What Genetics is Telling Us About Substance Use Disorders

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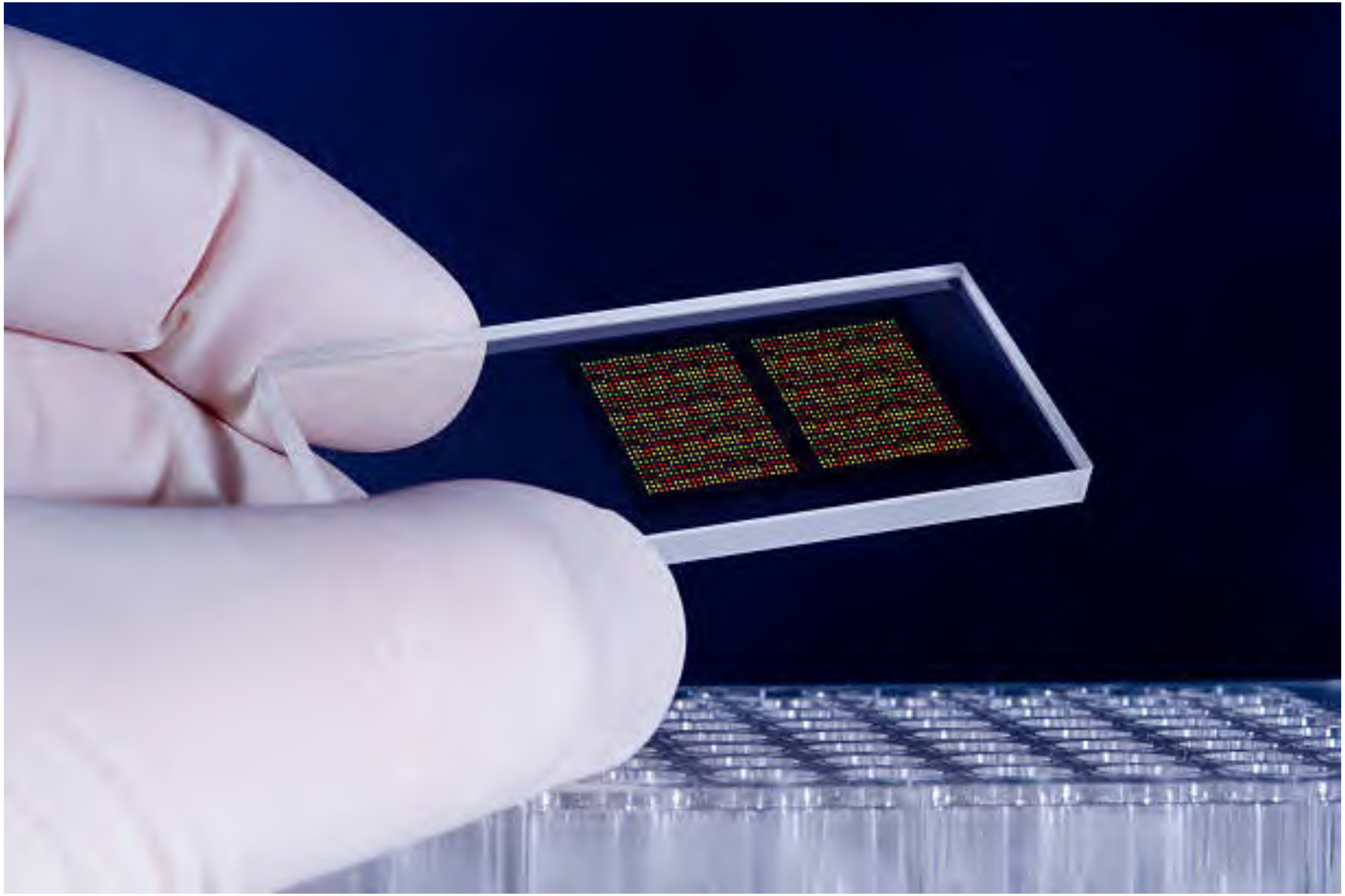
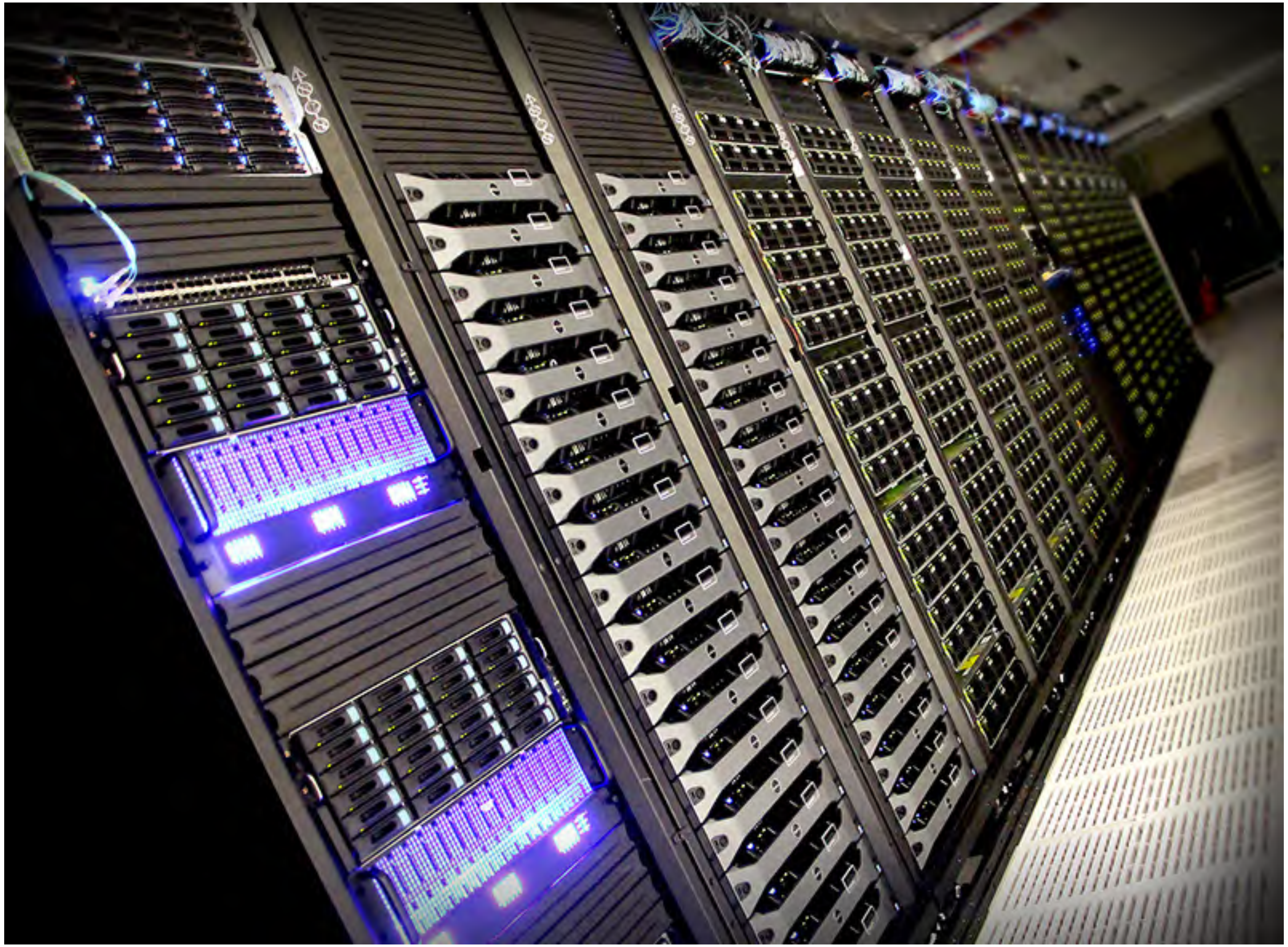
Substance use disorders are complex psychiatric conditions

Substance use disorder genetics

Advances in human genetics

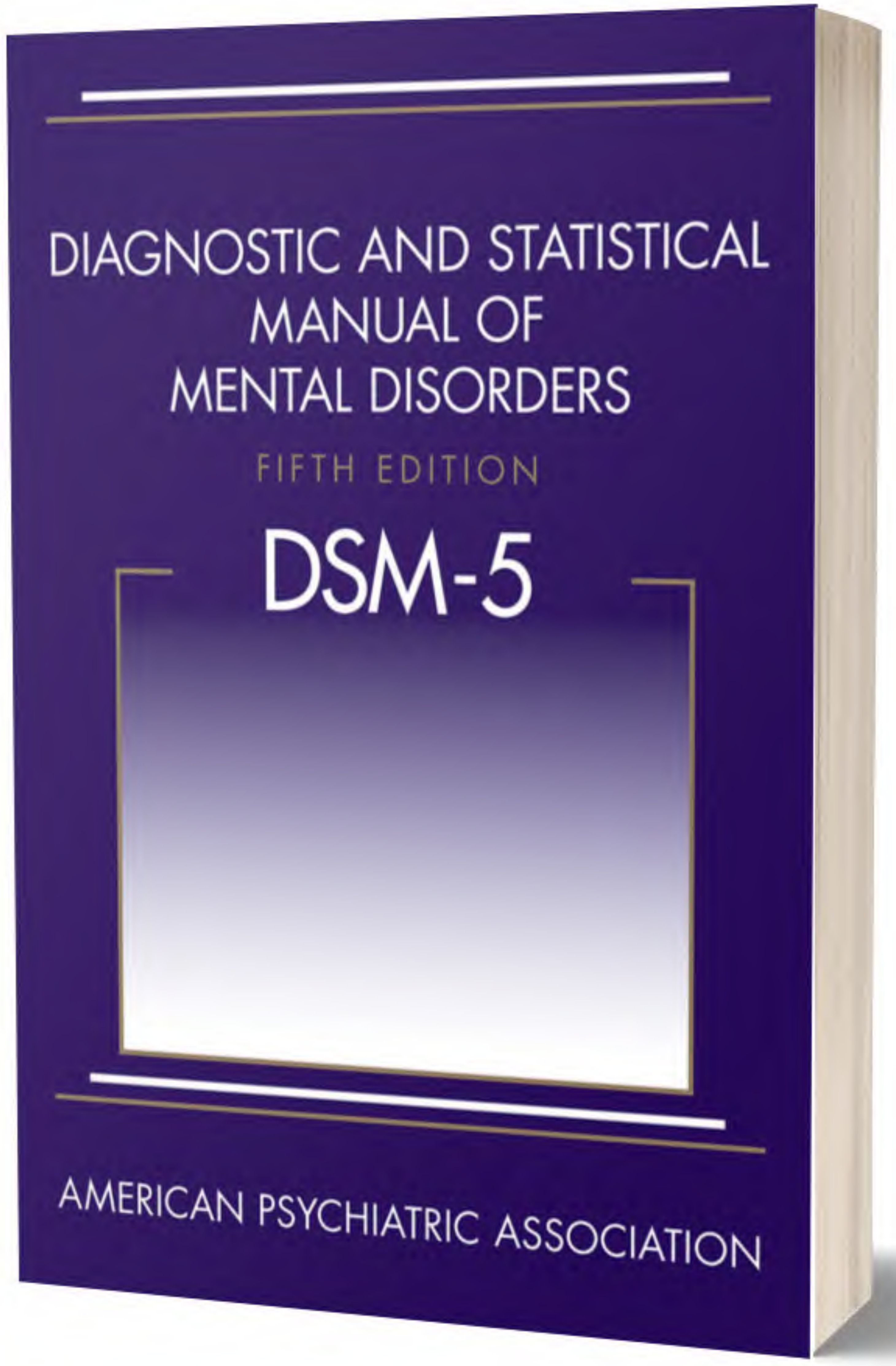
Genome-wide association studies
GWAS





How do we MEASURE substance use disorders?

20 40 60 80 100 120 140 160 180 200 220 240 260 280 300


DIAGNOSTIC AND STATISTICAL
MANUAL OF
MENTAL DISORDERS
FIFTH EDITION
DSM-5
AMERICAN PSYCHIATRIC ASSOCIATION

Substance Use Disorder (DSM-5)

1 Larger amounts or longer than intended

2 Unsuccessful efforts to cut down

3 Excessive time to obtain, use, or recover

4 Craving or strong desire to use

5 Failure to fulfill role obligations

6 Continued use despite recurrent problems

7 Important activities reduced due to use

8 Hazardous use

9 Continued use due to a problem caused by the substance

10 Tolerance

11 Withdrawal

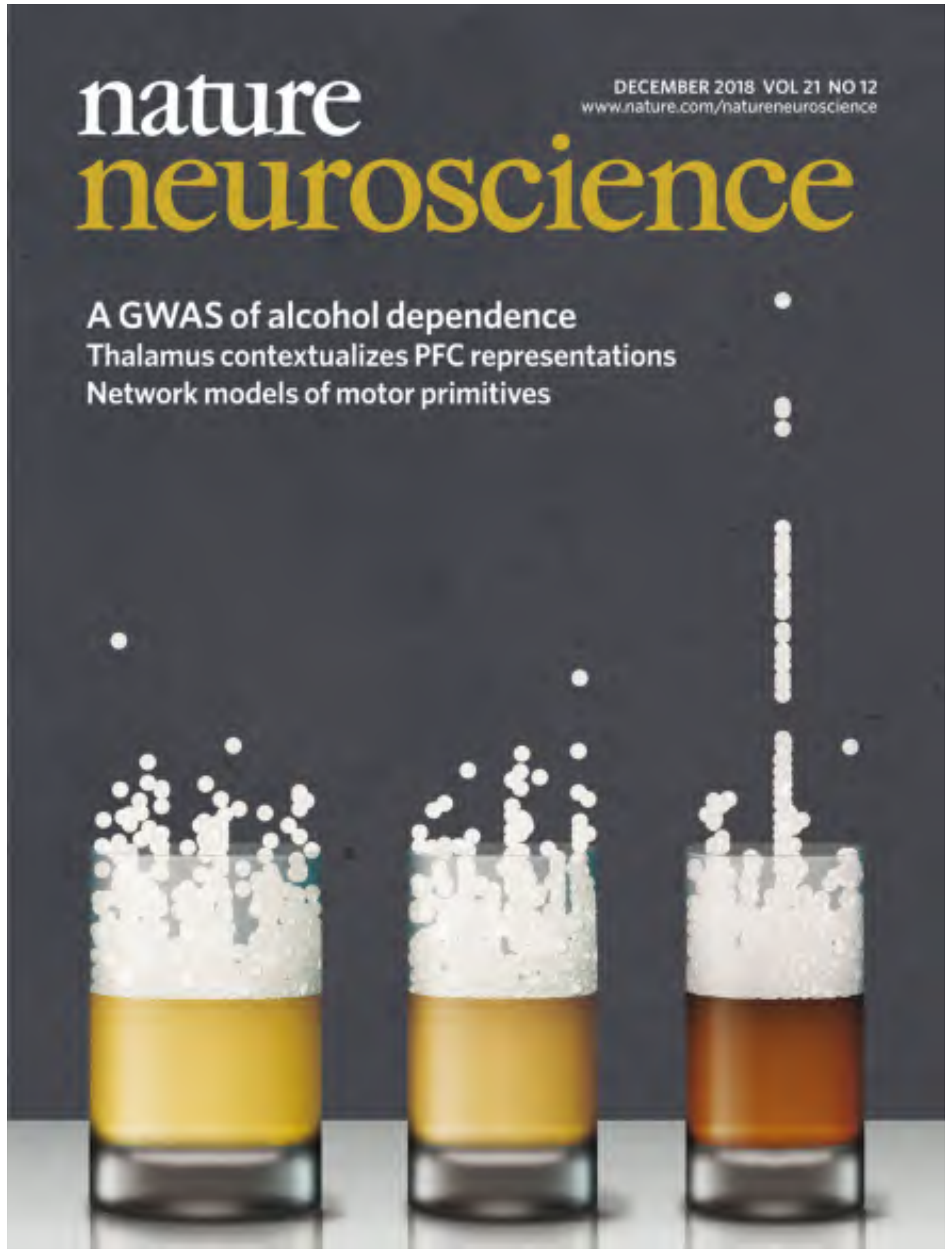
Mild 2-3 symptoms **Moderate** 4-5 symptoms **Severe** 6 or more symptoms

Clinical populations

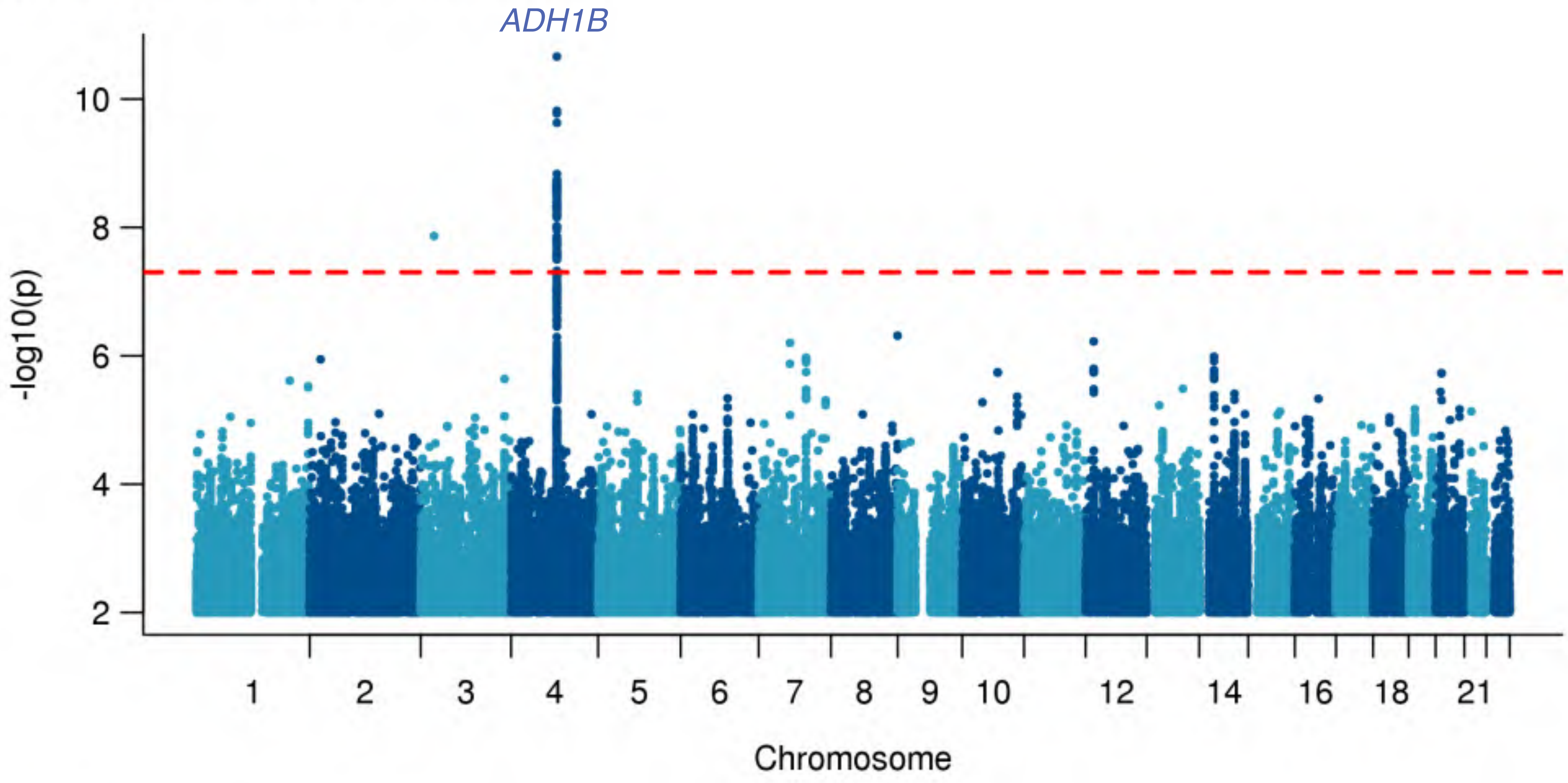
Substance Use Disorder Workgroup

PGC
Psychiatric Genomics Consortium

A multi-ancestral GWAS of alcohol dependence (14,904 cases, 37,994 controls)

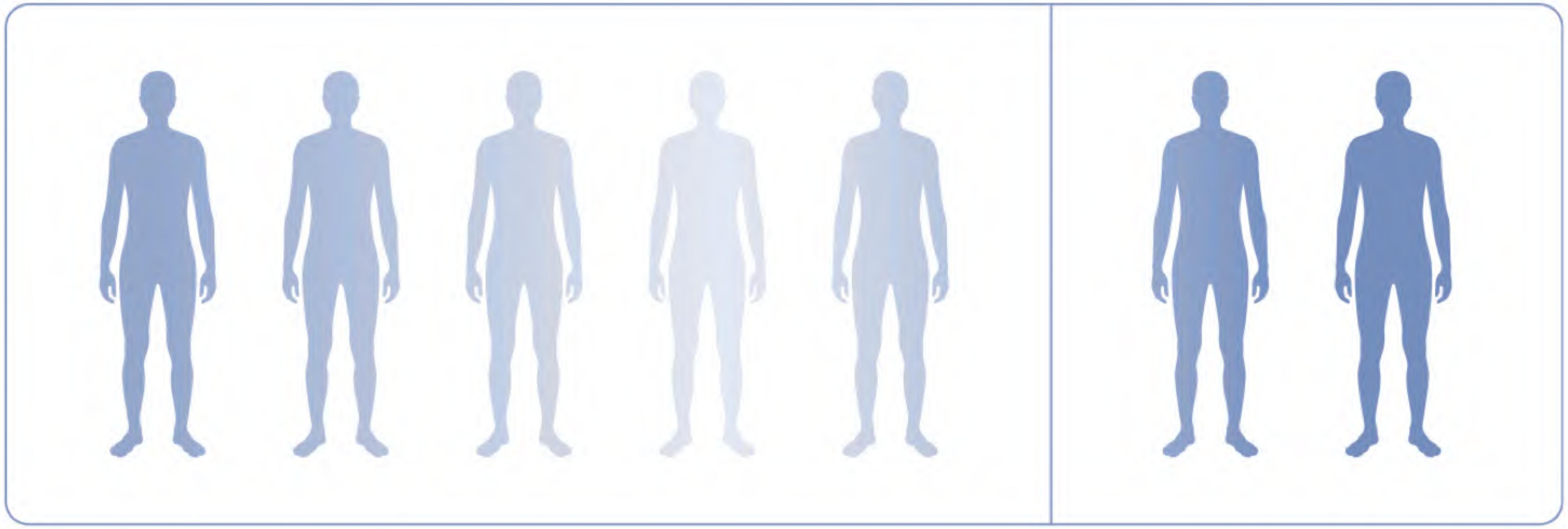


A multi-ancestral GWAS of alcohol dependence (14,904 cases, 37,994 controls) implicated *ADH1B*, an ethanol metabolizing gene



Walters et al PGC-Substance Use Disorder, *Nature Neuroscience*, 2018

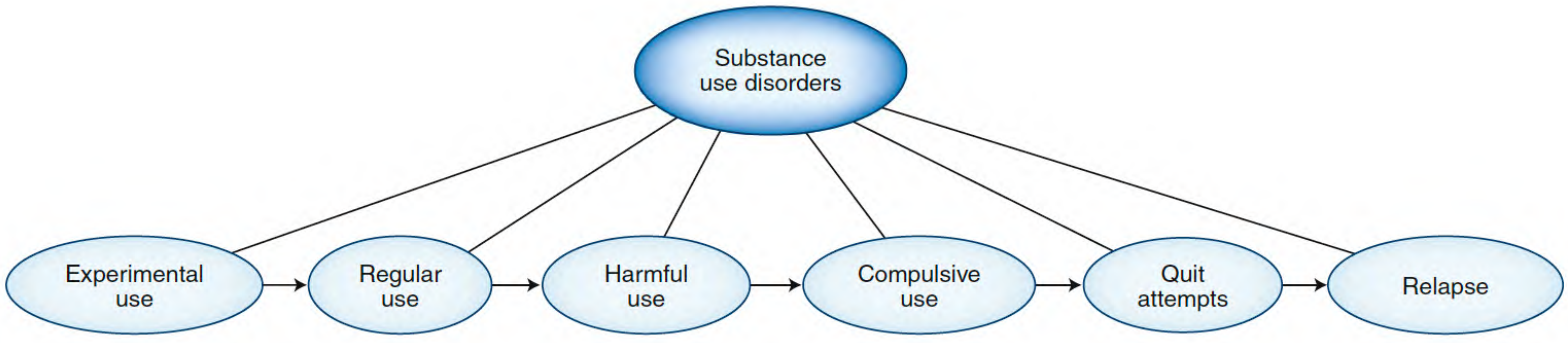
There are 2,036 unique combinations to receive a substance use disorder diagnosis



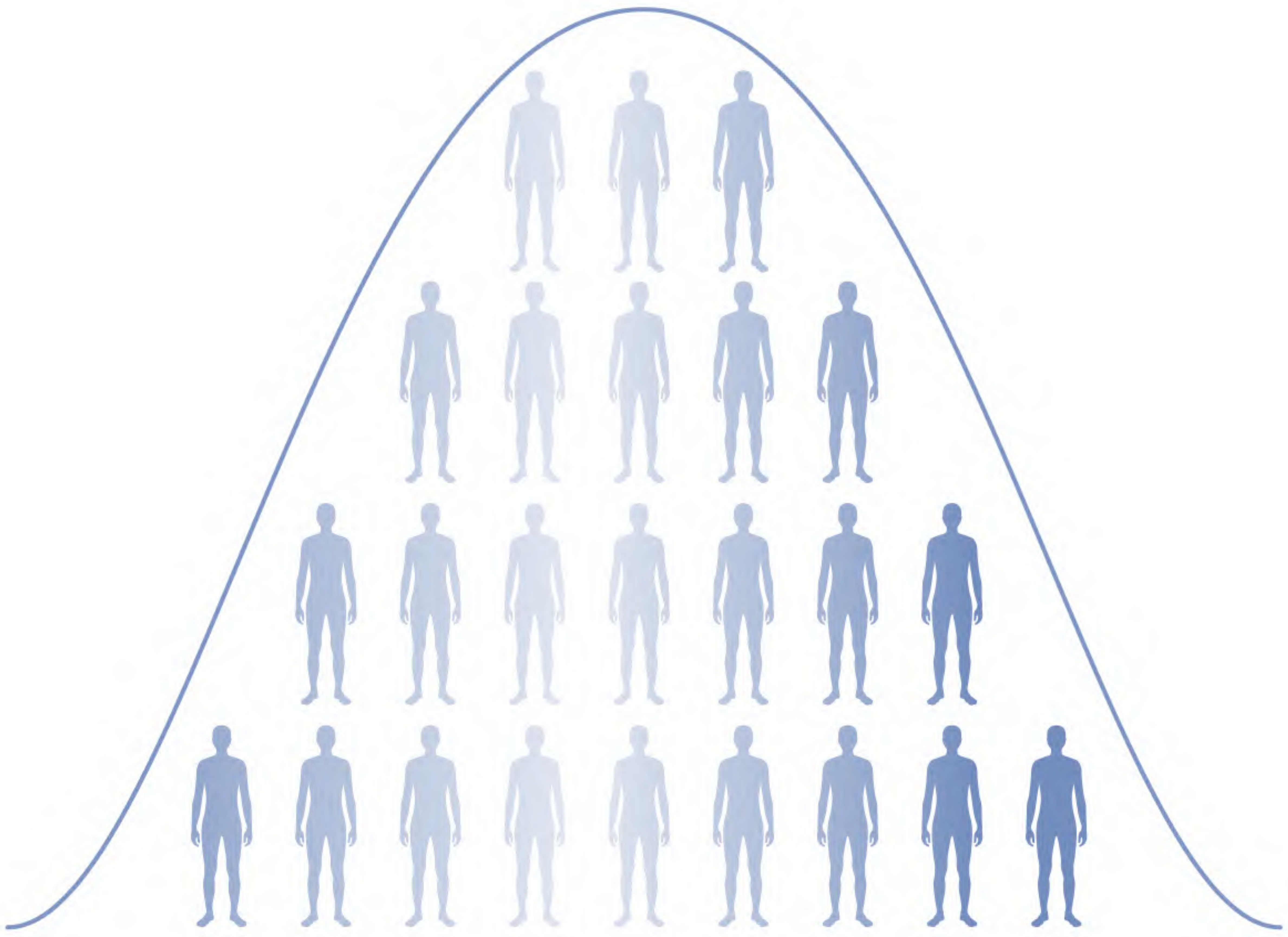
“controls” “cases”

