ChatGPT

Genetics of obsessive-compulsive disorder

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Zürich

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PGC TS-OCD
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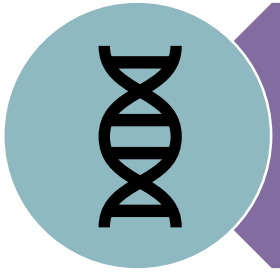
What is obsessive-compulsive disorder?



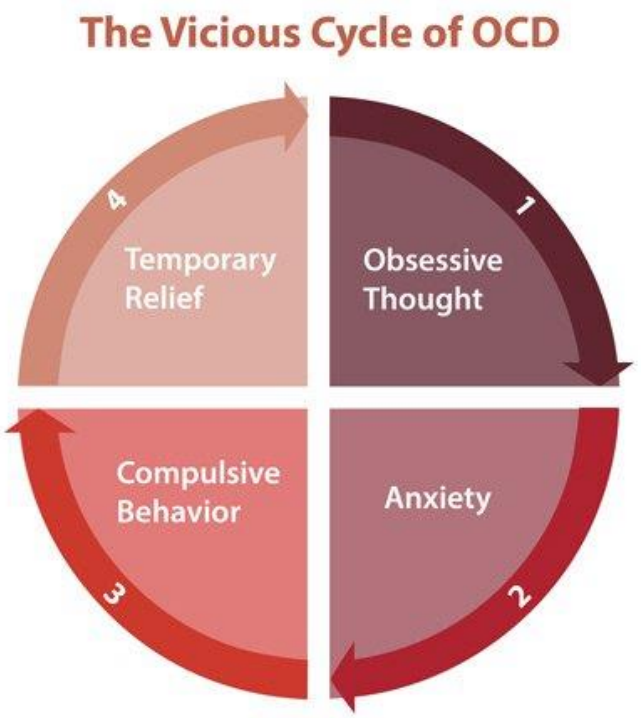
Types of genetic variation

Genetics of OCD – Insights from GWAS

Clinical translation

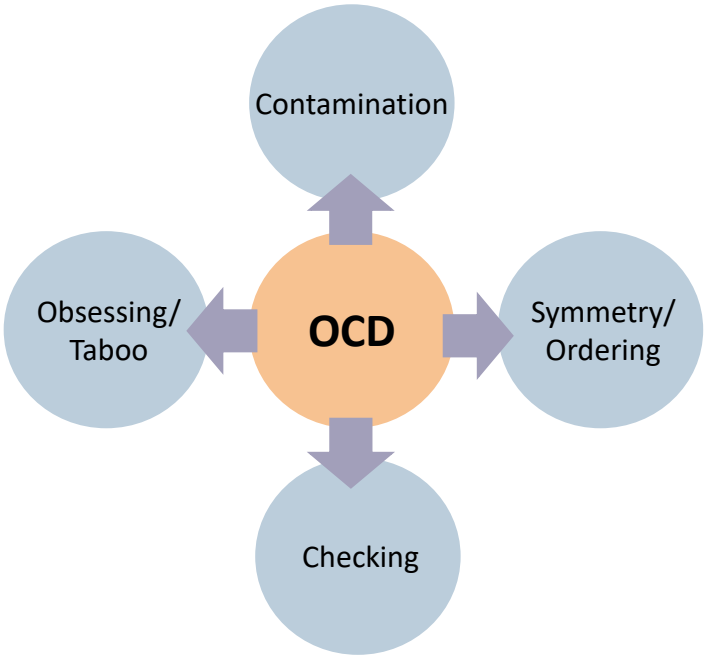
Obsessive-compulsive disorder (OCD)

Cycle of obsessions and/or compulsions



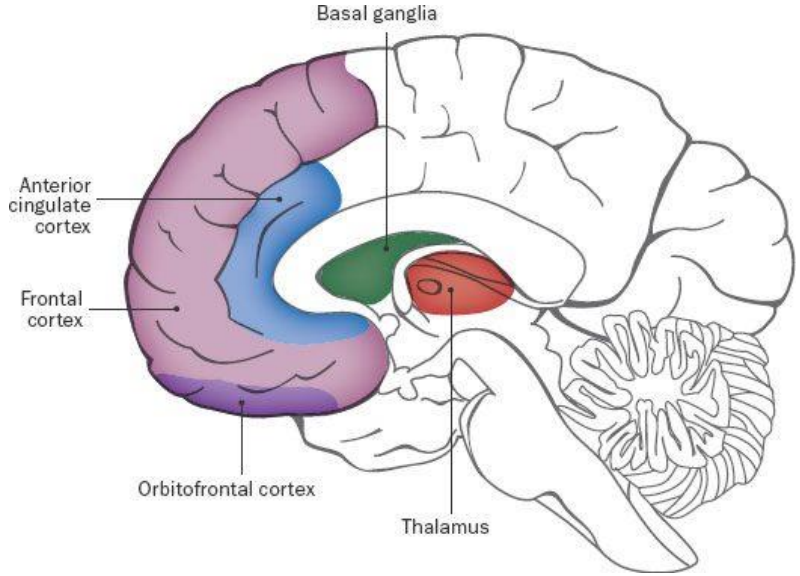
https://helpguide.org/

Variety of different symptoms in clusters



Strom, N.I.,et al. (2021). Transl Psychiatry

Cortico-striato-thalamo-cortical circuits



https://iocdf.org/

Obsessive-compulsive disorder (OCD)

Bimodal age of onset, sex differences in prevalence change with age

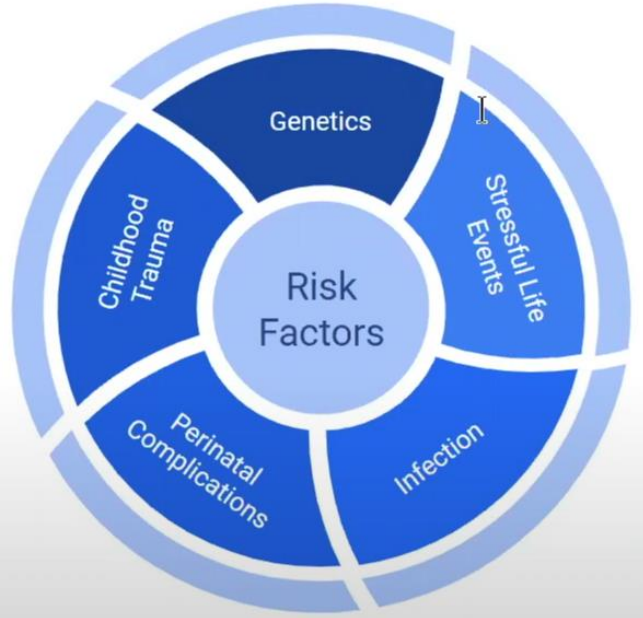
Treatment

Many different risk factors

Adapted from: Anholt, G., et al (2014). Psychological Medicine

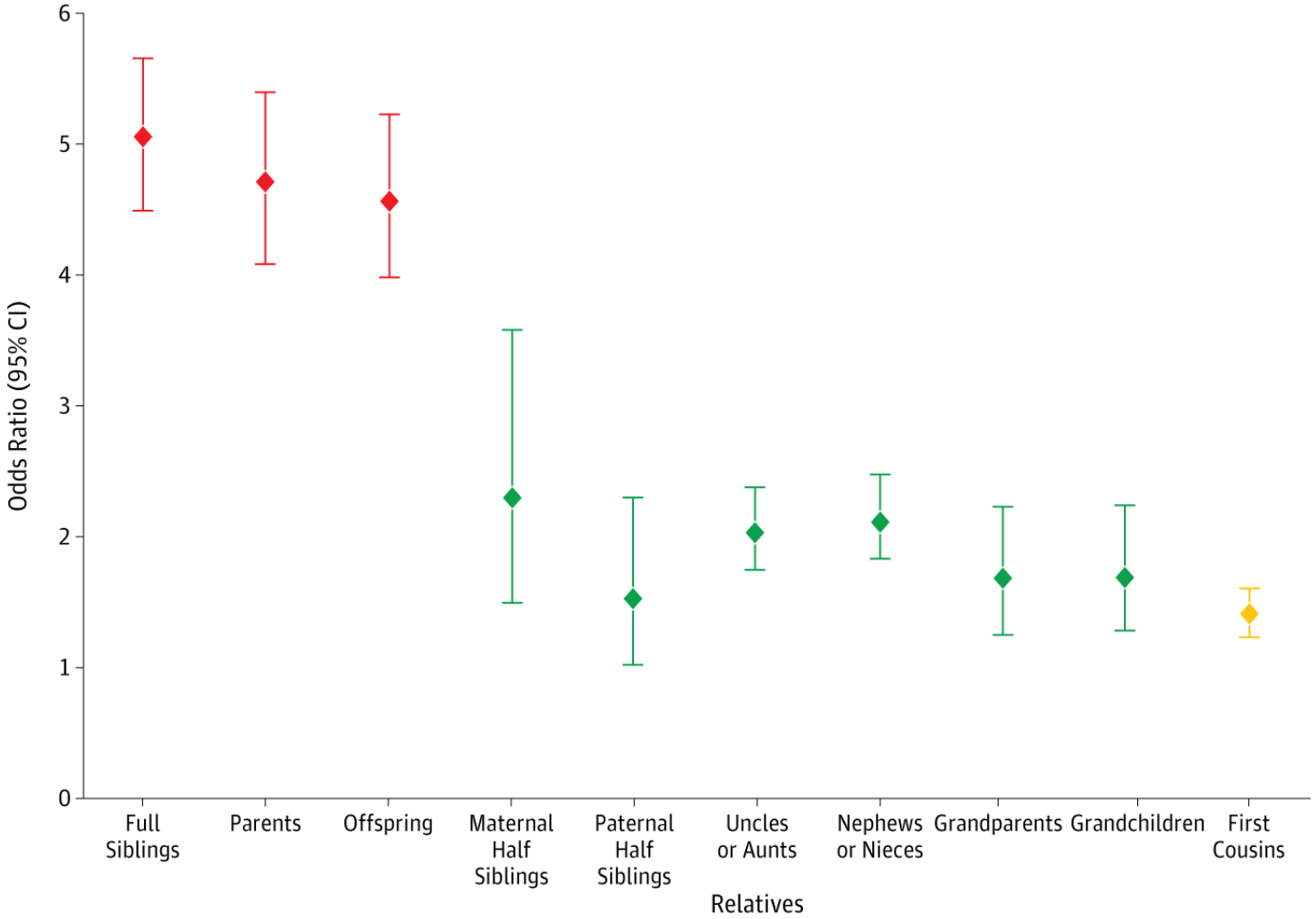
CBT: Exposure and response prevention

Medication: Serotonine reuptake inhibitors (SSRIs)



Heritability of OCD

Population-based, multigenerational family clustering study of obsessive-compulsive disorder



OCD: Genetic risk (or heritability) about 50%

Mataix-Cols D et al., Population-based, multigenerational family clustering study of obsessive-compulsive disorder, JAMA Psychiatry 2013

Monogenic vs. Polygenic disorders

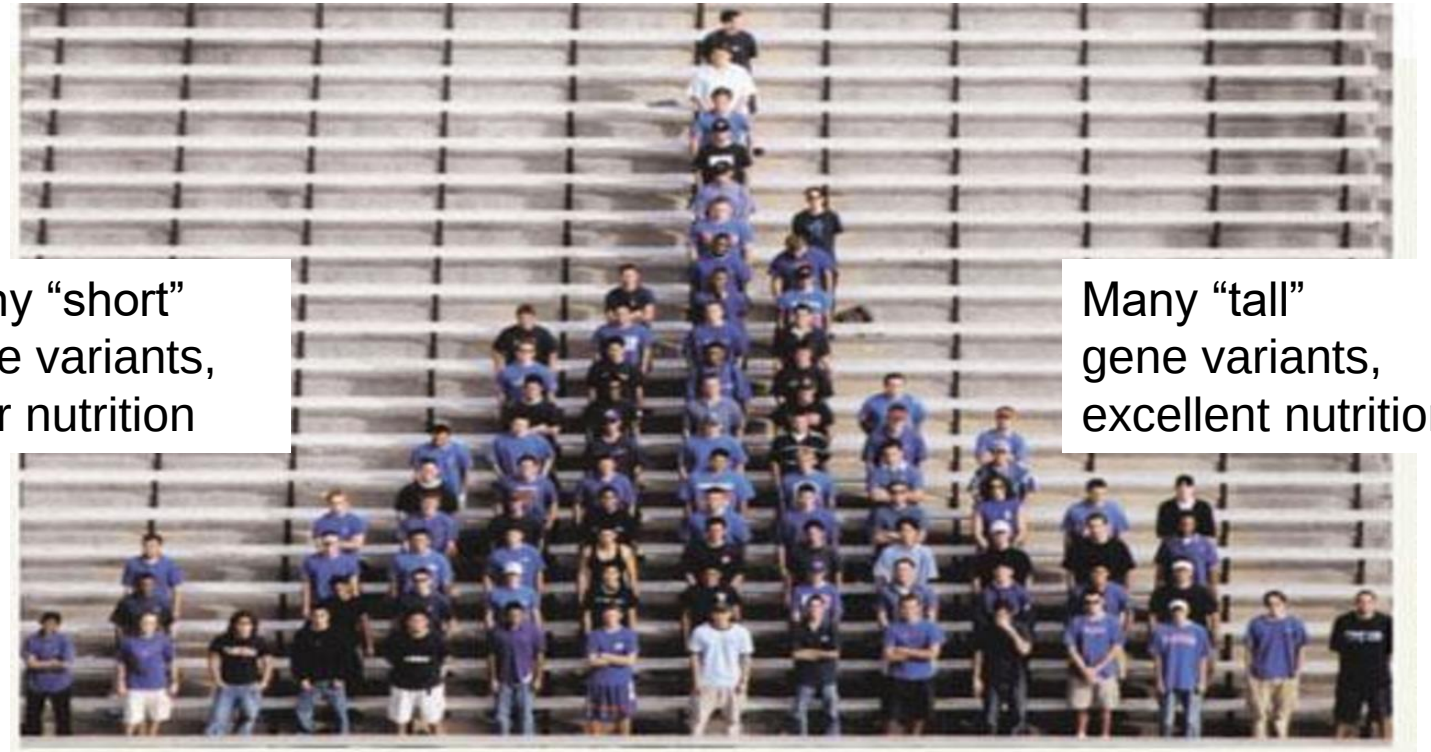
Monogenic: genetic v… in a single gene (a… quences on th… ect) leads to the d…

Very Complicated

Polygenic: genetic variation in/regulating multiple genes (and ist consequences on the gene products) can, in combination, lead to disease.

