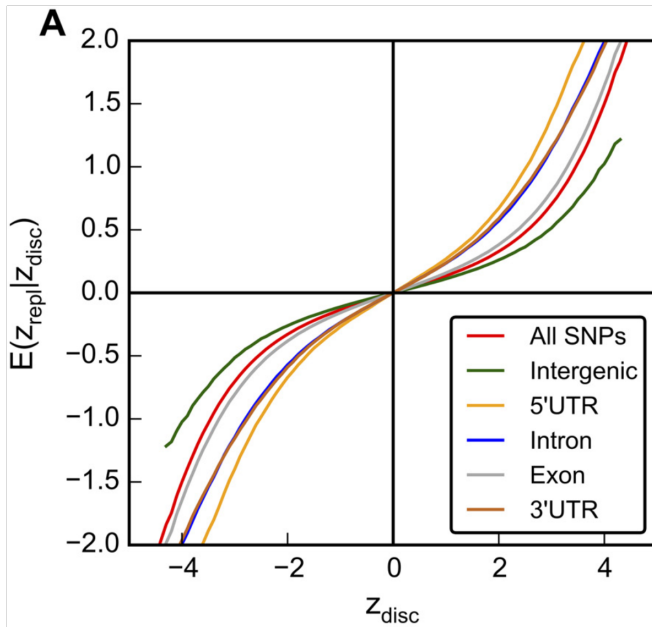


~ 0.5 million each of cases and controls needed to explain all chip heritability for SCZ



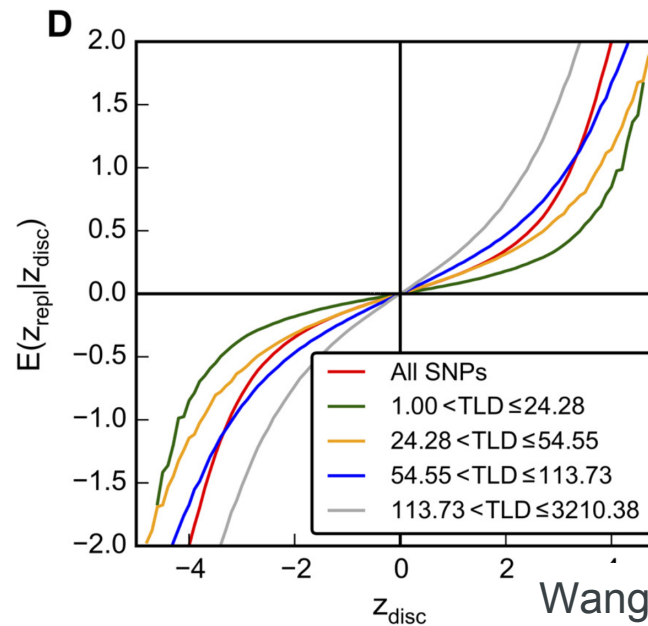
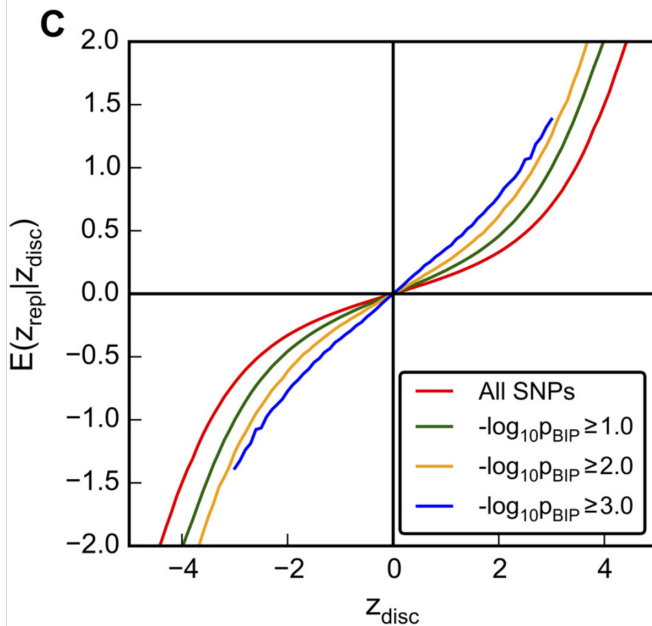
Holland et al 2016, Frontiers in Genetics