Sanchez-Roige and Palmer, *Nature Neuroscience*, 2020

Substance use disorder can be dissected into symptoms

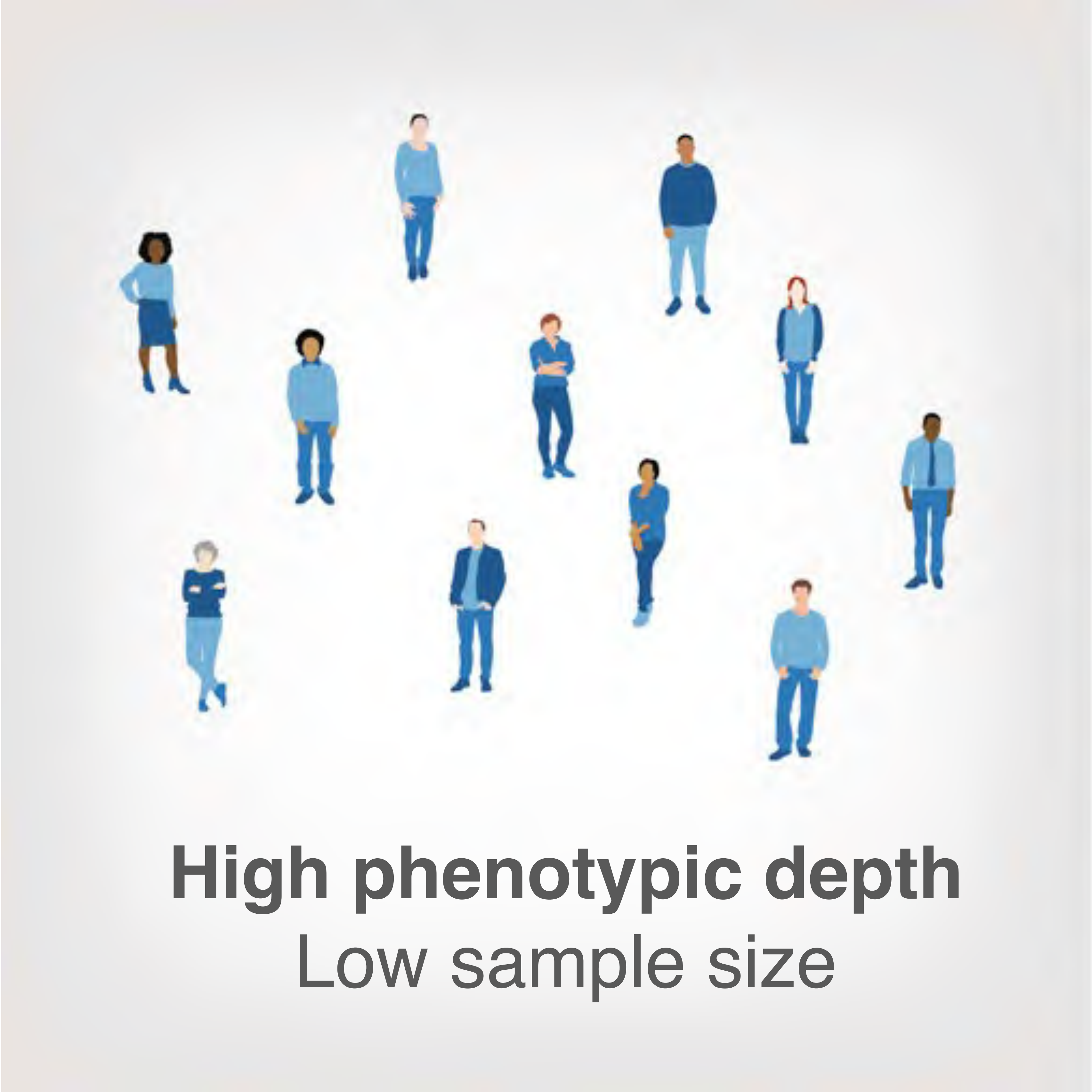


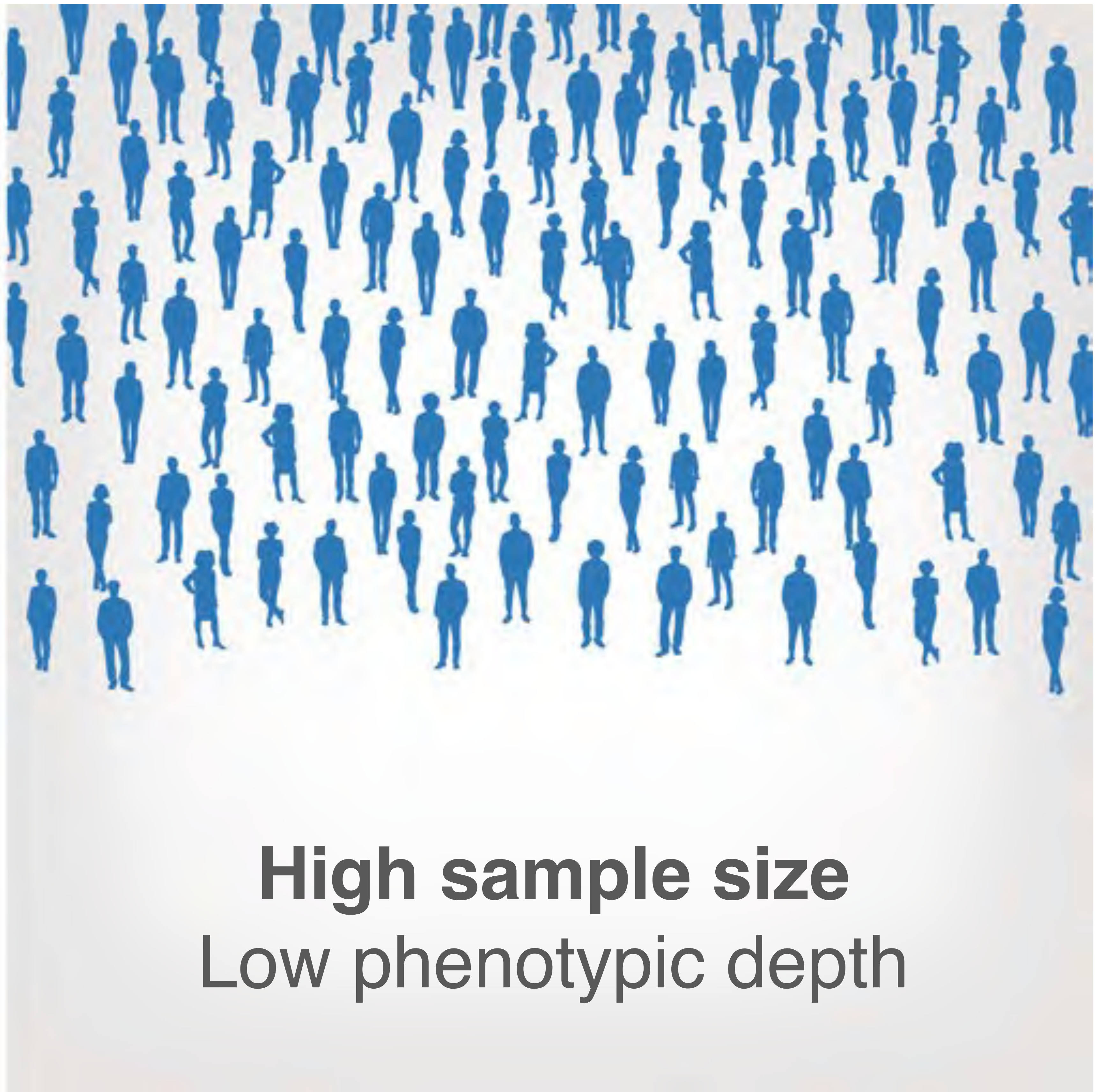
Sanchez-Roige and Palmer, *Nature Neuroscience*, 2020



Continuous traits measured in the general population

Sanchez-Roige and Palmer, *Nature Neuroscience*, 2020





Sanchez-Roige and Palmer, *Nature Neuroscience*, 2020

Where can we get high volumes of phenotypic and genotype data?

Abraham
Palmer

23andMe®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+
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Welcome to you®
saliva collection kit

We paid 23andMe to deploy an online survey

Abraham Palmer

Sarah Elson

Pierre Fontanillas

The survey included 139 questions from well-established questionnaires

James MacKillop

Harriet de Wit

The Alcohol Use Disorder Identification Test (AUDIT) is a **ten-item** screener that measures past year alcohol use

Saunders et al, *Addiction,* 1993

We collected AUDIT responses from 25,000 23andMe research participants

Abraham Palmer

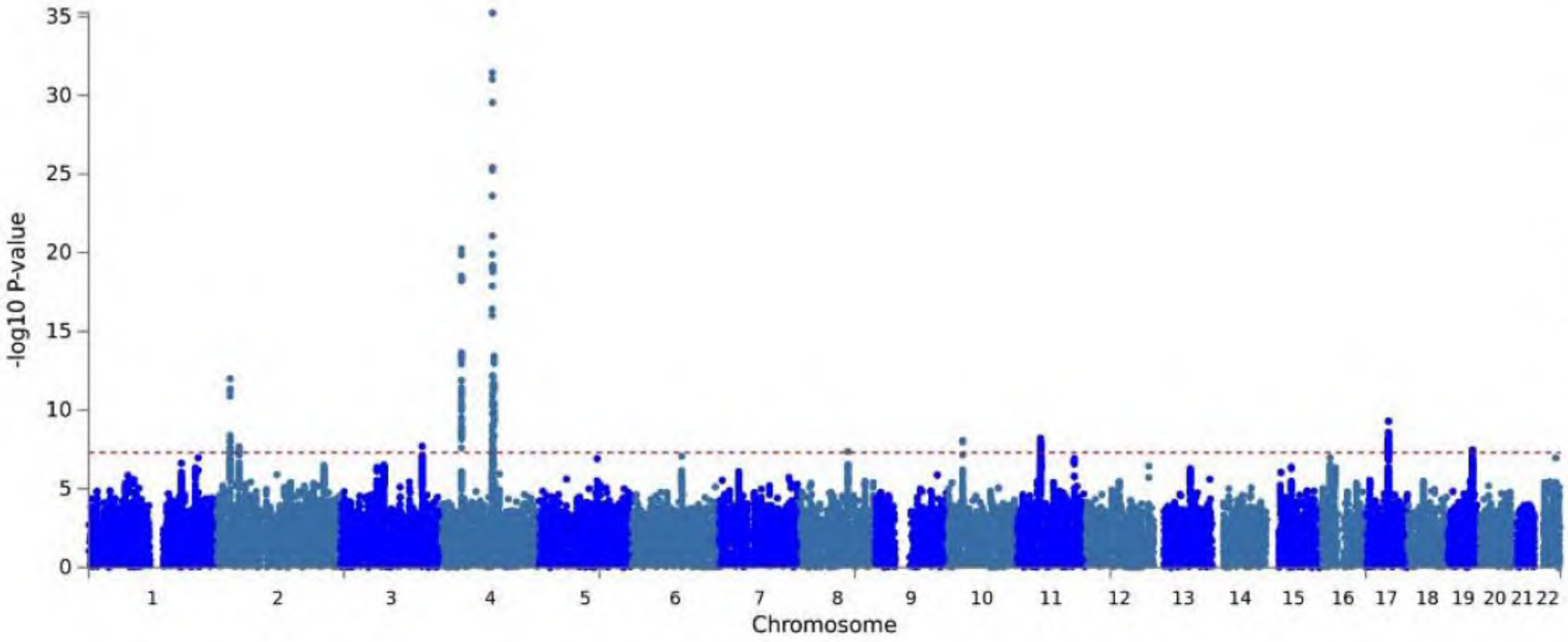
Sarah Elson

Pierre Fontanillas

biobank uk

Toni
Clarke

Meta-analysis of AUDIT using 23andMe and UK Biobank data (N=141,958) identified 10 loci



Sanchez-Roige et al, *American Journal of Psychiatry*, 2019

AUDIT captures aspects of alcohol use and misuse

Saunders et al, *Addiction*, 1993

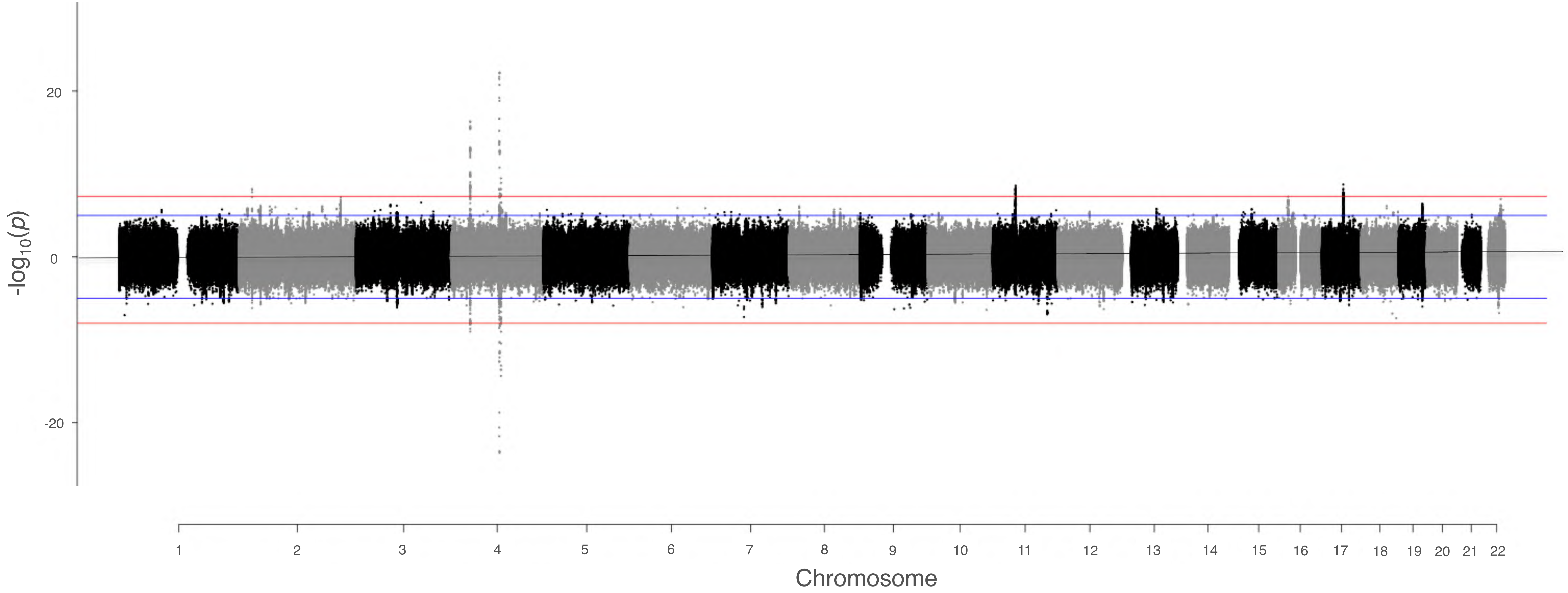
AUDIT-C	AUDIT-P
1 How often do you have a drink containing alcohol?	**4** How often have you found that you were not able to stop drinking once you had started?
2 How many drinks containing alcohol do you have on a typical day when you are drinking?	**5** How often have you failed to do what was expected from you because of drinking?
3 How often do you have six or more drinks on one occasion?	**6** How often have you needed a first drink in the morning to get yourself going after a heavy drinking session?
	7 How often have you had a feeling of guilt or remorse after drinking?
	8 How often have you been unable to remember what happened the night before because you had been drinking?
	9 Have you or someone else been injured as a result of your drinking?
	10 Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?

Saunders et al, *Addiction,* 1993

We performed separate GWAS for AUDIT-C and AUDIT-P in 121,604 UK Biobank participants

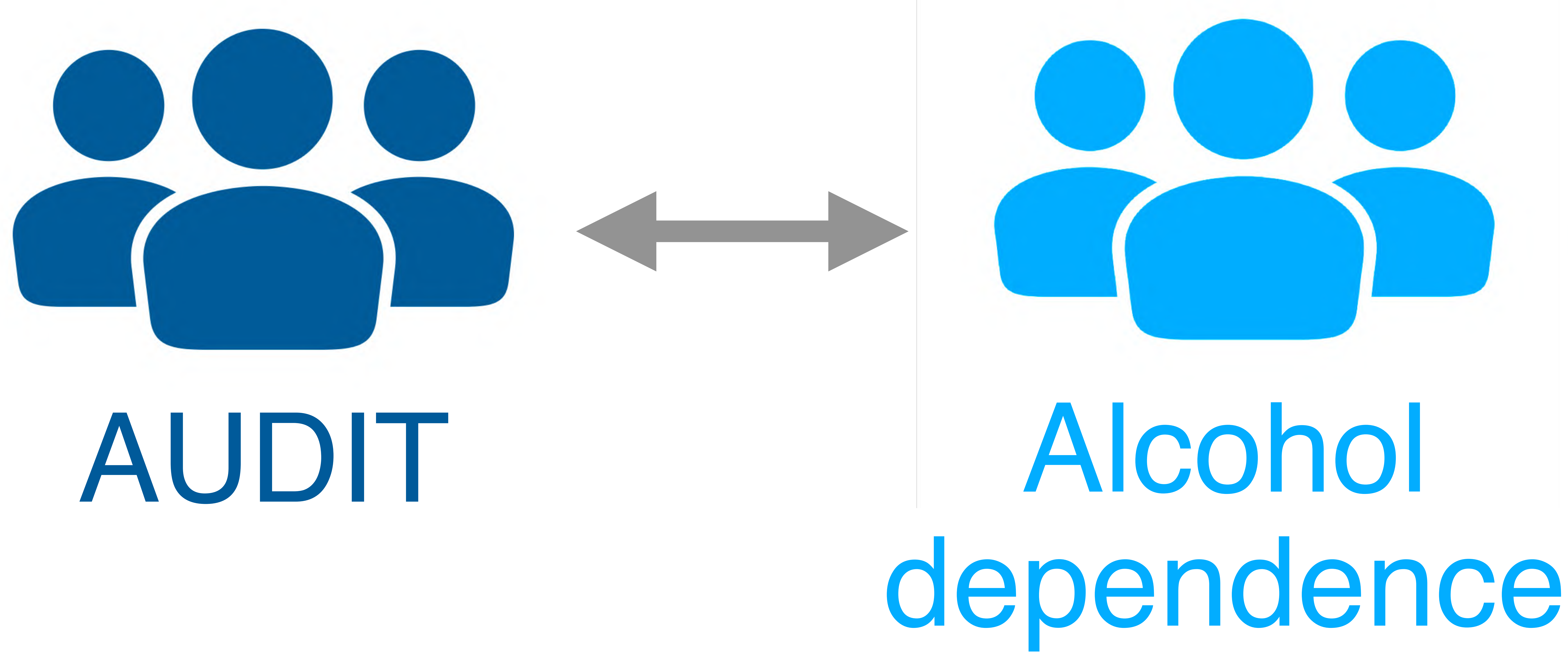
Sanchez-Roige et al, *American Journal of Psychiatry*, 2019

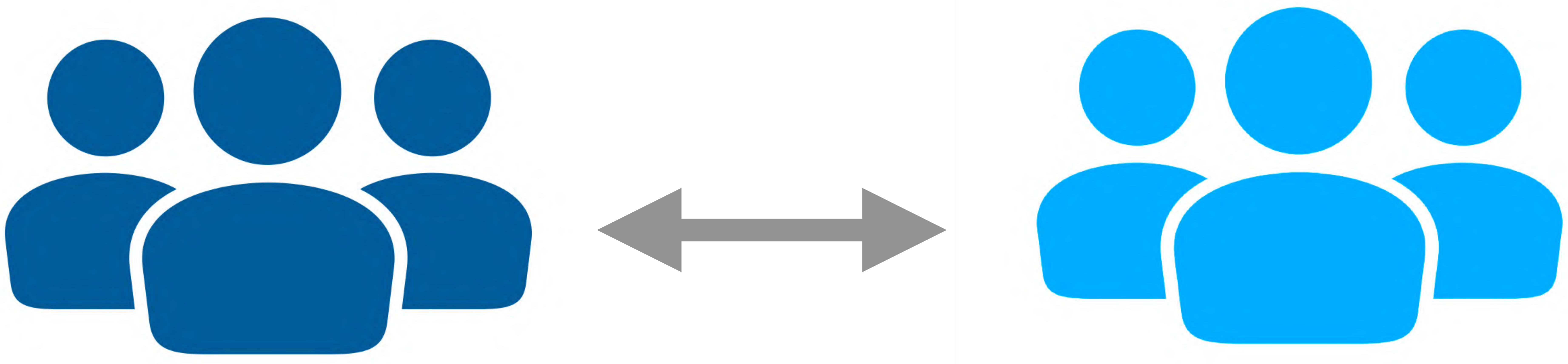
Genetic differences between AUDIT-C (top) and AUDIT-P (bottom)



Sanchez-Roige et al, *American Journal of Psychiatry*, 2019

The genetic basis of alcohol *consumption* and *problematic* alcohol use is distinct


AUDIT
Alcohol dependence



AUDIT

Alcohol dependence

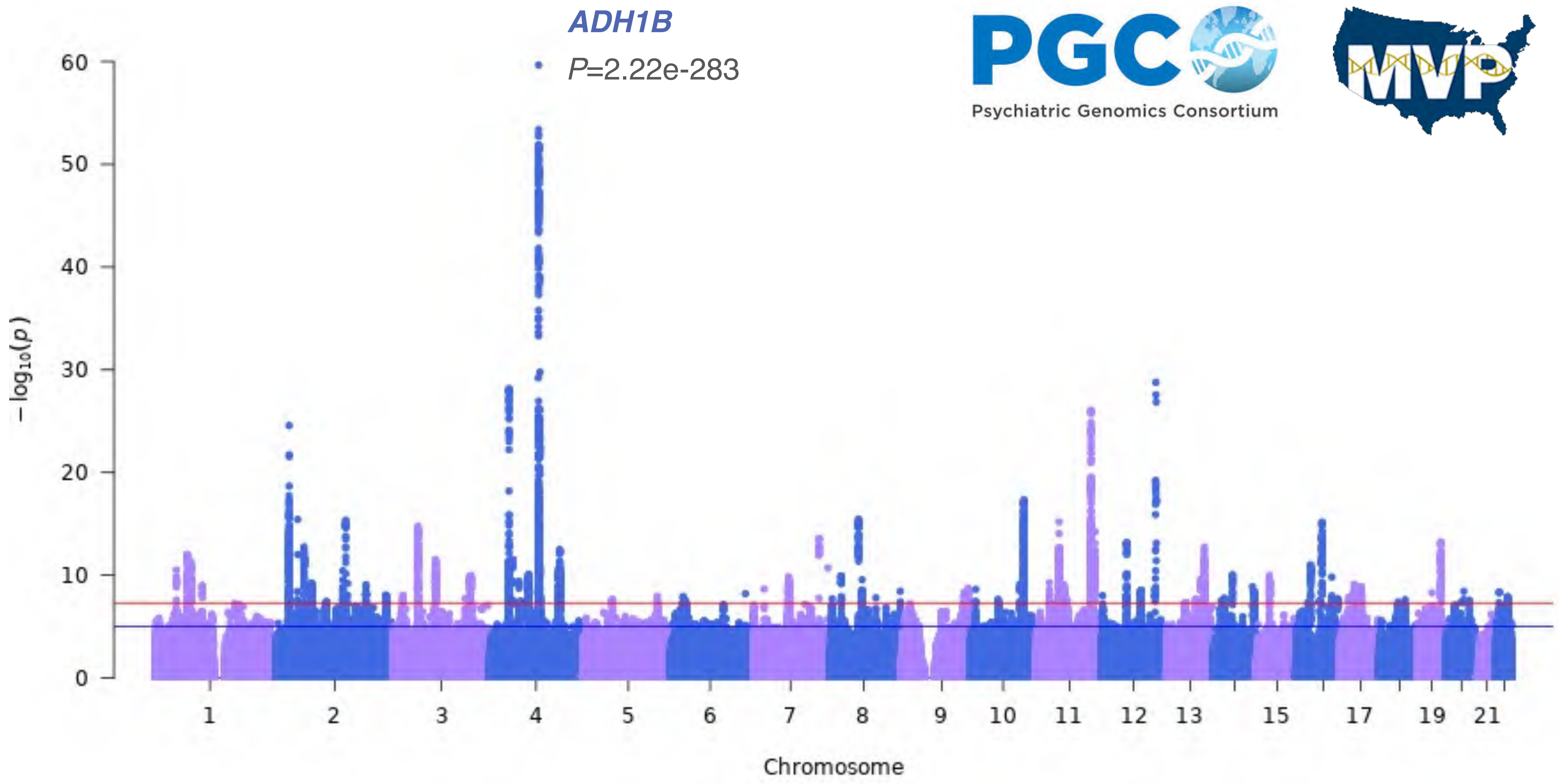
Mallard et al, *American Journal of Psychiatry*, 2022

Walters et al PGC-Substance Use Disorder, *Nature Neuroscience*, 2018

Positive genetic correlations between AUDIT phenotypes and clinically defined alcohol dependence

A research space where clinical and dimensional phenotypes coalesce

Meta-analysis of problematic alcohol use (AUDIT-P+AUD) in >1 million individuals identifies 110 risk variants



PGC
Psychiatric Genomics Consortium

MVP

BRAIN & BEHAVIOR
RESEARCH FOUNDATION
Awarding **NARSAD** Grants

2018 Young Investigator Grant to Dr. Hang Zhou

Link to blog article

Zhou et al, *medRxiv*, 2023

We can fractionate genetic signals for alcohol use disorders into symptoms (use, misuse), measured in population based cohorts

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Alcohol-related behaviors are extremely polygenic - not a single gene condition!

We can fractionate genetic signals for alcohol use disorders into symptoms (use, misuse), measured in population based cohorts

Alcohol-related behaviors are extremely polygenic - not a single gene condition!

Genetic studies benefit from team science

23andMe®

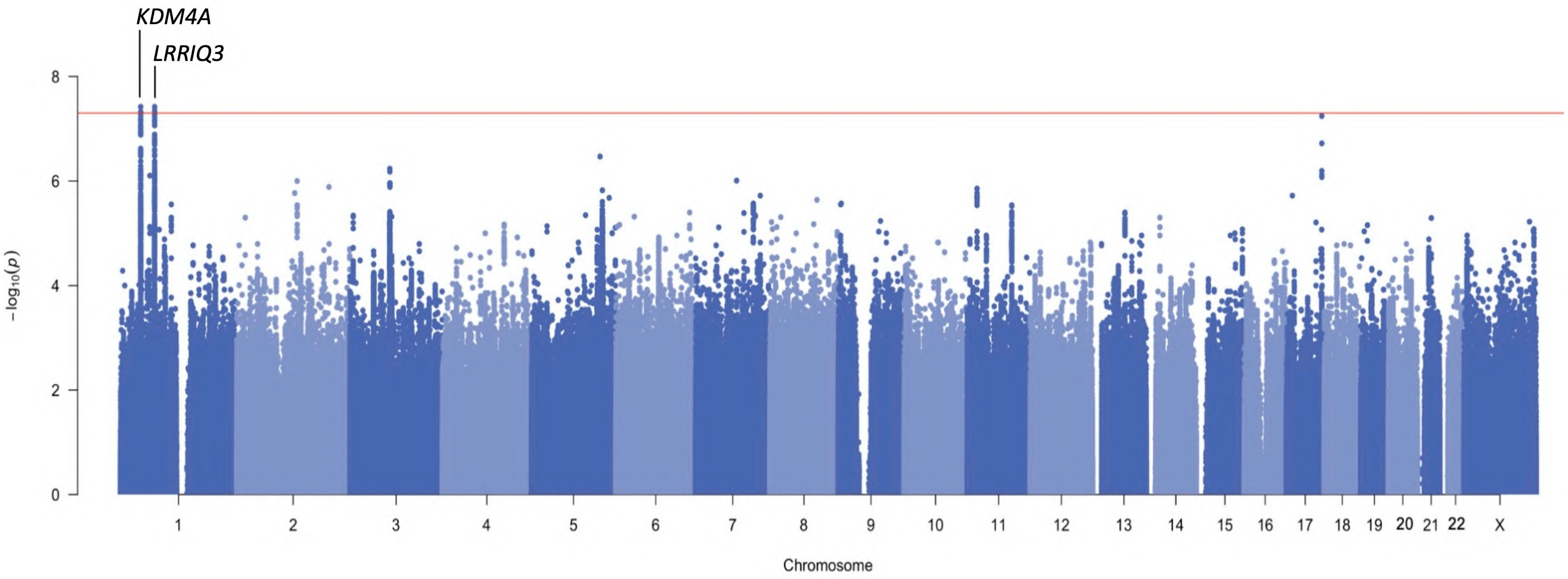
23andMe®

“Have you ever in your life used prescription painkillers (taken not as prescribed), e.g., Vicodin, Oxycontin?”