RA Fisher (1918), polygenic model:
If many genes affect a trait, and alleles at each gene are randomly sampled each generation, the effects of alleles at these genes are small and produce a continuous, normally distributed trait in the population.

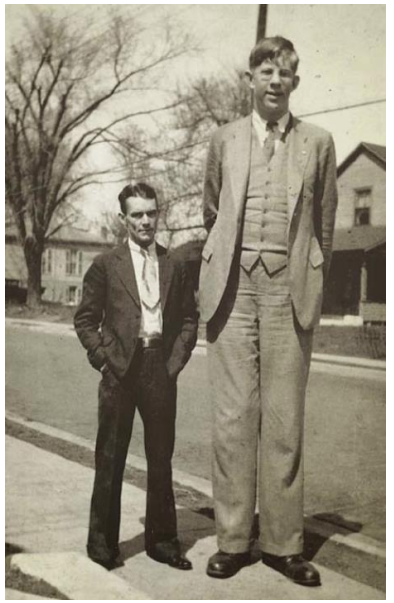
…or one major variant



Many "short" gene variants, poor nutrition

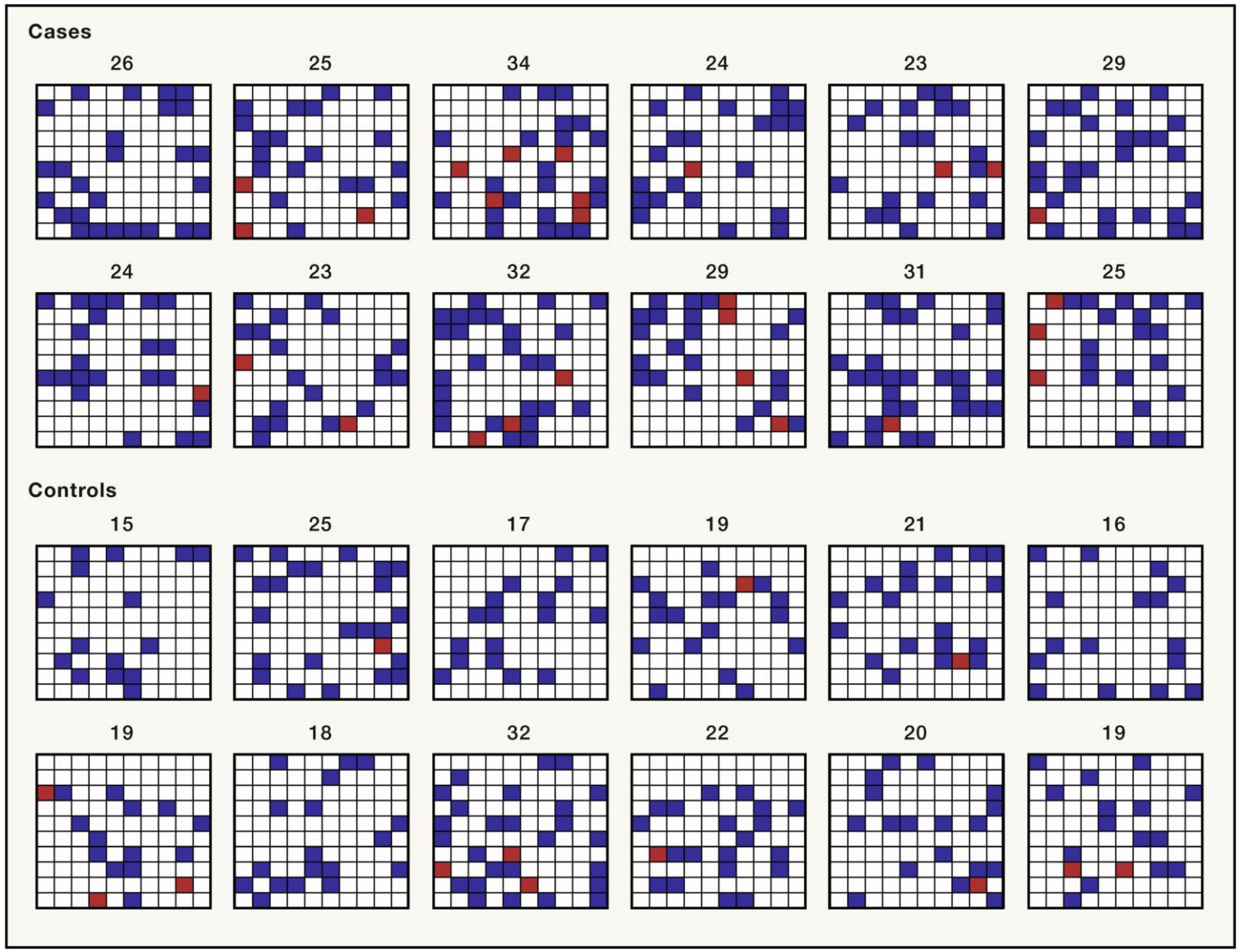
Many "tall" gene variants, excellent nutrition

Slide adapted from Jim Crowley



…or one major variant

Combinatorial effects



Disease risk is influenced by effects at 100 loci

Each box represents 1 risk locus
White = 0 risk alleles
Blue = 1 risk allele
Red = 2 risk alleles

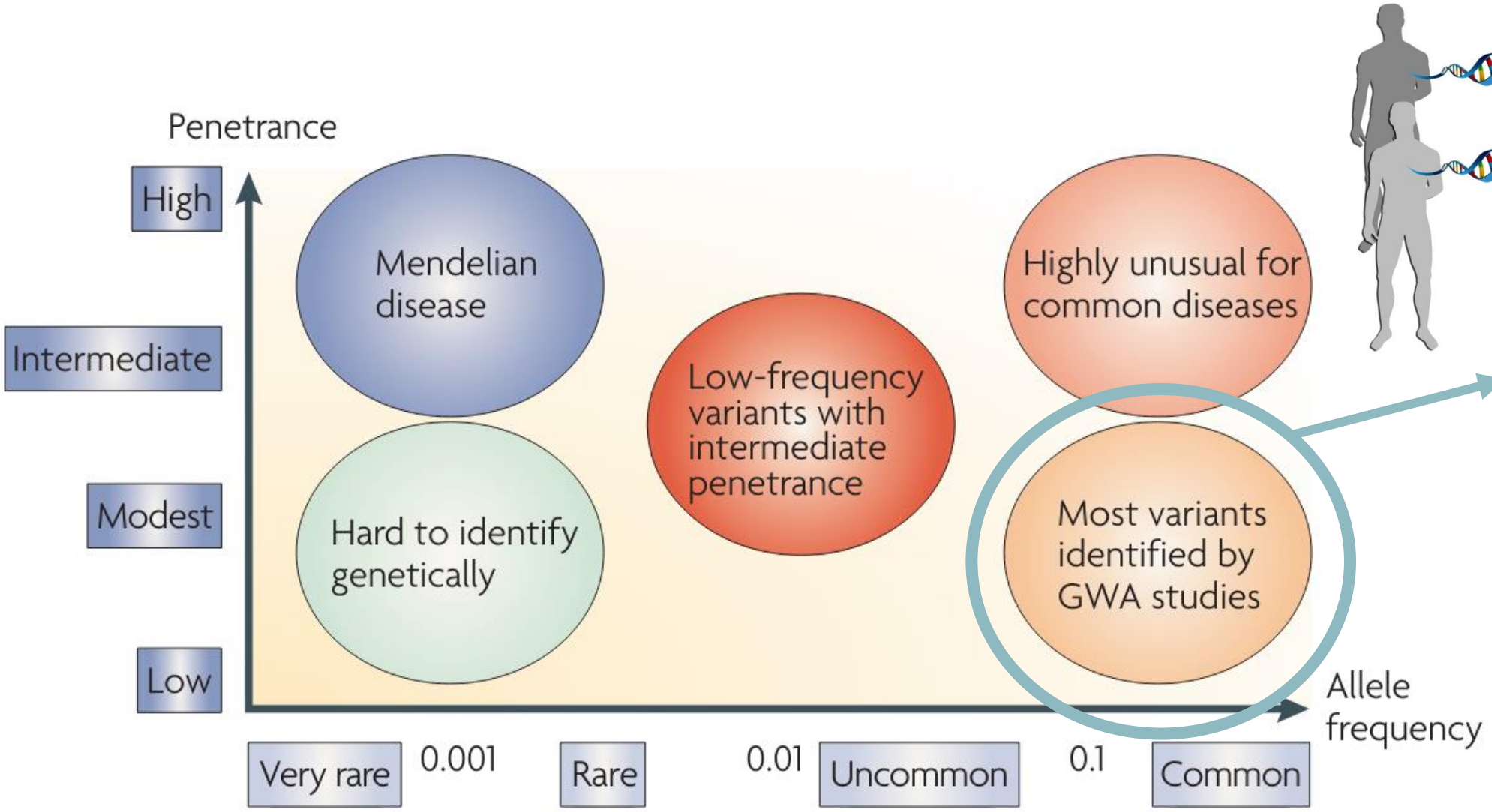
Cases don‘t look drastically different from controls!

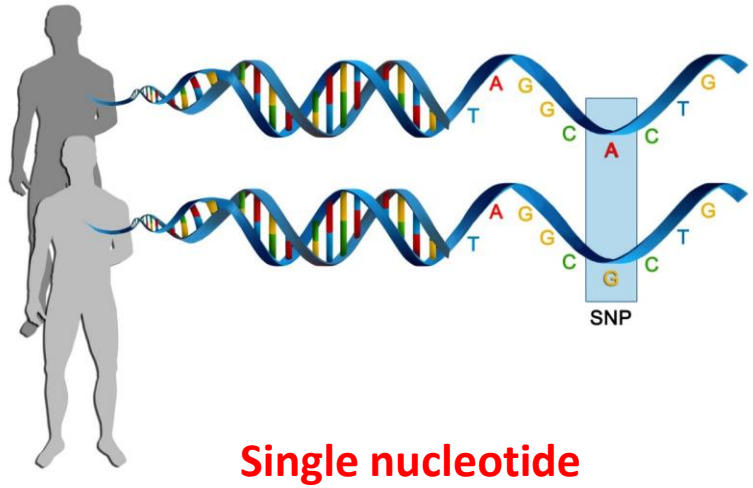
→ **Heterogeneity!**

- Cases look more different from other cases than we would think!
- This gets exponentially „worse“ as polygenicity increases.

