

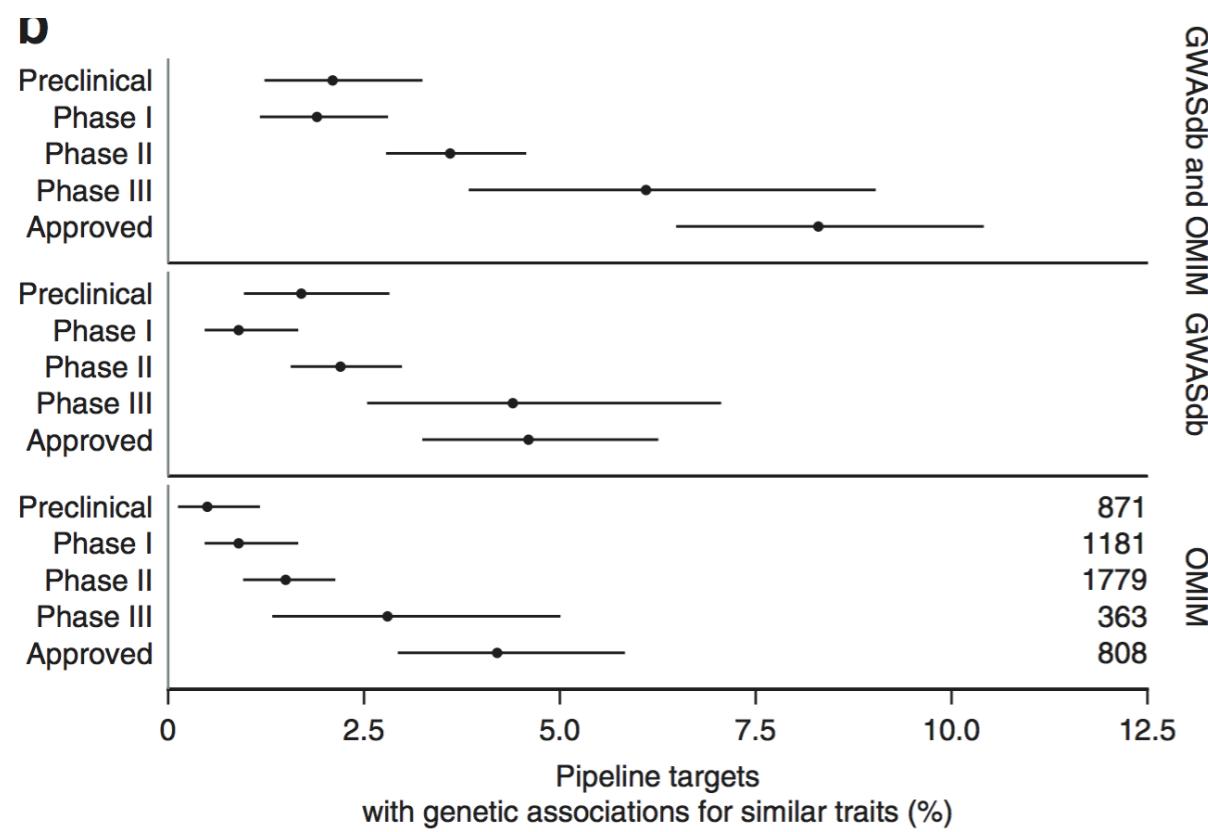
GENETICS OF SCHIZOPHRENIA

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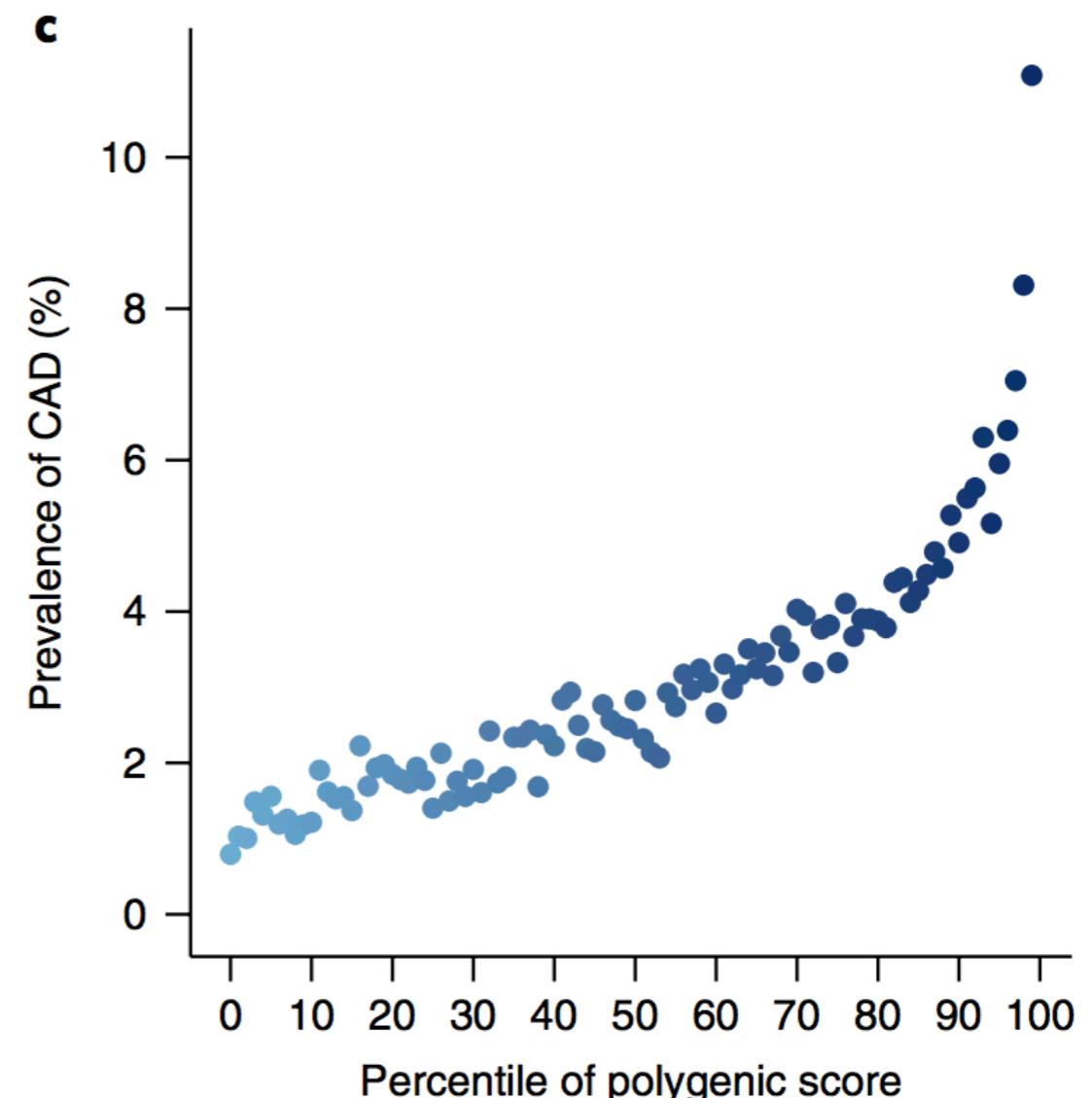
INTRO

THE POWER OF GENOMICS IN MEDICINE

Treatment



Prevention



INTRO

HERITABILITY



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INTRO

NOT EVERYTHING IS HERITABLE

Some things are genetic, but not heritable



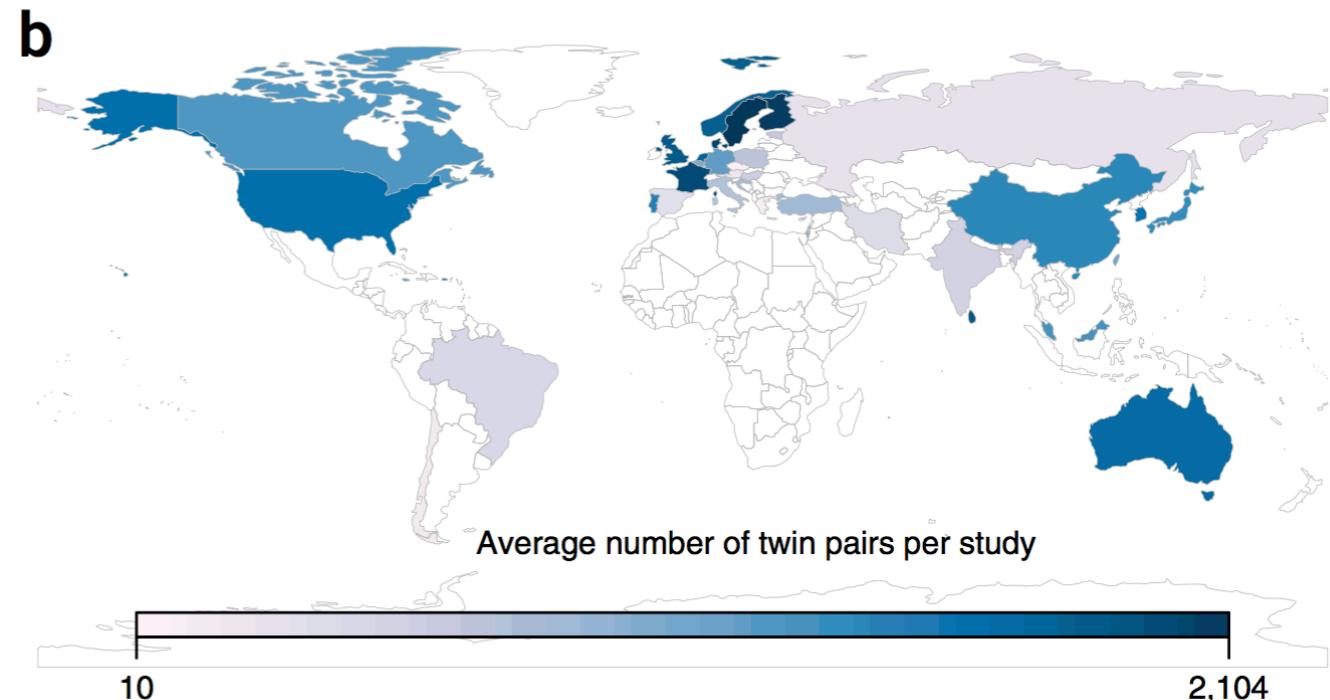
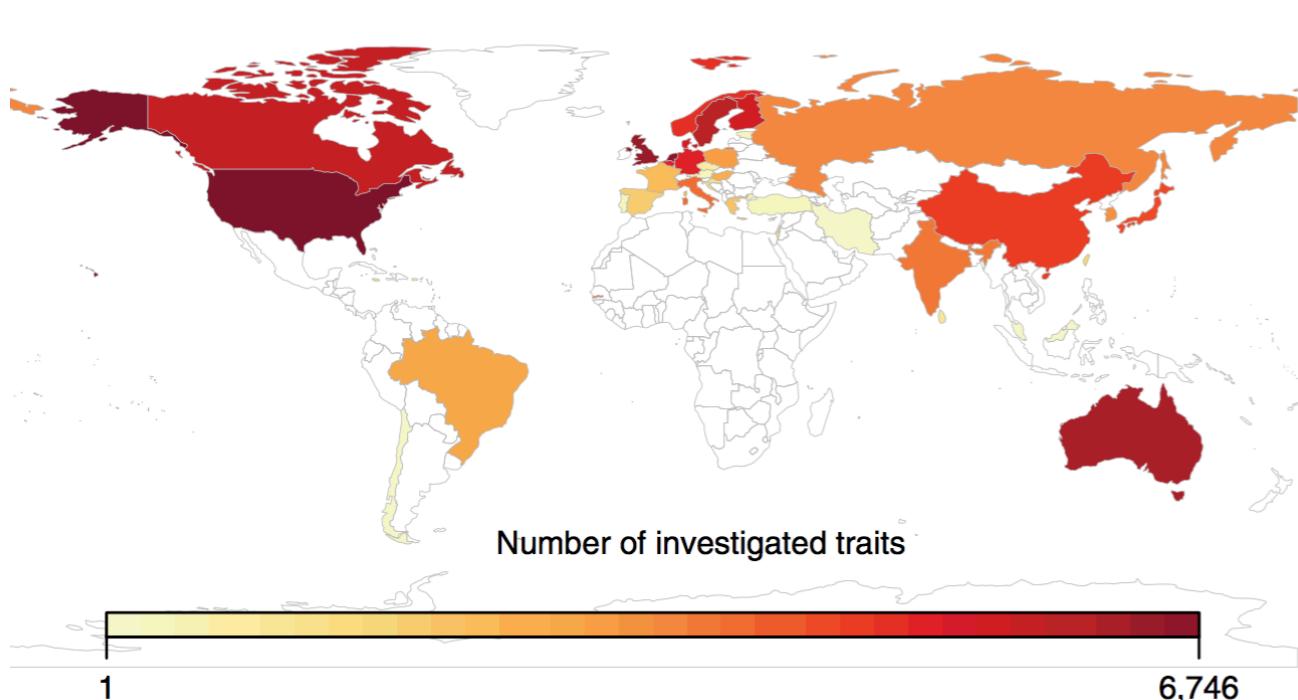
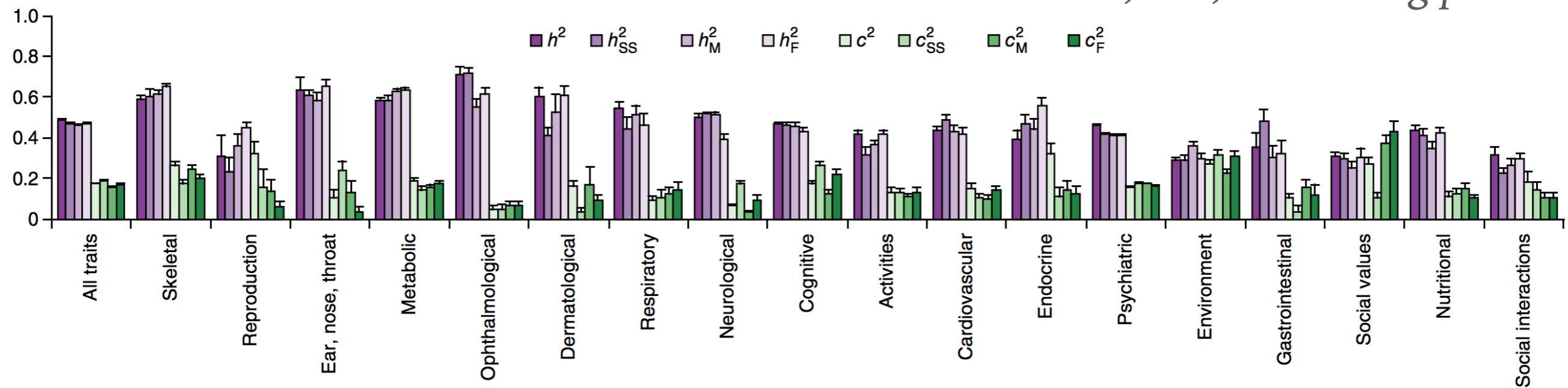
Some things are neither genetic, nor heritable (i.e., environmental)