Abraham Palmer

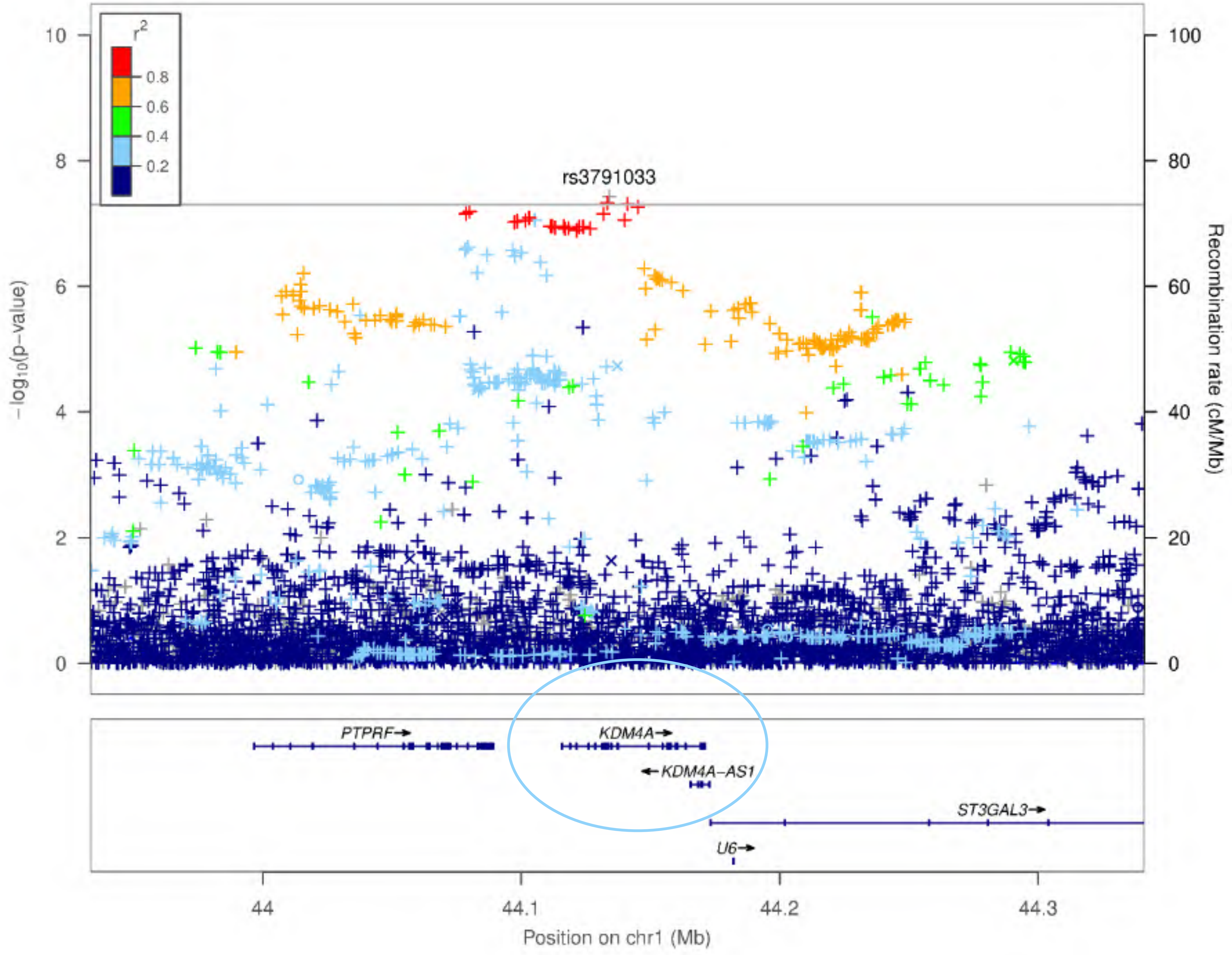
20% of 23andMe research participants (N=27,805) reported misuse of opioids

GWAS of problematic opioid use (POU) in 132,113 23andMe research participants of European ancestry



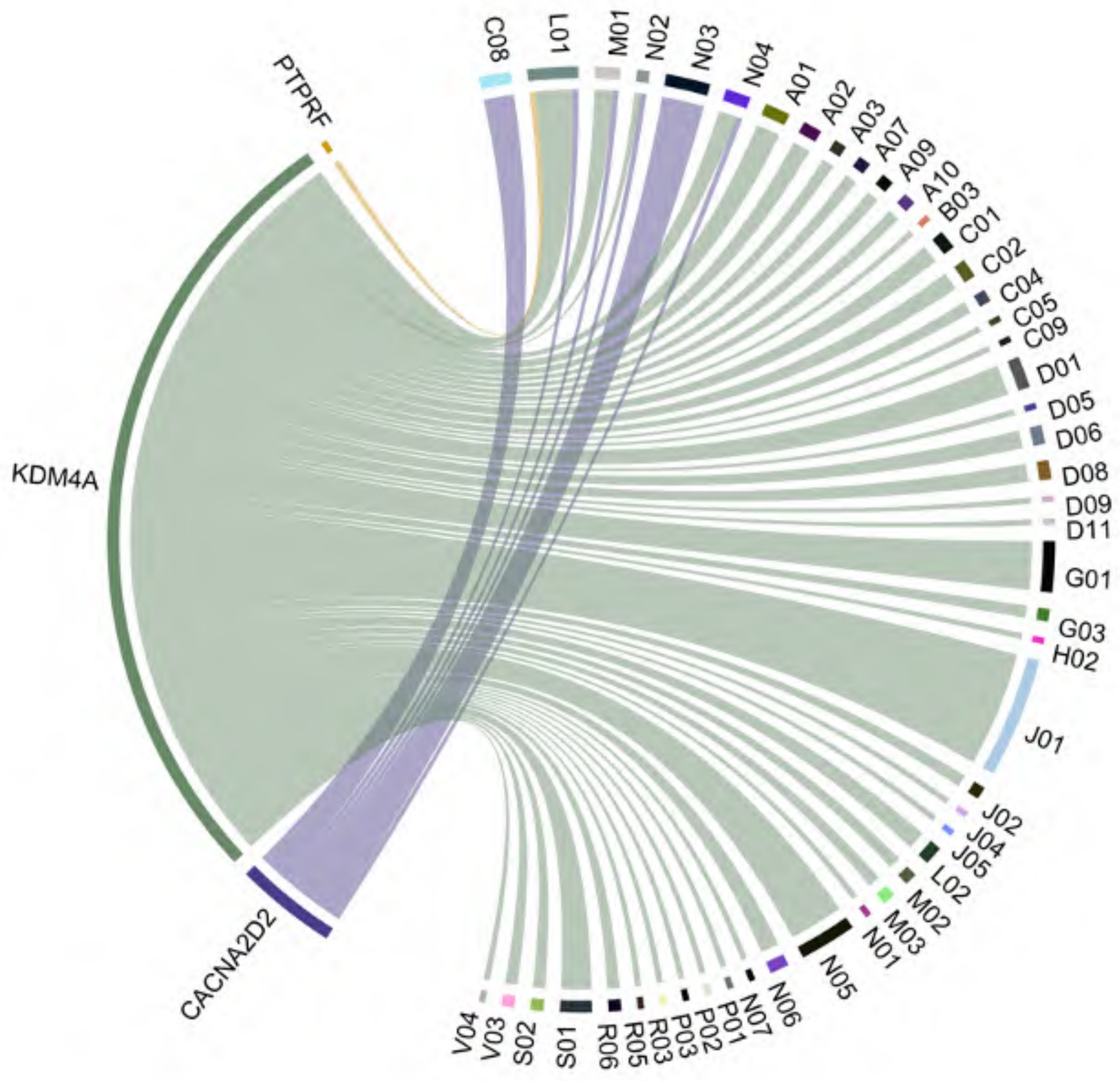
Sanchez-Roige et al, *Molecular Psychiatry*, 2021

KDM4A,
recently implicated in an independent opioid addiction GWAS



Sanchez-Roige et al, *Molecular Psychiatry*, 2021

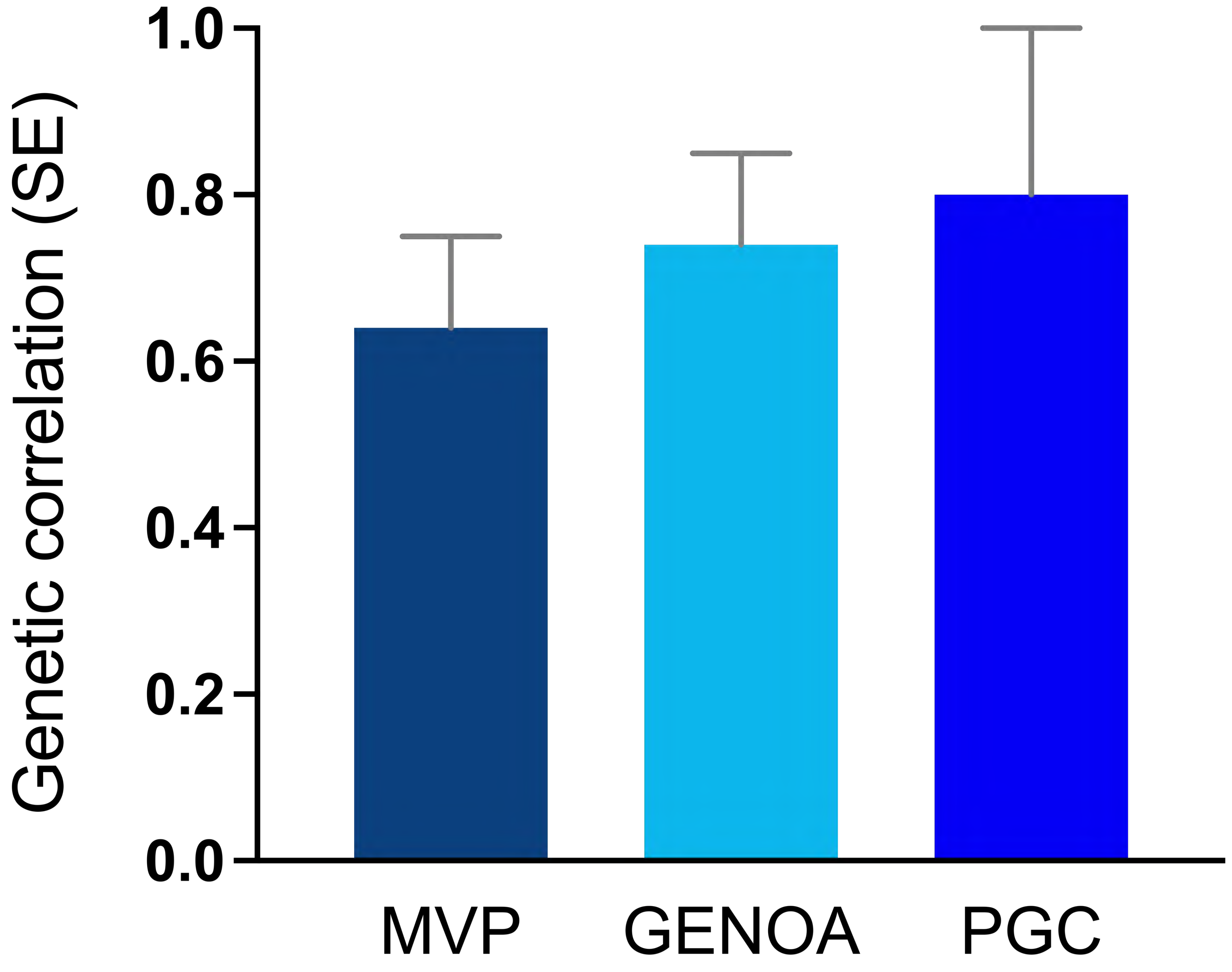
Chord diagram of genes significantly associated with POU and the Anatomical Therapeutic Chemical classifications of drugs



We found interactions between 3 genes and 464 drugs, including selective serotonin reuptake inhibitors and dopaminergic agents

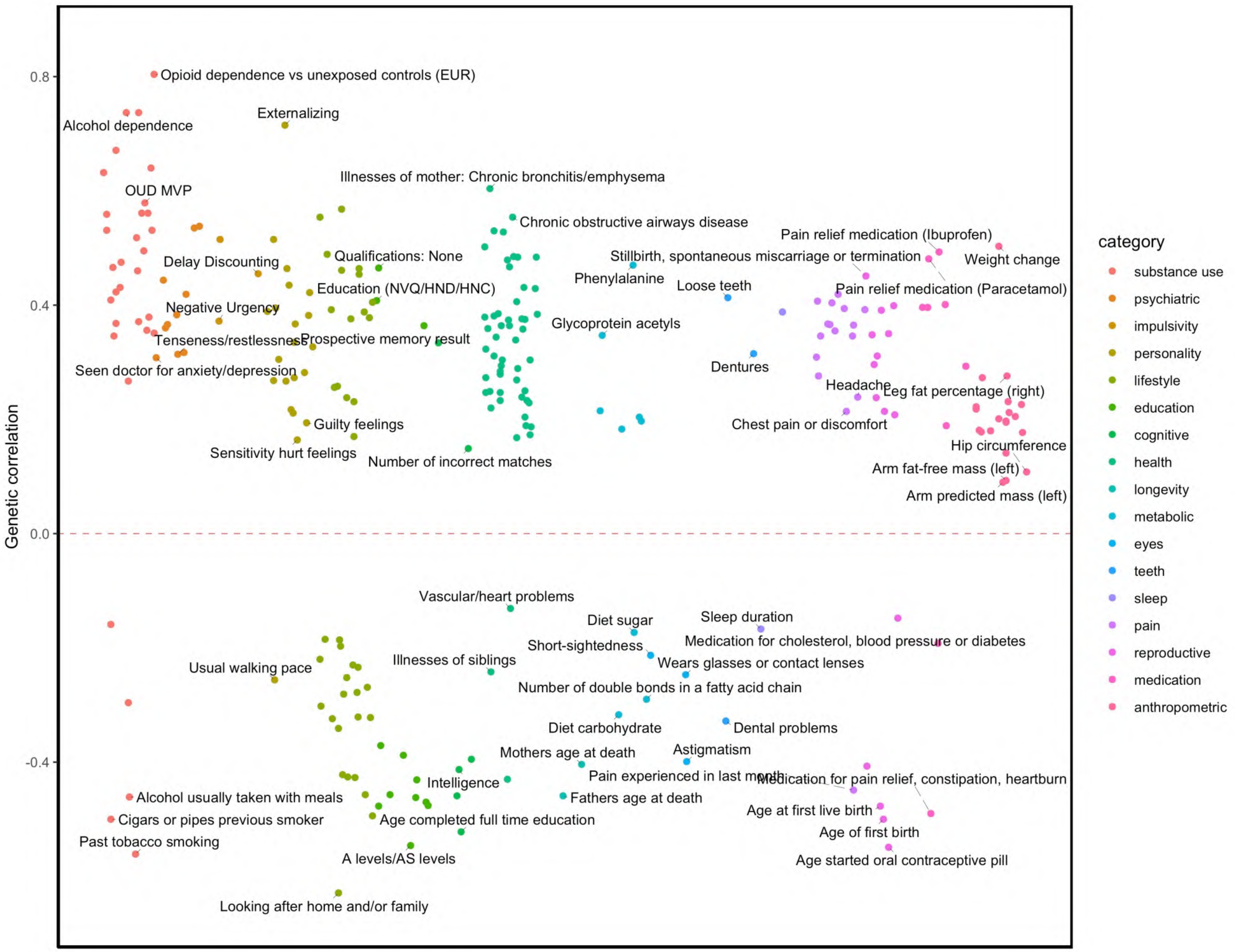
Sanchez-Roige et al, *Molecular Psychiatry*, 2021

Strong genetic correlations with the largest available GWAS of OUD



MVP (Million Veterans Program): Zhou et al, *JAMA Psychiatry*, 2020
GENOA (Genetics of Opioid Addiction): Gaddis et al, *Scientific Reports*, 2021
PGC (Psychiatric Genomics Consortium): Polimanti et al, *Molecular Psychiatry*, 2020

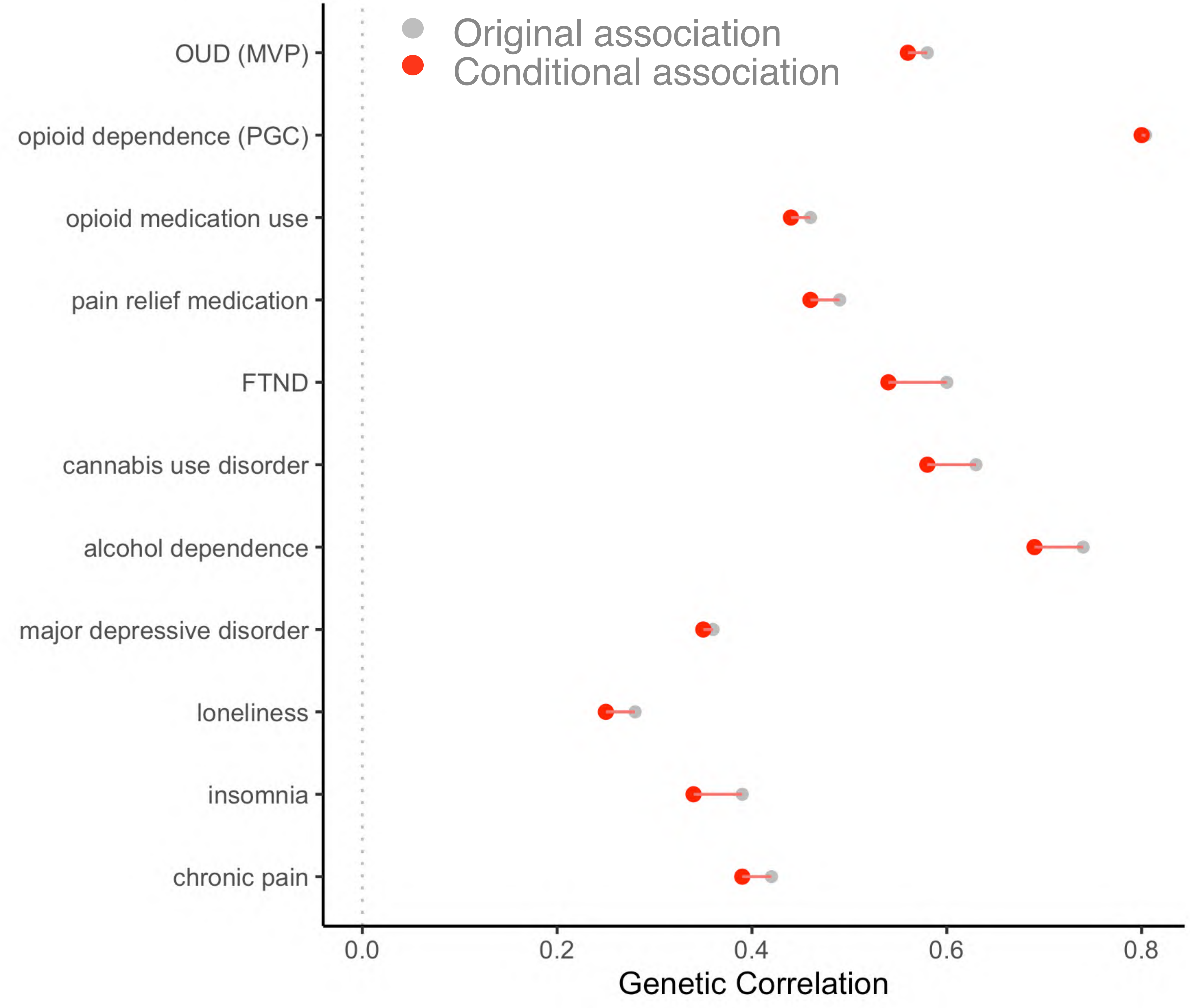
We identified strong genetic correlations between POU and other substance use traits, mental and physical outcomes

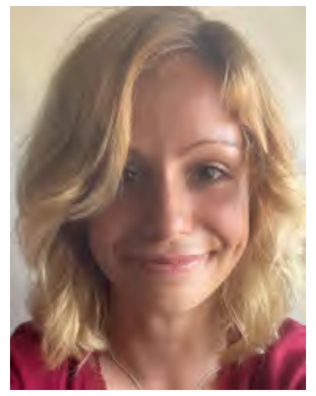


Sanchez-Roige et al, *Molecular Psychiatry*, 2021

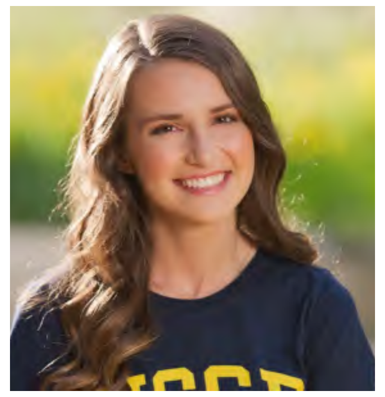
Is problematic opioid use simply a form of risky behavior?

Although POU was genetically correlated with risk-taking (r_g=0.35), conditioning on risk had little impact on these genetic associations





Mariela Jennings



Sevim Bianchi

Yuye Huang

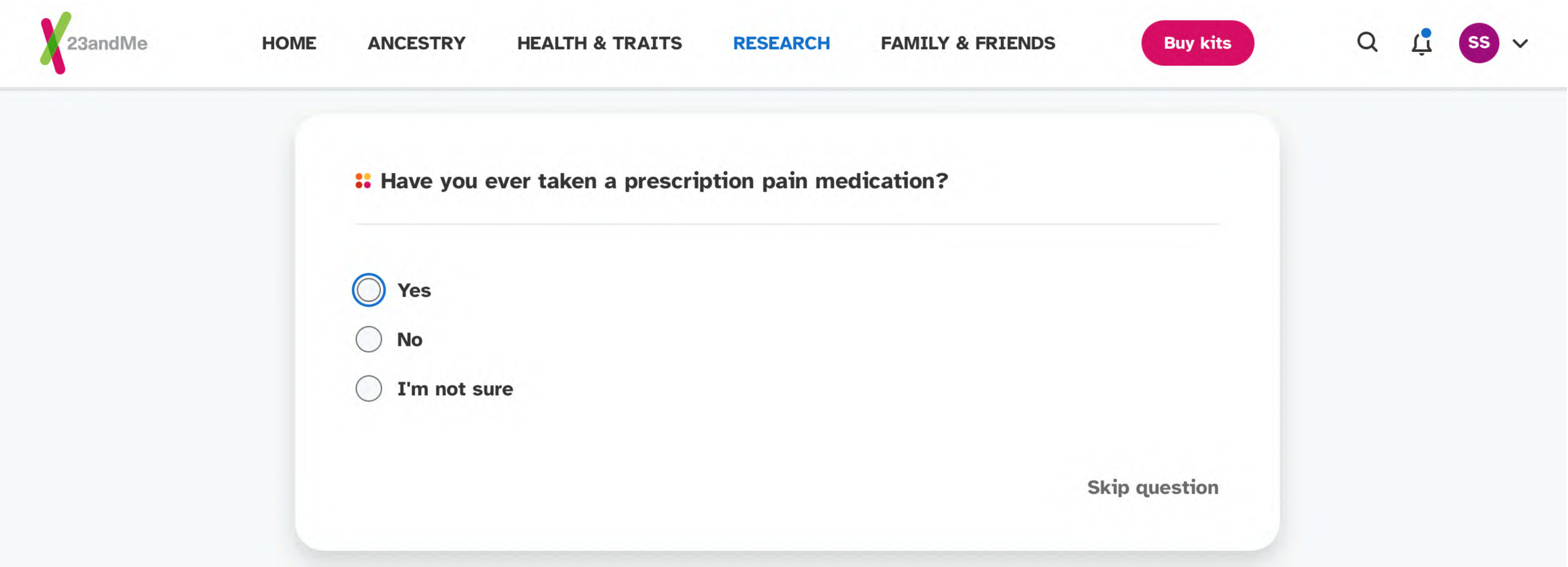
Sanchez-Roige et al, *Molecular Psychiatry*, 2021

Opioid misuse as a cost-effective strategy to augment the power of studies directly examining OUD

The Prescription Opioid Genetics Study

We are expanding our sample to
half a million individuals
of multiple ancestries and multiple
additional comorbid traits

The survey is already out!