Wray NR et al. Common Disease Is More Complex Than Implied by the Core Gene Omnigenic Model, Cell 2018

Allele frequency, effect size, types of variation





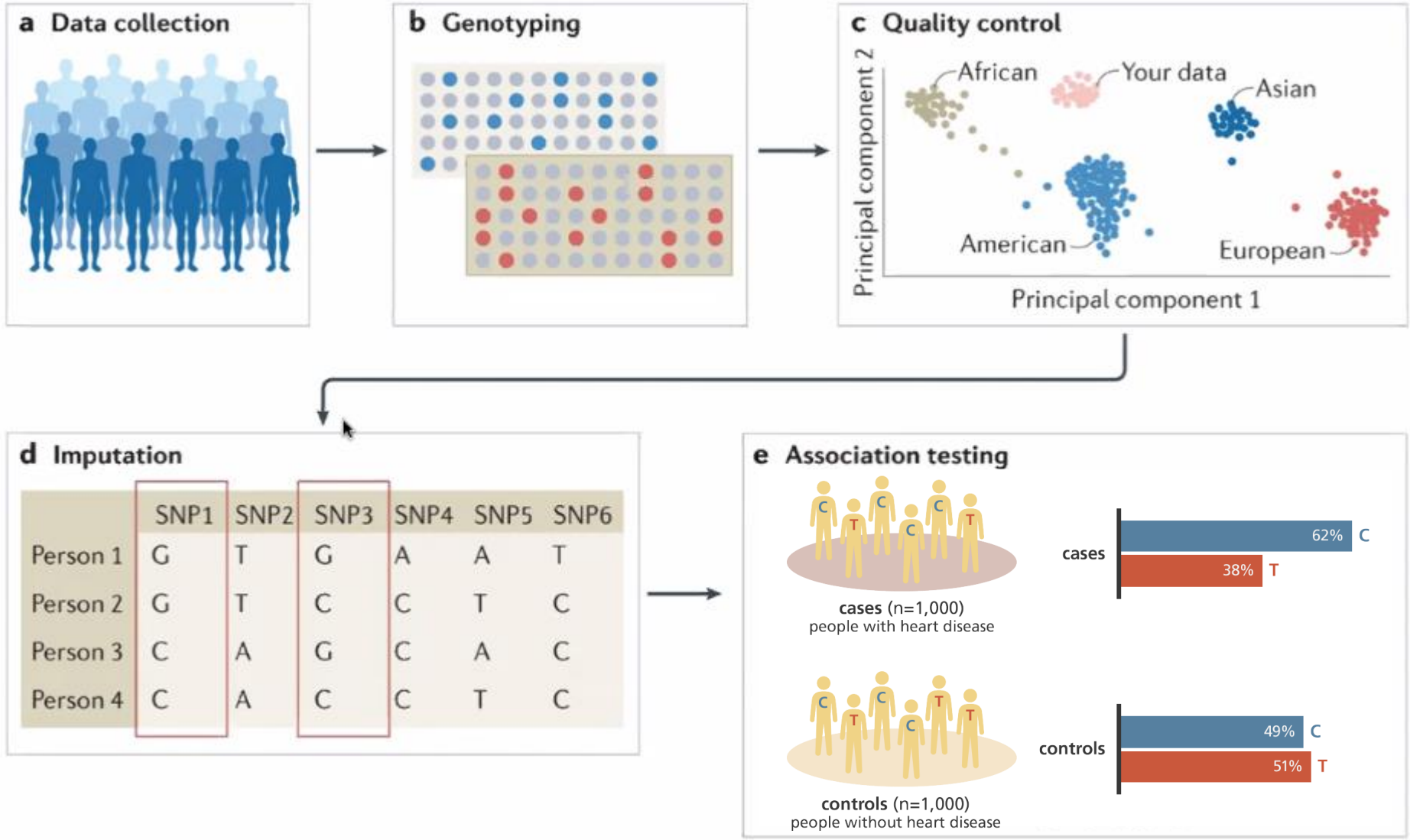
Single nucleotide polymorphisms (SNPs)

McCarthy MI et al. Genome-wide association studies for complex traits: consensus, uncertainty and challenges, Nature Reviews Genetics 2008

Genome-wide association study

Logistic regressions for each SNP comparing cases vs controls

P < 5x10-8

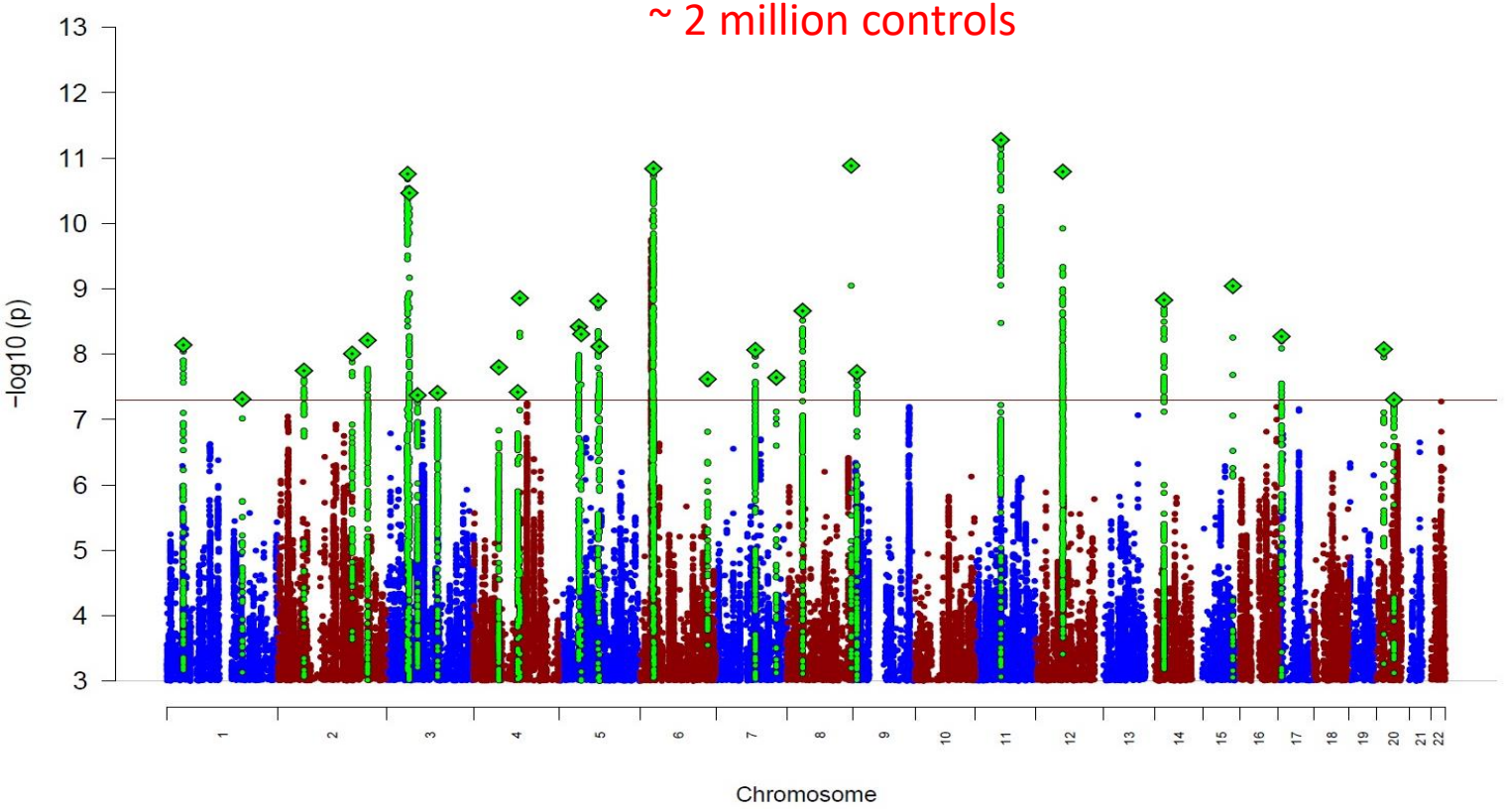


Adapted from: Uffelmann E et al., Genome-wide association studies, nature reviews methods primers 2021

OCD GWAS results

Meta-analysis of 28 cohorts identified 30 significant loci

53,660 cases with OCD
~ 2 million controls

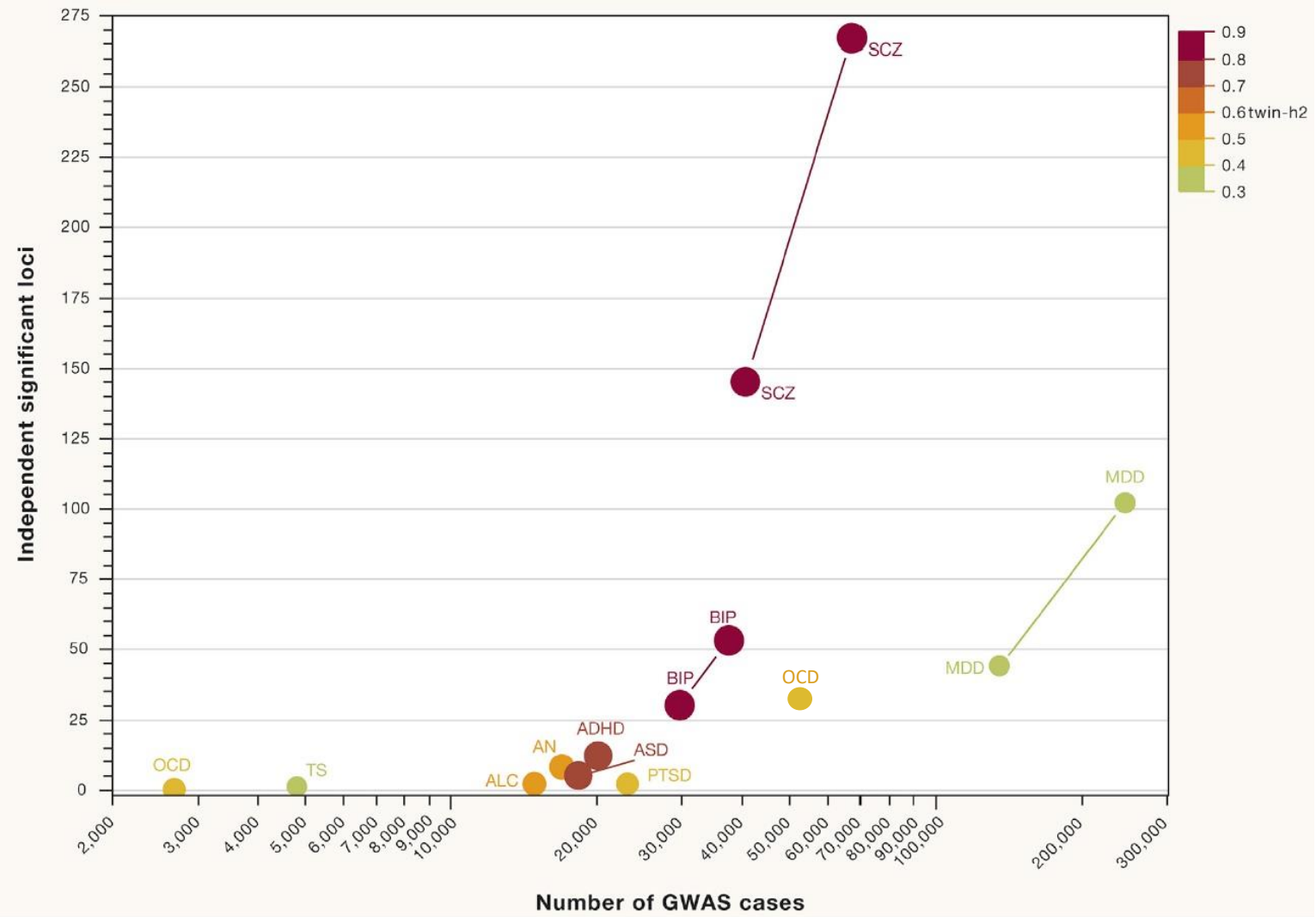


All participating cohorts:
23andMe
MVP
OCGAS
IOCDF
UKBB
NORDiC
EGOS
iPSYCH
AGDS/QIMR
bioVU
EstBB
FinnGen
HUNT
MoBa
Michigan/Toronto
YalePenn
Chop
Coga
EPOC
Würzburg
PsychBroad

Strom NI et al., Genome-wide association study identifies 30 obsessive-compulsive disorder associated loci, accepted at Nature Genetics, 2025