INTRO

BUT A LOT OF THINGS ARE

$N = 2,247,128$ sibling pairs



INTRO

OVERVIEW

- Heritability of schizophrenia
- Gene discovery and biological mechanisms
- Genetic prediction
- Into the future

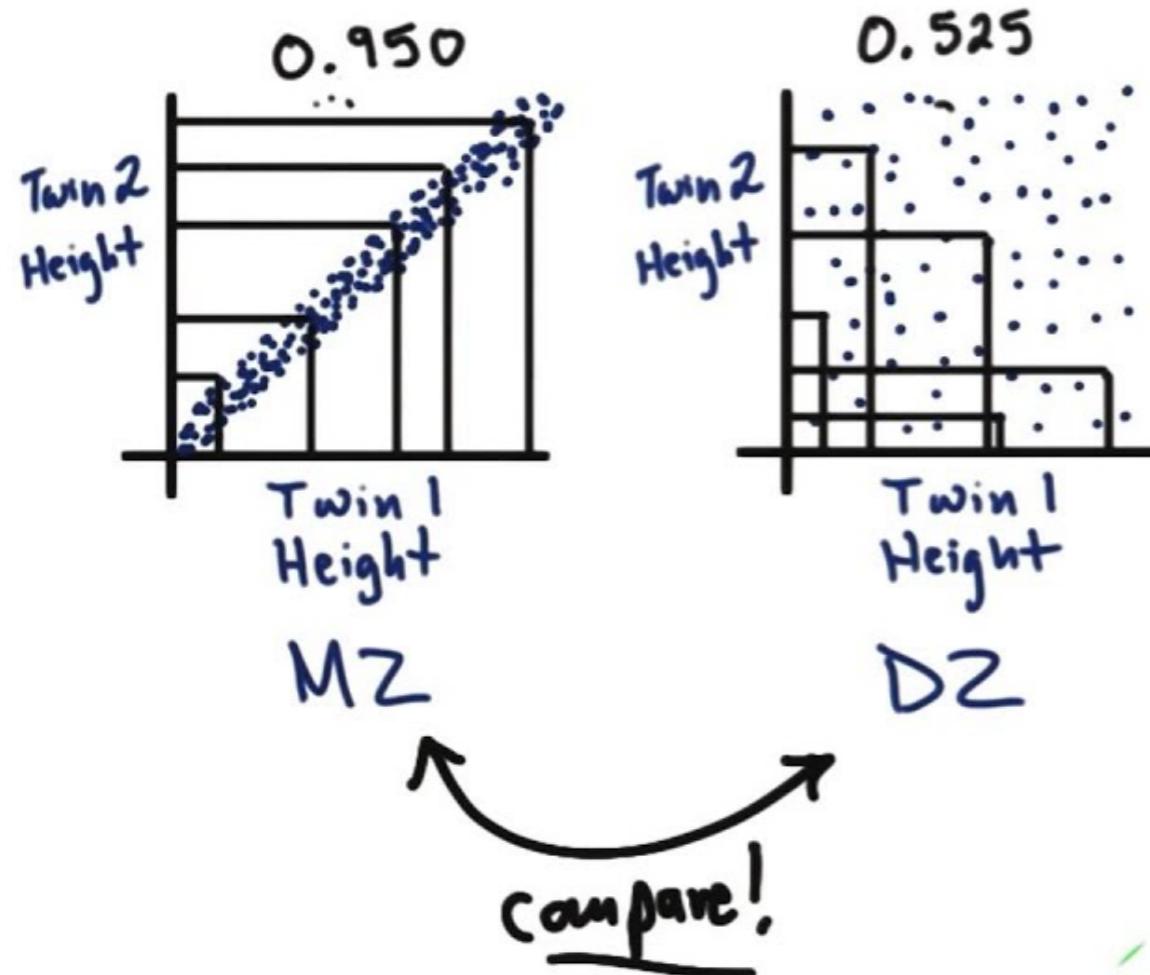
HERITABILITY

*How “genetic” is
schizophrenia?*

HERITABILITY

MEASURING HERITABILITY USING TWINS

Estimating Heritability



$$\begin{aligned}
 h^2 &= 2 \cdot (\text{MZ correlation} - \text{DZ correlation}) \\
 &= 2 \cdot (0.950 - 0.525) \\
 &= 2 \cdot (0.425)
 \end{aligned}$$

$$h^2 = 0.85$$

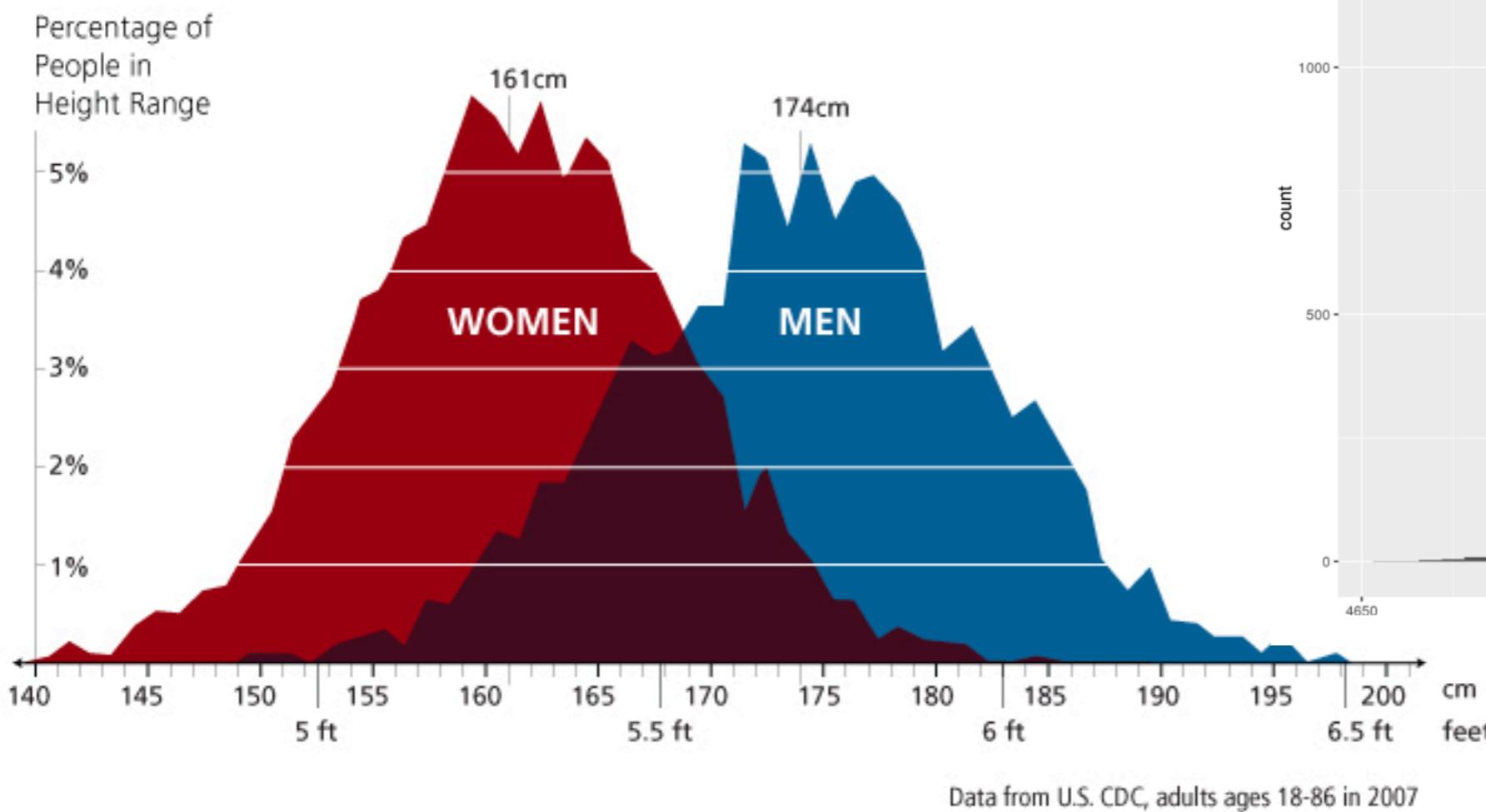
Which does this heritability indicate?