You can be one in half a million

Impulsivity

Impulsivity is a multifaceted construct

Impulsive choice; steeper reward discounting

Delay aversion

Lack of consideration when making decisions

Change in response criterion

Timing impairment

Motor disinhibition

Impaired ability to stop a response

Dalley, Everitt, Robbins, *Neuron*, 2012

Impulsivity is associated with multiple neuropsychiatric disorders

ADHD

Impulsive choice; steeper reward discounting

Motor disinhibition

Eating disorders

Delay aversion

Impaired ability to stop a response

Lack of consideration when making decisions

Mania

Change in response criterion

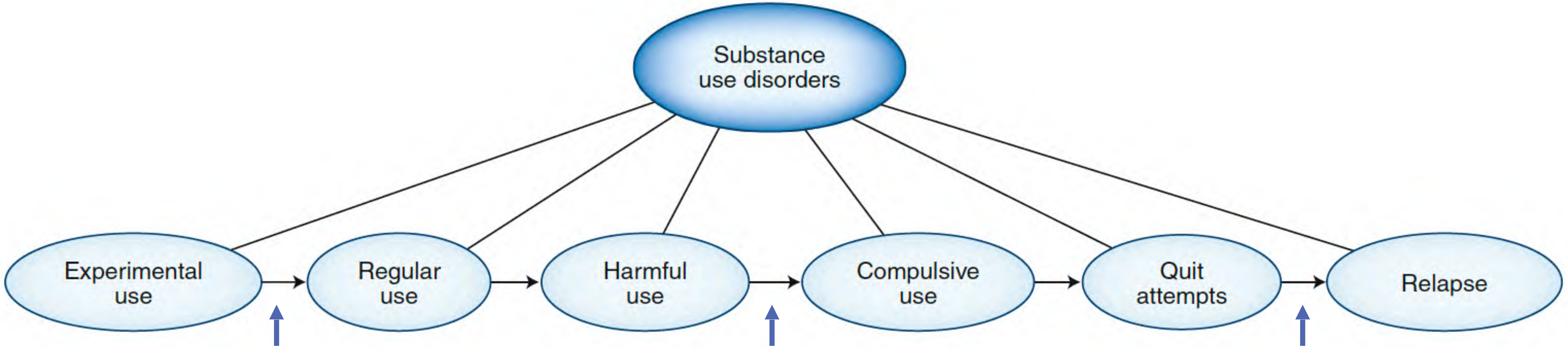
Timing impairment

Personality disorders

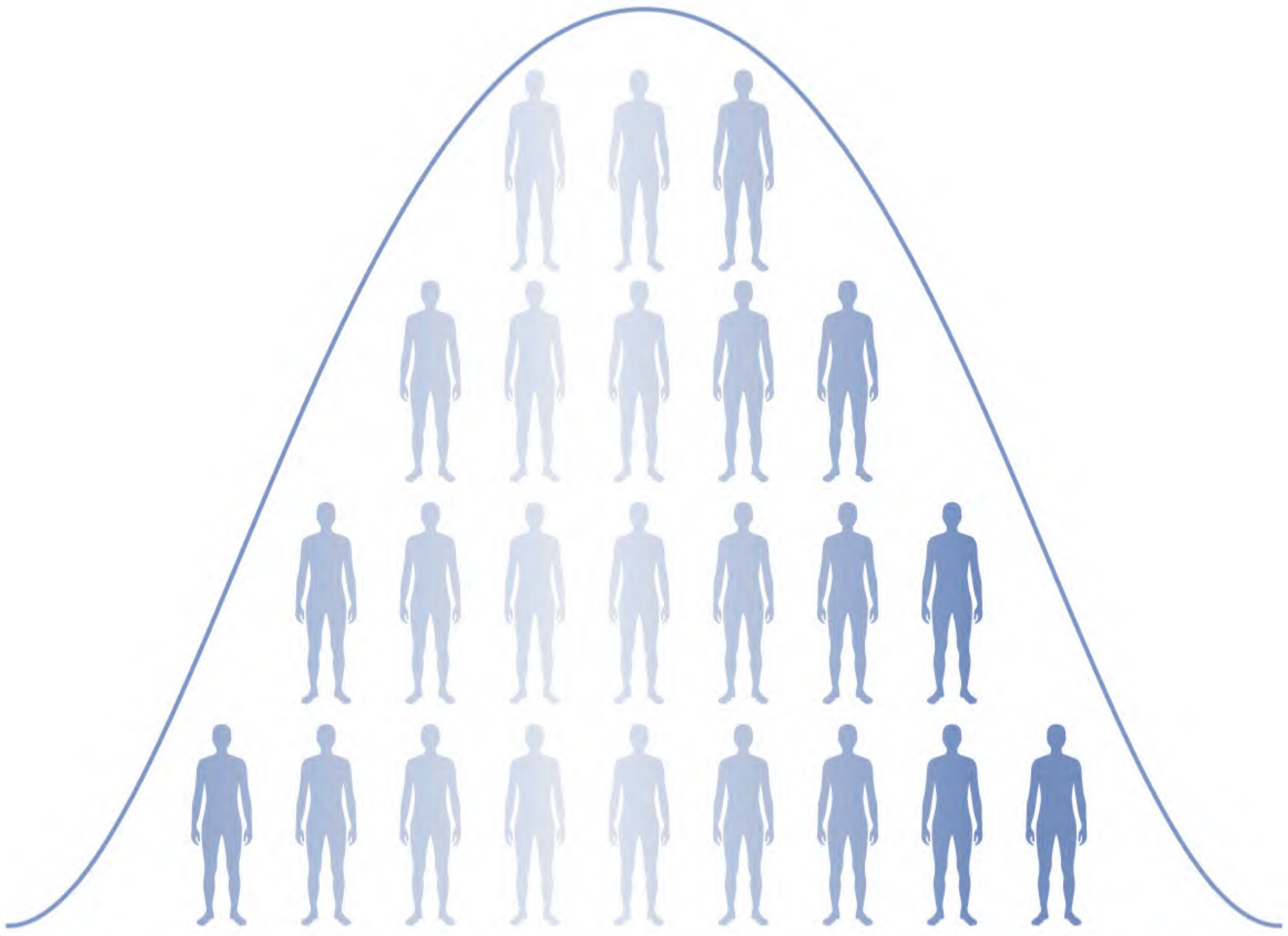
Substance use disorders

Dalley, Everitt, Robbins, *Neuron*, 2012

Impulsivity is involved in multiple stages of substance use vulnerability

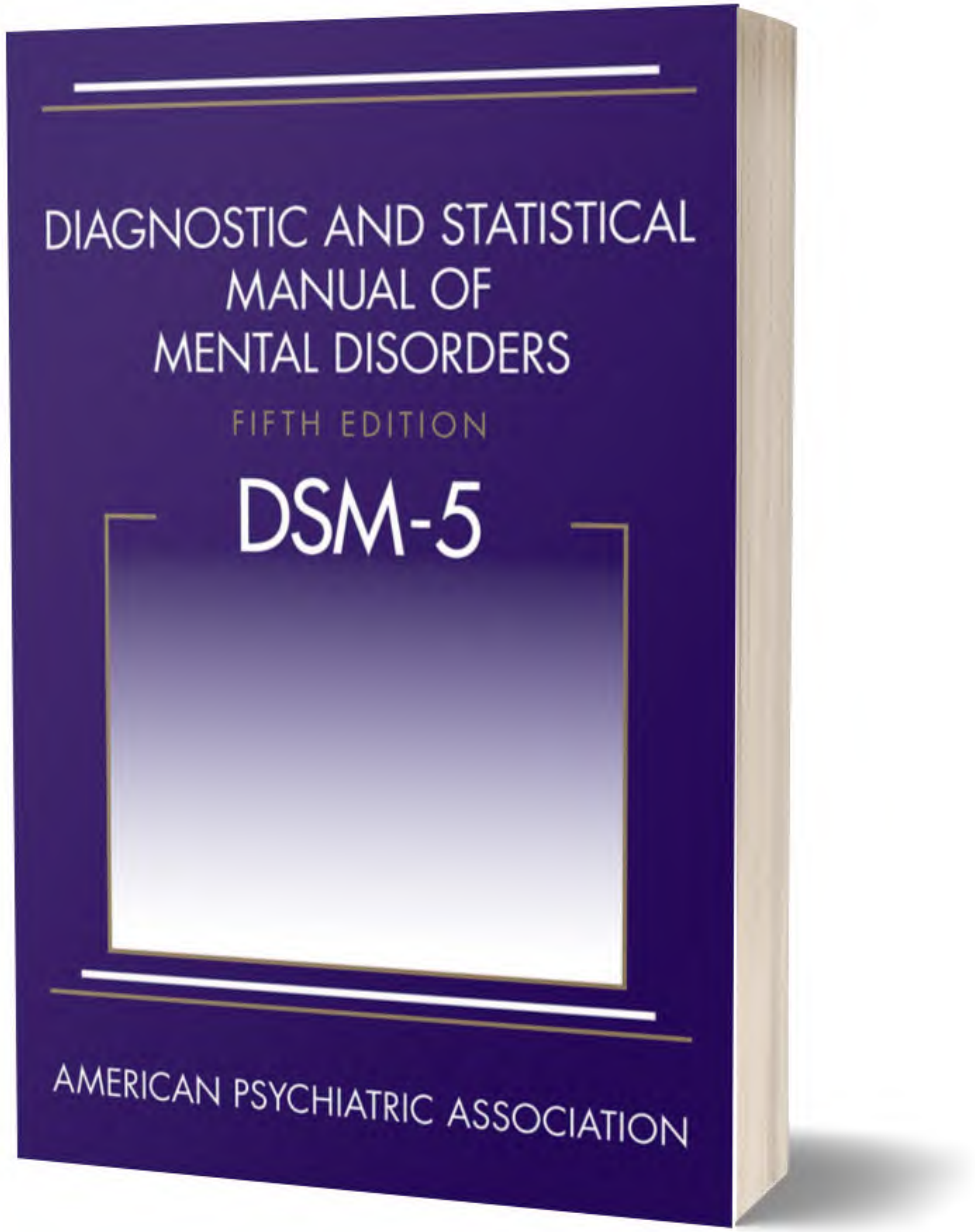


Sanchez-Roige and Palmer, *Nature Neuroscience*, 2020



Impulsivity levels

Sanchez-Roige and Palmer, *Nature Neuroscience*, 2020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Impulsive Behavior Scale (UPPS-P): Sensation Seeking, Premeditation, Positive Urgency, Negative Urgency, Perseverance

Whiteside and Lynam, *Personality and Individual Differences*, 2001

I quite enjoy taking risks

Barratt Impulsiveness Scale (BIS-11): Motor, Attention, Non-Planning

Patton, Stanford, Barratt, *Journal of Clinical Psychology*, 1995

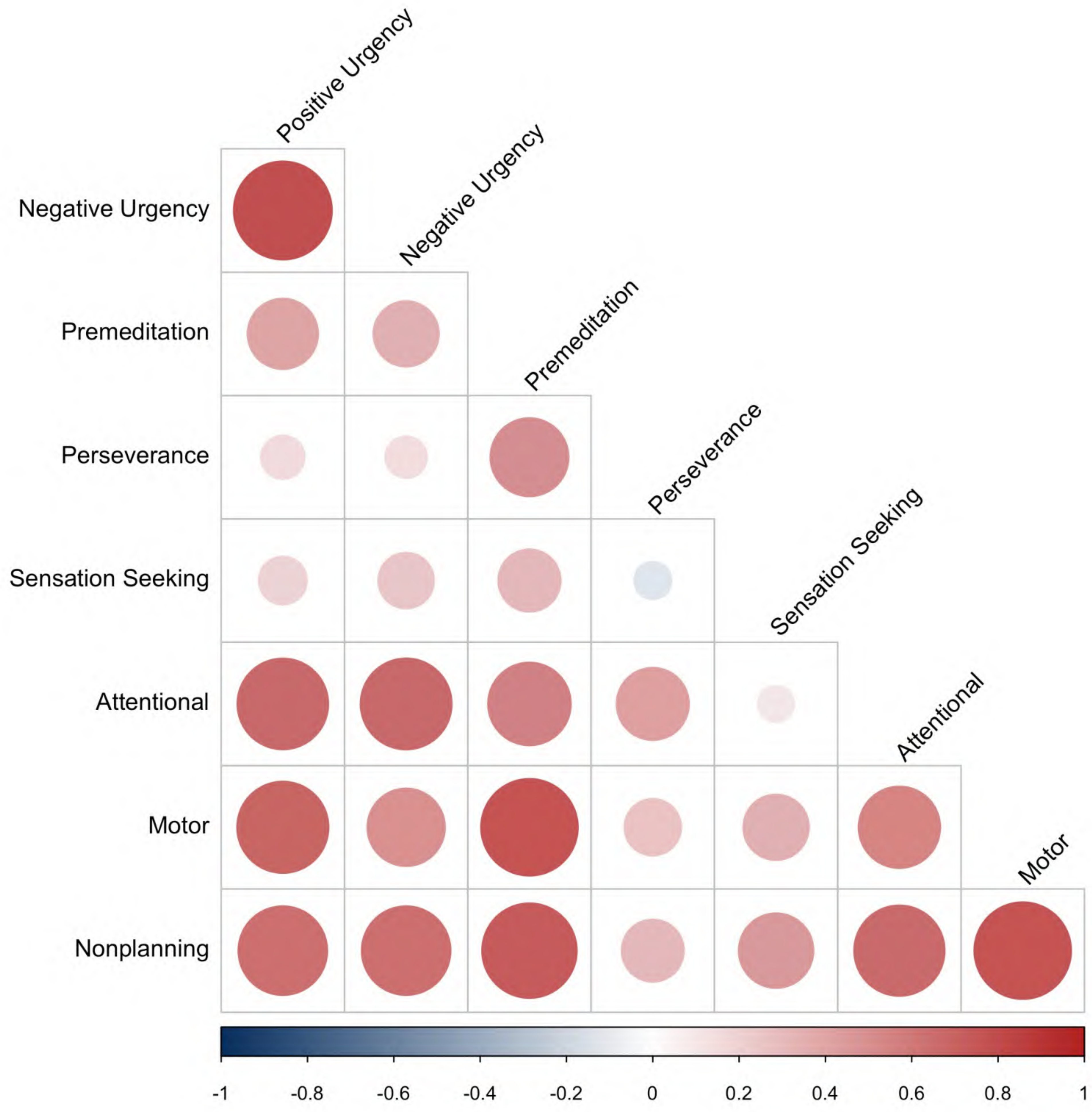
I do things without thinking

We collected 150,000 responses on 8 impulsive personality traits

Impulsivity is heritable
(~10%)

Sanchez-Roige et al, *Journal of Neuroscience*, 2019

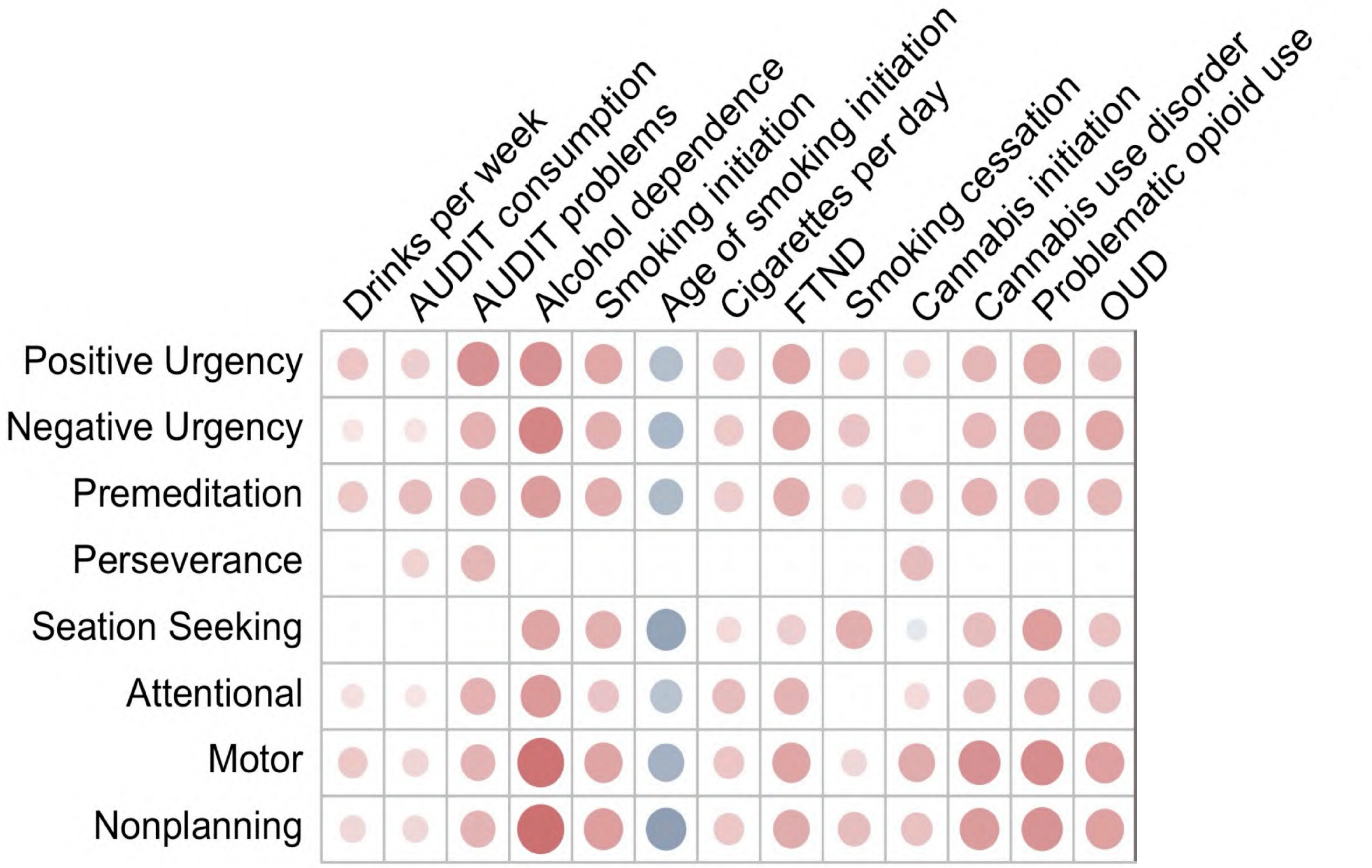
Genetic inter-correlations for the UPPSP and BIS subscales were high and positive



Sanchez-Roige et al, *Translational Psychiatry*, 2023

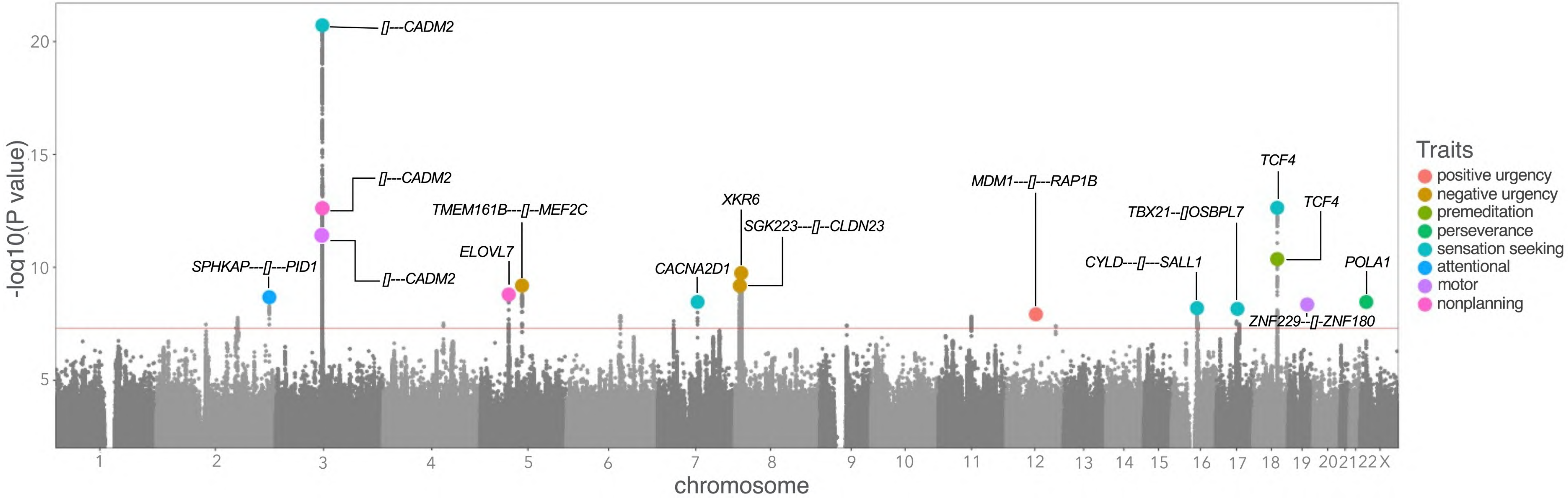
Genetic correlations between impulsivity and substance use

Genetic correlations between impulsivity and substance use and misuse



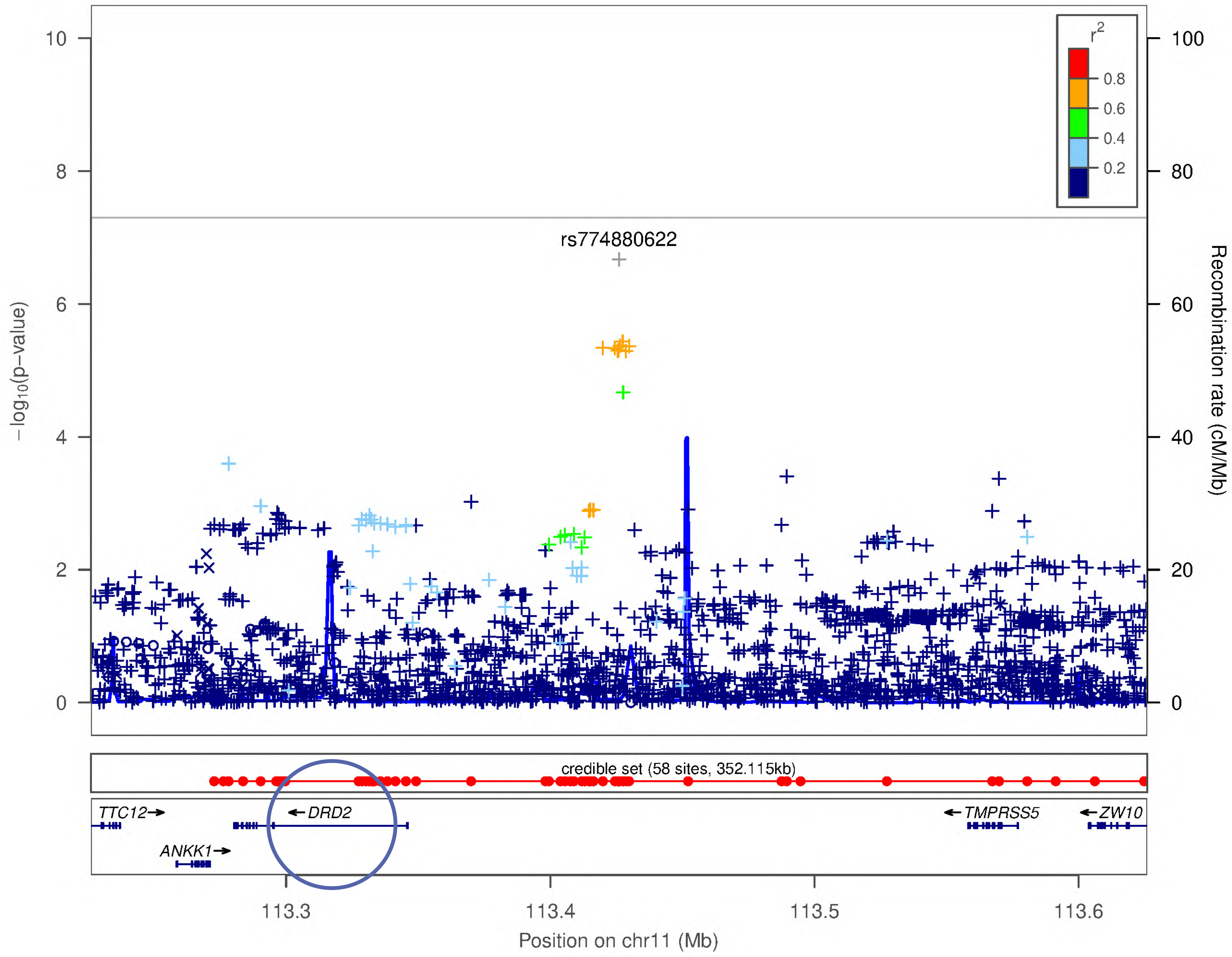
Sanchez-Roige et al, *Translational Psychiatry*, 2023

We identified 16 genome-wide associations that exceeded significance (p=5.0x10^{-8}) for the UPPSP and BIS subscales



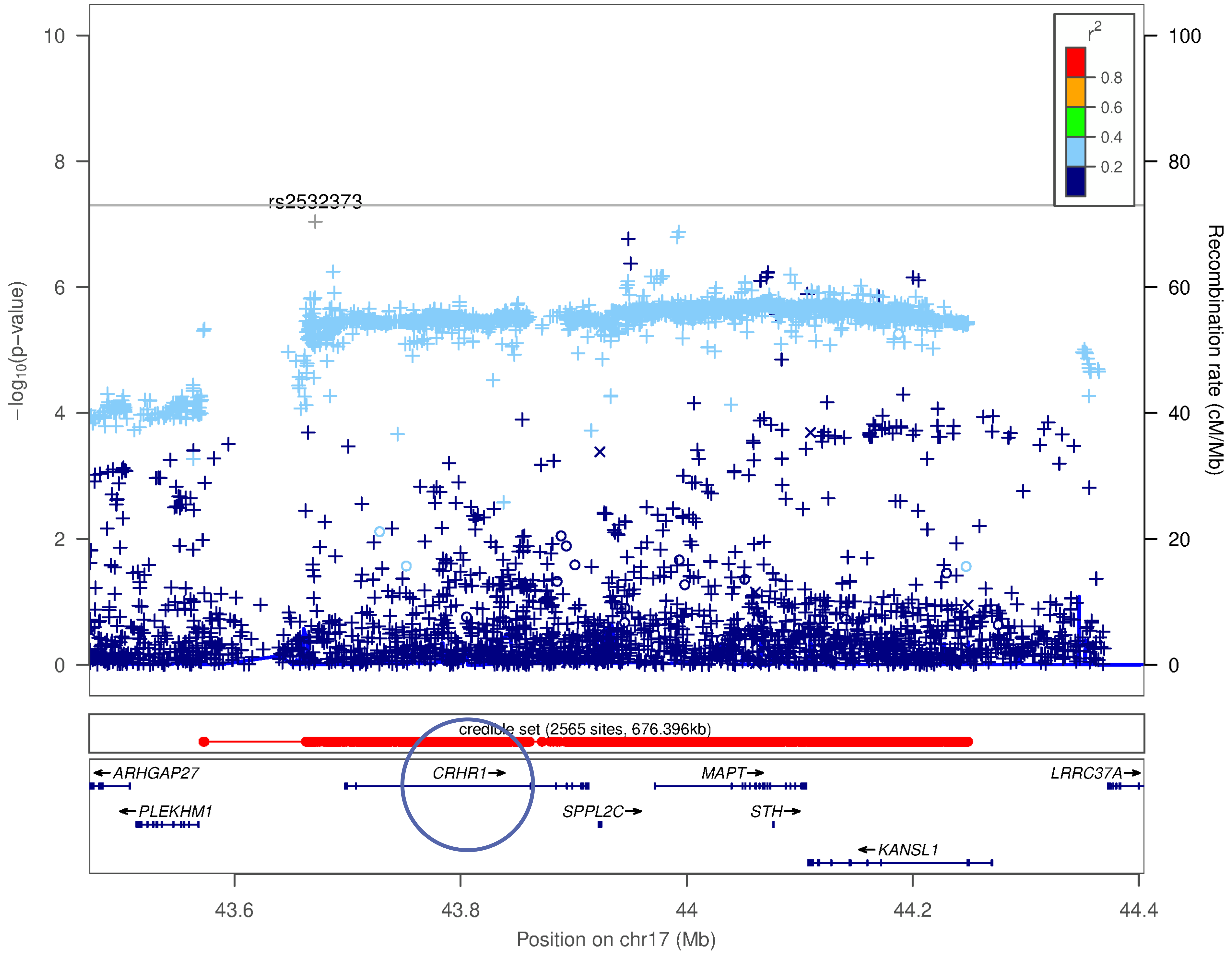
Sanchez-Roige et al, *Translational Psychiatry*, 2023

We noted a nominal association with rs774880622 (p=2.10E-07), near the Dopamine D2 receptor (*DRD2*) gene, and Premeditation



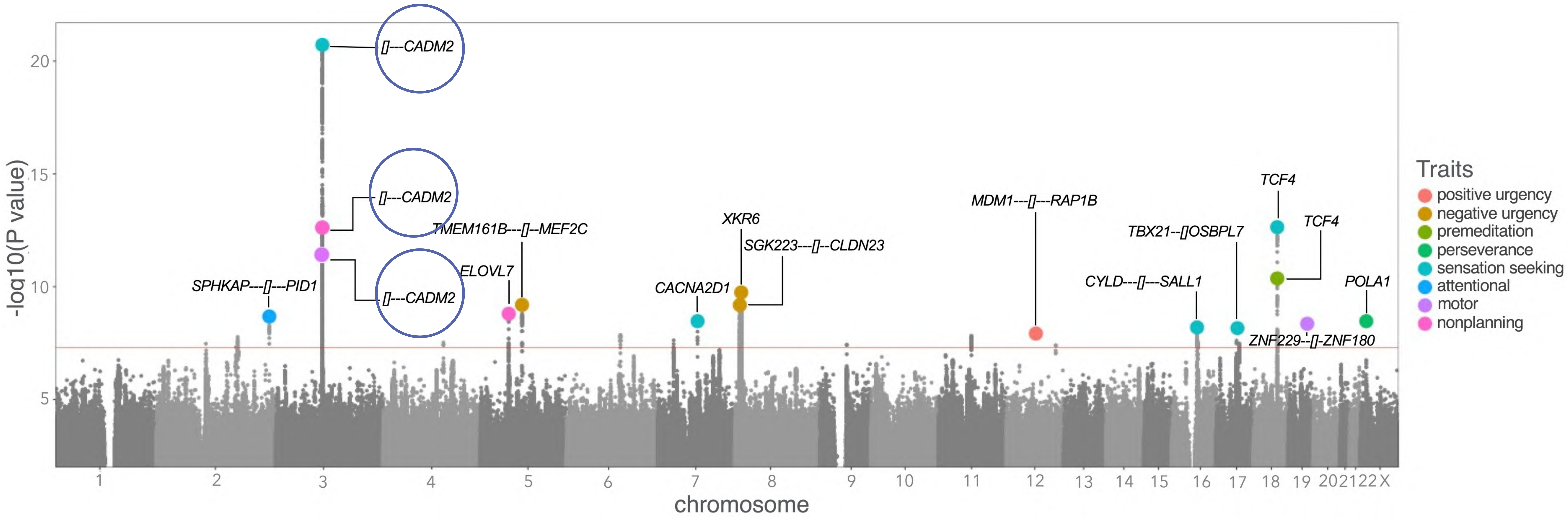
Sanchez-Roige et al, *Translational Psychiatry*, 2023

We also noted a nominal association with rs2532373 (p=9.10E-08), near the corticotropin receptor (*CRHR1*) gene, and Negative Urgency



Sanchez-Roige et al, *Translational Psychiatry*, 2023

One of the most consistent loci was located on chromosome 3, near the gene cell adhesion molecule 2 (*CADM2*)



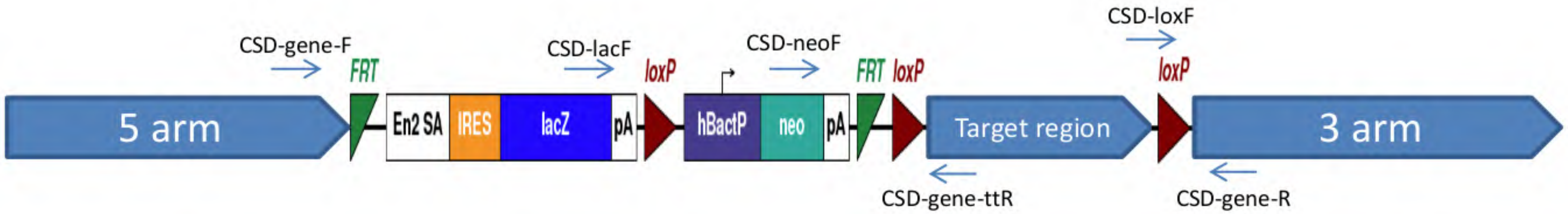
Sanchez-Roige et al, *Translational Psychiatry*, 2023

CADM2 has a profound effect on human behavior:
ADHD, drug experimentation, alcohol and cannabis use, BMI, smoking, neuroticism, age at first sex, among others
(see GWAS Catalog www.ebi.ac.uk/gwas/)

GWAS produce novel biological insights but do not themselves produce actionable new knowledge