All SNPs are not created equal



Some loci are more likely to harbor true effects*

Not exploited by standard GWAS approach



*Literature

Hindorff et al 2011, PNAS

Maurano et al 2012, Science

Schork et al 2013, Plos Genetics

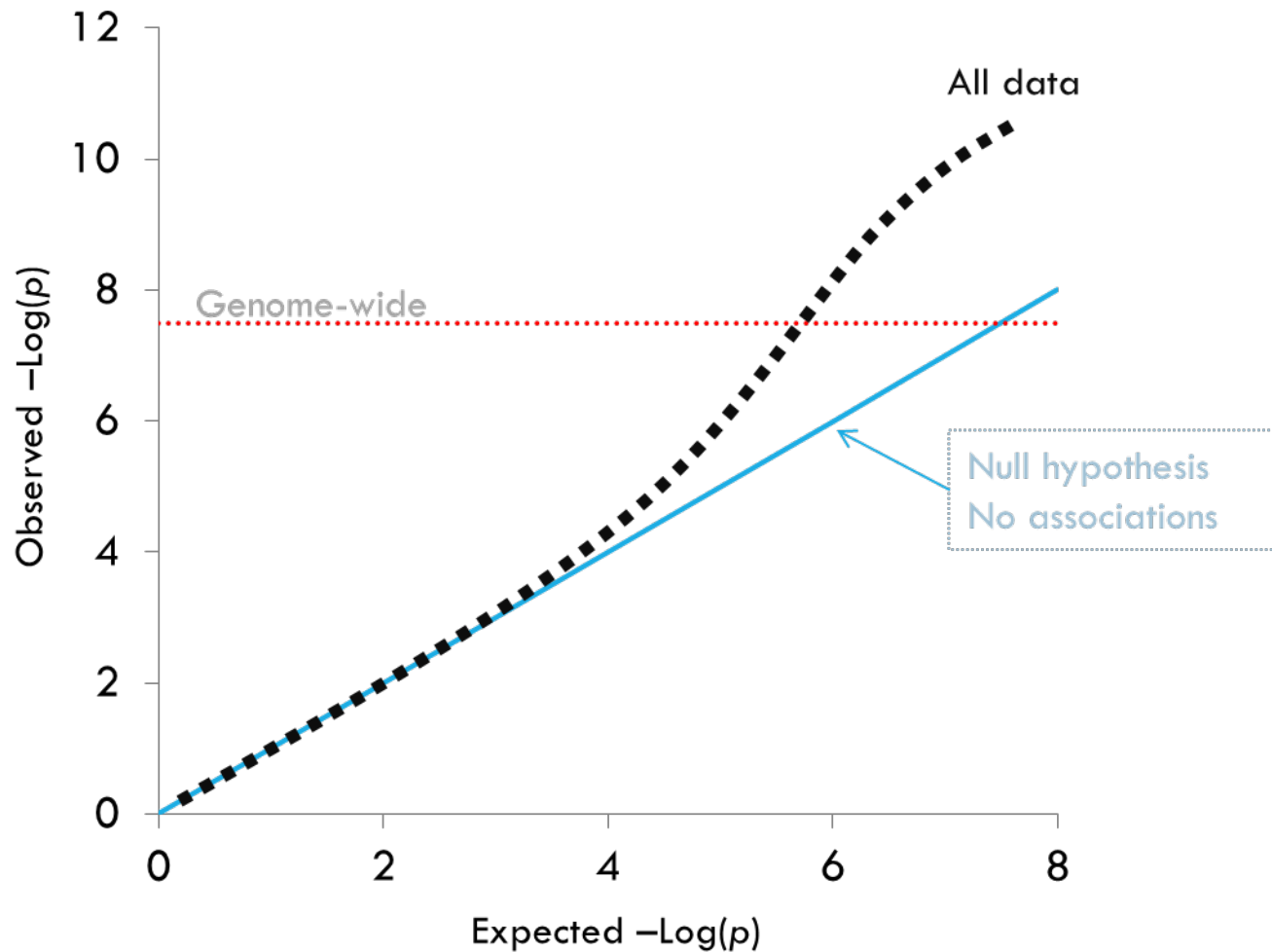
Finucane et al 2015, Nature Genetics

Sveinbjornsson et al 2016, Nature Genetics

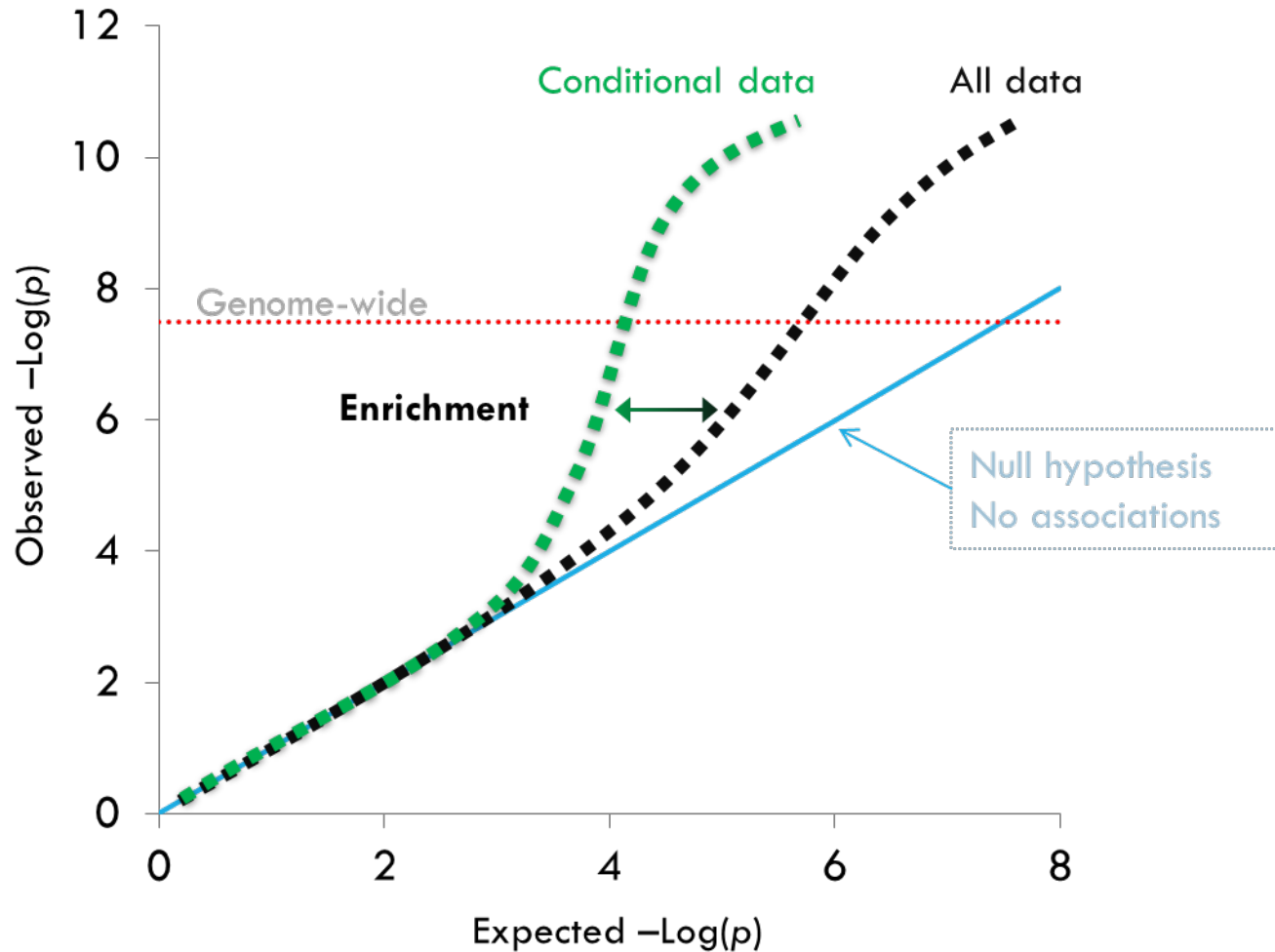
Nat Gen

Wang et al 2016, Plos Genetics

Conditional FDR – leveraging pleiotropic enrichment



Conditional FDR – leveraging pleiotropic enrichment



Schizophrenia and cognitive function – shared genetic basis?

- Unaffected relatives have cognitive impairments
- Heritabilities of SCZ and cognitive impairment covary
- PGRS for SCZ associated with worse cognitive performance, and vice versa
- Negative correlation between SCZ and cognitive traits using LD score regression