- Larger environmental influence
- Larger genetic influence

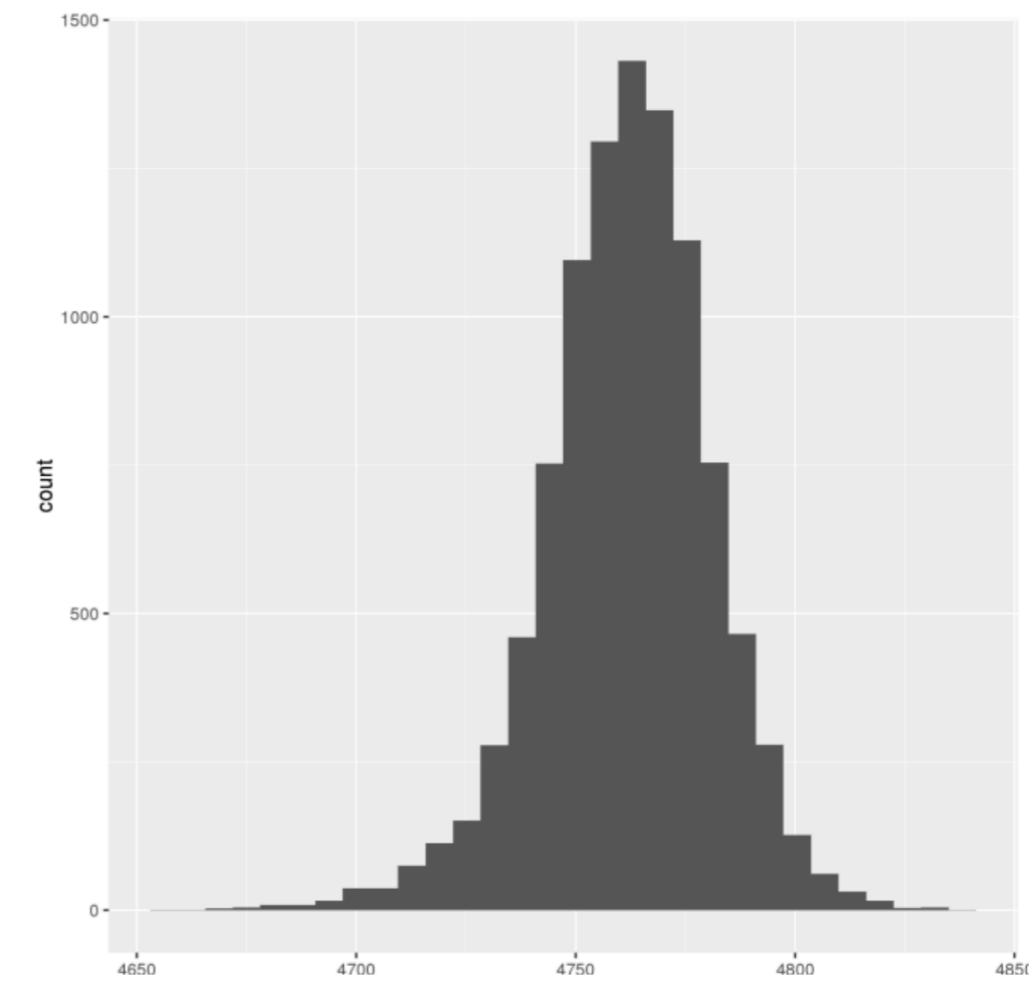
HERITABILITY

MEASURING HERITABILITY USING SNPs

Height in US Adults



Genetic variation related to height



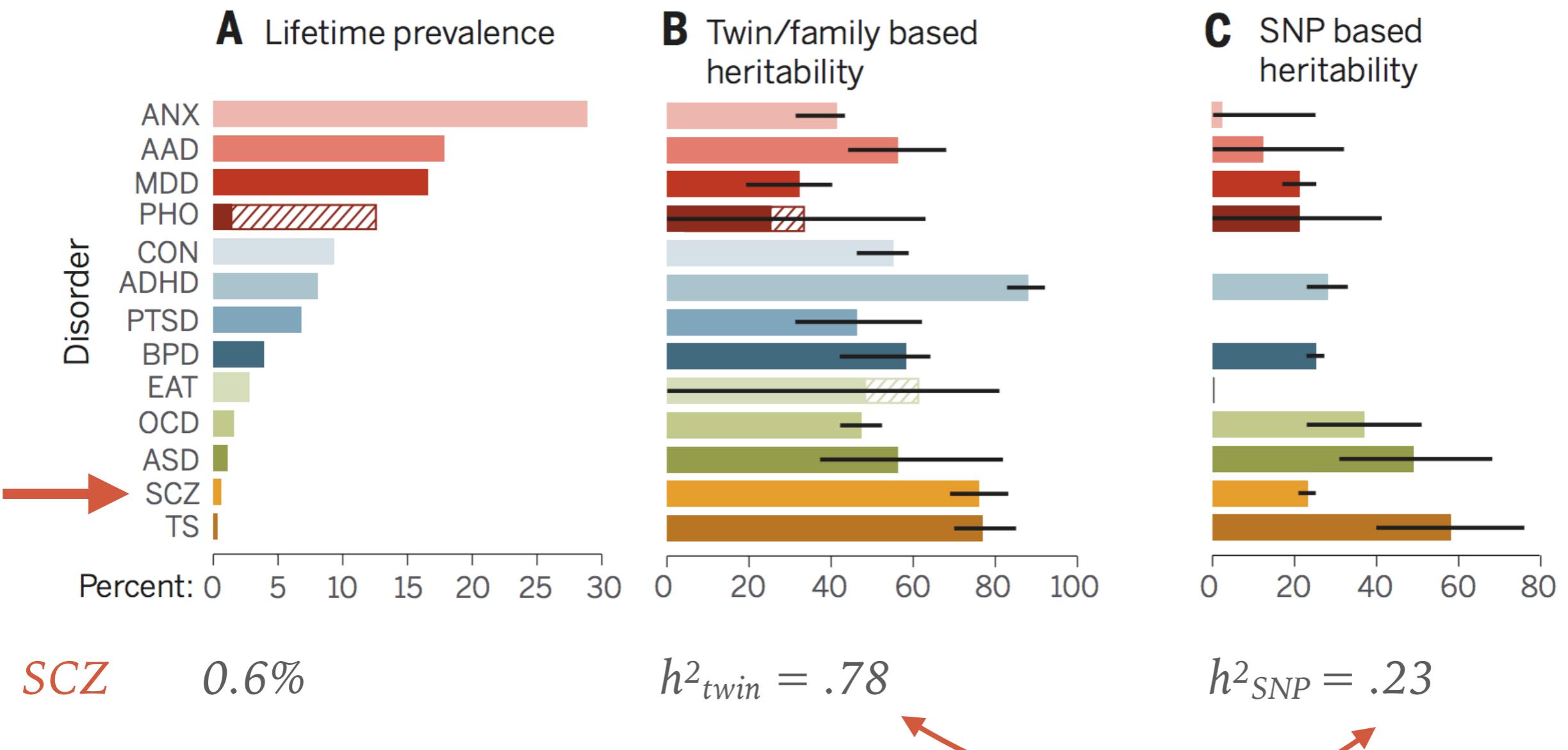
253,288 individuals
2.5 million SNPs

For more, see here: [http://www.nealelab.is/blog/2017/9/13/
heritability-201-types-of-heritability-and-how-we-estimate-it](http://www.nealelab.is/blog/2017/9/13/heritability-201-types-of-heritability-and-how-we-estimate-it)

Wood et al., 2014, *Nature Genetics*

HERITABILITY

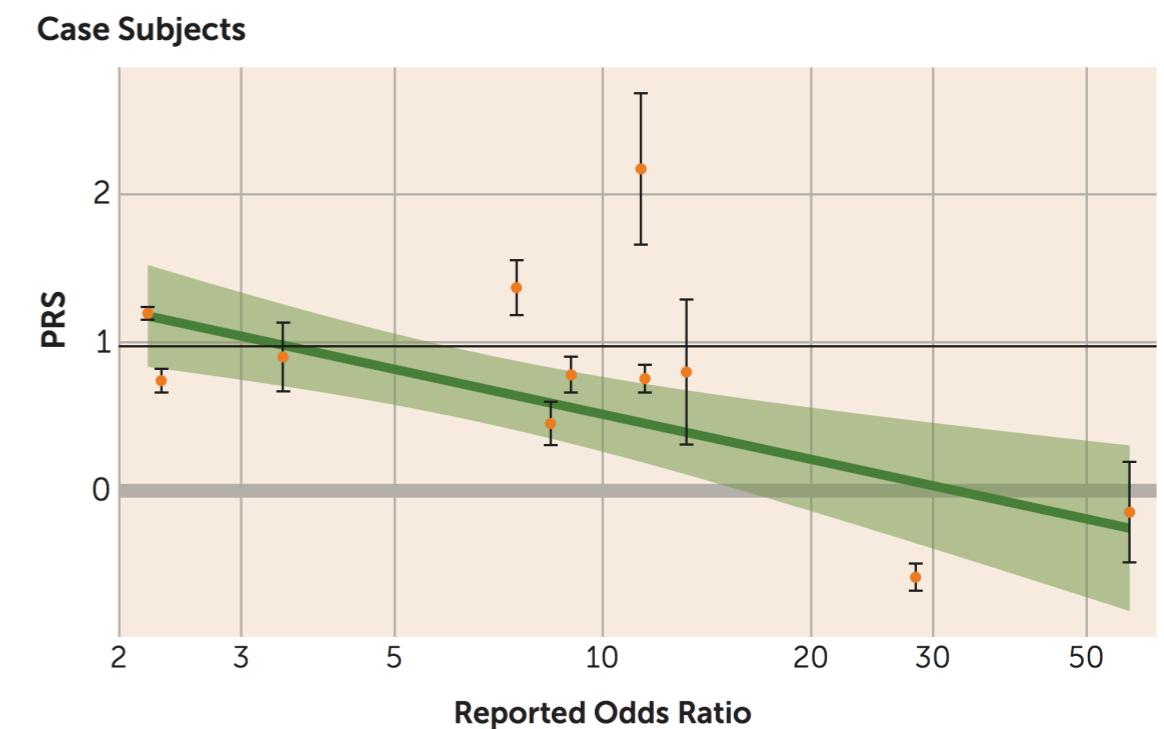
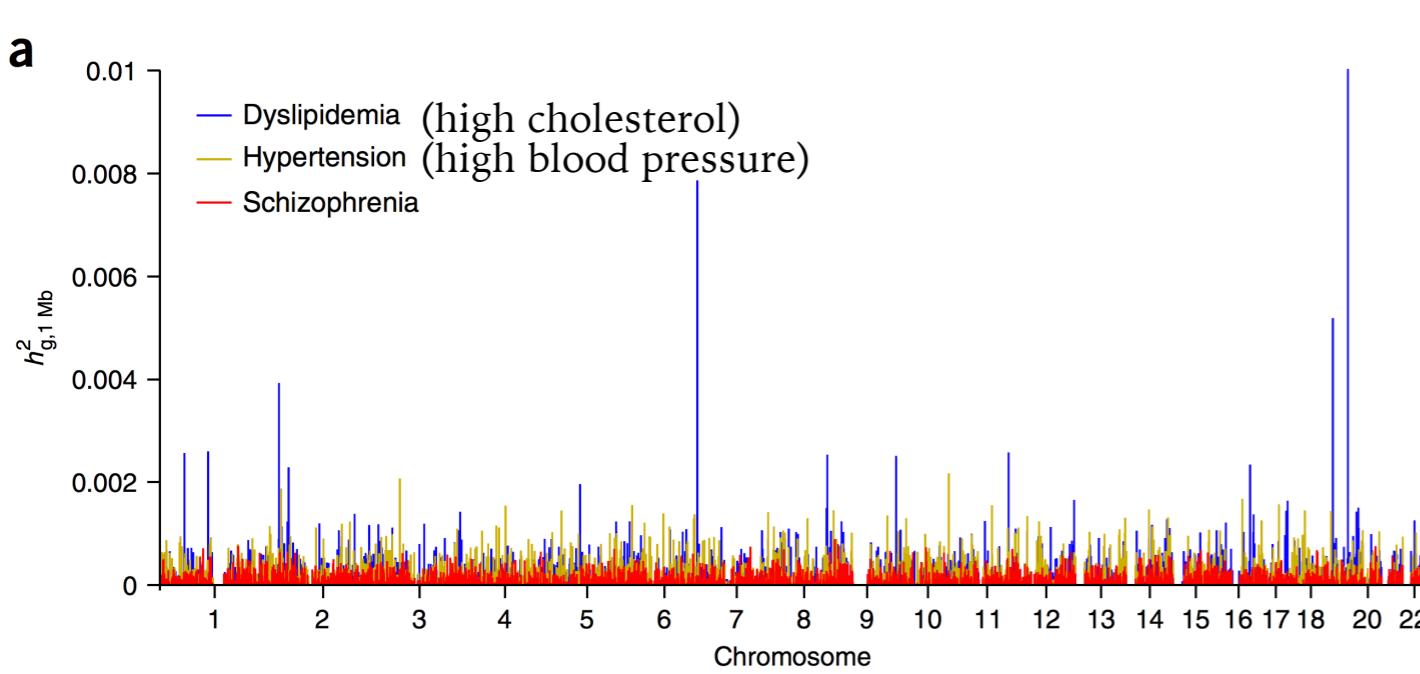
HERITABILITY OF SCHIZOPHRENIA