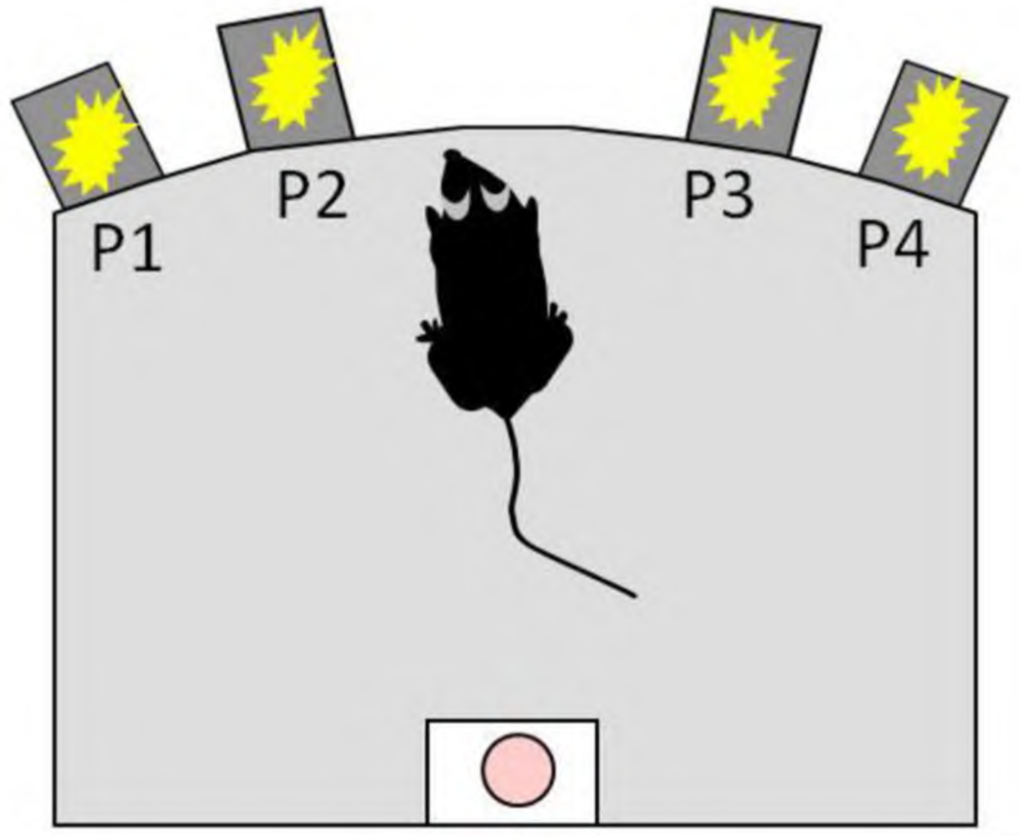
FAMILIES FOR BORDERLINE PERSONALITY DISORDER RESEARCH

BRAIN & BEHAVIOR RESEARCH FOUNDATION
Awarding **NARSAD** Grants

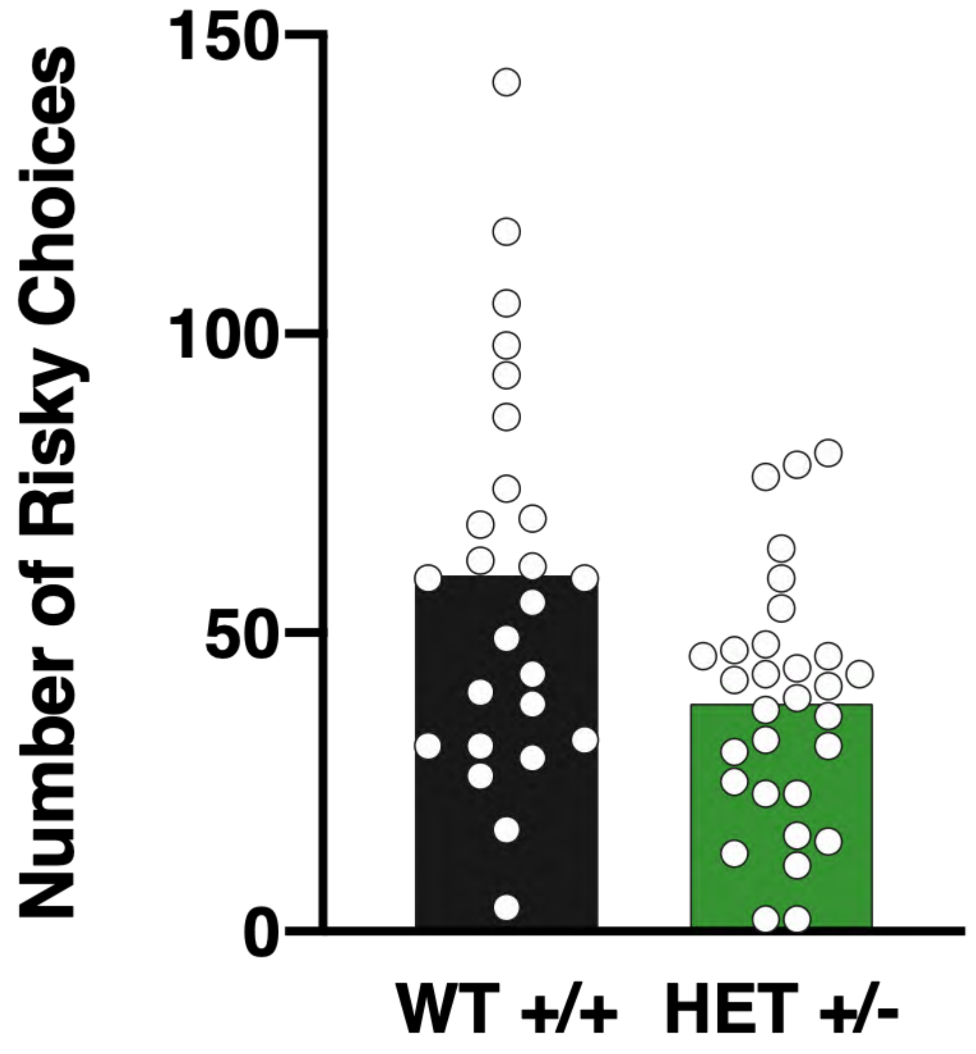


We produced mice that expressed a null allele $Cadm2^{tm1a(KOMP)Mbp}$ on an otherwise isogenic (inbred) background (C57BL/6N) under homogeneous environmental conditions

Decreased expression of *Cadm2* is associated with low risky responding in the mouse IOWA gambling task



Mice had to choose between disadvantageous ("risky") options (higher reward but less often) vs advantageous options (lower reward, but more frequently)

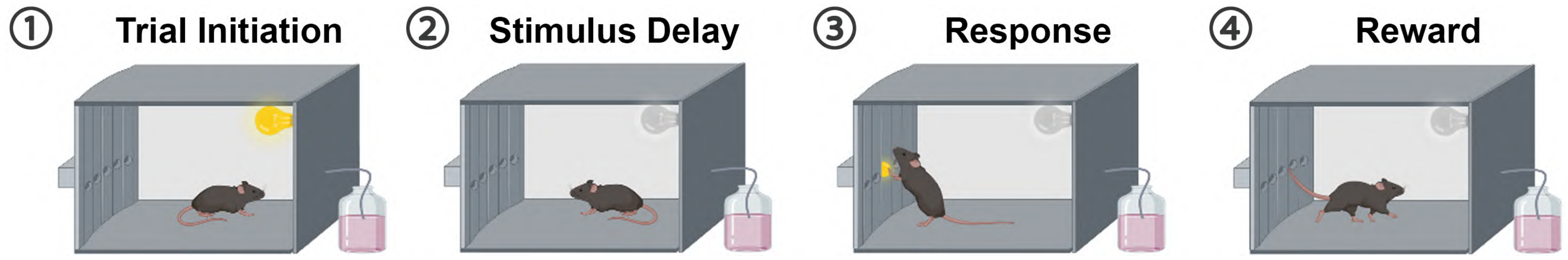


Lieke van der Werf

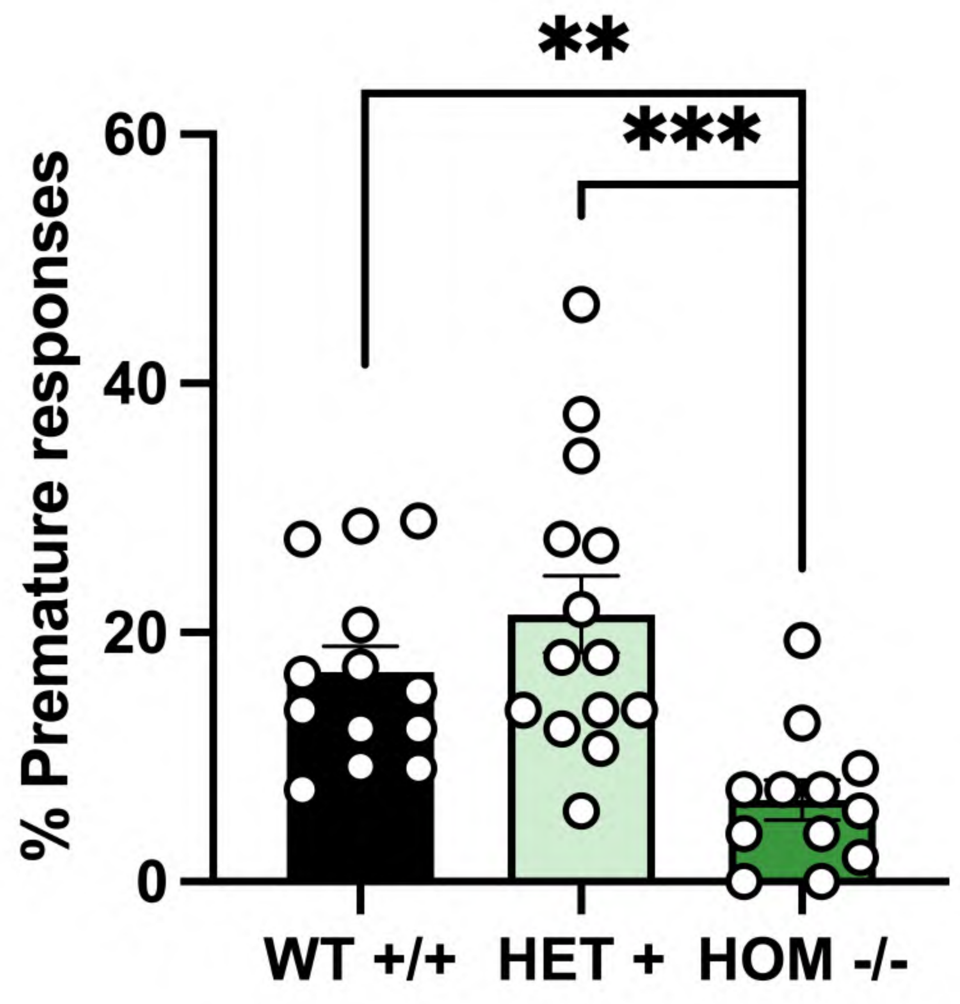
Jared Young

Sanchez-Roige et al, *Translational Psychiatry*, 2023

Decreased expression of *Cadm2* is associated with low motoric impulsivity in the 5-Choice Serial Reaction Time Task



Mice have to respond to a stimulus light in order to get a food reward. If they "cannot wait" and make a premature response, they are punished by loosing the reward. Premature responses are a form of "motoric" impulsivity



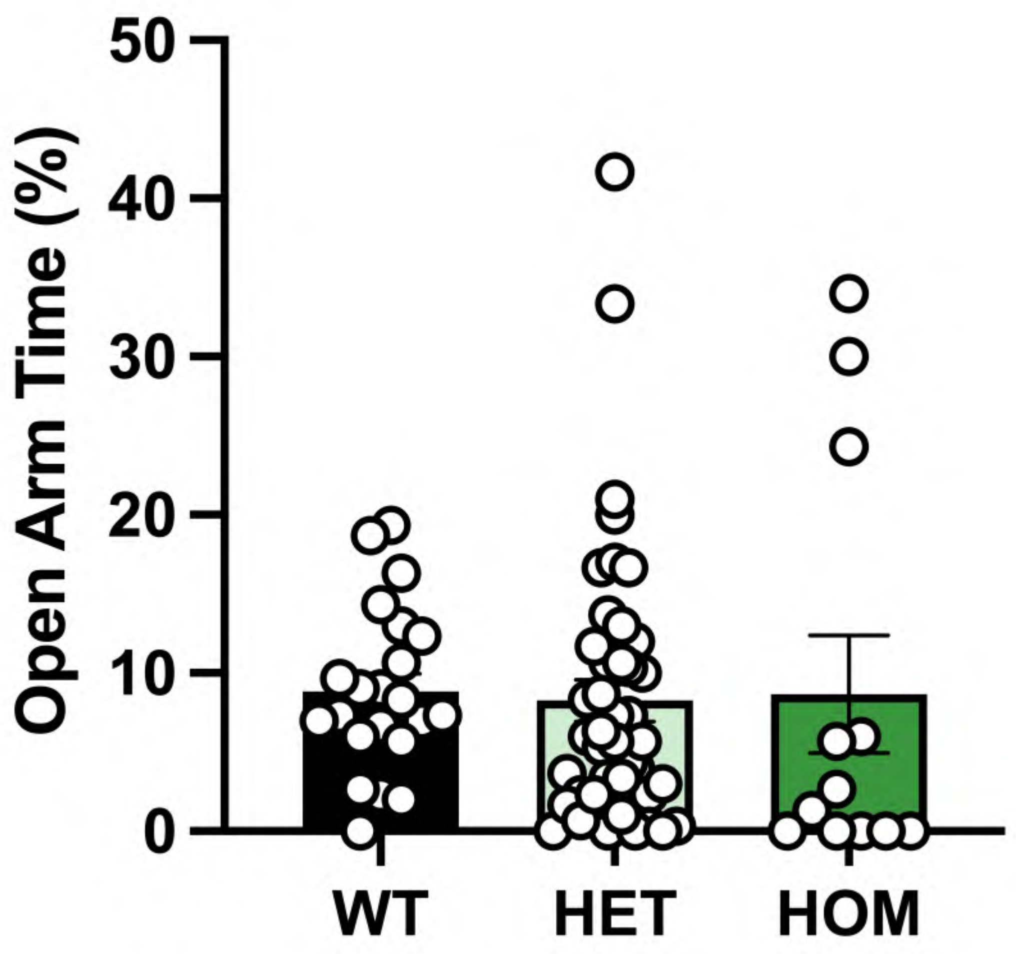
Hayley Thorpe

Jibran Khokhar

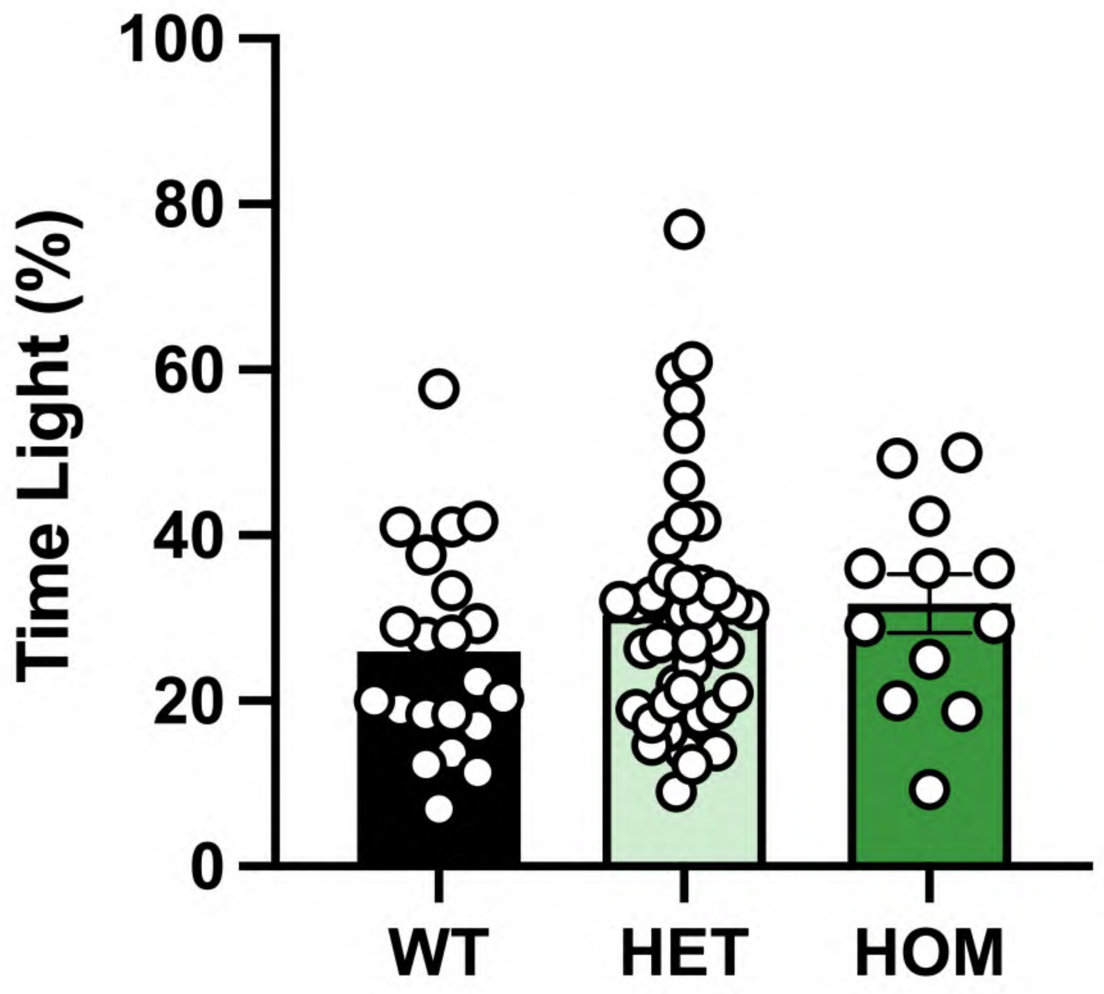
Sanchez-Roige et al, *Translational Psychiatry*, 2023

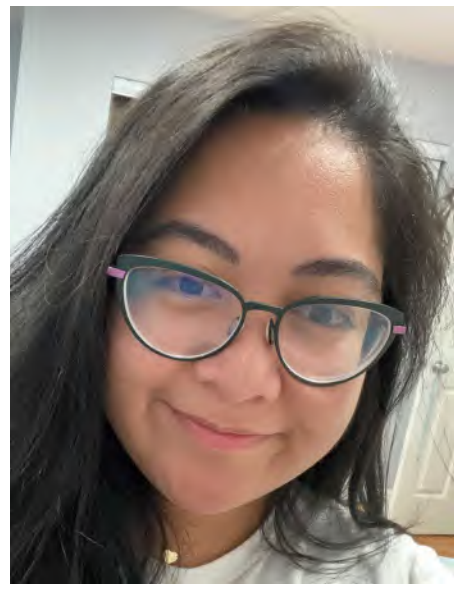
Decreased expression of Cadm2 was not associated with general anxiety-like behavior in mice

Elevated Plus Maze



Light-Dark Box



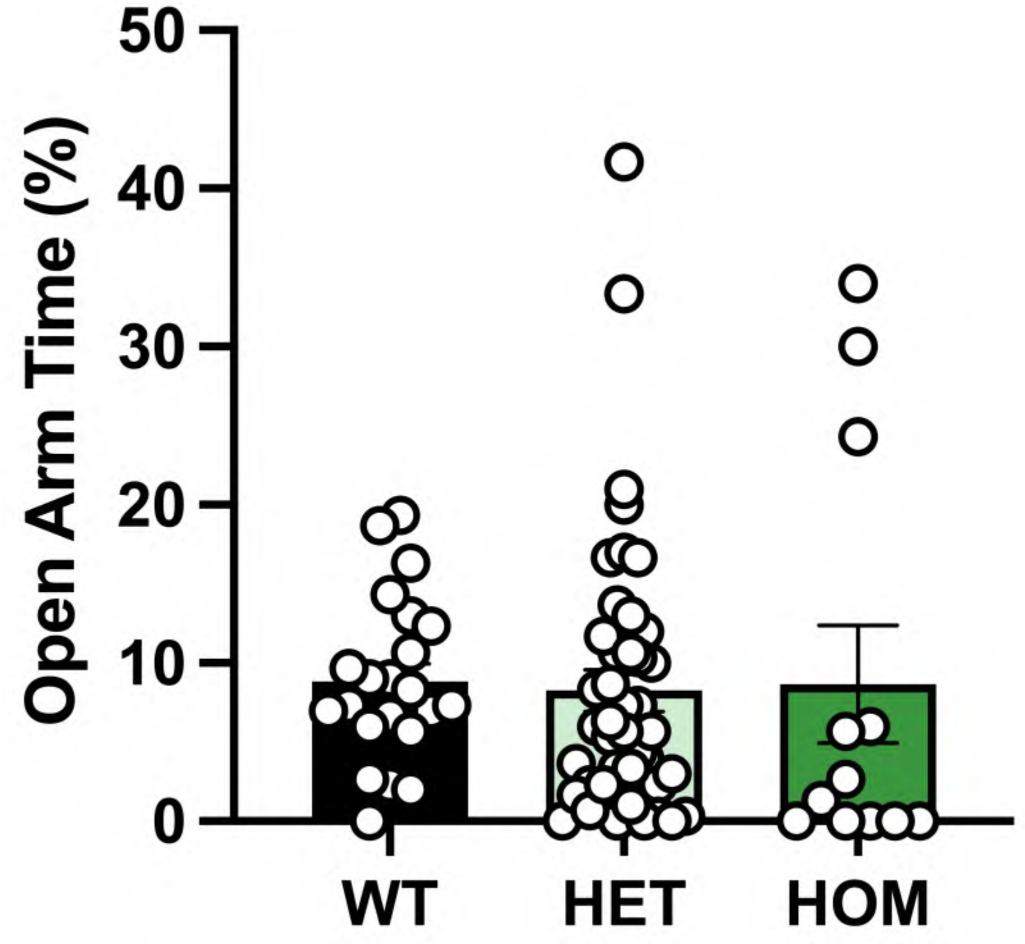


Jazlene Mallari

Sanchez-Roige et al, *Translational Psychiatry*, 2023

Decreased expression of Cadm2 was not associated with general anxiety-like behavior or ethanol consumption in mice

Elevated Plus Maze



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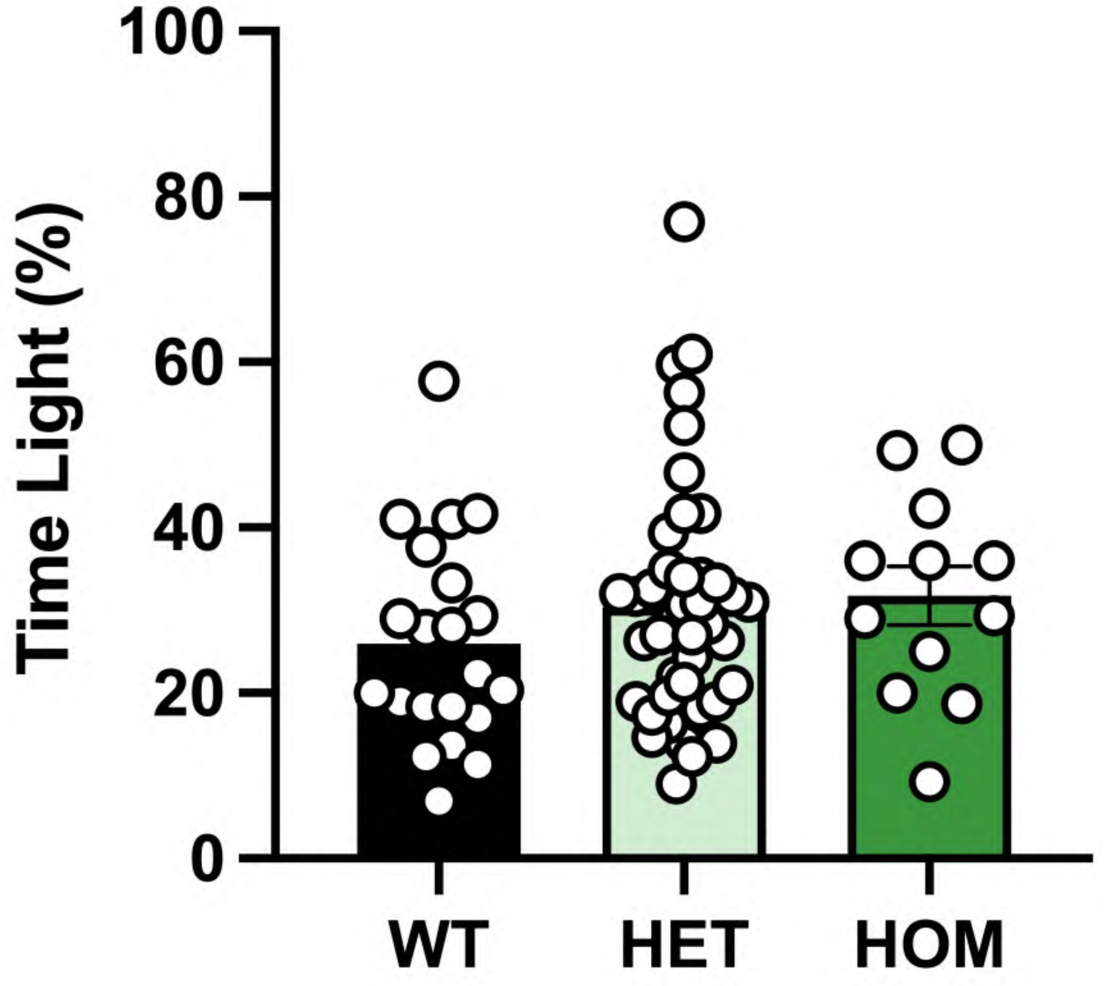
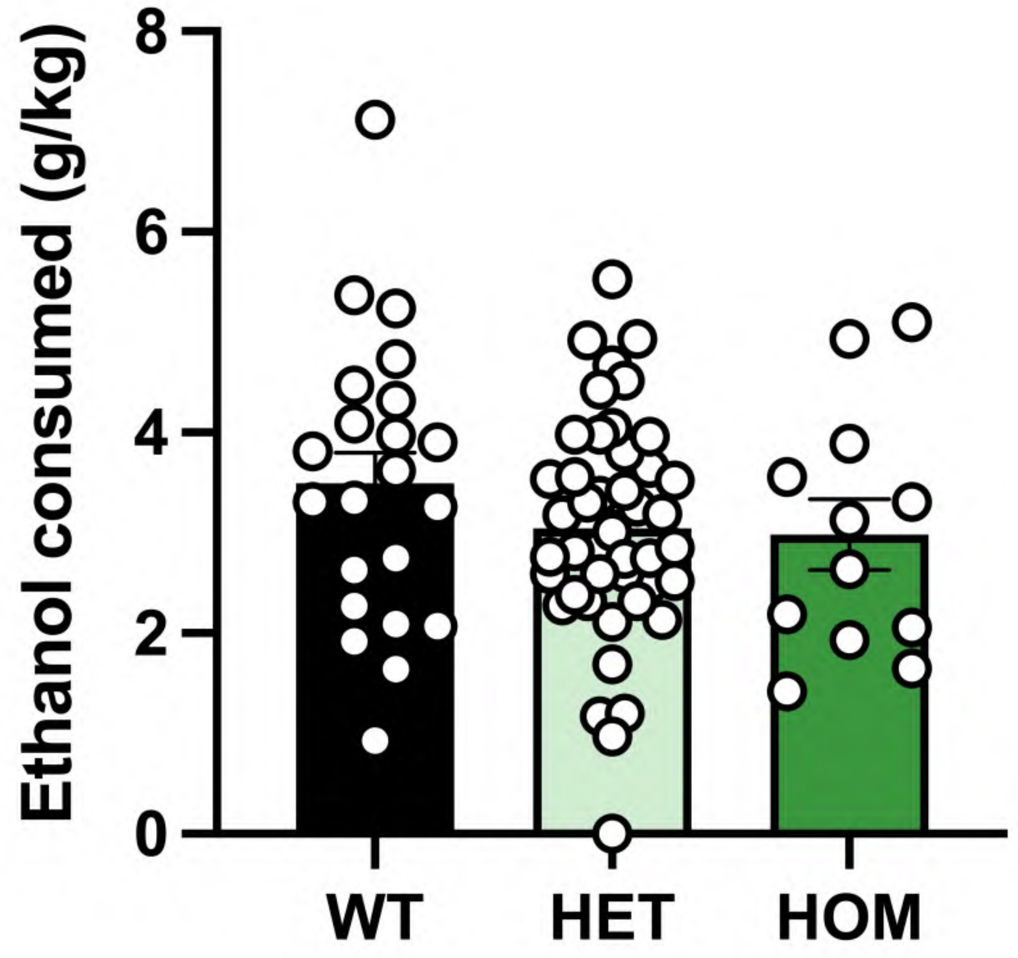
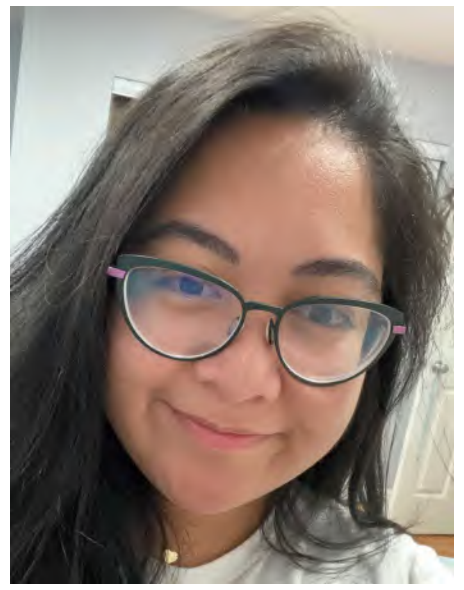