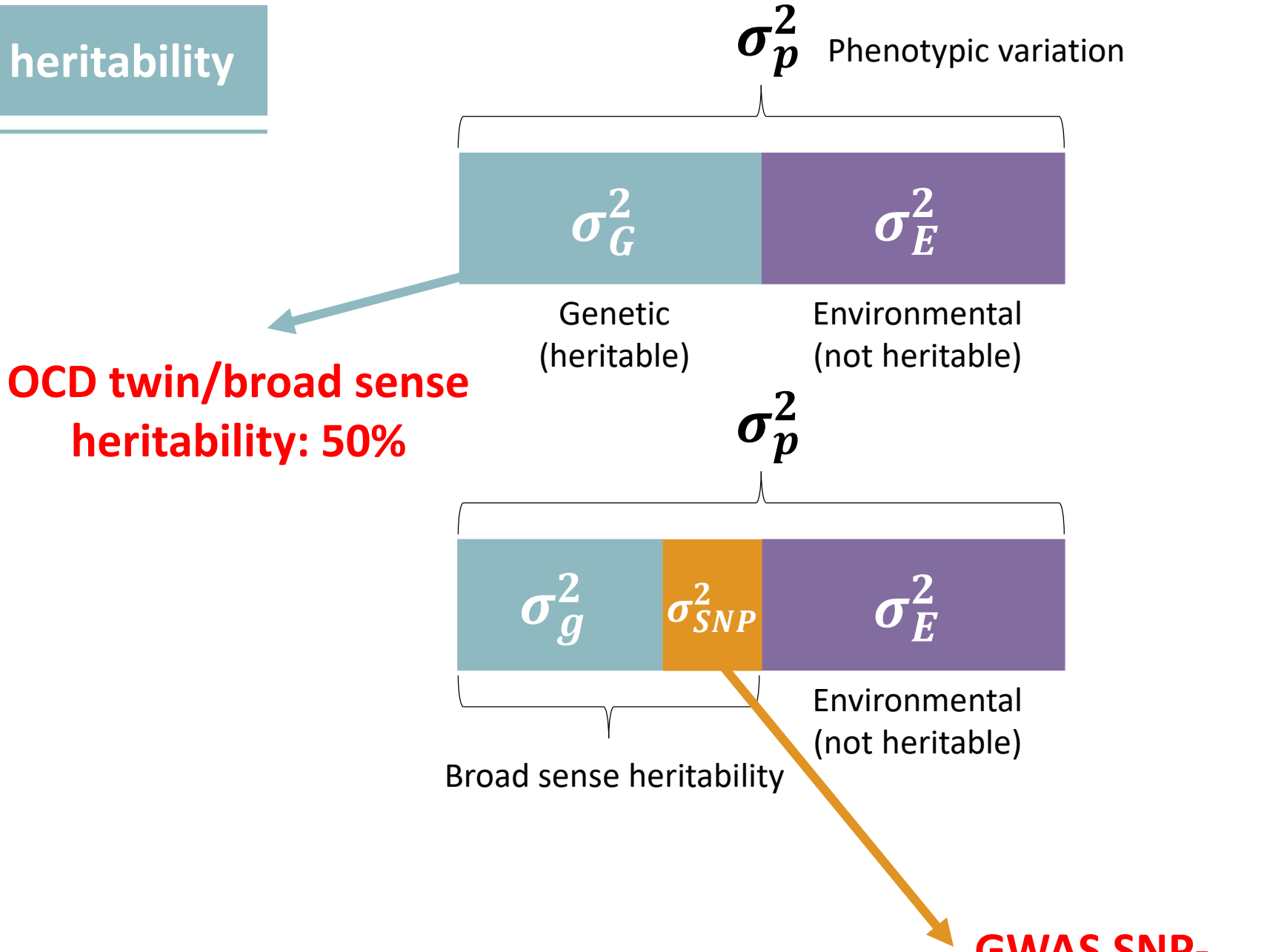
Genetics of psychiatric disorders

Relationship between N_{cases} in GWAS and significant loci



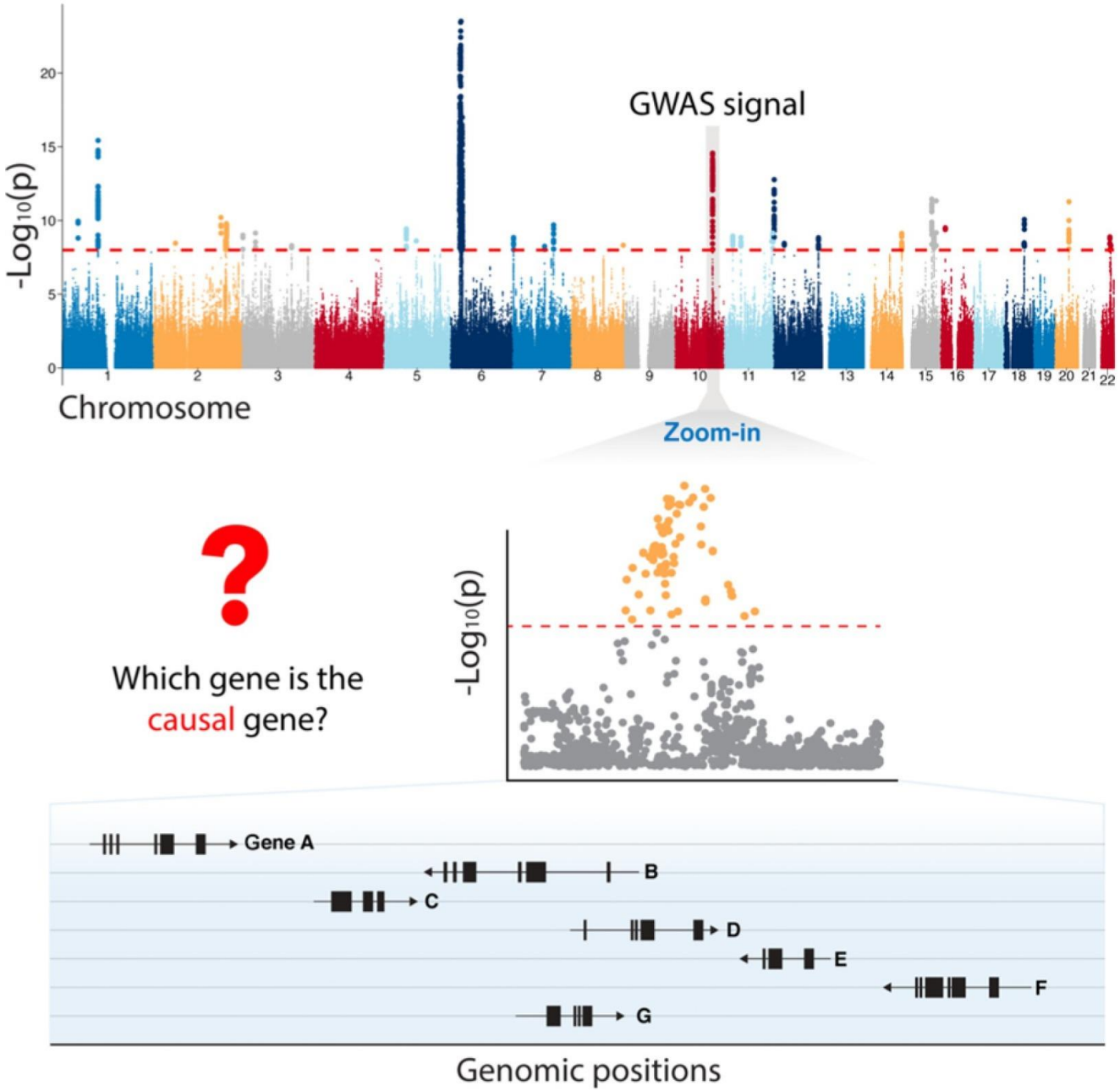
P Sullivan & D Geschwind Defining the Genetic, Genomic, Cellular, and Diagnostic Architectures of Psychiatric Disorders (2019), Cell

OCD SNP heritability



Finding causal genes

Mapping is very complicated

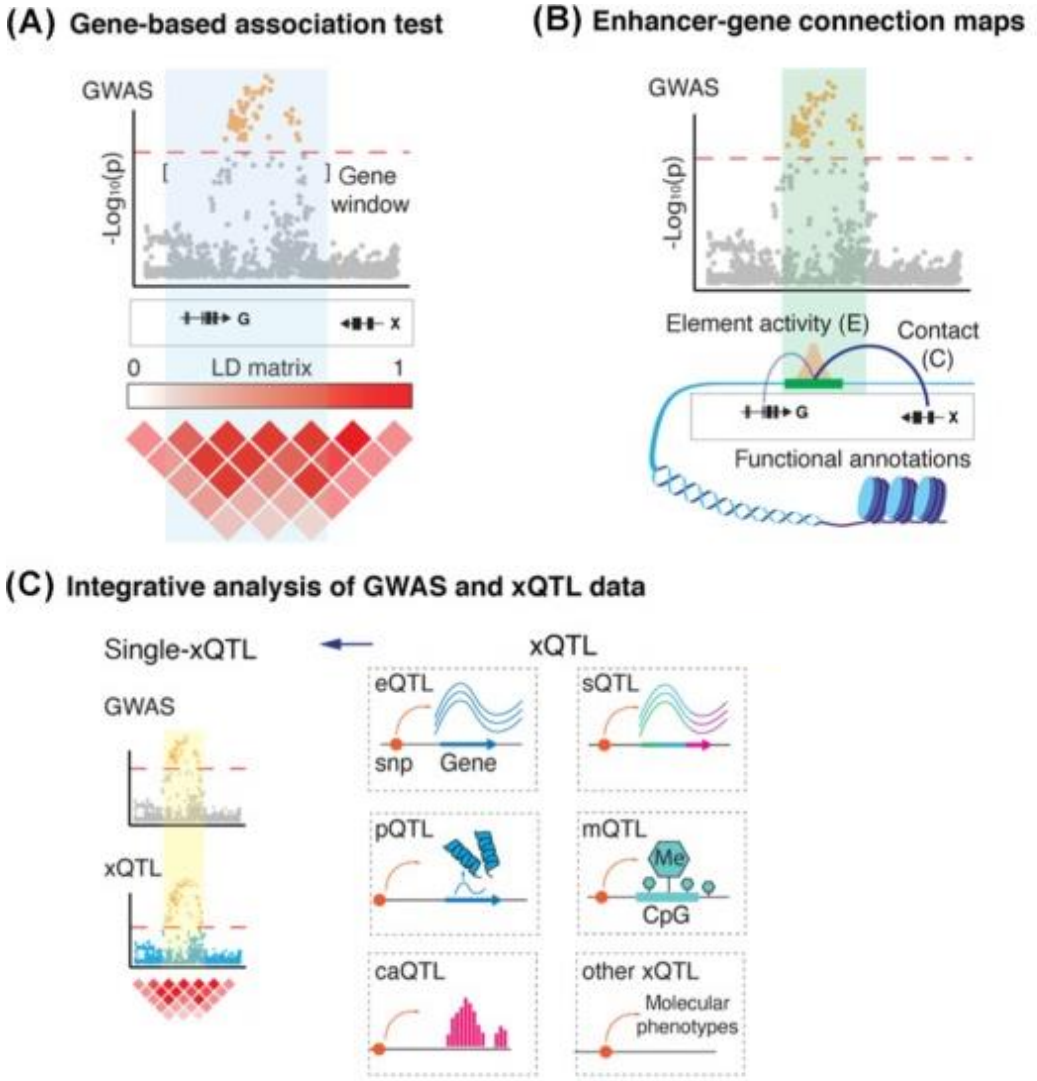


- Low mapping resolution (many correlated SNPs in one locus)
- Primarily non-coding
- Gene regulation

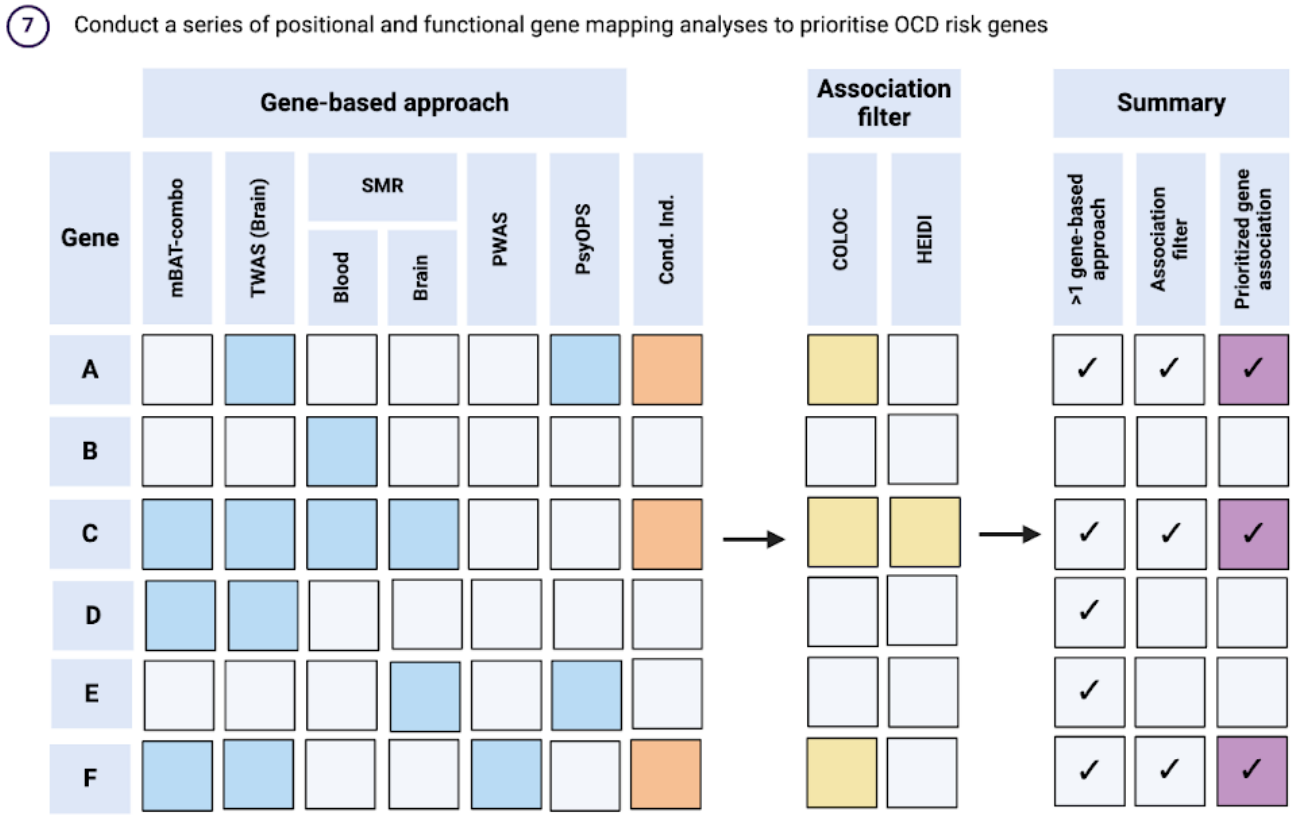
Trends in Genetics

Qi T et al., From genetic associations to genes: methods, applications, and challenges, Trends in Genetics 2024