HERITABILITY

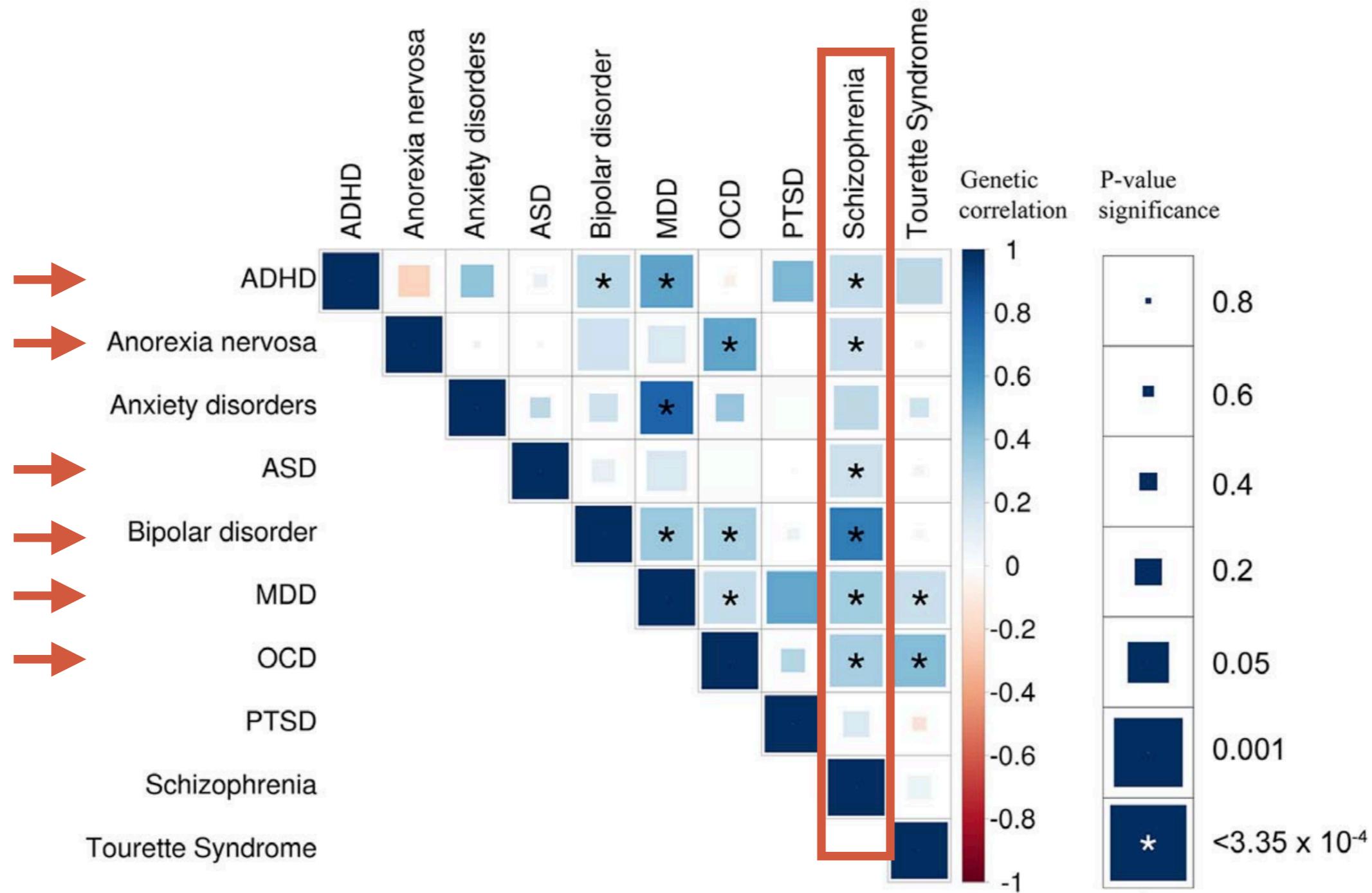
THE CASE OF THE MISSING HERITABILITY

- Extremely polygenic = extra small effects
- Contributions of rare or interactive effects
- Heterogeneity within schizophrenia cases



HERITABILITY

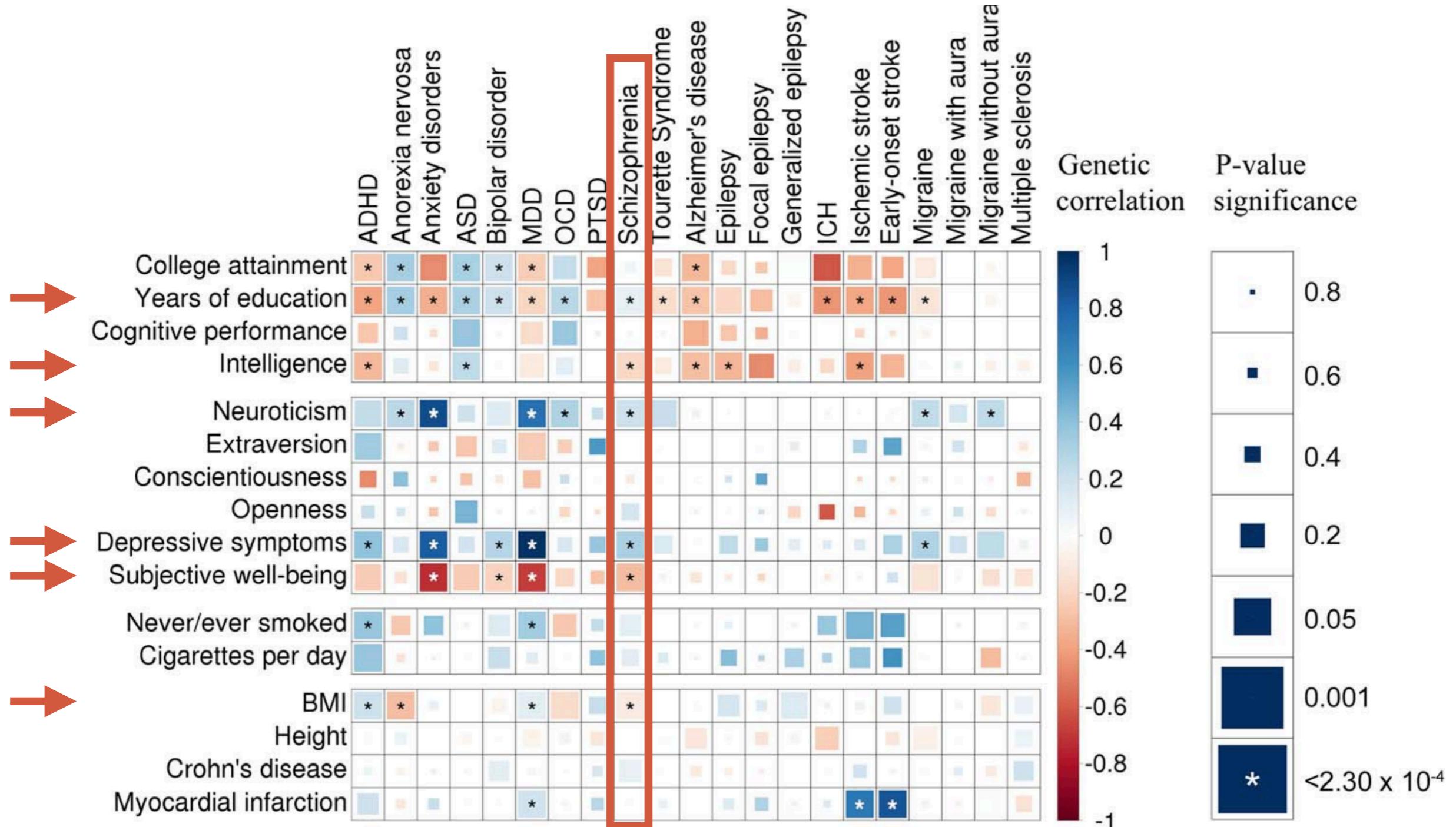
GENETIC CORRELATIONS BETWEEN DISEASES



Genes for schizophrenia also increase risk for other psychiatric disorders

HERITABILITY

GENETIC CORRELATIONS BETWEEN TRAITS

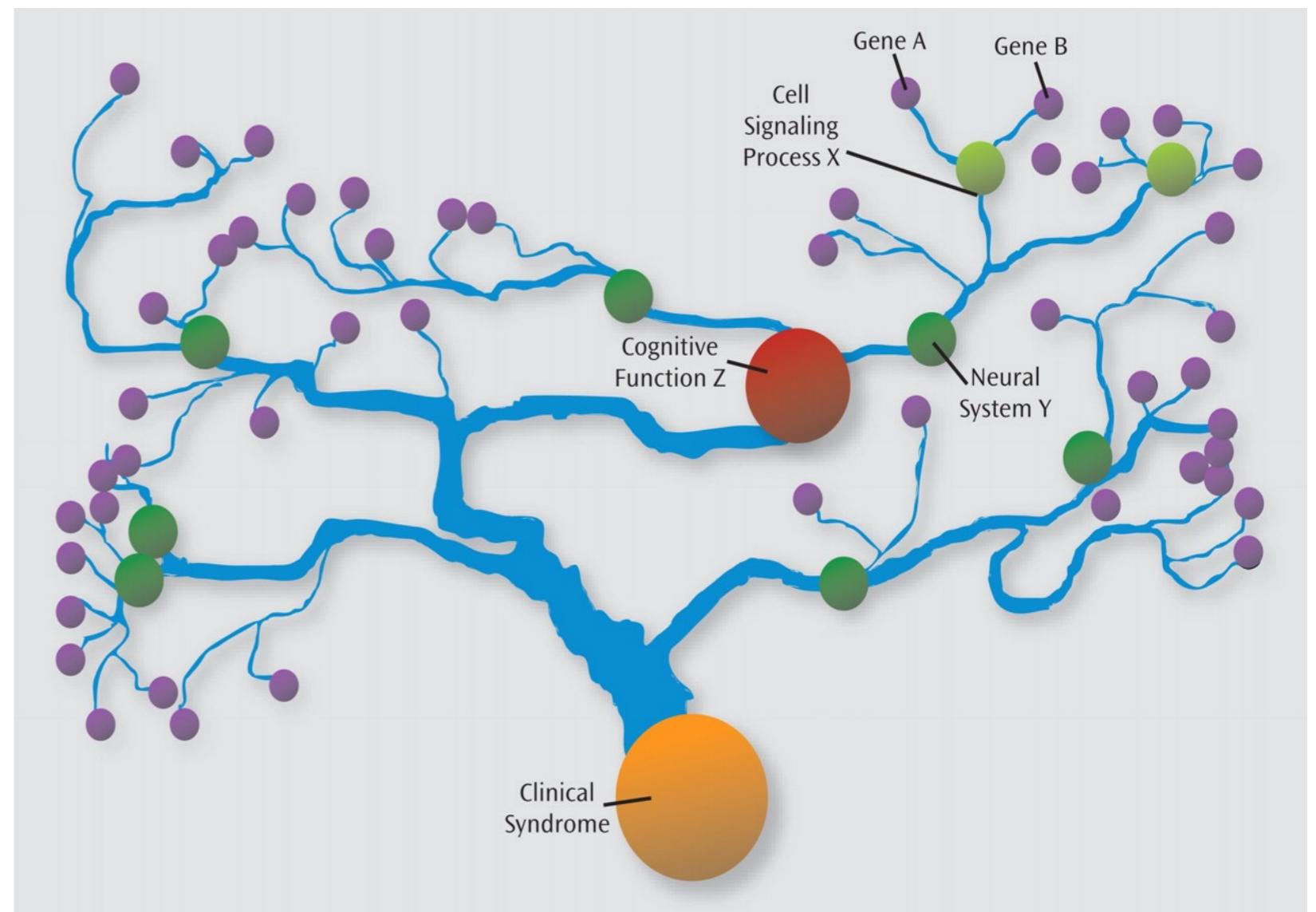
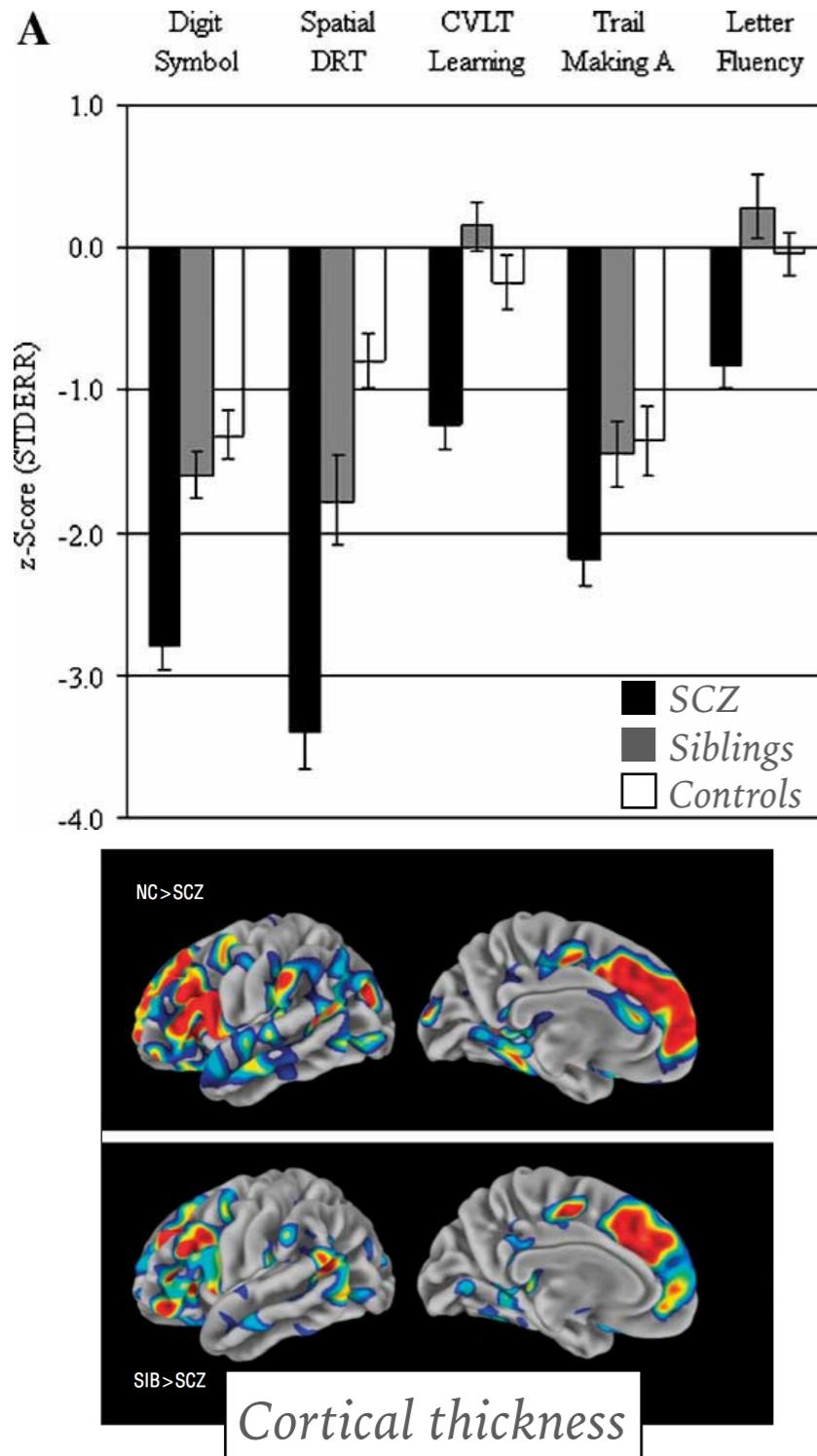