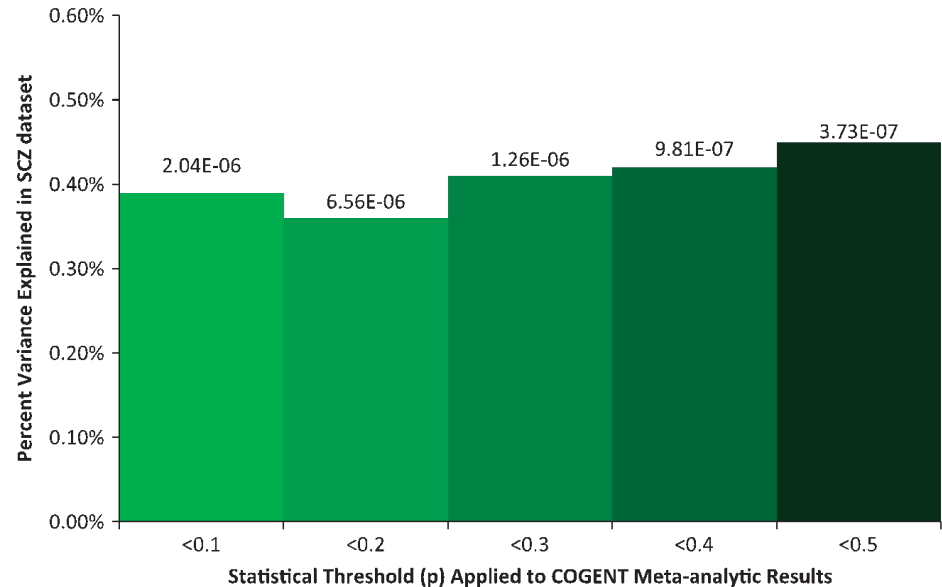


Figure 2. Polygenic overlap between cognitive allele scores (derived from the Cognitive Genomics consortium (COGENT) meta-analysis thresholded at varying P -values) and schizophrenia (SCZ) case-control status in the Molecular Genetics of Schizophrenia (MGS) European-American cohort.

Lencz et al 2014, *Mol Psychiatry*

Conditional FDR: SCZ vs Cognitive traits

GWAS summary data (p-values and z-scores)

SCZ: PGC, n=79,757, SCZ Working Group 2014

General cognitive function: CHARGE, n=53,949, Davies et al 2015, and COGENT, n=27,888, Trampush et al 2017

Verbal-numerical reasoning: UK Biobank, n=36,035, Davies et al 2016

Reaction time: UK Biobank 2016, n=111,483, Davies et al 2016

Memory: UK Biobank 2016, n=112,067, Davies et al 2016

Conditional Q-Q plots

Conditional FDR Manhattan plot: Test-statistics for COG re-ordered using SCZ GWAS

Loci shared between SCZ and cognitive traits at conjunctional cFDR < 0.05

Conclusions

All SNPs are not created equal

- Enrichment categories can be leveraged to increase discovery of genetic variants

Analysis of GWAS data on SCZ and cognitive traits using conditional FDR uncovered 21 overlapping loci. For 18 loci, SCZ risk alleles were associated with worse cognitive performance

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CHARGE

W David Hill

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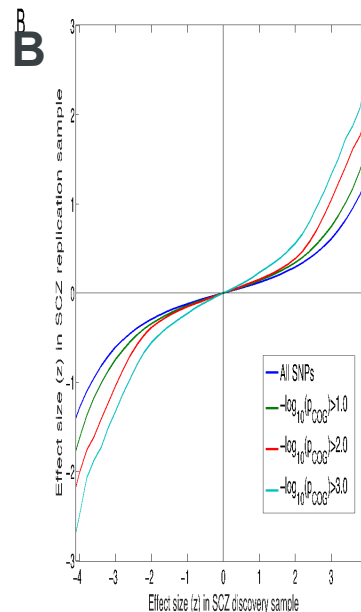
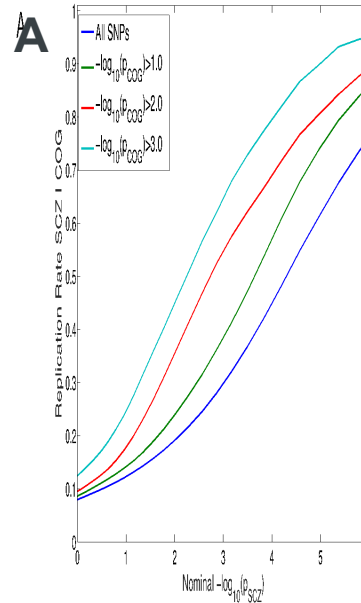
Replication plots

SCZ | General cognitive function

Individual cohorts contributing to the SCZ GWAS meta-analysis randomly distributed into discovery and replication groups across 500 permutations.

A) Rate of replication (SNPs with $p < 0.05$) assessed across 1000 discovery bins

B) Direct evaluation of the relationship of replication effect size of the discovery samples versus replication samples for each SNP



Mixture distribution GWAS