Finding causal genes



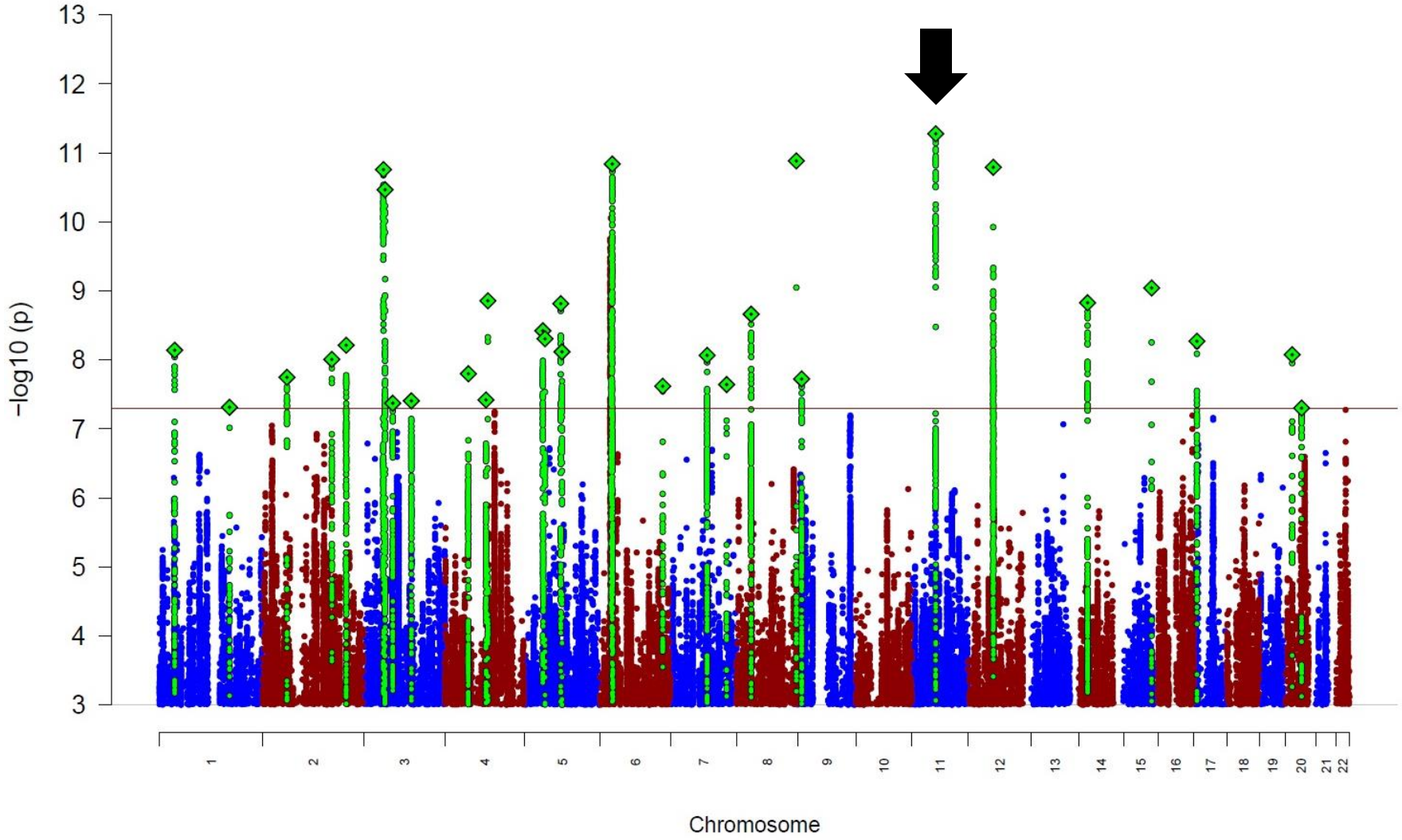
Qi T et al., From genetic associations to genes: methods, applications, and challenges, Trends in Genetics 2024



Strom NI et al., Genome-wide association study identifies 30 obsessive-compulsive disorder associated loci, accepted at Nature Genetics, 2025

OCD GWAS results

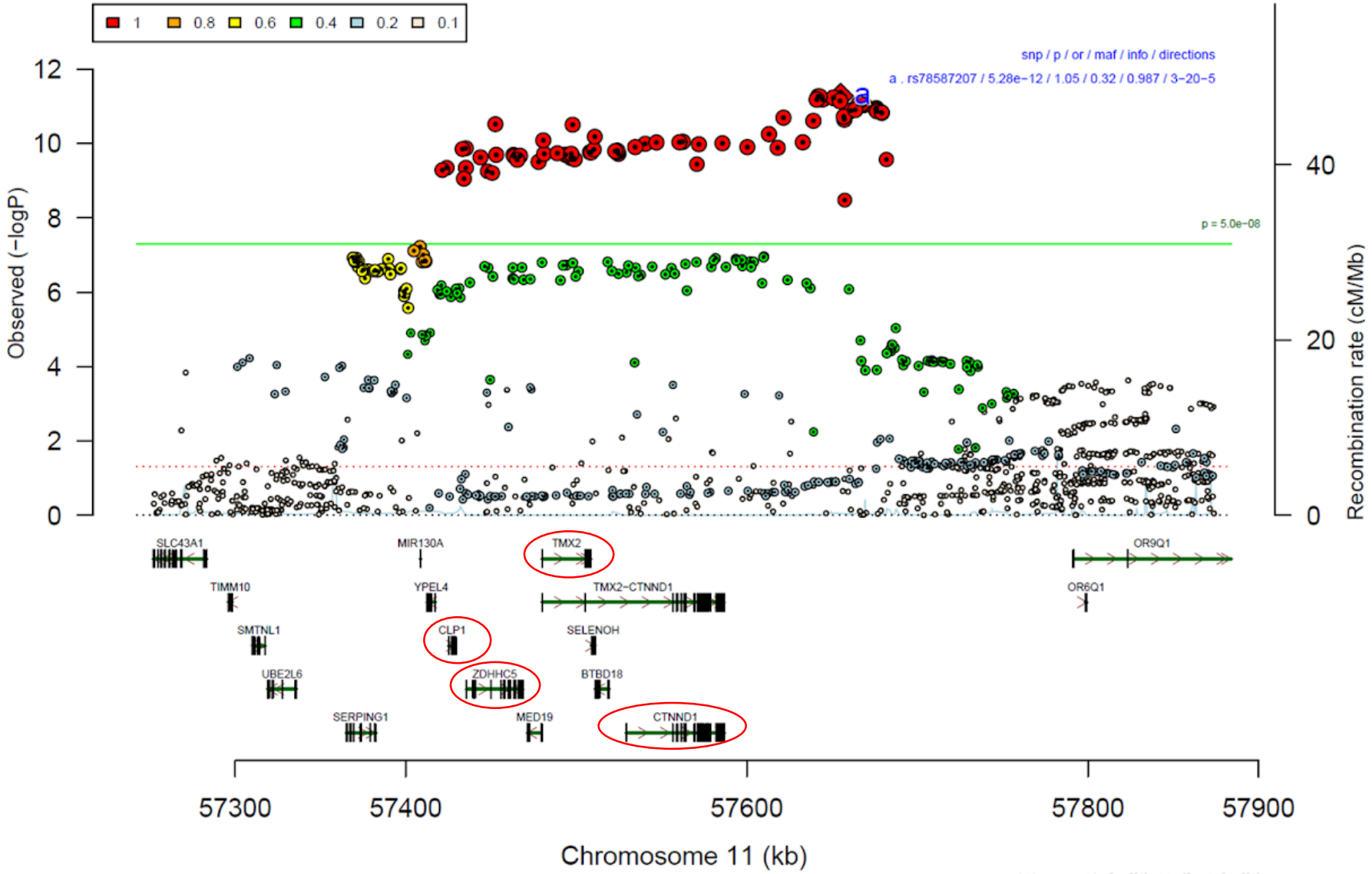
Closer look at significant regions



Strom NI et al., Genome-wide association study identifies 30 obsessive-compulsive disorder associated loci, accepted at Nature Genetics, 2025

Zooming in

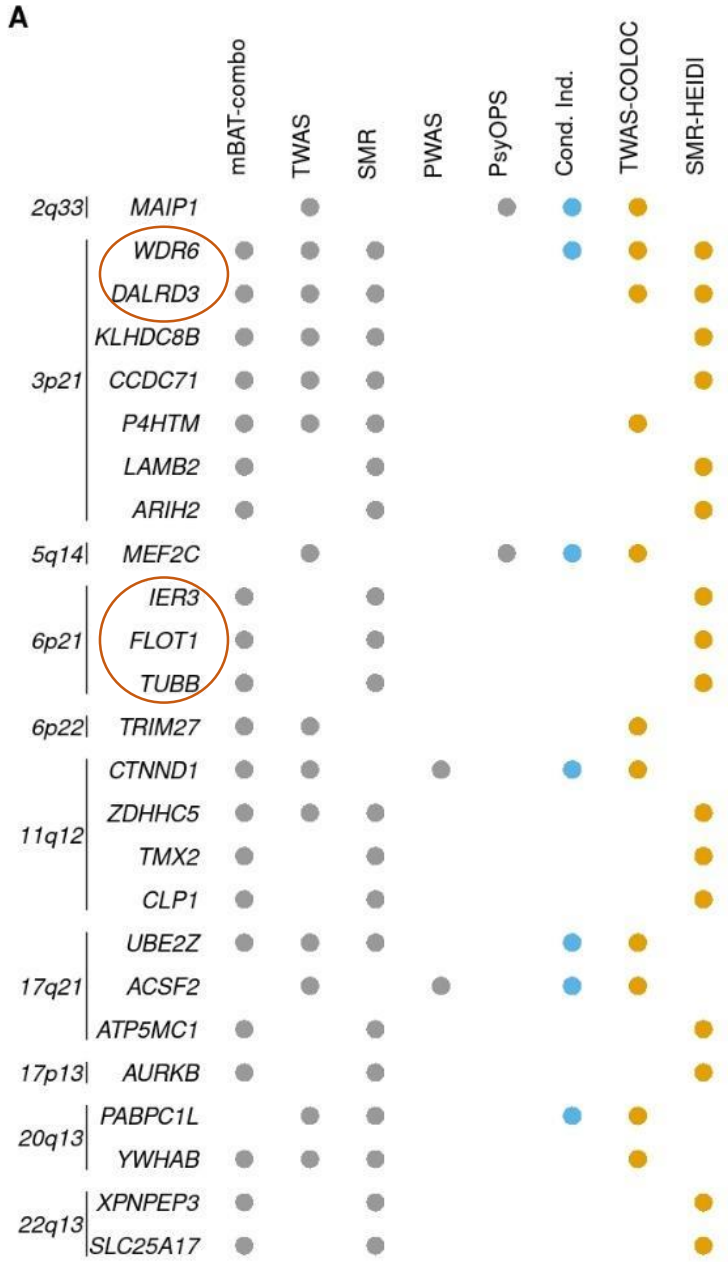
SNP rs78587207: 4 putative causal genes: *CTNND1*, *CLP1*, *TMX2*, *ZDHHC5*



Strom NI et al., Genome-wide association study identifies 30 obsessive-compulsive disorder associated loci, accepted at Nature Genetics, 2025