Genes for schizophrenia also affect other traits

Brainstorm Consortium et al., 2018, *Science*

HERITABILITY

ENDOPHENOTYPES



Genetics of endophenotypes ultimately were no less complex than schizophrenia

Glahn et al., 2006, Amer Journal of Med Gen, Part B, Neuropsychiatric Genetics; Goldman et al., 2009, JAMA Psychiatry; Cannon & Keller, 2006, Annual Review of Clinical Psychology

DISCUSSION: GENOTYPE TO PHENOTYPE

- “Using the watershed analogy, is the point that while exploring the various streams and rivers (endophenotypes) that feed into the watershed (schizophrenia itself) is no less complex, the hope is that operating at this intermediary level can allow researchers to avoid getting bogged down in parsing the thousands of discrete SNPs that contribute to schizophrenia?”
- “Given the genetic overlap with bipolar and schizoaffective disorder, is it likely that the genes that supposedly confer risk for schizophrenia actually confer risk for psychiatric illness more generally? Could individual differences in aggregation of these risk alleles explain why individuals develop different psychiatric disorders, or even why individuals may present differently within the same disorder?”

GENE DISCOVERY

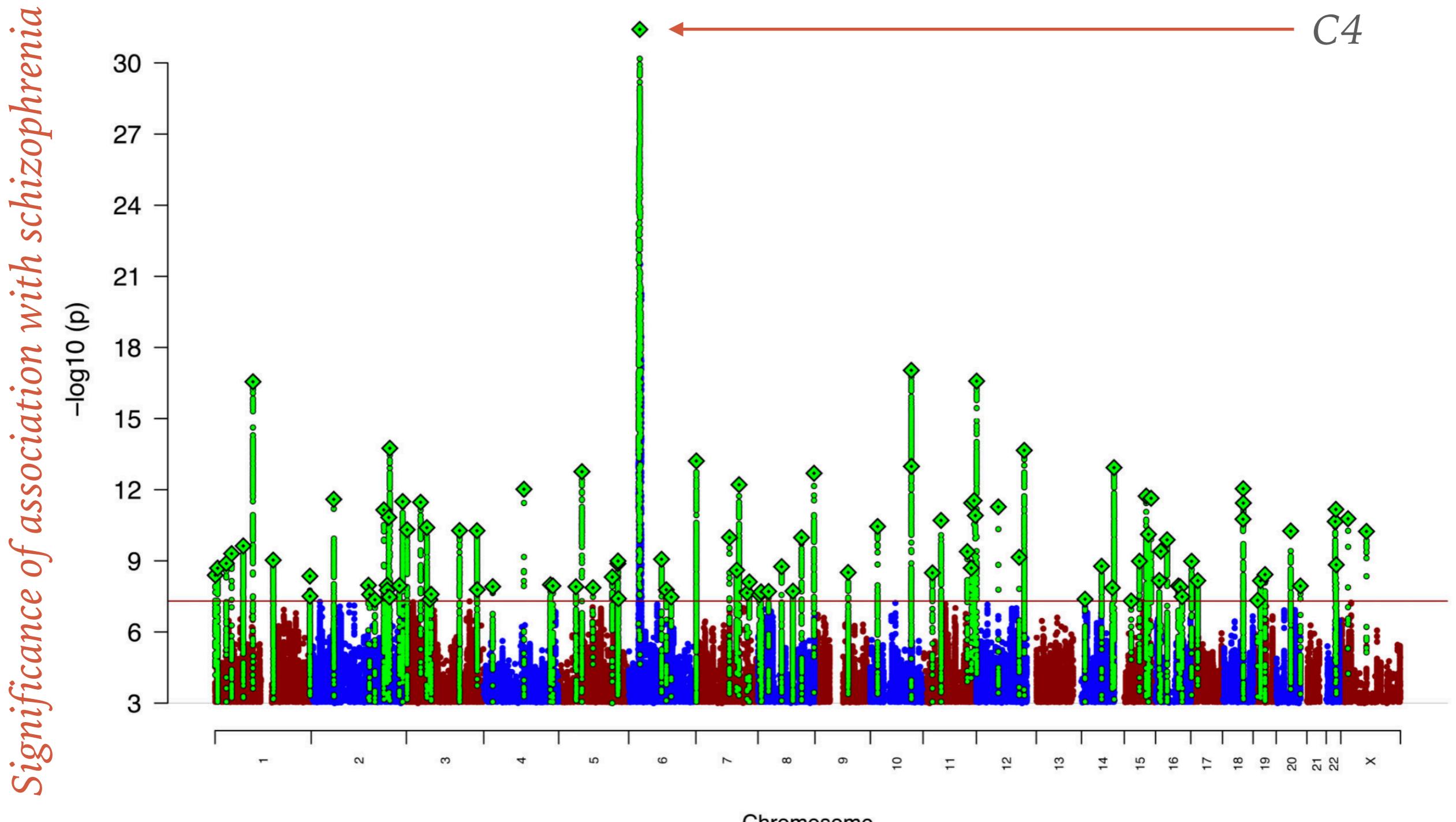
*What genes cause
schizophrenia?*

GENE DISCOVERY

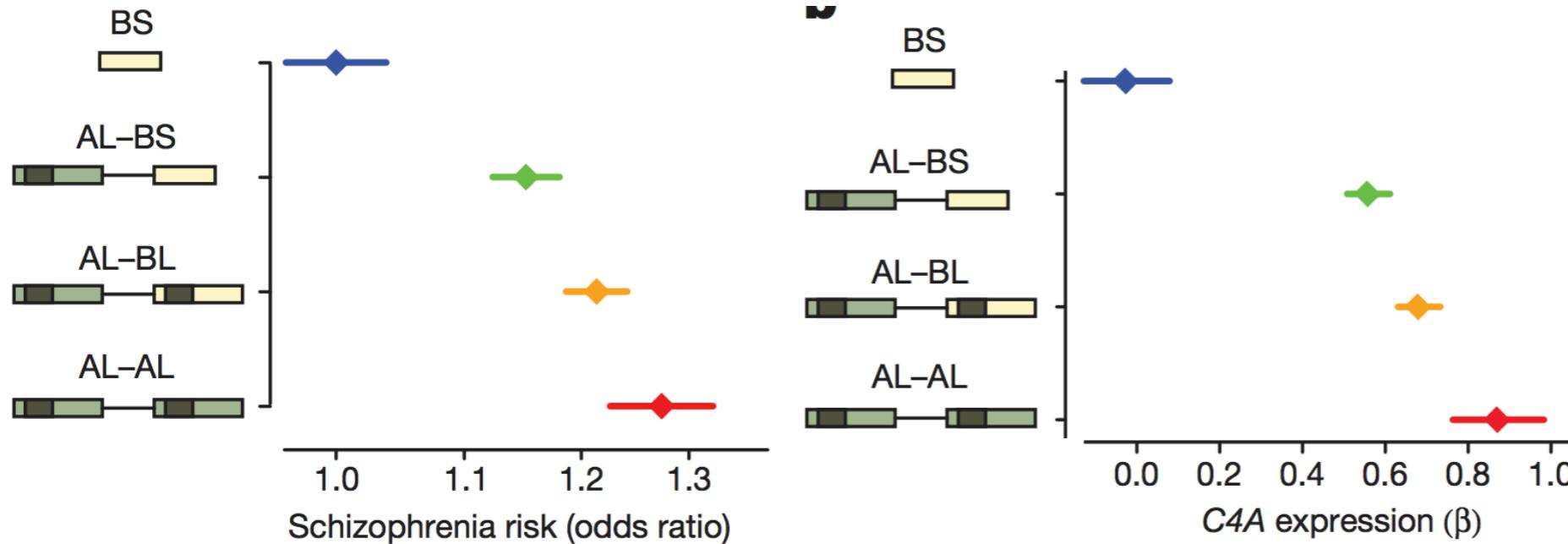
HISTORY



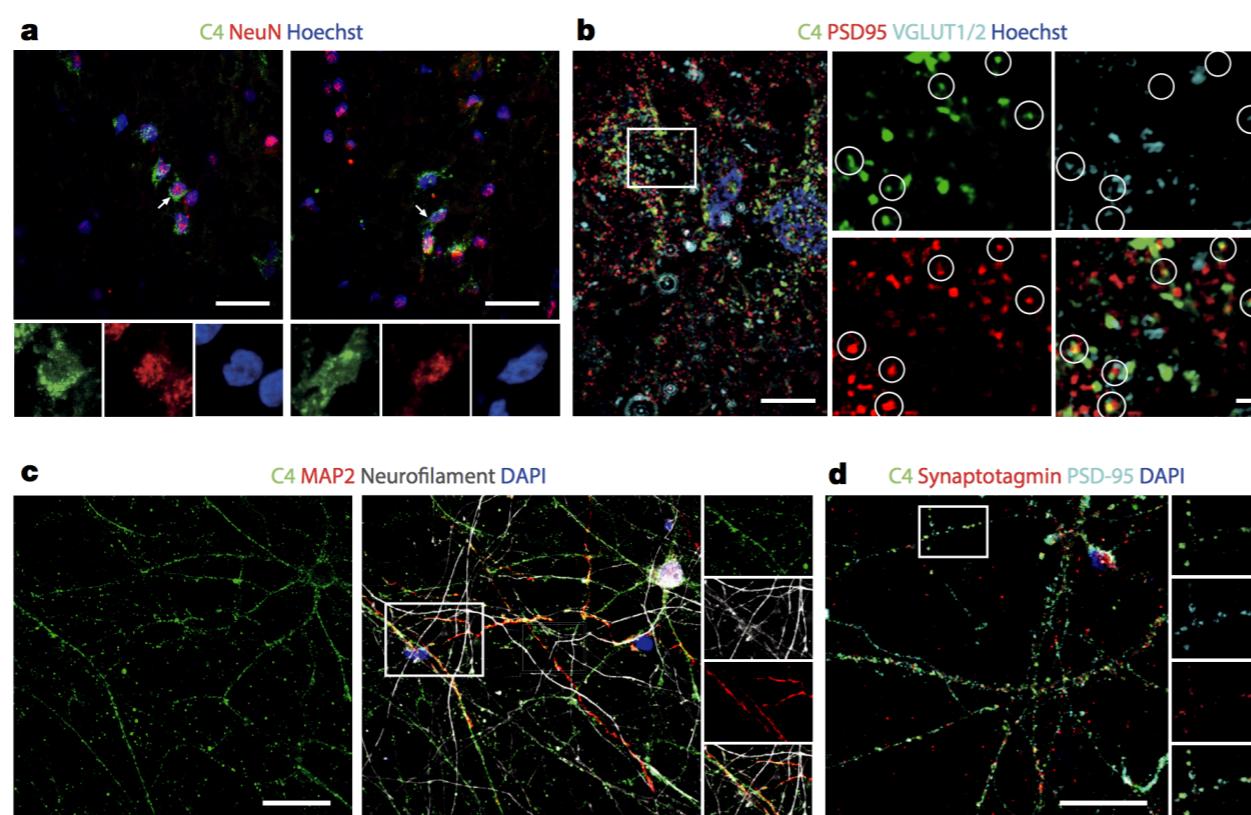
GENOME-WIDE ASSOCIATION STUDIES



FROM GENES TO BIOLOGY: C4

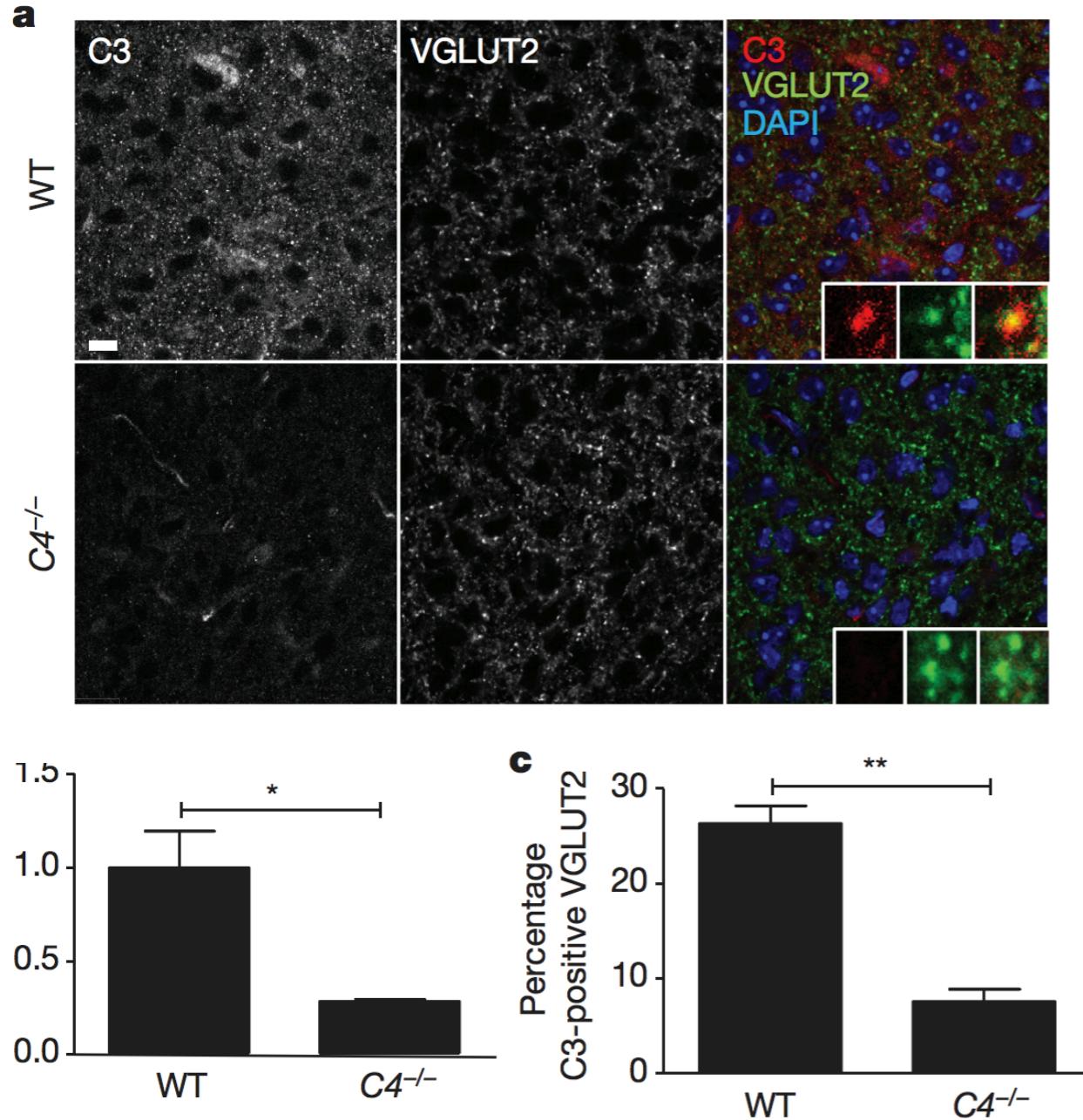


C4 associated with schizophrenia and correlates with gene expression

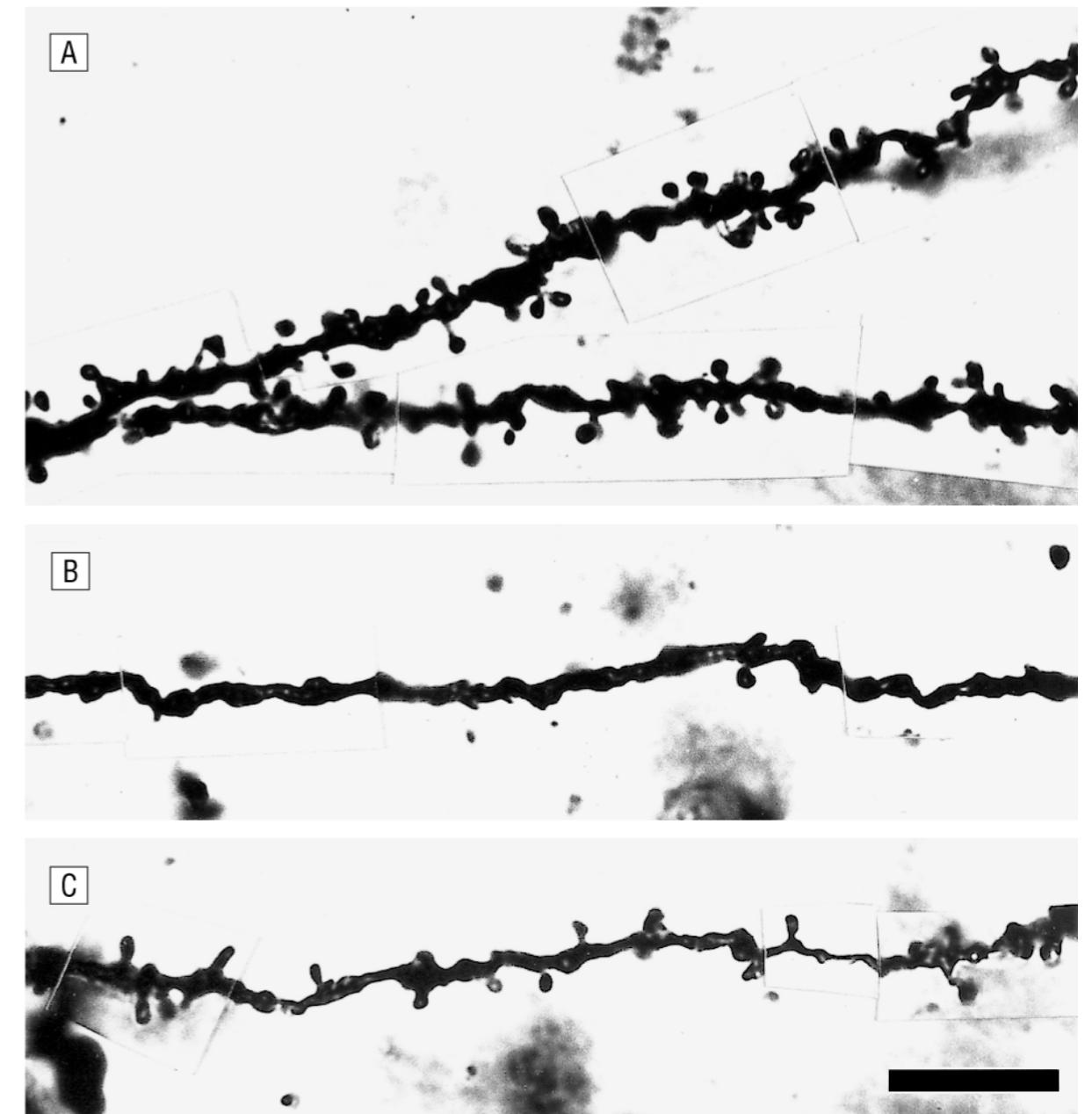


C4 protein is found on neurons, near synapses

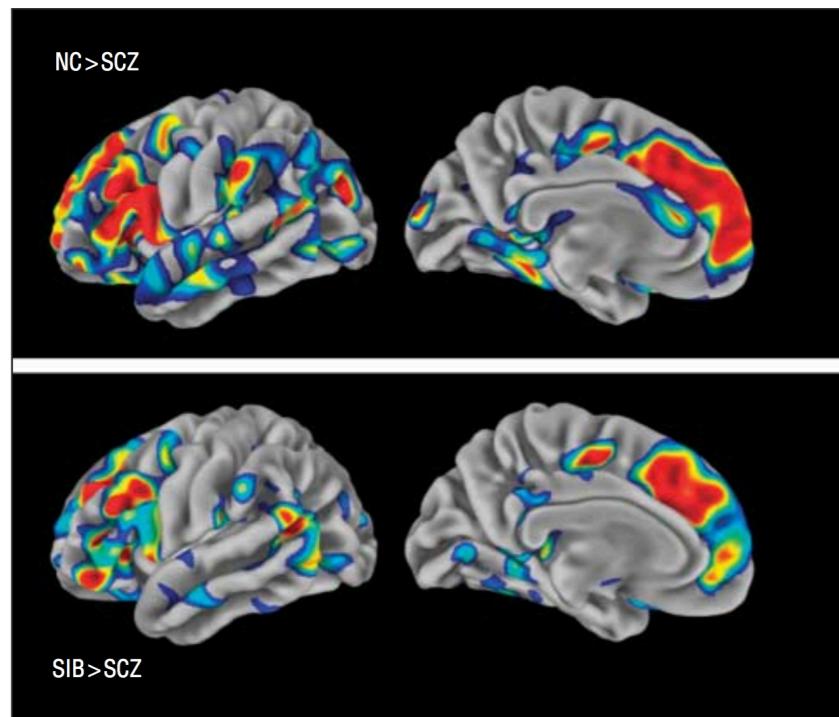
ROLE OF C4 IN THE (MOUSE) BRAIN



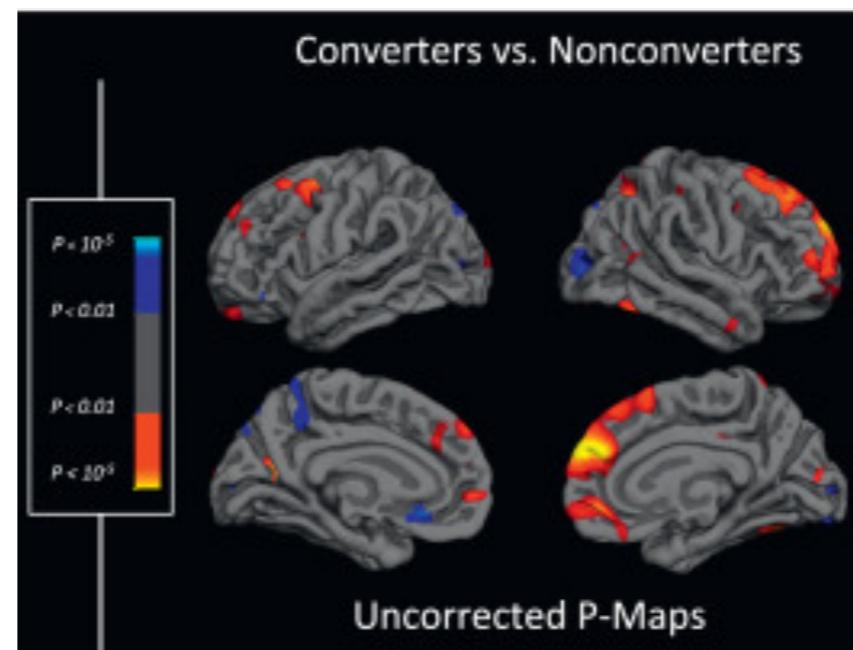
C4 promotes C3, which tags synapses to prune
C4 deficient mice have reduced synaptic pruning