Drinking-in-the-dark paradigm





Jazlene Mallari

Sanchez-Roige et al, *Translational Psychiatry*, 2023

The role of *Cadm2* at the molecular, cellular and circuit level

Link to the article

Dimensional phenotypes complement traditional ascertainment strategies: they can dissect aspects of substance use disorders and can be inexpensively measured in large cohorts

The use of dimensional phenotypes enables translational research

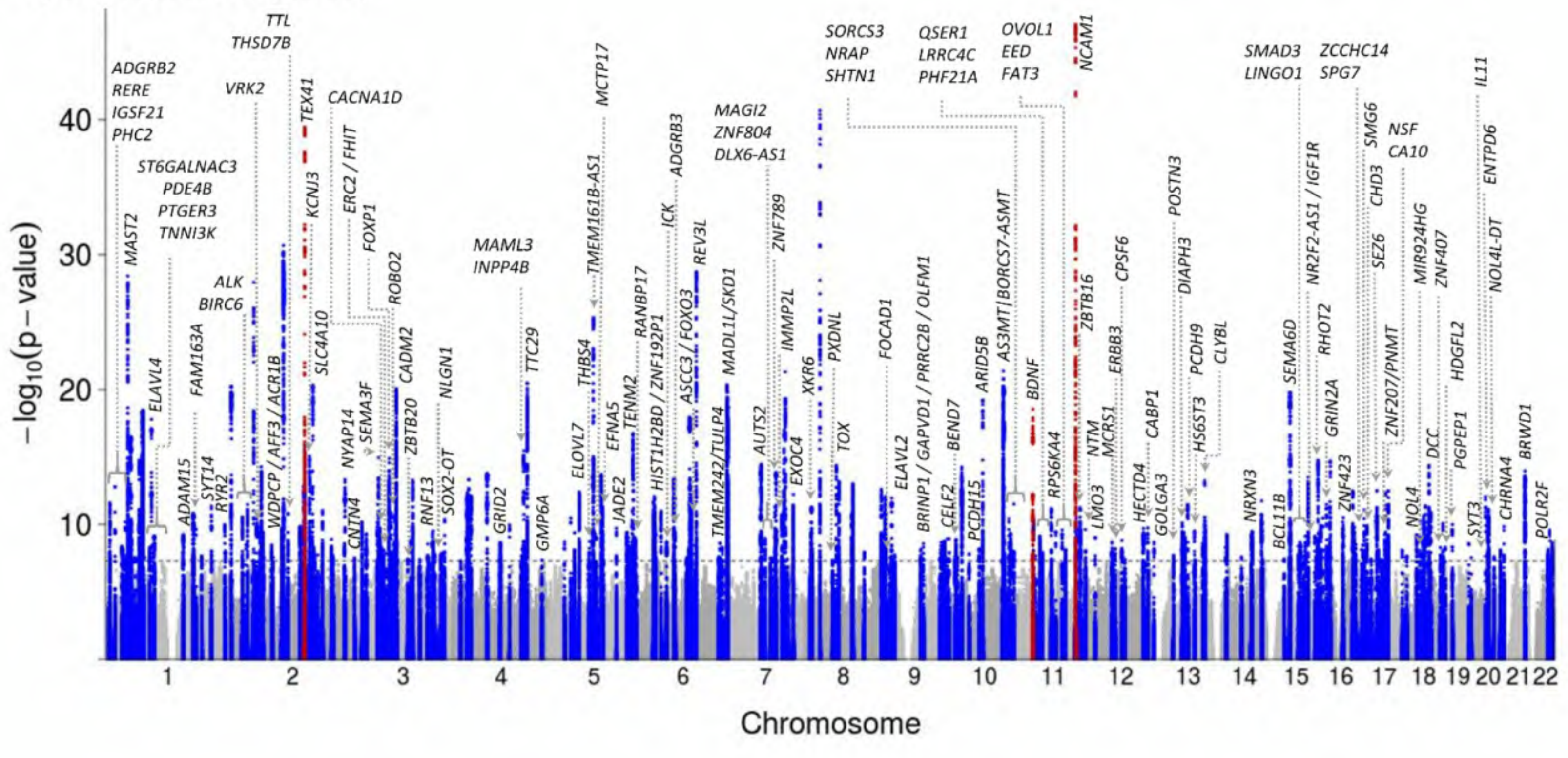
Reach out if you'd like to use the GWAS summary statistics!

sanchezroige@ucsd.edu

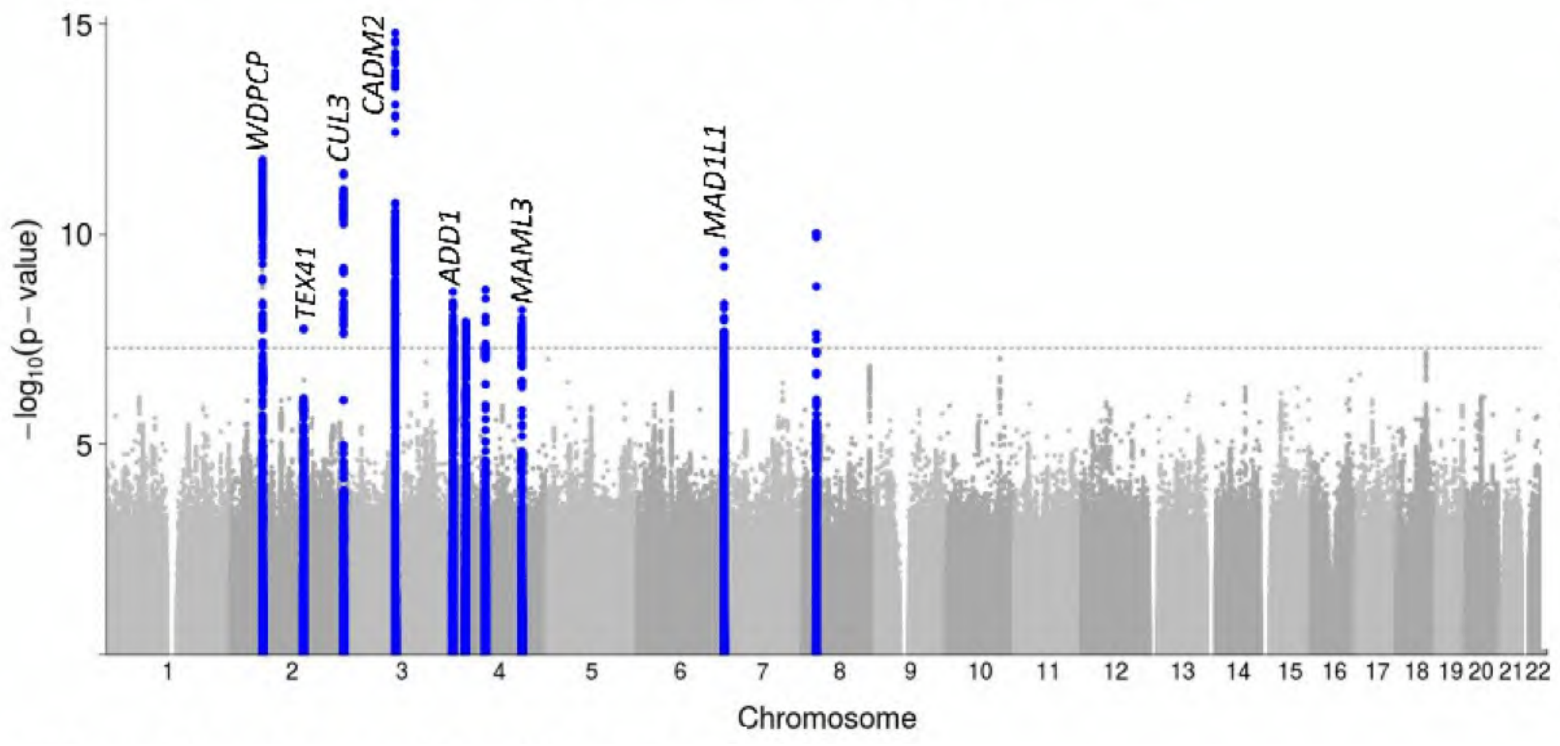
Multi-ancestry meta-analysis of tobacco use disorder based on electronic health records

Big strides for understanding aspects of smoking behaviors via GWAS

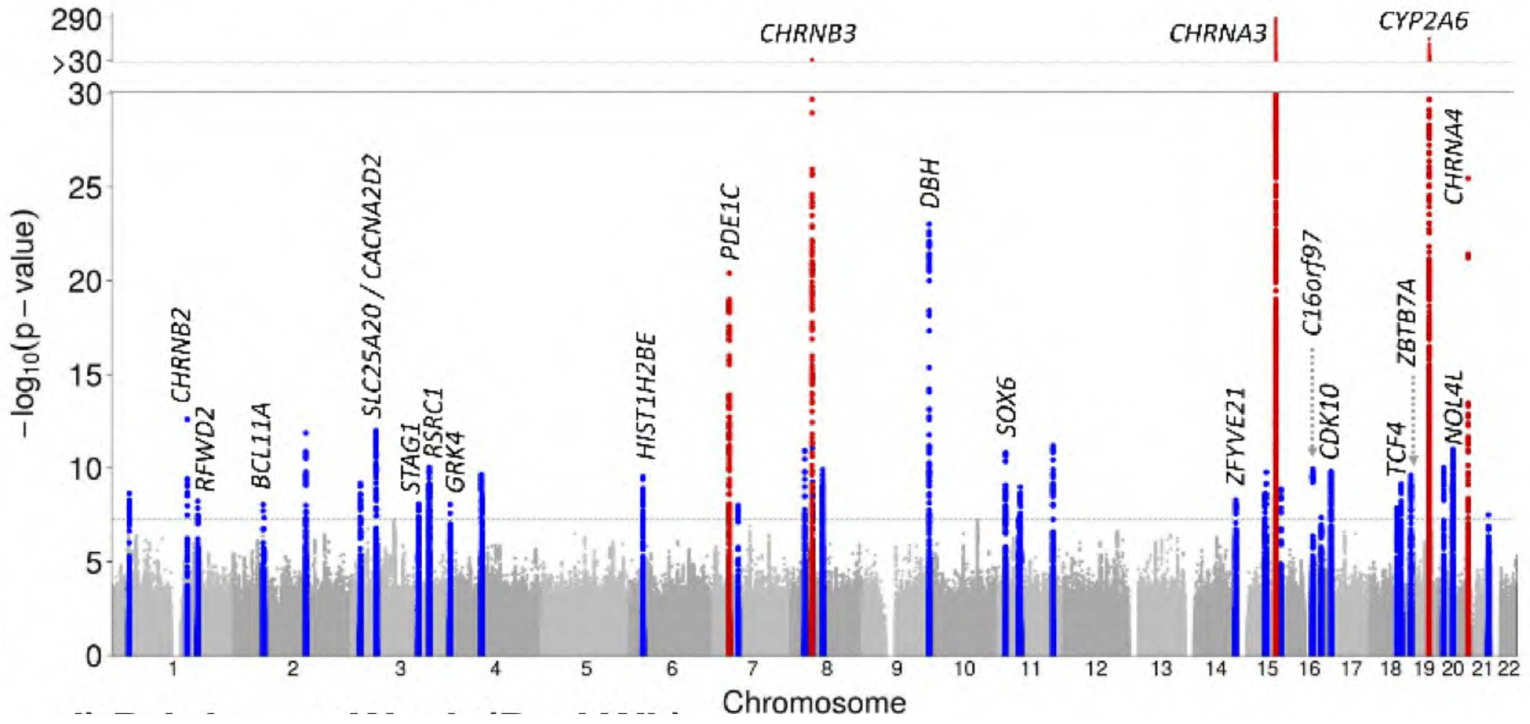
Smoking Initiation



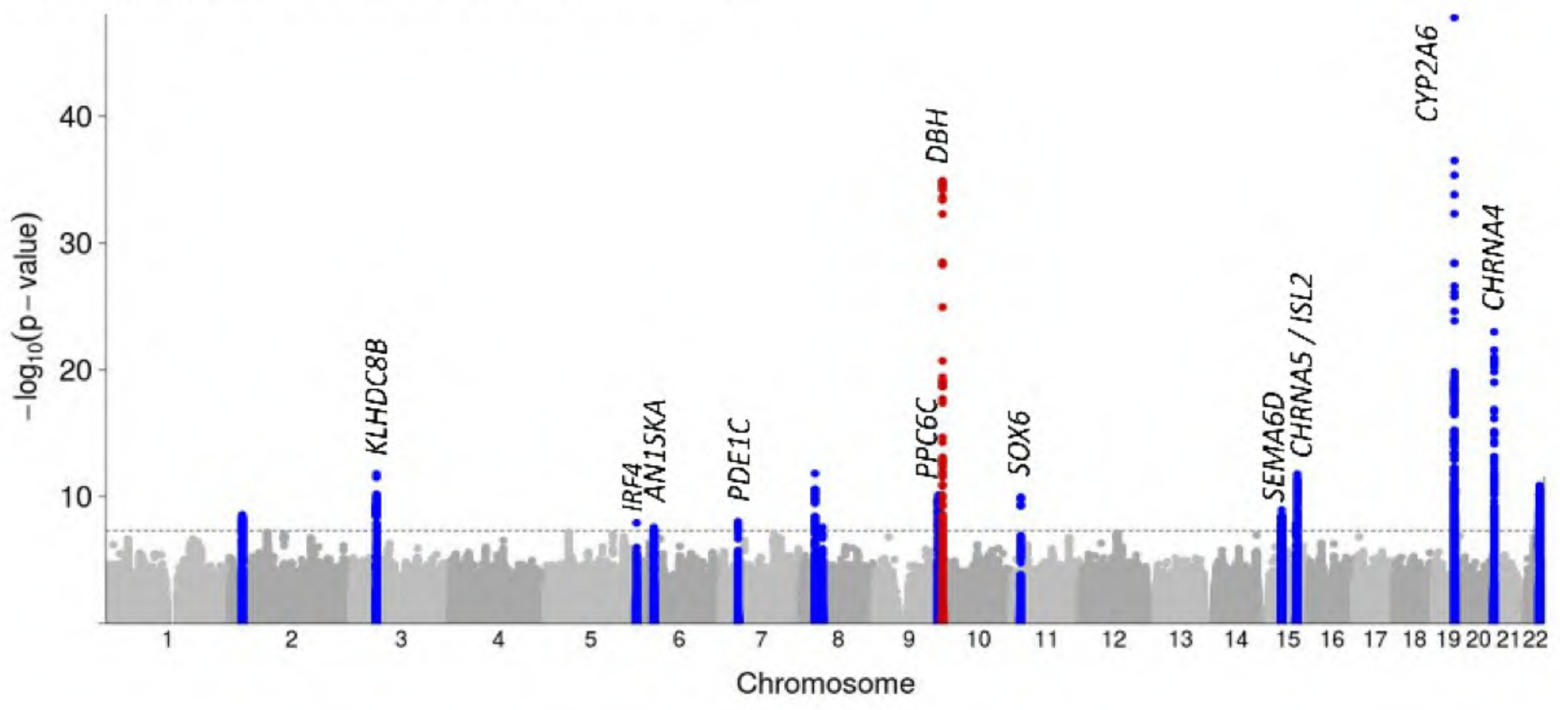
Age at Initiation



Cigarettes per Day



Smoking Cessation



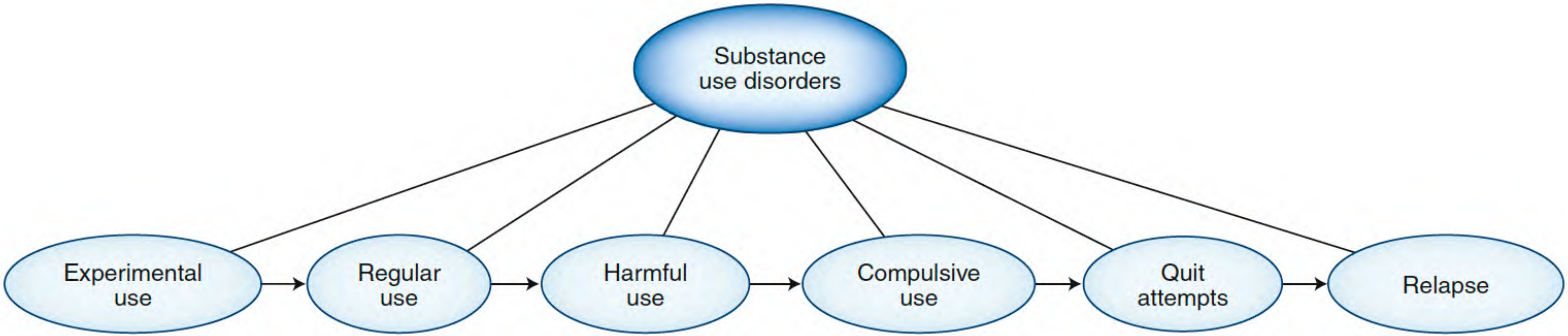
GWAS and Sequencing Consortium of Alcohol and Nicotine (GSCAN), *Nature Genetics*, 2018

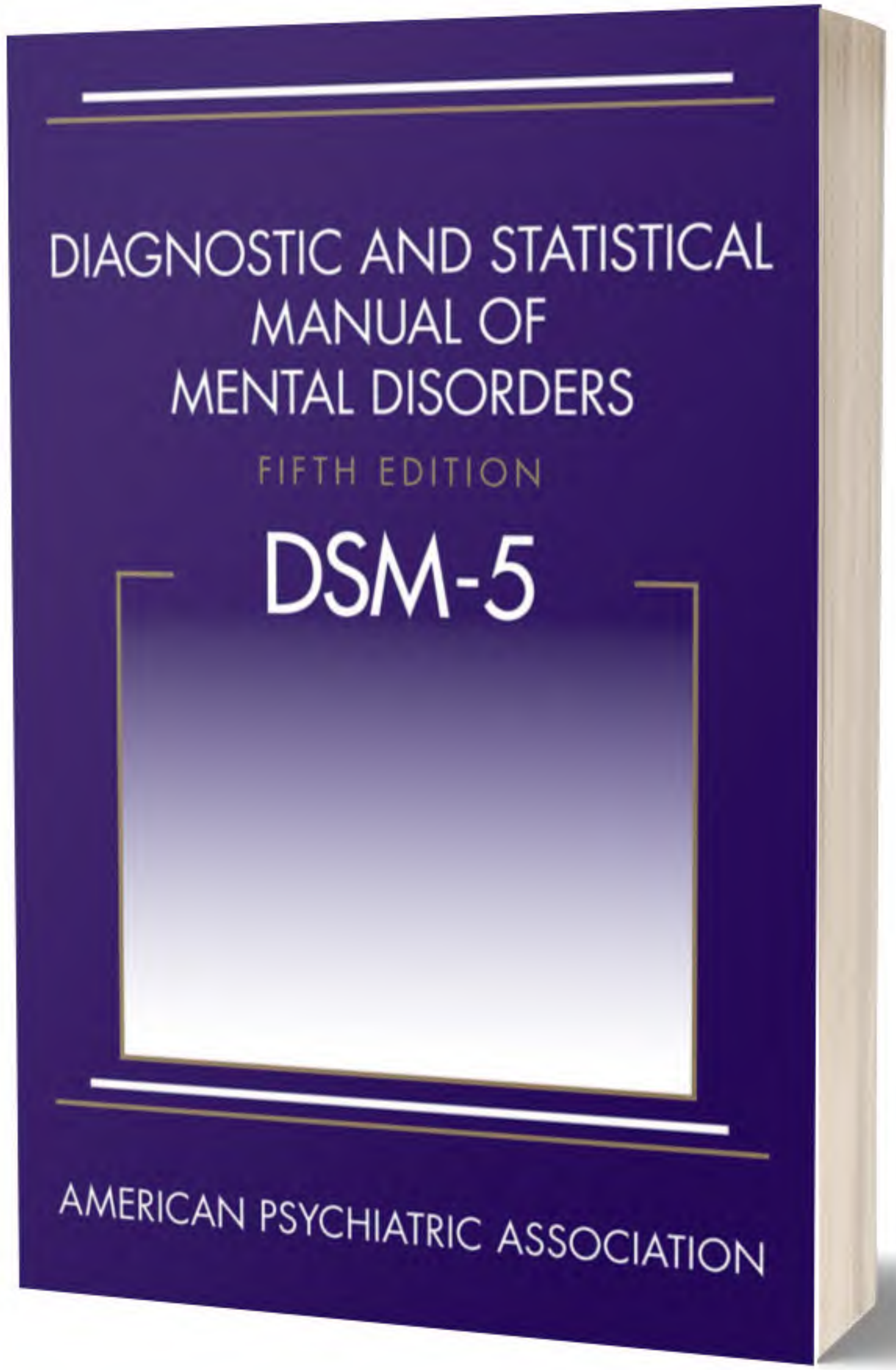
2,143 loci

associated with tobacco use

GWAS and Sequencing Consortium of Alcohol and Nicotine (GSCAN), *Nature*, 2022

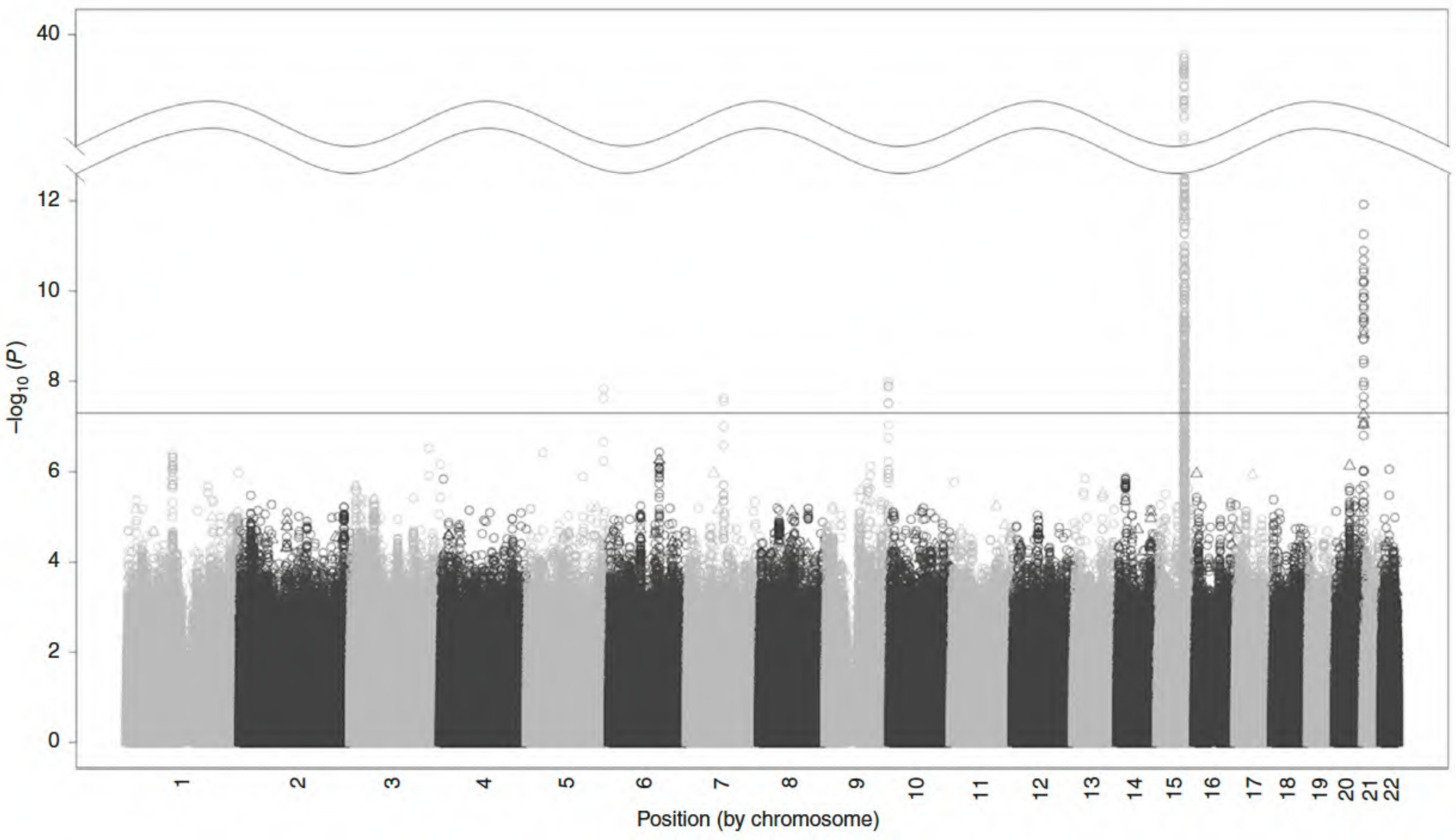
GWAS of tobacco use disorder (TUD) have been largely unexplored




DIAGNOSTIC AND STATISTICAL
MANUAL OF
MENTAL DISORDERS
FIFTH EDITION
DSM-5
AMERICAN PSYCHIATRIC ASSOCIATION

Fagerström Test for Nicotine Dependence (FTND) GWAS in 58,000 European and African ancestry smokers identified 5 loci

1. Time to first cigarette after waking
2. Cigarettes per day
3. Difficulty to refrain from smoking in forbidden places
4. Cigarette most hated to give up (morning or others)
5. Smoke during the first hours after waking
6. Smoke when ill



iNDiGO Consortium; Quach et al, *Nature Communications*, 2020

Larger and diverse samples are needed to uncover more loci

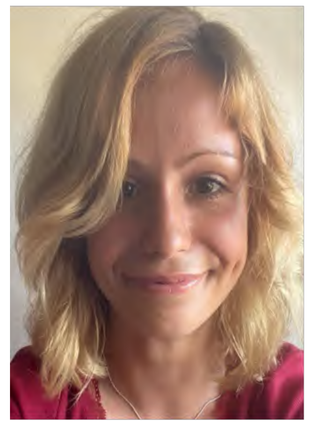

CYTOSINE
GUANINE
ADENINE
THYMINE
Cardiovascular diseases
Pulmonary disease
Diseases of the digestive system
Liver disease
Diseases of the musculoskeletal system
Neurological diseases

PsycheMERGE

(Psych) Electronic Medical Record
and GEnomics Network

Substance Use Disorder Workgroup


Vanessa Troiani


Mariela Jennings

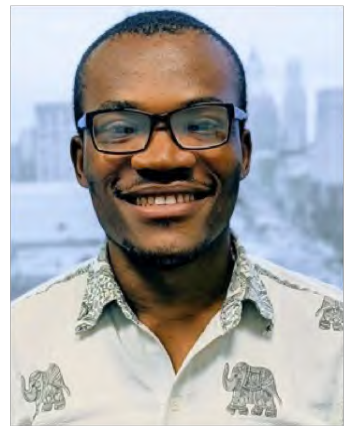

Lea Davis


Maria Niarchou

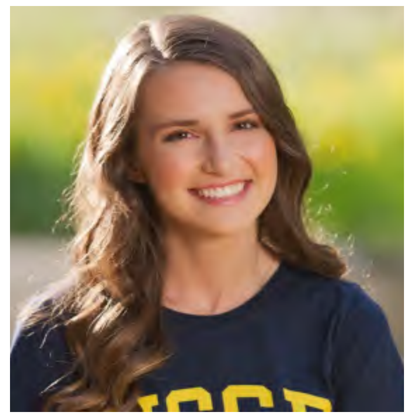

Hyunjoon Lee


Travis Mallard


Jordan Smoller


Sylvanus Toikumo


Rachel Kember


Sevim Bianchi


Brandon Coombes


Yirui Hu


Lori Schirle


David Samuels


Alvin Jeffery


Melissa Poulson


Colin Walsh


Laura Vilar-Ribo


Natasia Courchesne-Krak


Renata Cupertino


Kritika Singh


Rick Crist

Can we use EHR data for genetic studies of TUD?