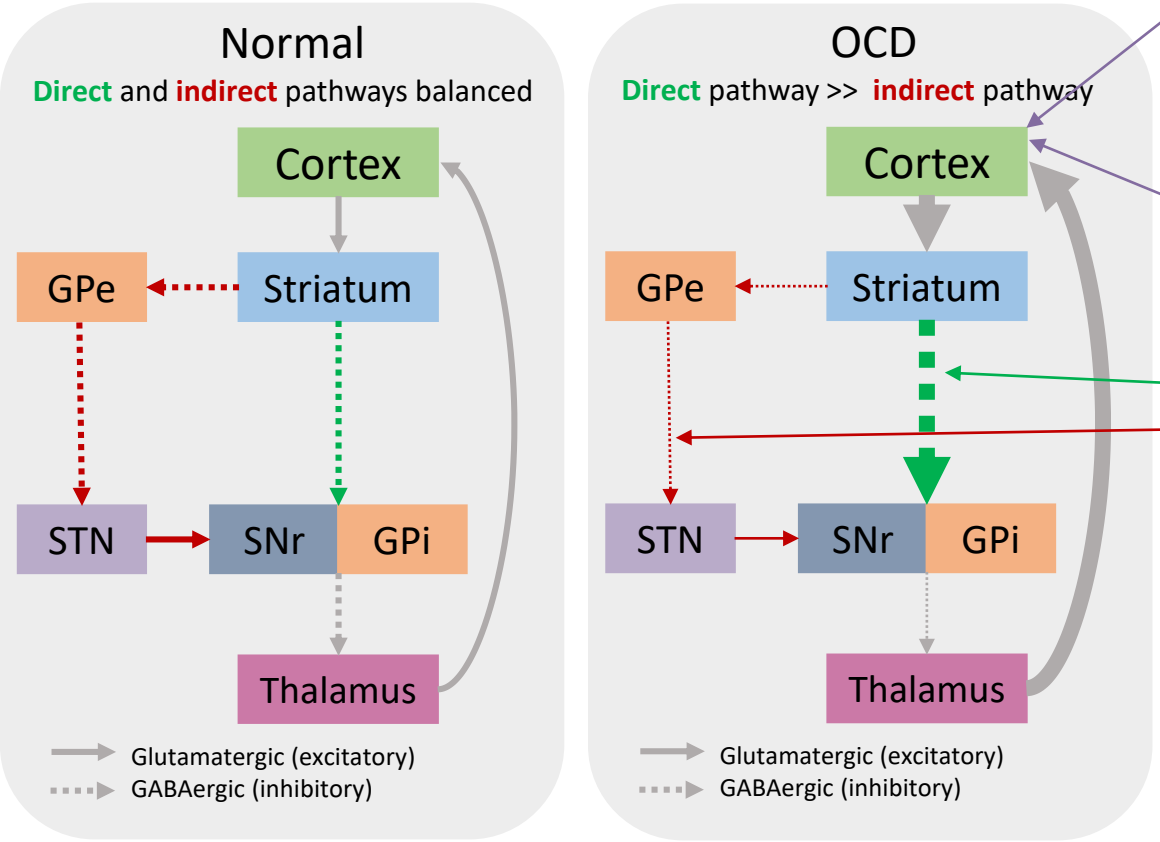
Gene-based results

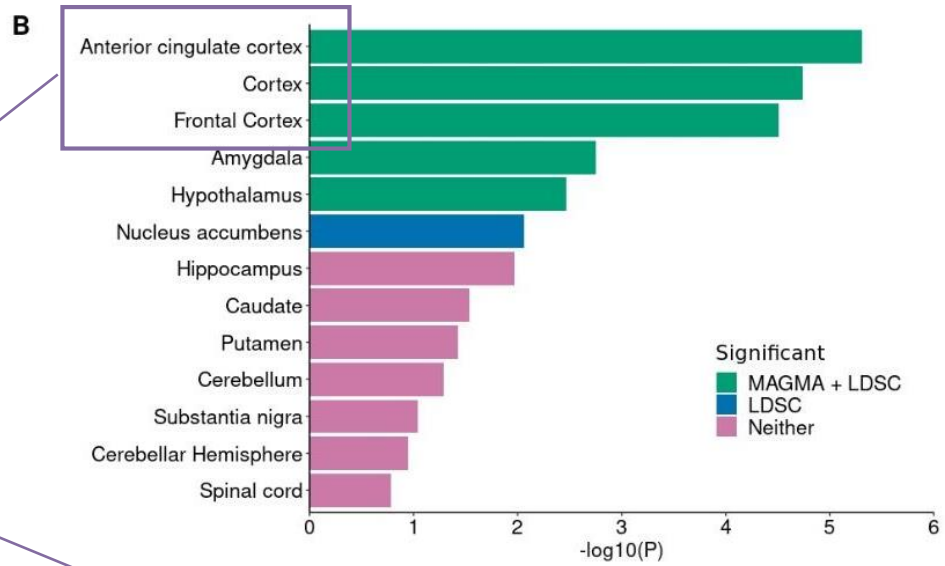
25 likely causal genes

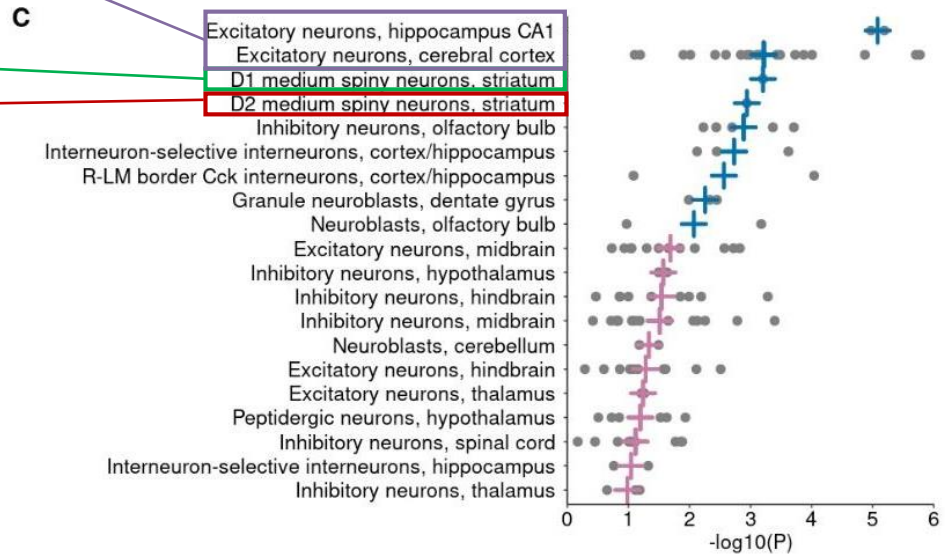


Strom NI et al., Genome-wide association study identifies 30 obsessive-compulsive disorder associated loci, accepted at Nature Genetics, 2025

Tissue expression



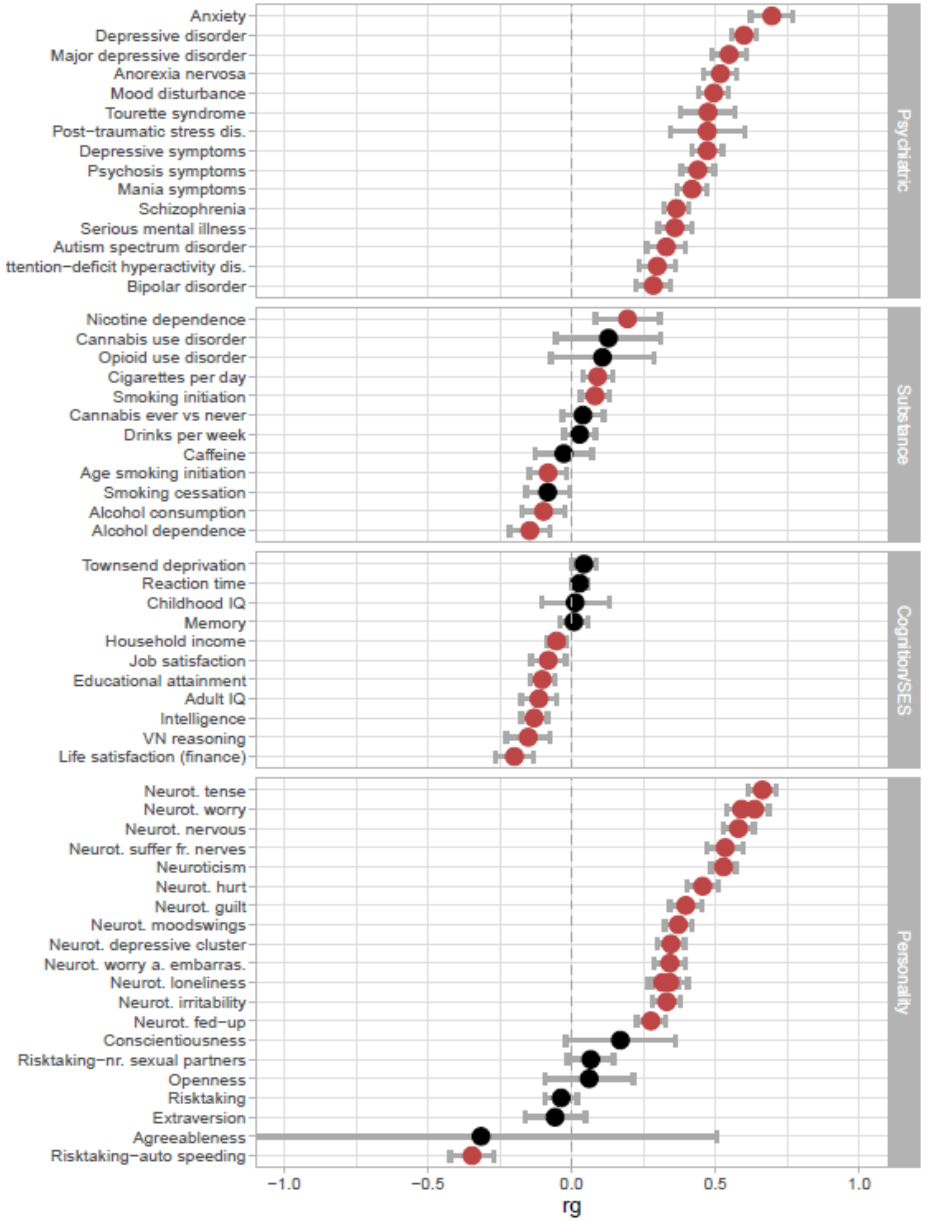


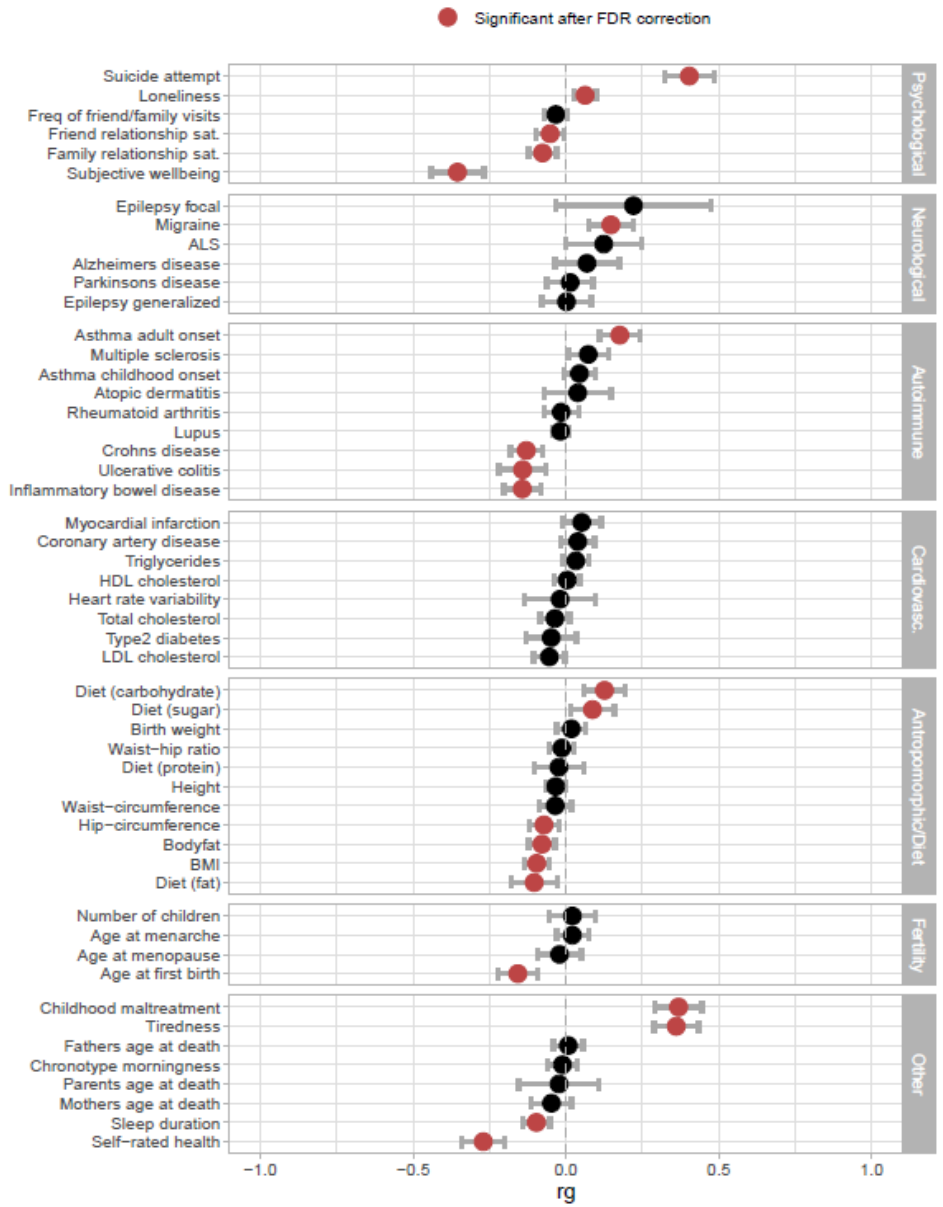


Strom NI et al., Genome-wide association study identifies 30 obsessive-compulsive disorder associated loci, accepted at Nature Genetics, 2025