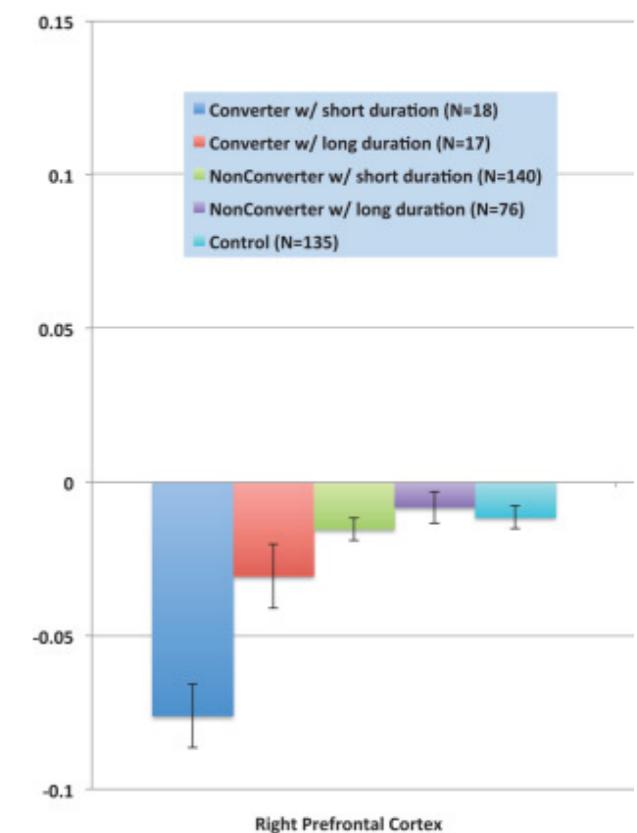
CORTICAL THICKNESS & THINNING



Cortical thickness in schizophrenia, unaffected siblings, and controls



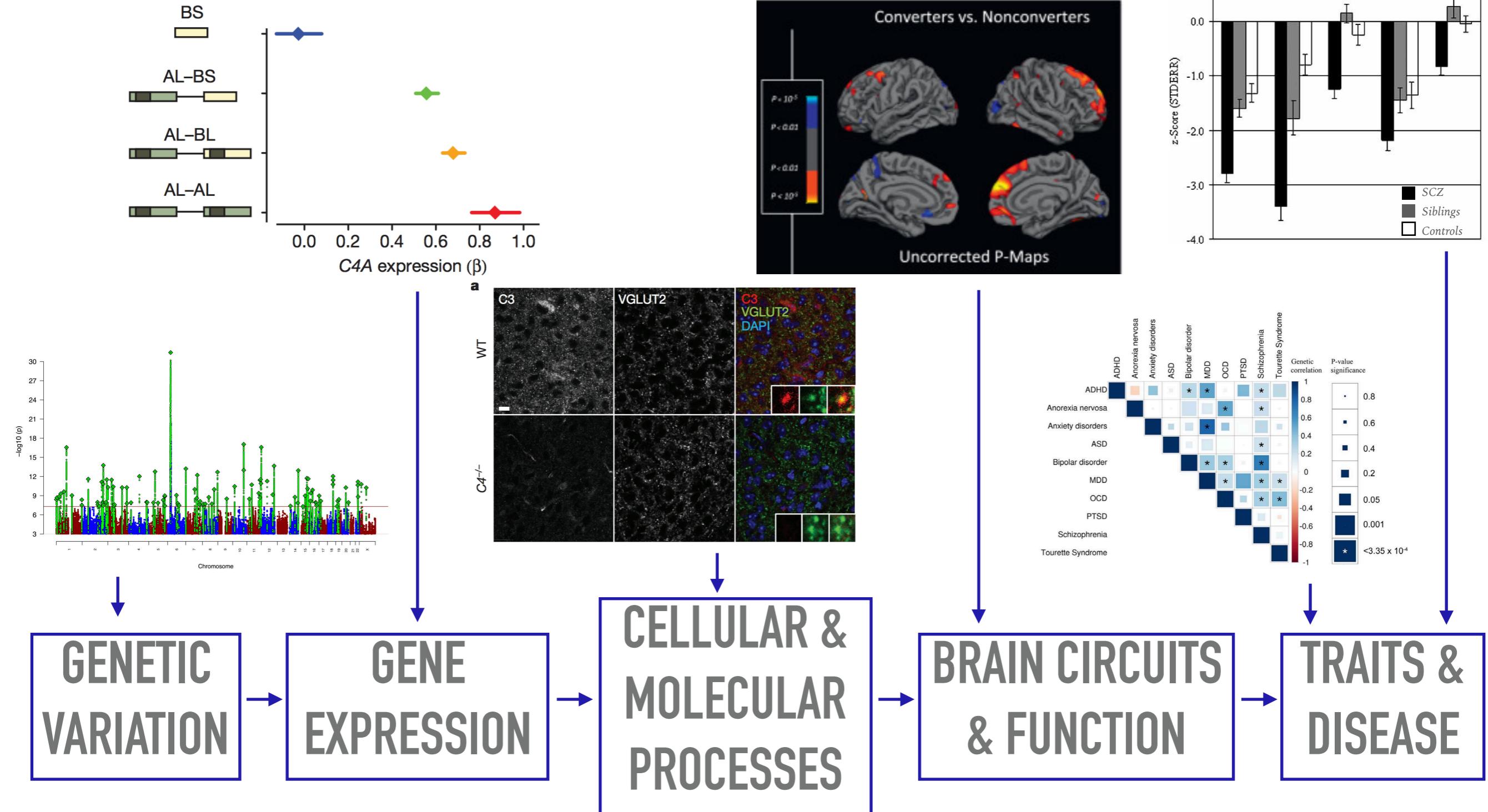
Cortical thickness in individuals at clinical high risk for psychosis



Rate of cortical thinning across clinical high risk groups

GENE DISCOVERY

MAPPING GENES TO BEHAVIOR



DISCUSSION: BIOLOGY OF SCHIZOPHRENIA

- “Even if we could map out all of the common risk variants for schizophrenia, most of its genetic variance would still be unexplainable. Why exactly is this? Do you think there ever will be a time when schizophrenia’s genetic variances can be completely explained?”
- “Though there are estimated to be 8,400 SNPs that potentially play a role in the development of schizophrenia, are there any that we know must be present for the disease to occur?”
- “Can medication target risk alleles by targeting the brain functions they’re involved with? Would there always be too many genetic risk alleles for it to matter?”
- “Are there network effects in terms of a few amount of nucleotides that can cause cascades which consequently have an impact on the resulting expression (“butterfly-effect”), so that it may not be necessary to understand the function of every single molecule?”

GENETIC RISK PREDICTION

*Which individuals are at
high risk for schizophrenia?*

CLINICAL GENOMICS

American College of Medical Genetic & Genomics

ACMG STATEMENT

KALIA et al | Updated secondary findings recommendations

Table 1 ACMG SF v2.0 genes and associated phenotypes recommended for return of secondary findings in clinical sequencing

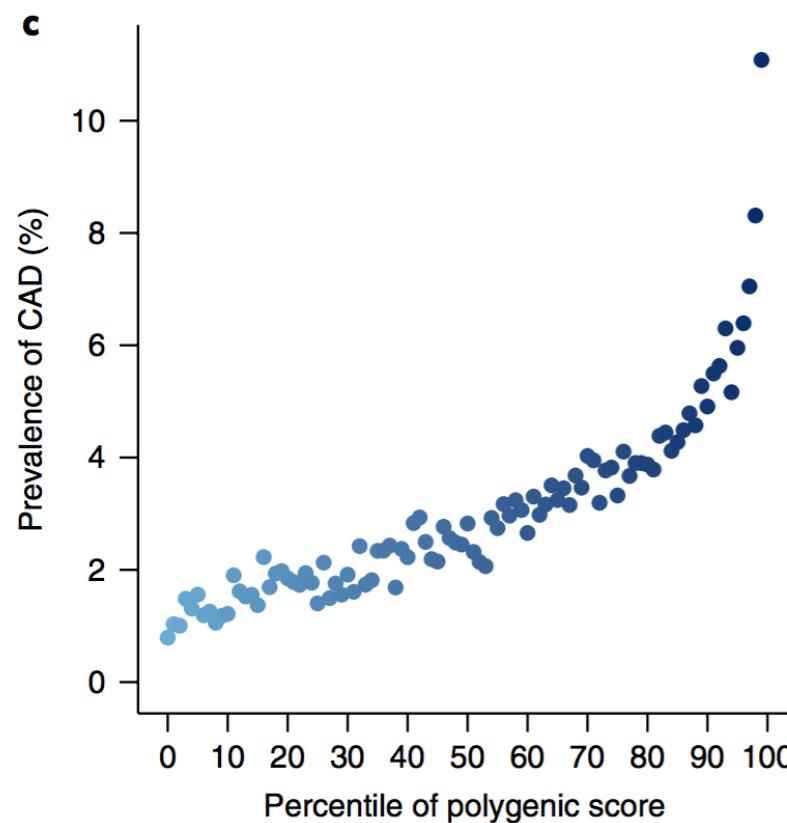
Phenotype	MIM disorder	PMID Reviews entry	Typical age of onset	Gene	MIM gene	Inheritance ^a	Variants to report ^b
Hereditary breast and ovarian cancer	604370 612555	20301425	Adult	<i>BRCA1</i> <i>BRCA2</i>	113705 600185	AD	KP and EP
Li-Fraumeni syndrome	151623	20301488	Child/adult	<i>TP53</i>	191170	AD	KP and EP
Familial hypercholesterolemia	143890 603776	No GeneReviews entry	Child/adult	<i>LDLR</i> <i>APOB</i> <i>PCSK9</i>	606945 107730 607786	SD SD AD	KP and EP KP
Wilson disease	277900	20301685	Child	<i>ATP7B</i>	606882	AR ^c	KP and EP
Ornithine transcarbamylase deficiency	311250	24006547	Newborn (male), child (female)	<i>OTC</i>	300461	XL	KP and EP (hemi, het, hom)
Malignant hyperthermia susceptibility	145600	20301325	Child/adult	<i>RYR1</i> <i>CACNA1S</i>	180901 114208	AD	KP

0.4% of population; 3-fold increased risk

59 genes total =
“ACMG 59”

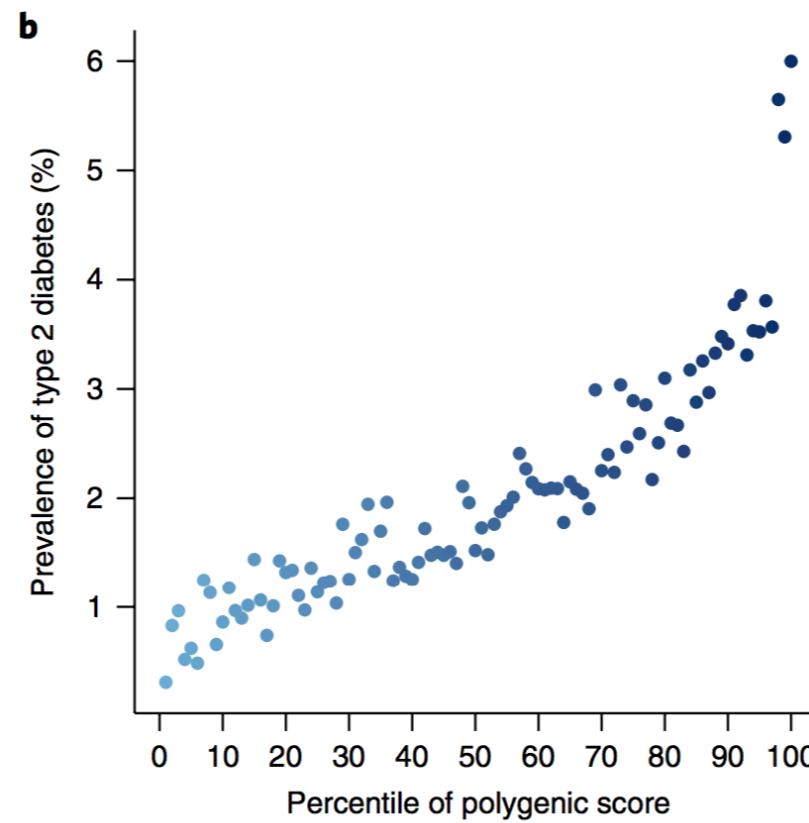
POLYGENIC RISK SCORES

Coronary artery disease



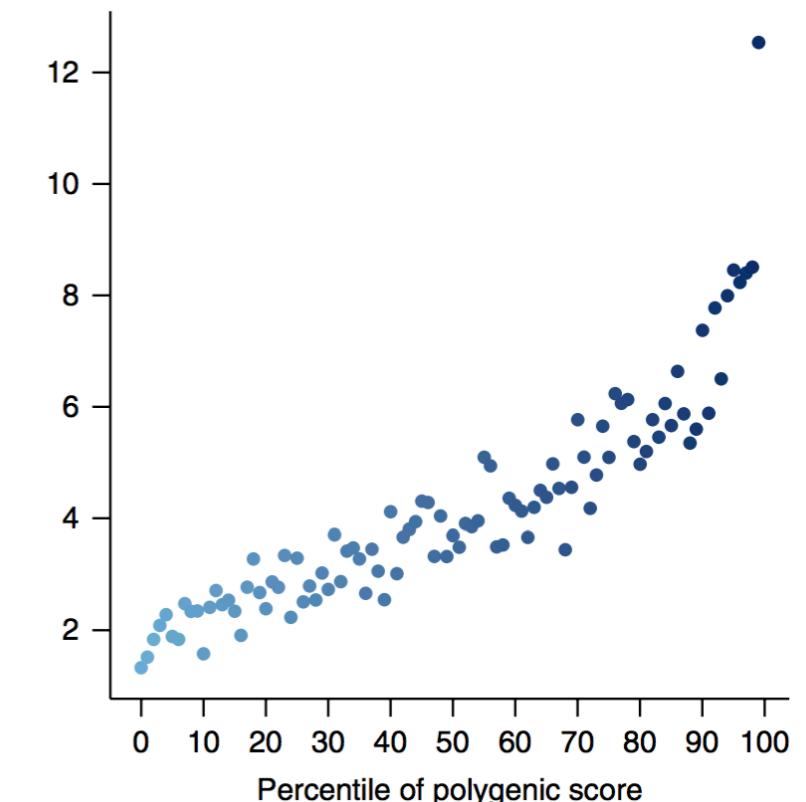
20x as many people at same level of risk as FH (8% of population)