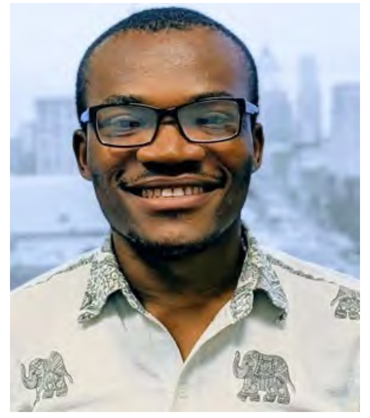
TUD Phecodes (318*)

For a full list of codes

653,790 individuals across four sites from the psycheMERGE network

BioVU DNA REPOSITORY	Mass General Brigham	PMBB Penn Medicine BioBank	MVP
46,905 (EUR)	22,268 (EUR)	28,999 (EUR) 10,088 (AFR)	396,833 (EUR) 104,332 (AA) 44,365 (LA)

Mariela Jennings



Sylvanus Toikumo

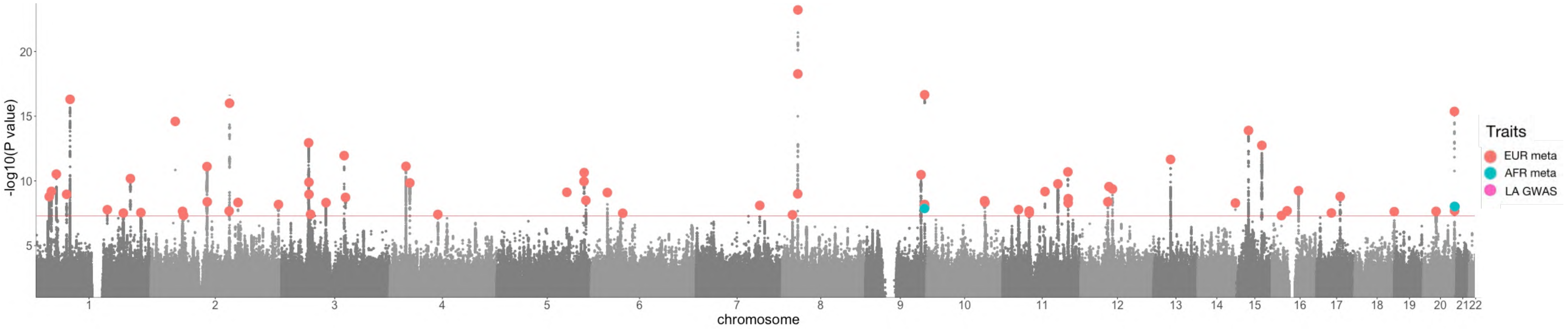
Hyunjoon Lee

EUR European; AFR African;
AA African American; LA Latin American

High genetic correlations across sites (mean r_g=0.74, EUR; r_g=0.86, AFR)

Toikumo*, Jennings* et al, *medRxiv*, 2023

Ancestry-specific meta-analyses identified 55 loci (EUR) and 2 loci (AFR)
No significant loci were found in LA (N= 44,365)



Mariela Jennings

Sylvanus Toikumo

Hyunjoon Lee

Toikumo*, Jennings* et al, *medRxiv*, 2023

The multi-ancestral meta-analysis identified 97 lead SNPs in 72 independent loci

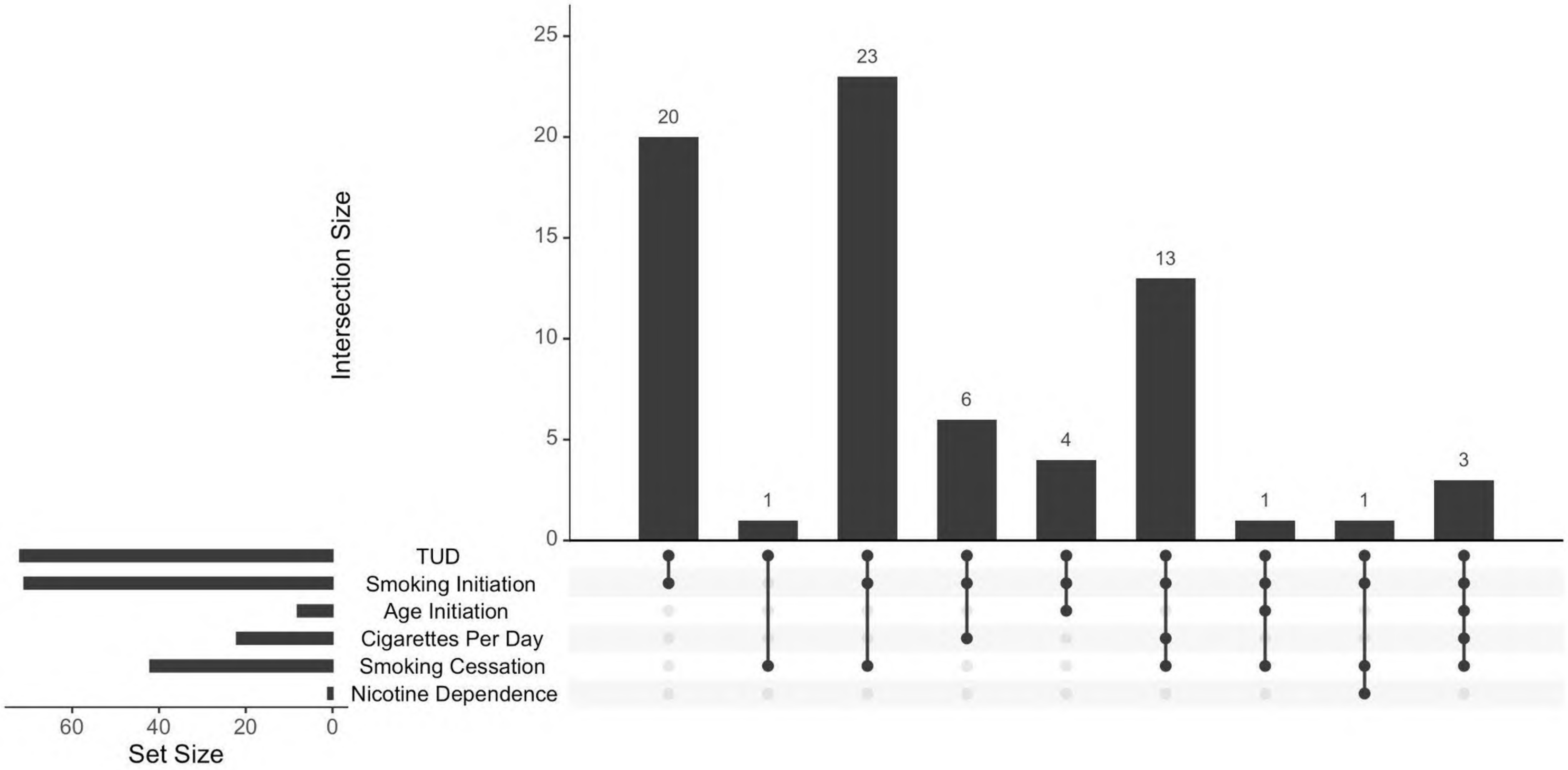
Sylvanus Toikumo

Toikumo*, Jennings* et al, *medRxiv*, 2023

All GWS associations replicated the findings identified in the recent GSCAN study

Toikumo*, Jennings* et al, *medRxiv*, 2023

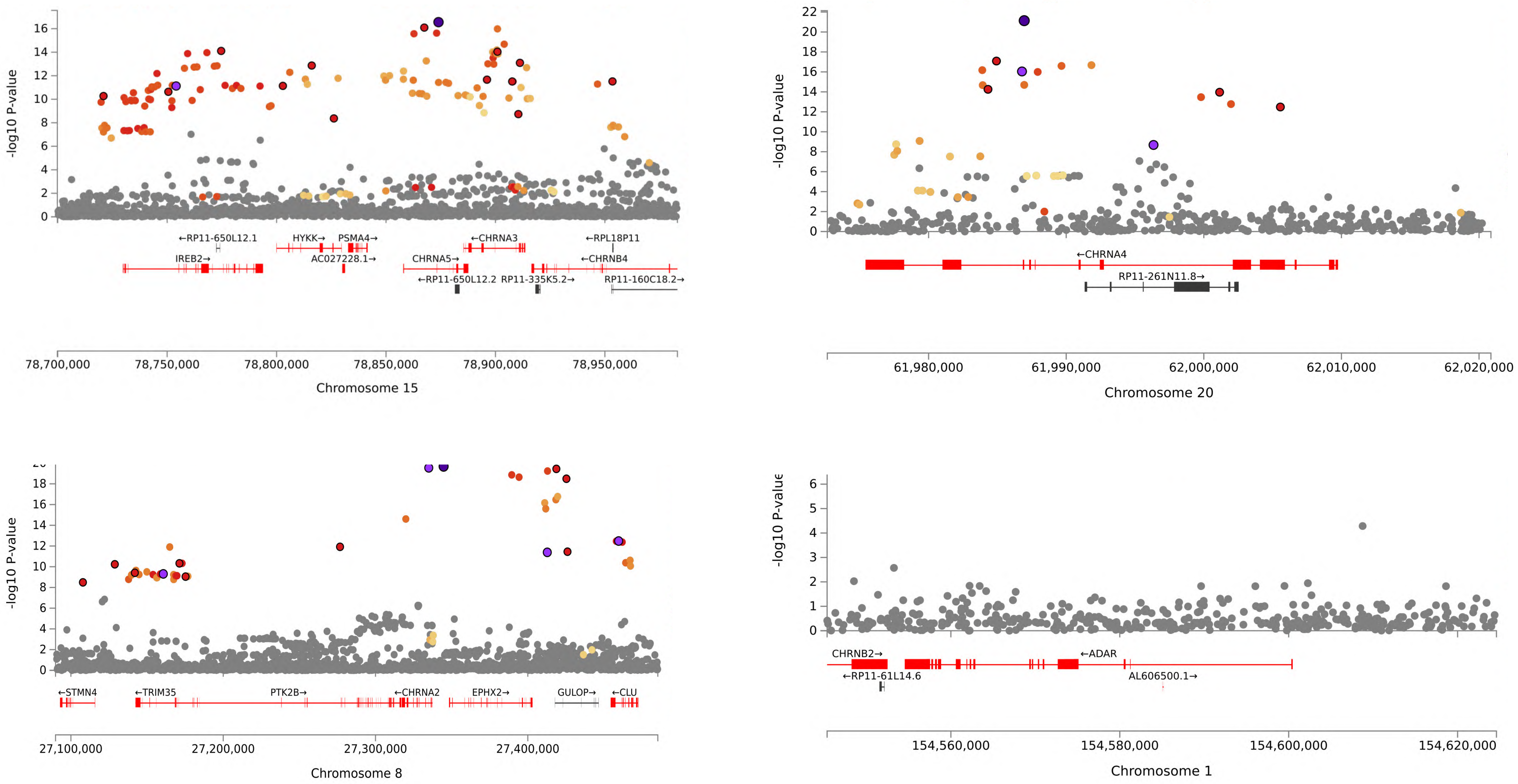
We replicate previously known associations with smoking traits, from initiation, to consumption, to cessation, to dependence



Toikumo*, Jennings* et al, *medRxiv*, 2023

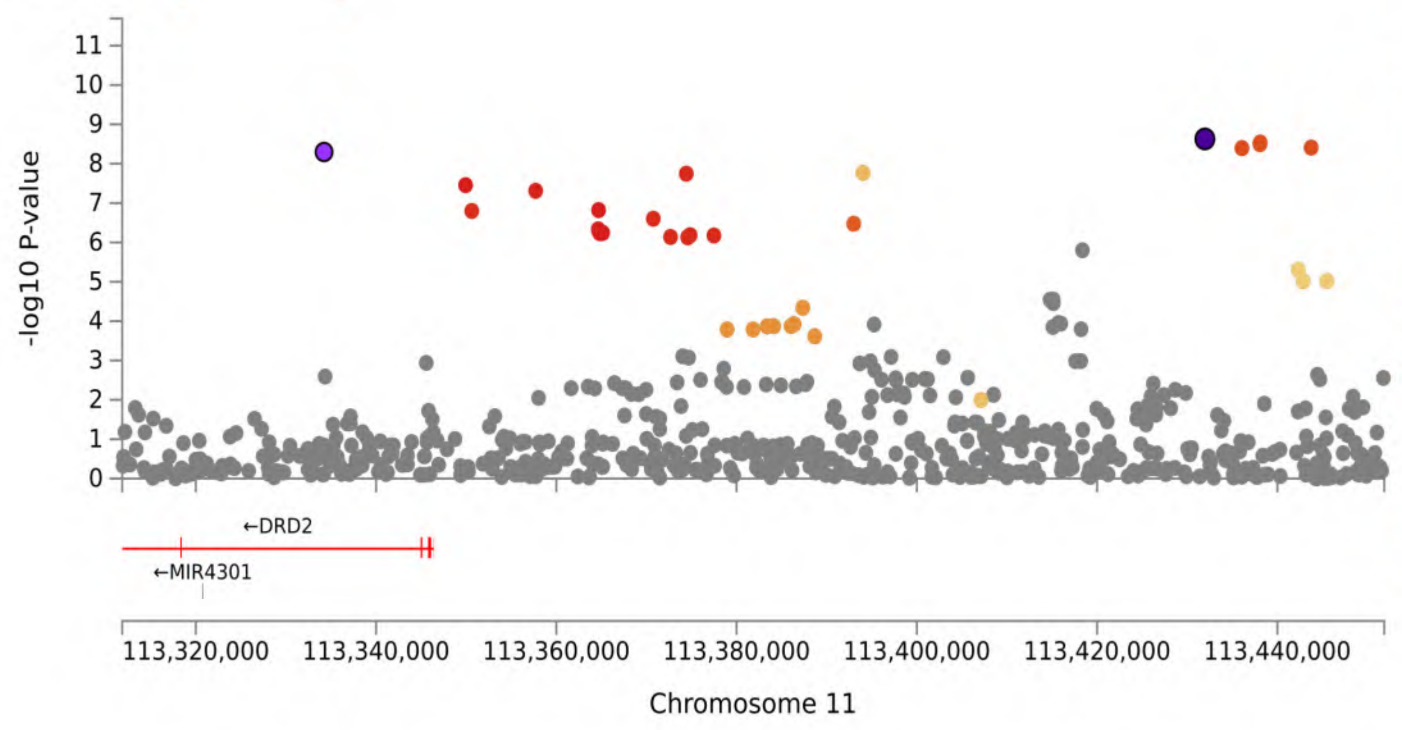
Associations with previous candidate genes with overwhelming biological evidence of involvement in tobacco use disorder

Corroborative support for the involvement of nicotinic acetylcholine receptor genes (*CHRNA5-A3-B4, CHRNB2*, *CHRNA2, CHRNA4*)

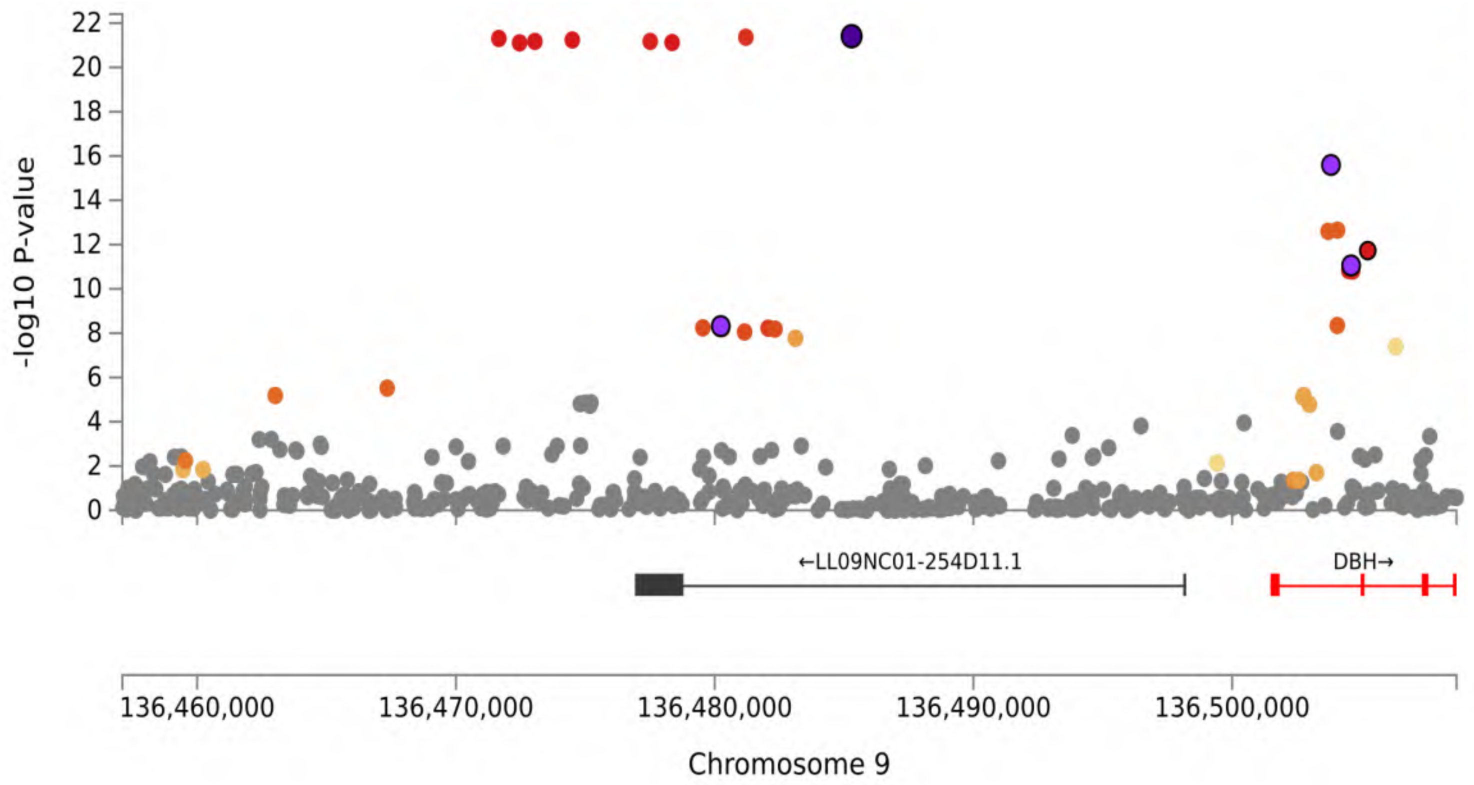


Toikumo*, Jennings* et al, *medRxiv*, 2023

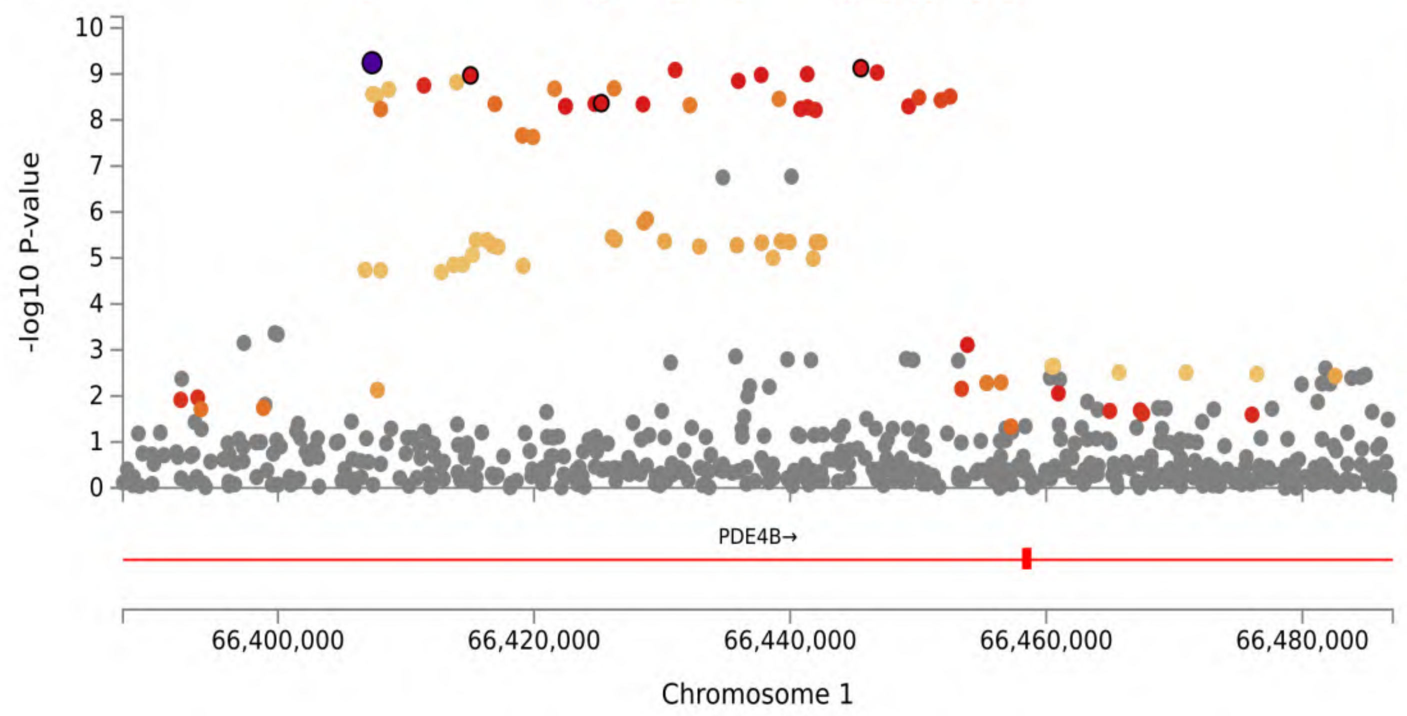
We identified associations with variants in several genes that modulate dopaminergic transmission



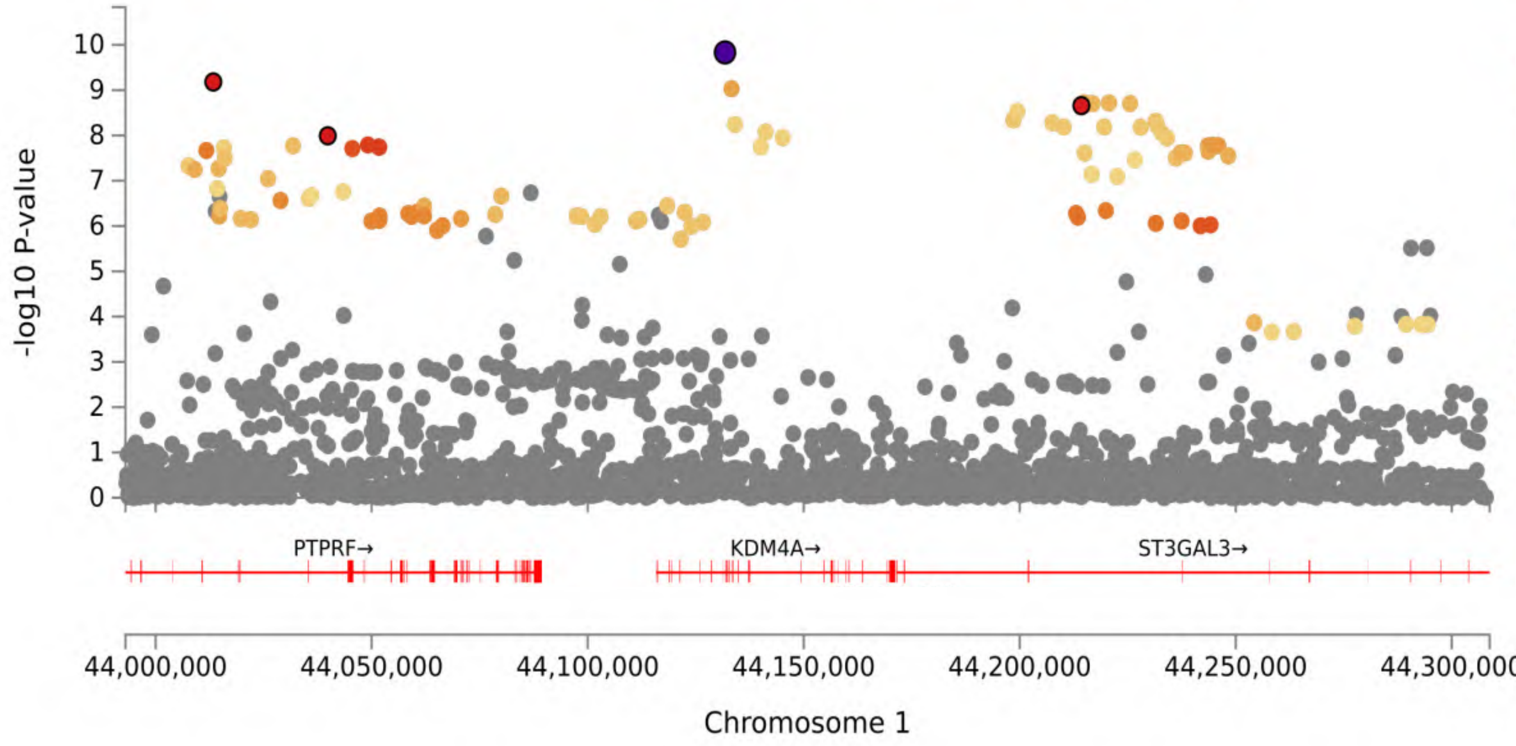
Dopamine Receptor D2 gene; dopaminergic transmission is central to reward and reinforcement learning



DBH encodes a dopamine β-hydroxylase enzyme necessary to convert dopamine to norepinephrine



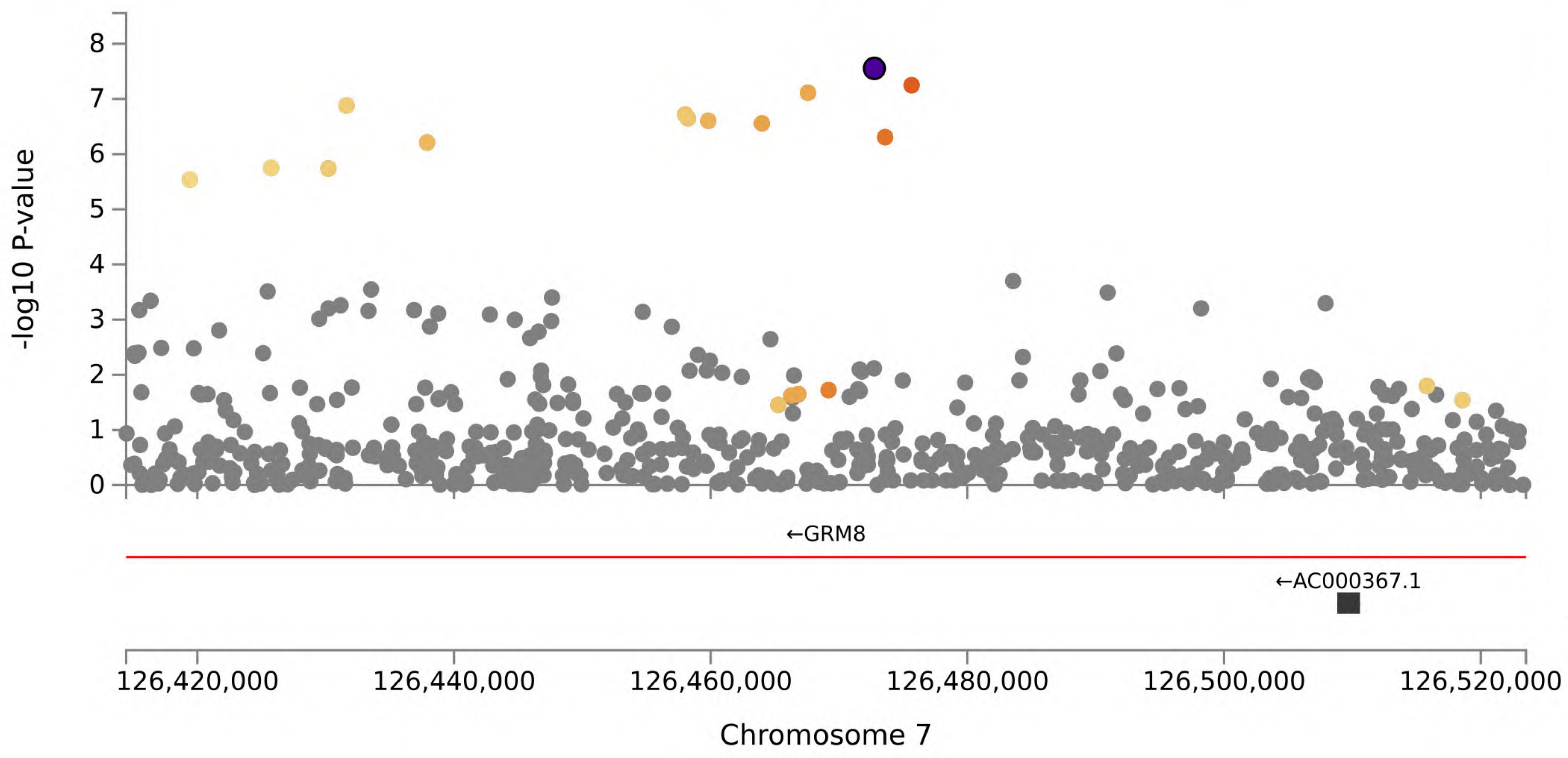
PDE4B has regulatory effects on dopaminergic pathways