Genetic relatedness

Genetically correlated with 63/112 phenotypes

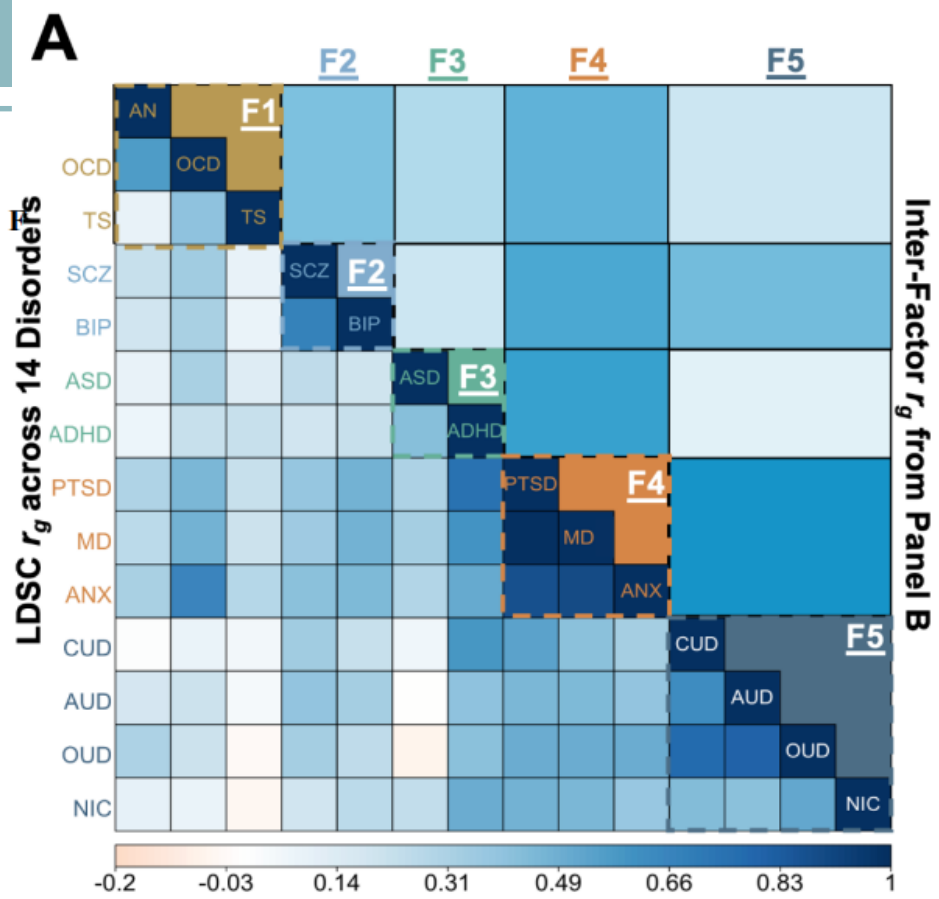


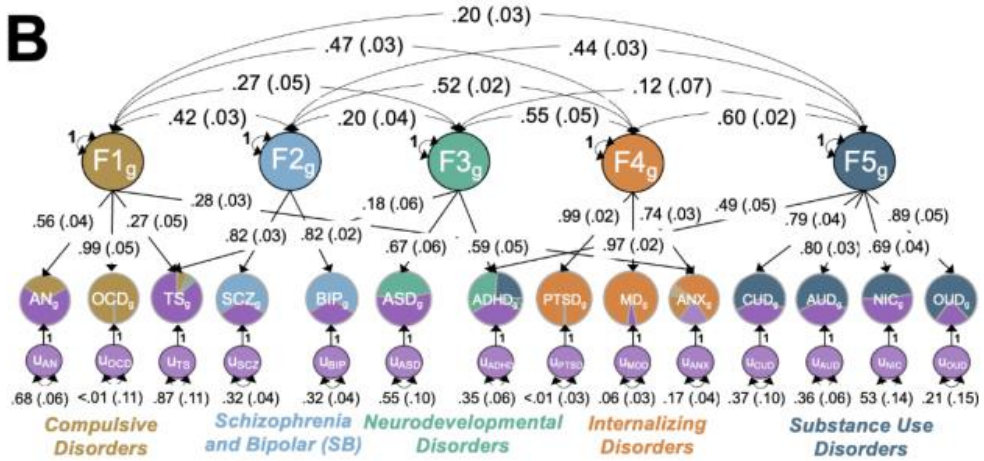


Strom NI et al., Genome-wide association study identifies 30 obsessive-compulsive disorder associated loci, accepted at Nature Genetics, 2025

Genetic relatedness

OCD clusters together with Anorexia and Tourette syndrome

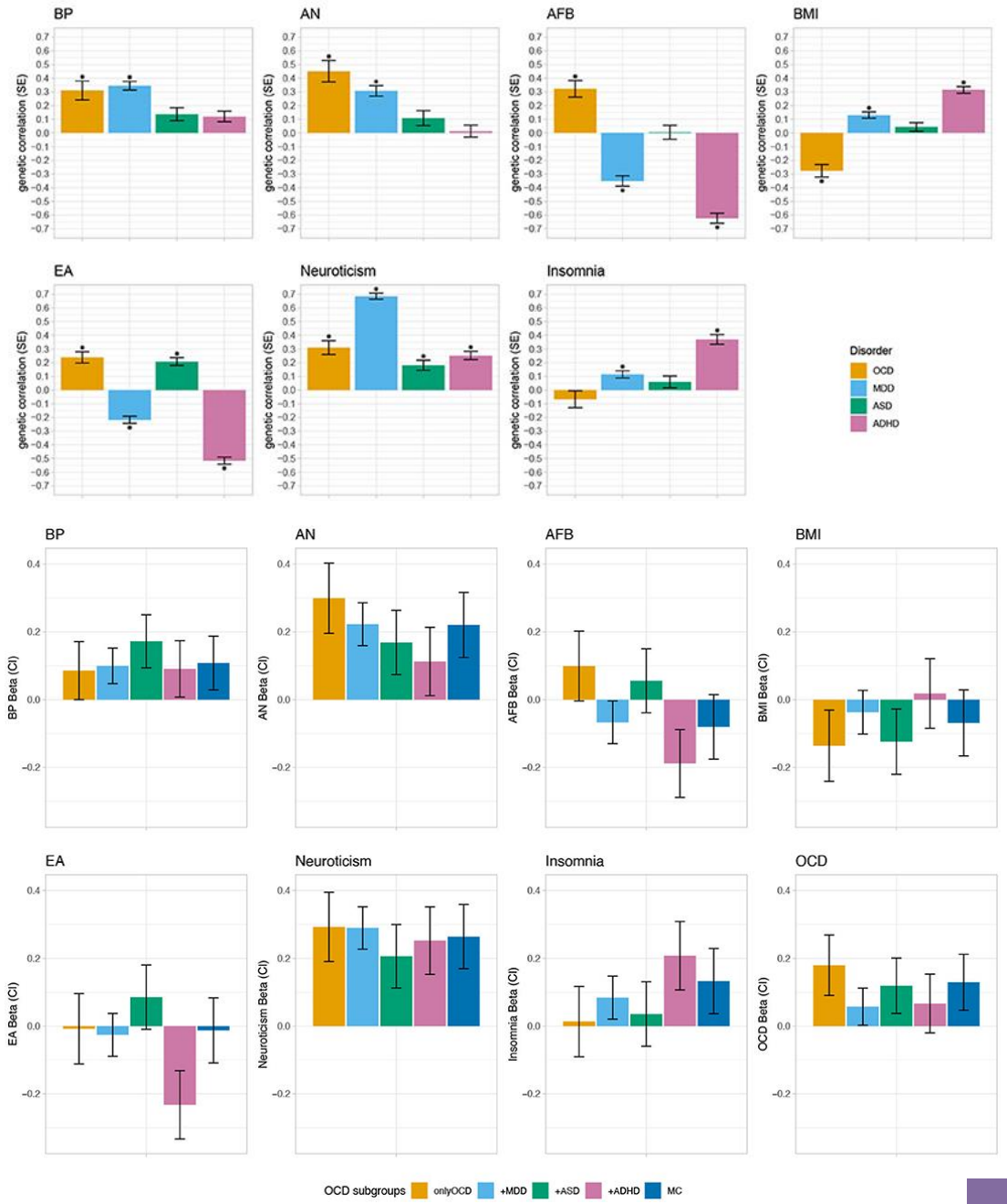




Grotzinger AD et al., The Landscape of Shared and Divergent Genetic Influences across 14 Psychiatric Disorders, medRxiv 2025

Comorbidity

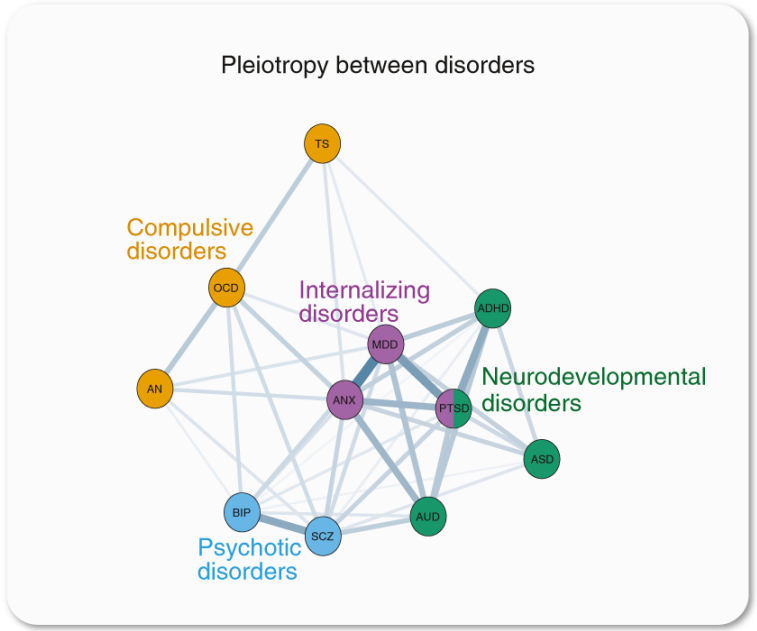
iPSYCH sample
onlyOCD: 366cases
OCD+MDD: 1052 cases
OCD+ASD: 388 cases
OCD+ADHD: 443 cases
OCD+multiple: 429 cases