Type 2 diabetes



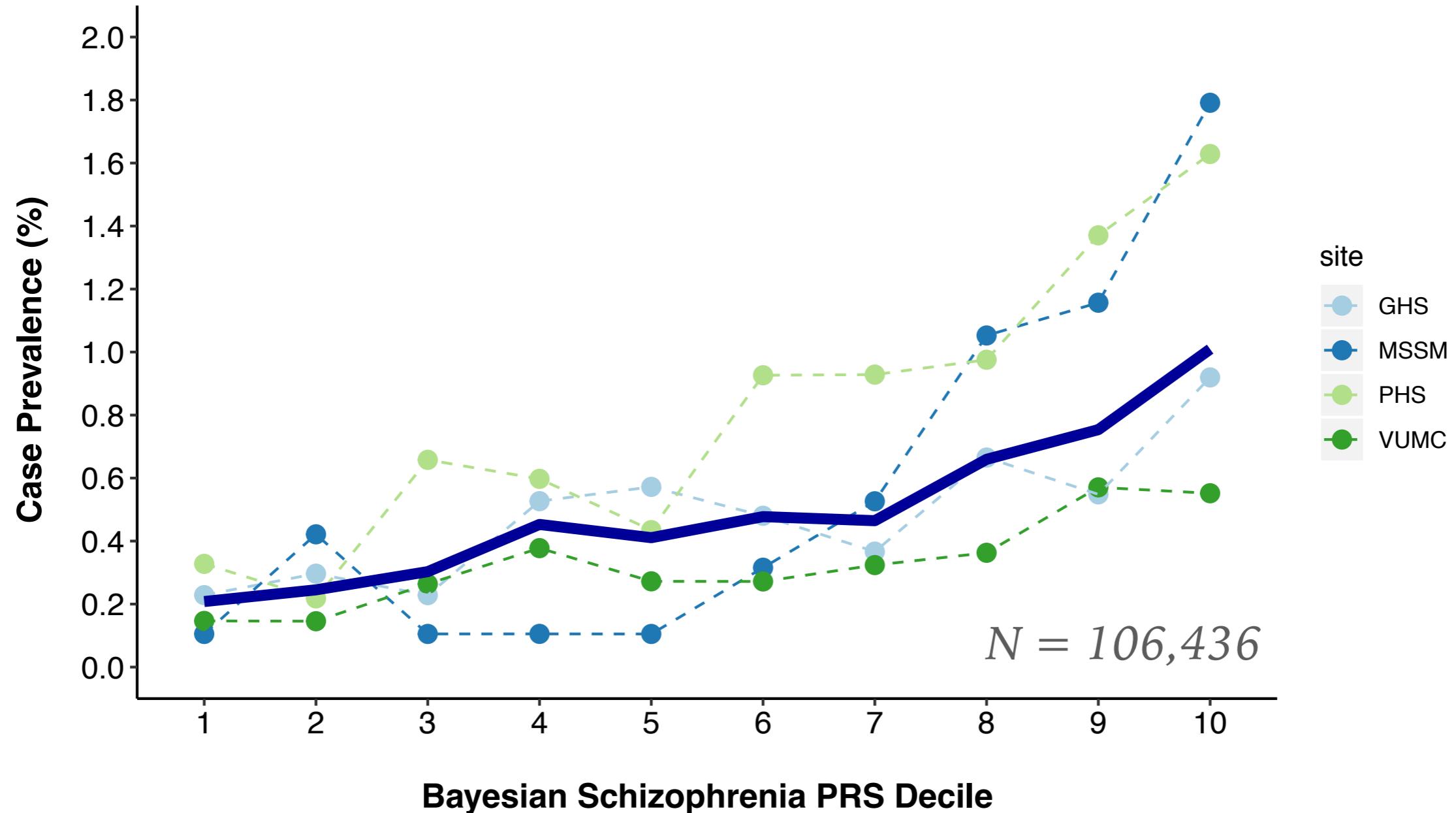
Top 1% has 3.3x the risk as bottom 99%

Breast cancer



Top 0.1% has prevalence of 19% compared to 4.2% in bottom 99.9%

SCHIZOPHRENIA PRS



Top 10% twice as likely as bottom 90% to have schizophrenia; four times as likely as bottom 10%

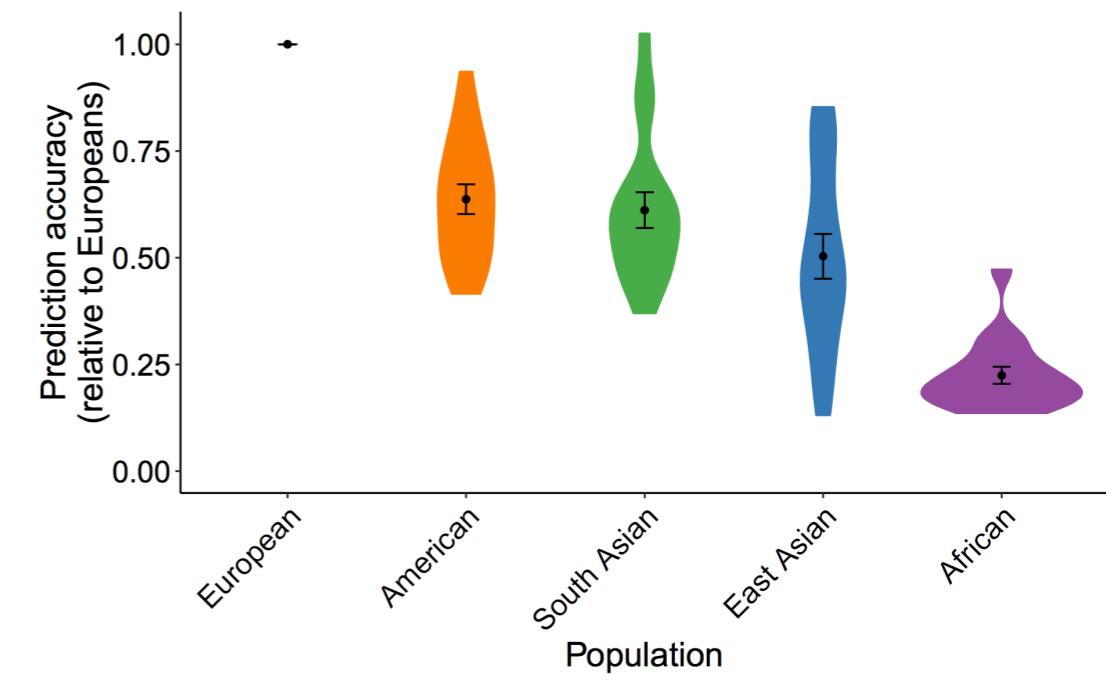
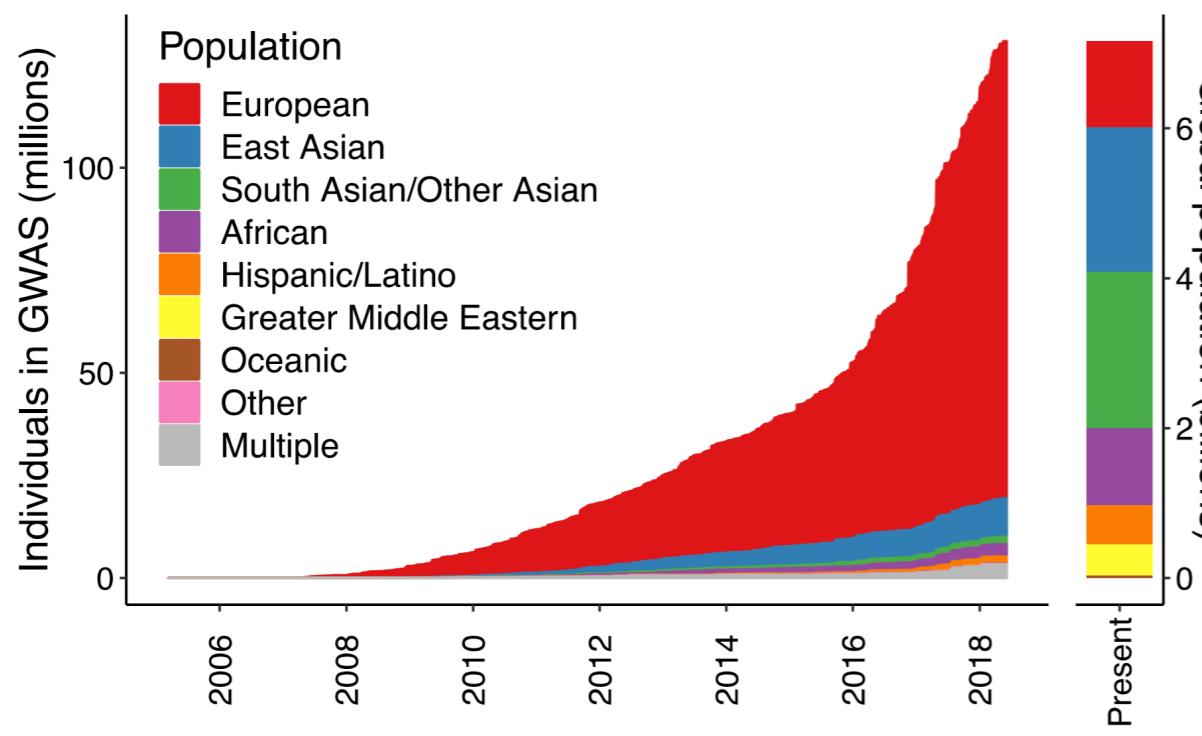
DISCUSSION: HOW GOOD ARE PSYCHIATRIC PRS?

- “Why is there such a stark difference between certain medical diseases vs. psychiatric disorders?”
- “Since there is such a high overlap between schizophrenia and other disorders (such as bipolar disorder), how reliable do we think polygenic risk scores will be in determining the risk of schizophrenia alone?”
- “Assuming that the individuals studied are diagnosed used an iteration of the DSM or the ICD, how does the arbitrary nature and definition of schizophrenia within these diagnostic manuals affect the validity of genetic testing on the population and generalization of results to a wider population?”
- “With the hopes of having more genetic information about psychiatric disorders, would more individualized care cause for the creation of a lot of new therapies to treat the specific diagnosis? Or would patients be treated with a combination of pre-existing treatments?”

INTO THE FUTURE

GENOMIC MEDICINE

- Extensive follow up on other genes of interest, which may lead to the development of new treatments
- Improvements in genetic risk stratification, which could lead to improvements in early intervention



DISCUSSION: DISCLOSING GENETIC RISK

- “As we have also talked about in class, to what extent does the class think we should focus on heritability when talking to patients about their risk of illness or current illness? Since heritability does not account for the whole story, could this induce undue stress?”
- “Does focusing on the genetic and biological risk factors for schizophrenia increase or reduce stigma? And how does this in turn change patient perceptions of potential treatment outcomes?”
- “Should patients be able to find out their PRSs from doctors? What would be the positive and negative repercussions of this availability?”
- “How helpful would an early genetic screening be if it isn’t helping the people that are more likely to develop mental health disorders (low SES people)?”
- “What are the protective factors preventing these healthy populations from expressing a schizophrenic phenotype?”



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