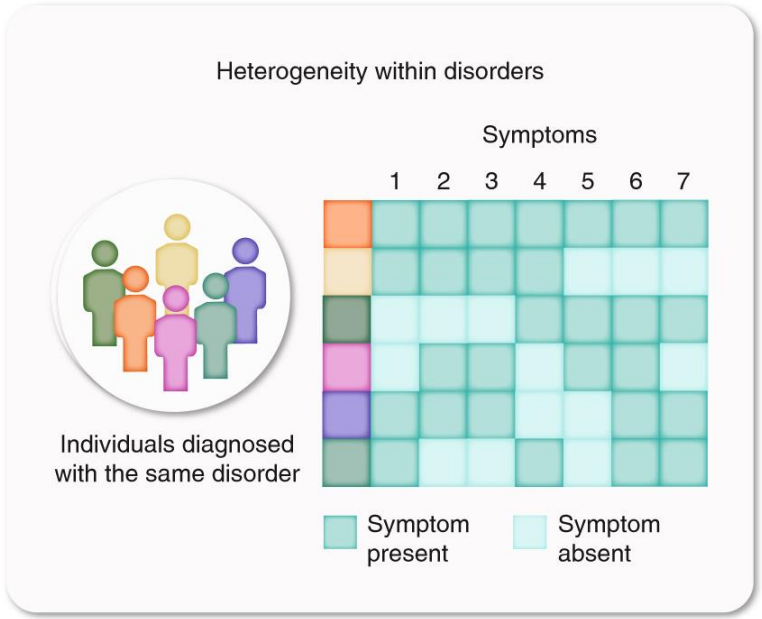


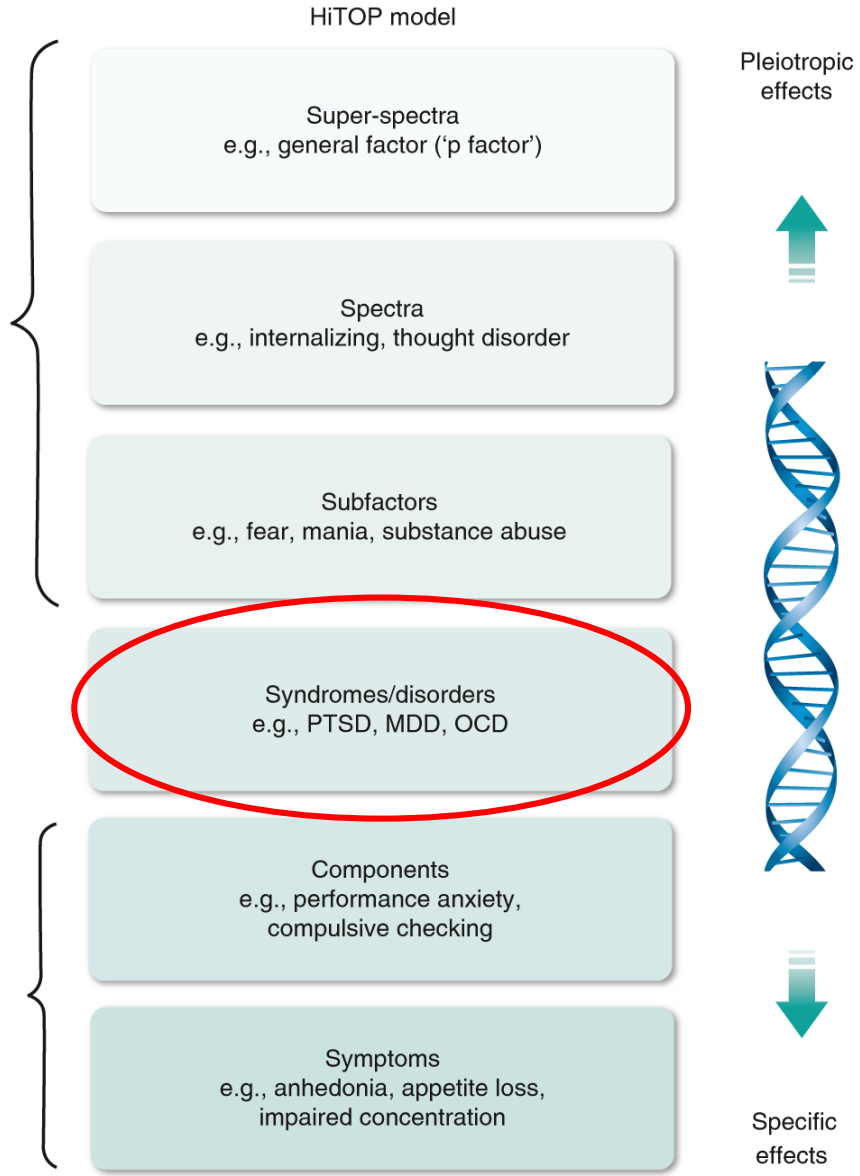
Strom NI et al., Polygenic Heterogeneity Across Obsessive-Compulsive Disorder Subgroups Defined by a Comorbid Diagnosis, Frontiers in Genetics, 2021

Specificity

Genetic risk acts on different levels from very broad (general psychiatric risk) to very specific (symptoms)







Derks E et al., Ten challenges for clinical translation in psychiatric genetics, nature genetics perspective, 2022

Rare genetic signal in OCD

~1 in 20 OCD cases have a rare coding variant that substantially contributes to their disorder

nature neuroscience
ARTICLES
https://doi.org/10.1038/s41593-021-00876-8
Check for updates

Exome sequencing in obsessive-compulsive disorder reveals a burden of rare damaging coding variants

OCD cases = 1313 (trios)
+ 644 additional cases

Small rare genetic variants:

- Rare coding single nucleotide variants (SNVs)
- indels

Halvorsen MW et al., Exome sequencing in obsessive-compulsive disorder reveals a burden of rare damaging coding variants, Nature Neurocience 2021

Molecular Psychiatry
www.nature.com/mp

ARTICLE OPEN
Check for updates

A burden of rare copy number variants in obsessive-compulsive disorder

OCD cases = 2248

Large rare genetic variants:

- Rare copy number variants (CNVs)

Halvorsen MW et al., A burden of rare copy number variants in obsessive-compulsive disorder, Molecular Psychiatry 2024

Summary OCD genetics

We identified the first genetic variants ever associated with OCD

- OCD is highly genetic
  - Twin studies: 50% heritability
  - GWAS: 7% heritability
- We found 30 loci associated with OCD (common SNPs)
- 25 credible genes implicated
- Rare genetic variants also seem to have an impact (less studied)
- Genes expressed in brain areas and cell types involved in the CSCT-circuitry
- Genetically correlated with other traits, especially with Tourette syndrome, anorexia & anxiety

Limitations:

- Mechanistic understanding from gene → disorder still limited
- Many samples not deeply phenotyped (self-reported diagnosis)
- Individuals only from European ancestry

Drug target discovery/repurposing

Drug development including evidence from human genetics are twice as successful

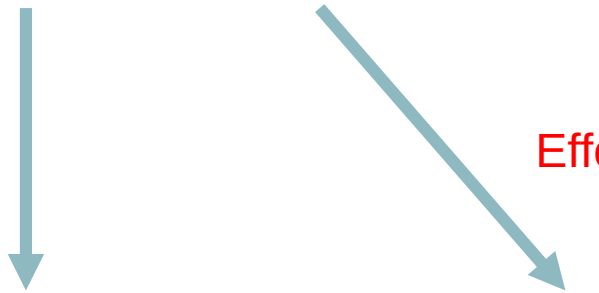
- **Depression GWAS** identified possible new therapeutic targets:
  - anti-cancer therapies,
  - modafinil (reduces daytime sleepiness)
  - pregabalin (pain management)

MDD Consortium of the PGC. Trans-ancestry genome-wide study of depression identifies 697 associations implicating cell types and pharmacotherapies. *Cell* 2025.

Pharmacogenetics

Using genetic variants to predict a patient's response to a particular drug

CYP2D6 and ***CYP2C19*** for antidepressants and antipsychotics



Effects on antidepressants

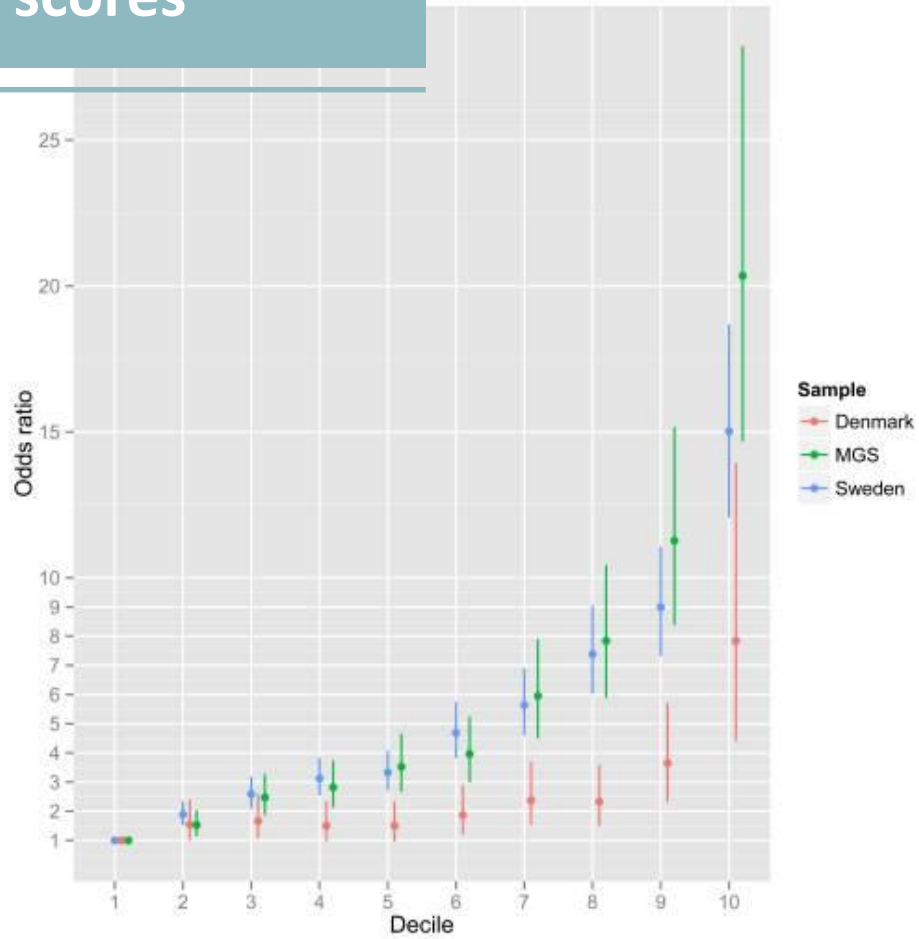
Metabolism of venlafaxine, fluoxetine, paroxetine

Metabolism of escitalopram, citalopram, sertraline (poor metabolizers increased side effects, ultrarapid metabolizers

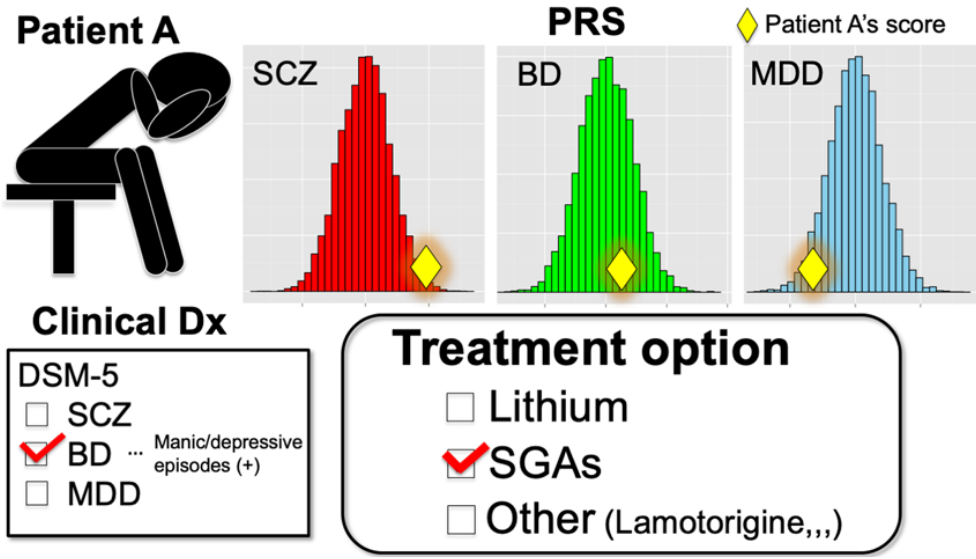
Zai G, Pharmacogenetics of Obsessive-Compulsive Disorder: An Evidence-Update, The Neurobiology and Treatment of OCD: Accelerating Progress 2021

Polygenic risk scores

Common genetic findings are not commonly used in clinical pratice



SCZ working group of the PGC. *Nature*, 2014



Ikeda et al., Polygenic risk score as clinical utility in psychiatry: a clinical viewpoint. Journal of human genetics, 2020

But they might help to guide differential diagnosis (not used in the clinic yet!).

Genetic risk scores (from **GWAS**) do not have sufficient power for future diagnosis

Genetic testing and counseling

Genetic testing of rare genetic findings might be useful for some psychiatric disorders

- Known **rare genetic variants** for neurodevelopmental disorders and schizophrenia are of relevance in genetic counselling
- European network: **EnGagE** (Enhancing Psychiatric Genetic Counseling, Testing, and Training in Europe)

Koido et al., Lack of guidelines and translational knowledge is hindering the implementation of psychiatric genetic counseling and testing within Europe – A multi-professional survey study. European journal of medical genetics, 2023

Thank you!

All participating cohorts:
23andMe
MVP
OCGAS
IOCDF
UKBB
NORDiC
EGOS
iPSYCH
AGDS/QIMR
bioVU
EstBB
FinnGen
HUNT
MoBa
Michigan/Toronto
YalePenn
Chop
Coga
EPOC
Würzburg
PsychBroad

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Dr. Zac Gerring


Dr. Dongmei Yu


Dr. Matthew Halvorsen


Dr. Manuel Mattheisen


Dr. Jeremiah Scharf


Dr. Eske Derks


Dr. Carol Mathews

& many more!

International OCD Foundation

Questions?

O.C.D comics – Lily Williams