KDM4A has known interactions with dopamine agents

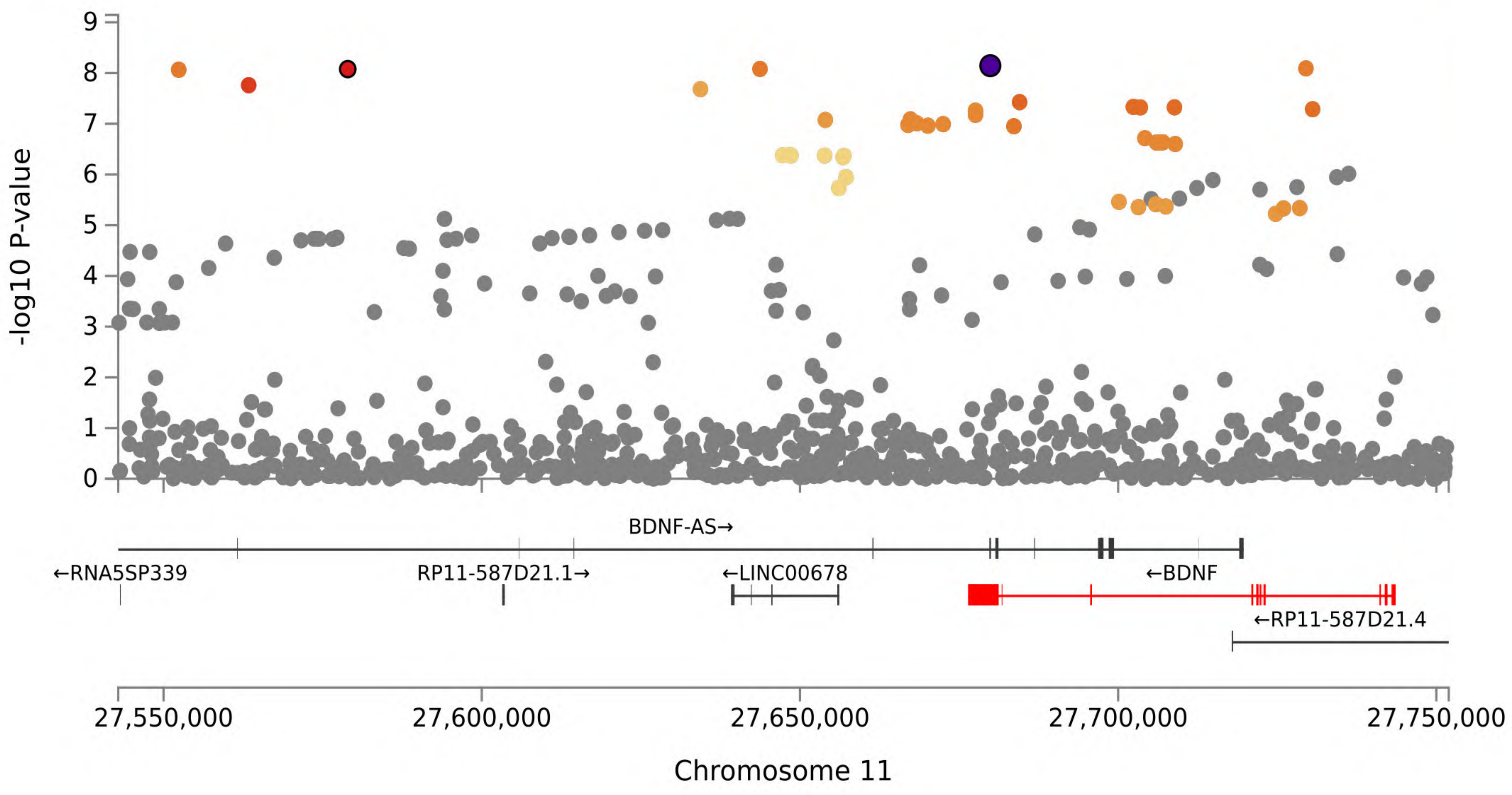
Toikumo*, Jennings* et al, *medRxiv*, 2023

We identified variants in *GRM8* (Glutamate Metabotropic Receptor 8), important for mediating reward-related learning and memory



Toikumo*, Jennings* et al, *medRxiv*, 2023

We identified variants in the gene *BDNF*, a robust candidate gene in substance use disorders for its role in synaptogenesis and memory



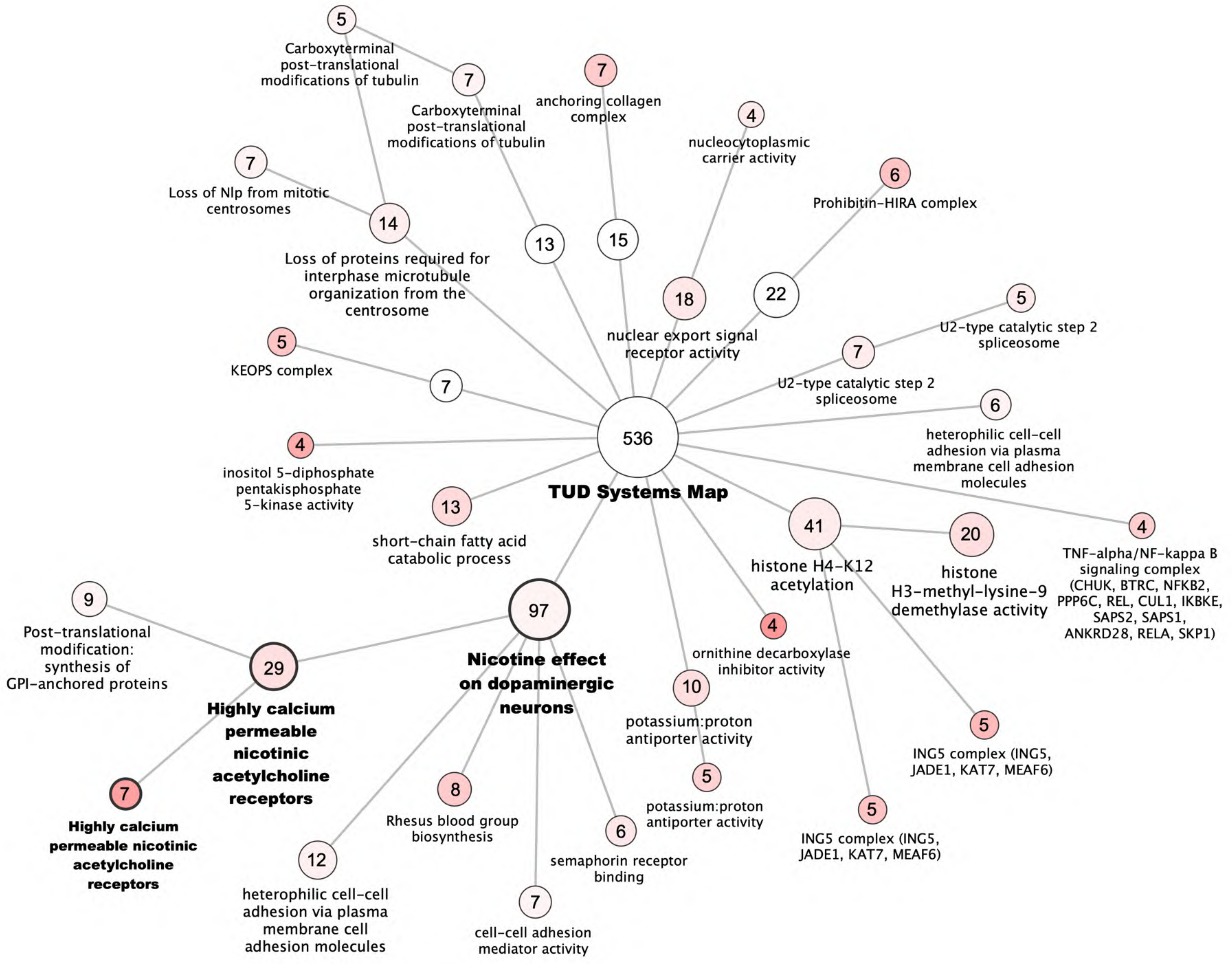
Toikumo*, Jennings* et al, *medRxiv*, 2023

Mapping variants to genes identified

330 TUD risk genes

Toikumo*, Jennings* et al, *medRxiv*, 2023

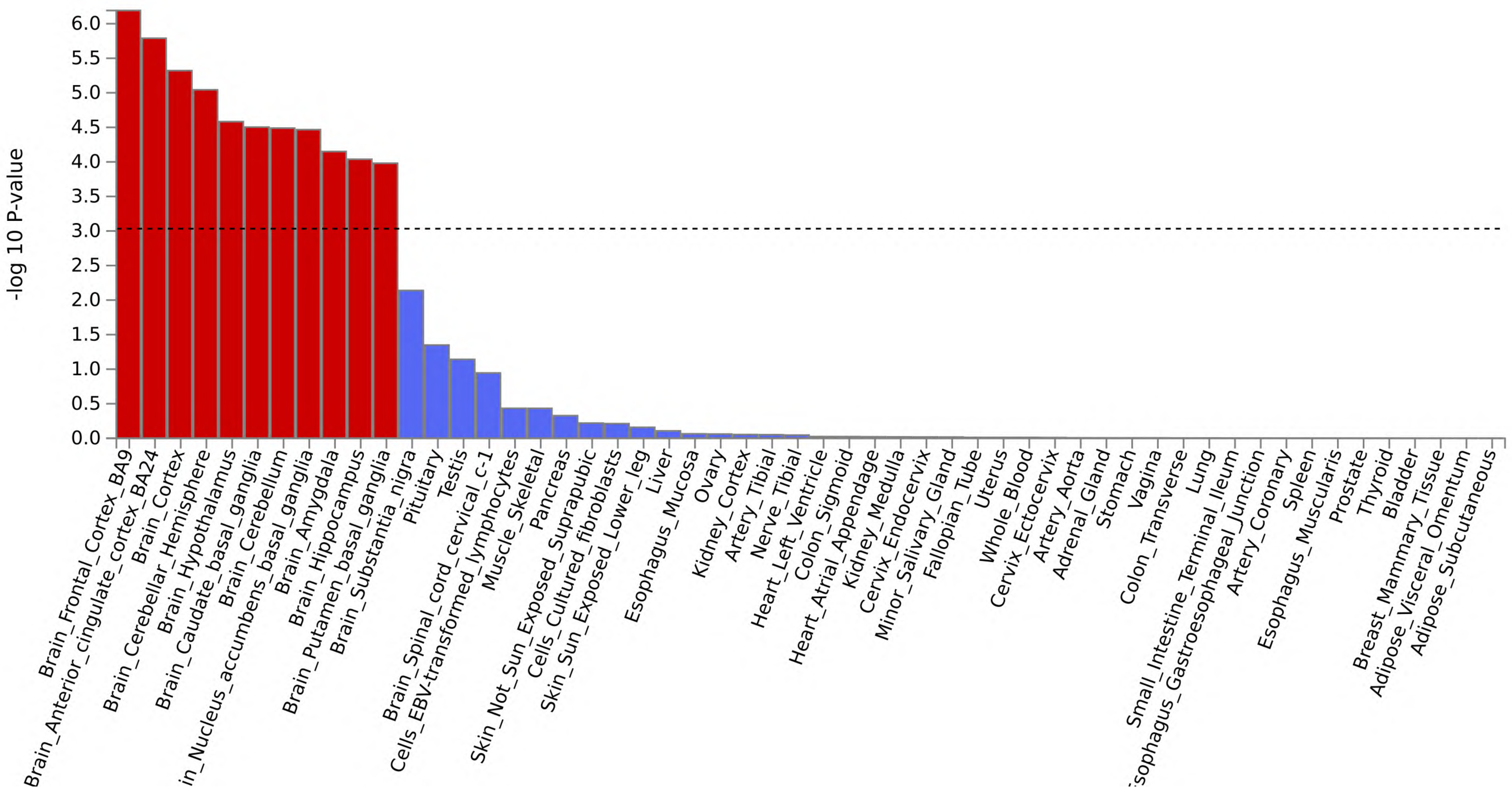
Pathways involved in cholinergic and dopamine transmission

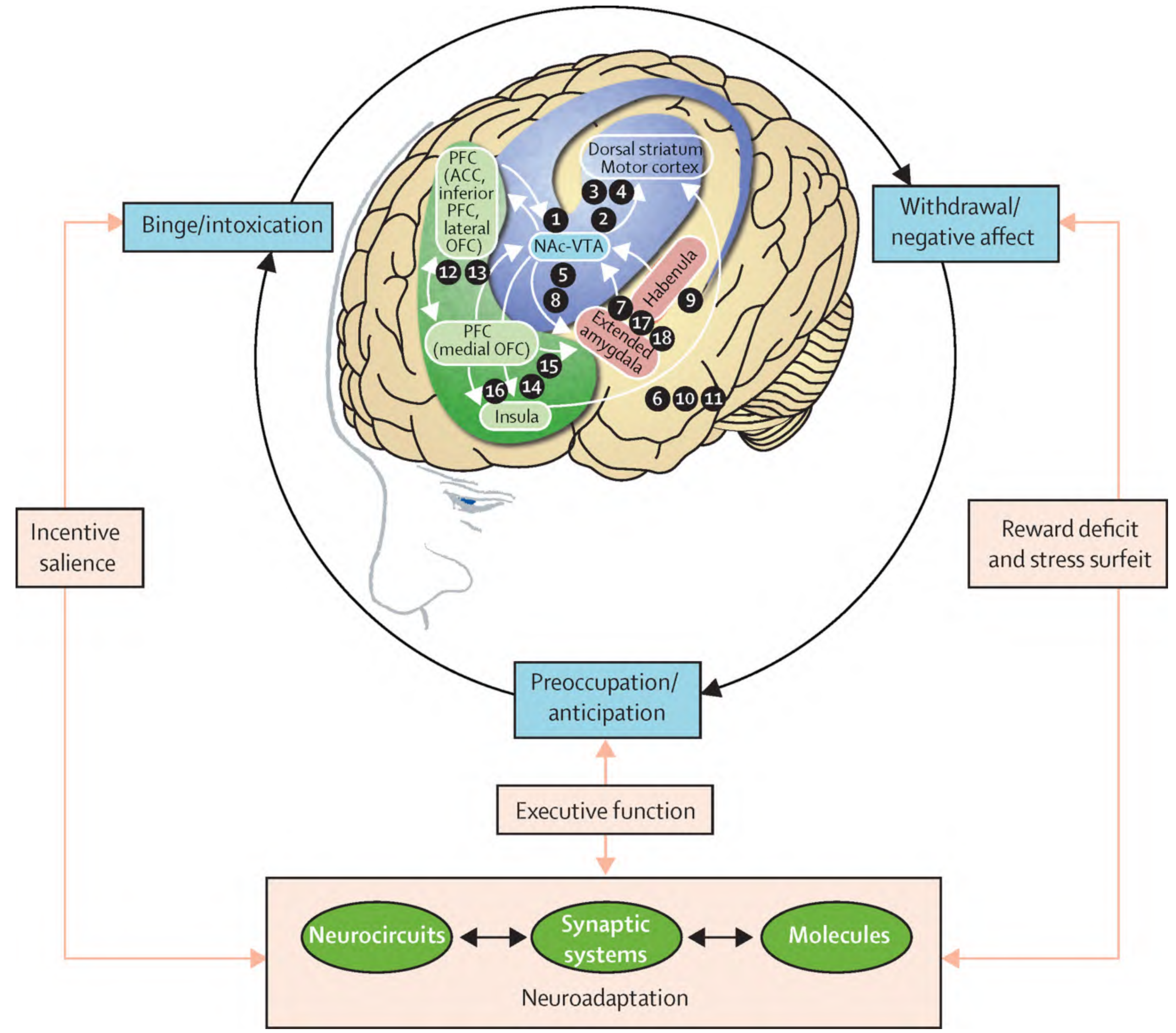


Brittany Leger

Toikumo*, Jennings* et al, *medRxiv*, 2023

Enrichment for TUD in brain tissues, including regions previously associated with substance use disorders

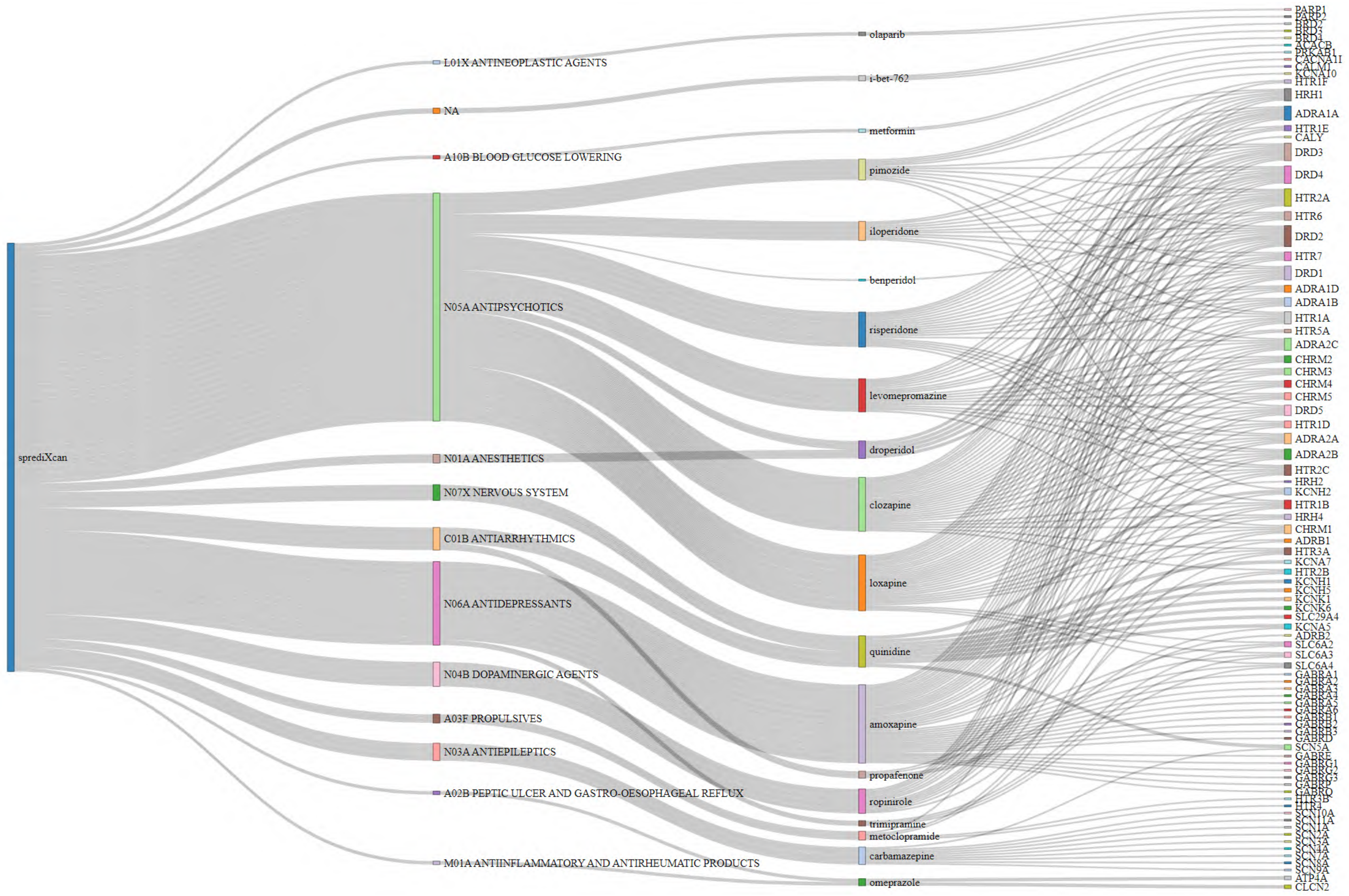




Toikumo*, Jennings* et al, *medRxiv*, 2023

Koob and Volkow, *The Lancet Psychiatry*, 2016

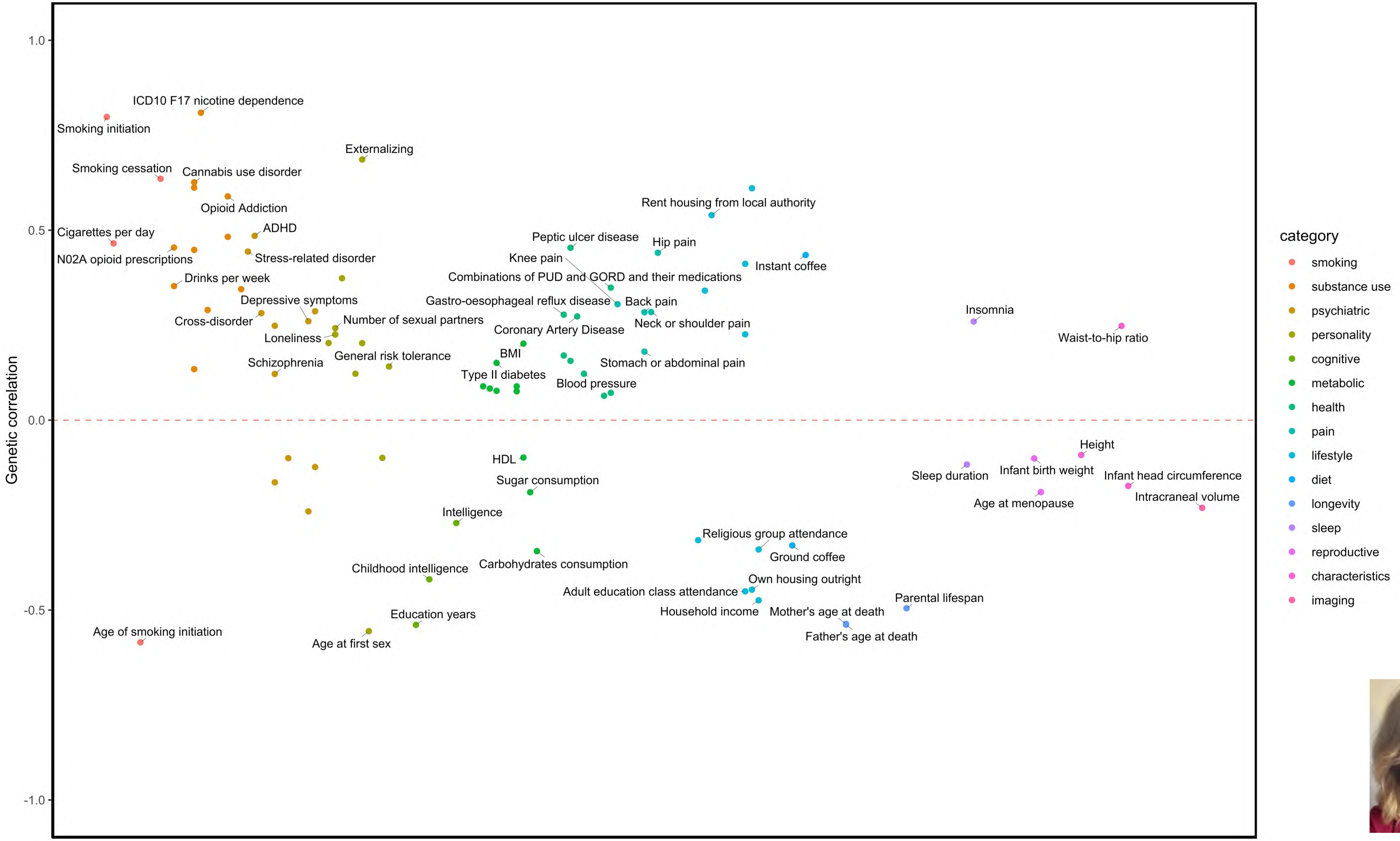
Significant signal enrichment was found in genes encoding targets of antipsychotics, antidepressants, dopaminergic agents, among others*, including varenicline (an FDA approved drug for smoking cessation)



*Library of Integrated Network-Based Cellular Signatures (LINCS) database

Ben Pham

Significant genetic correlations with 86 comorbid traits



Toikumo*, Jennings* et al, *medRxiv*, 2023

Mariela Jennings

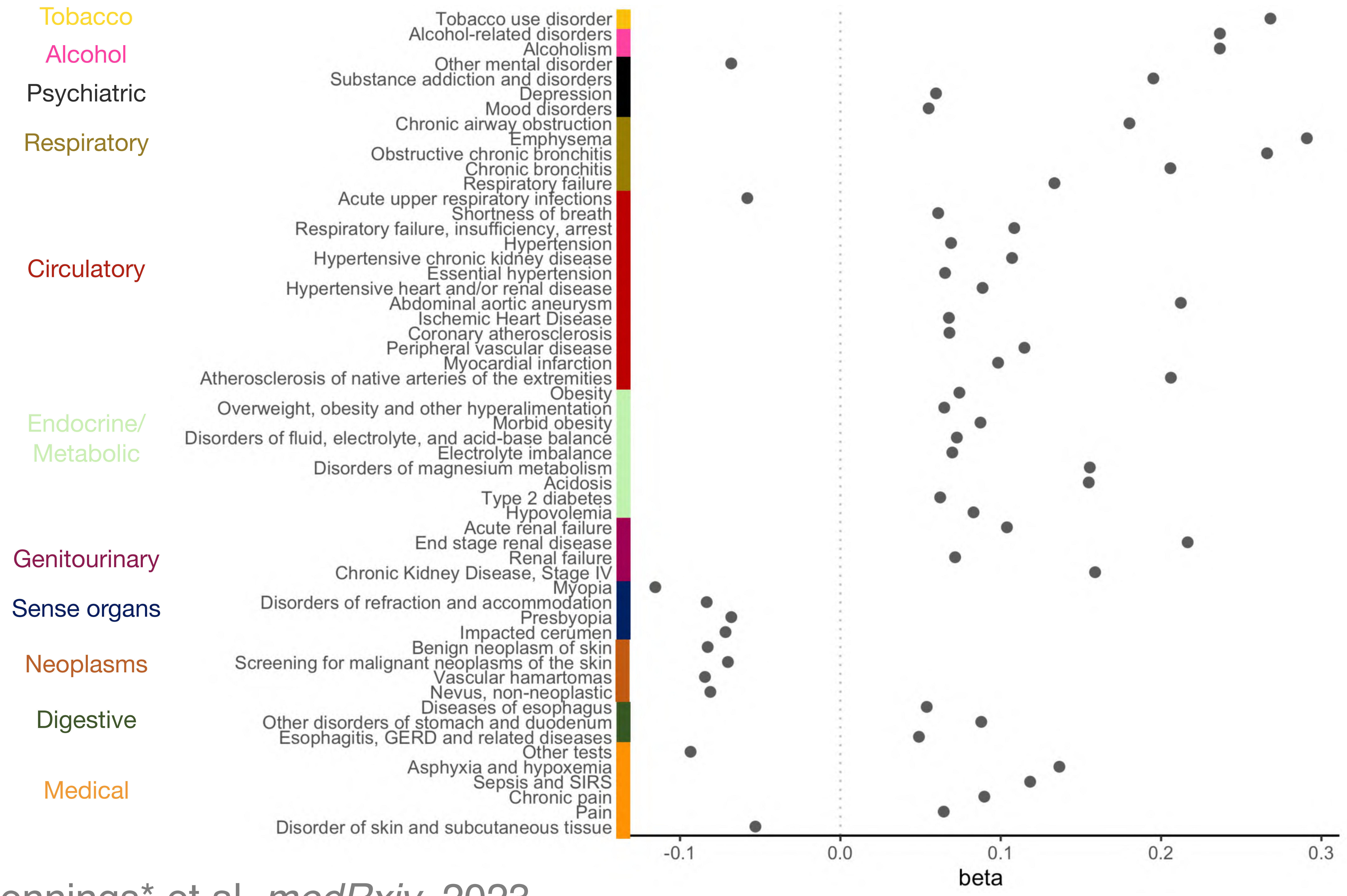
TUD Polygenic Score (PGS) phenome-wide association analysis (PheWAS) in >57k Mayo Clinic individuals

MAYO CLINIC

Brandon Coombes

Joanna Biernacka

TUD PGS was associated with 54 medical conditions (selected traits below), including tobacco use disorder as defined by phecodes (European cohort)



Toikumo*, Jennings* et al, *medRxiv*, 2023

Vanessa Pazdernik

Yale-Penn:
deeply phenotyped sample for substance use disorders

Joel Gelertner

Hank Kanzler

Kember et al, *Biological Psychiatry*, 2022

TUD Polygenic Score (PGS) PheWAS in >10k Yale-Penn individuals

TUD PGS was associated with 202 comorbid traits (selected traits below), including nicotine dependence as defined by DSM-IV (European cohort)

Toikumo*, Jennings* et al, *medRxiv*, 2023

Sylvanus Toikumo

Rachel Kember

TUD PGS (African) was also significantly associated with nicotine dependence as defined by DSM-IV in the African Yale-Penn cohort

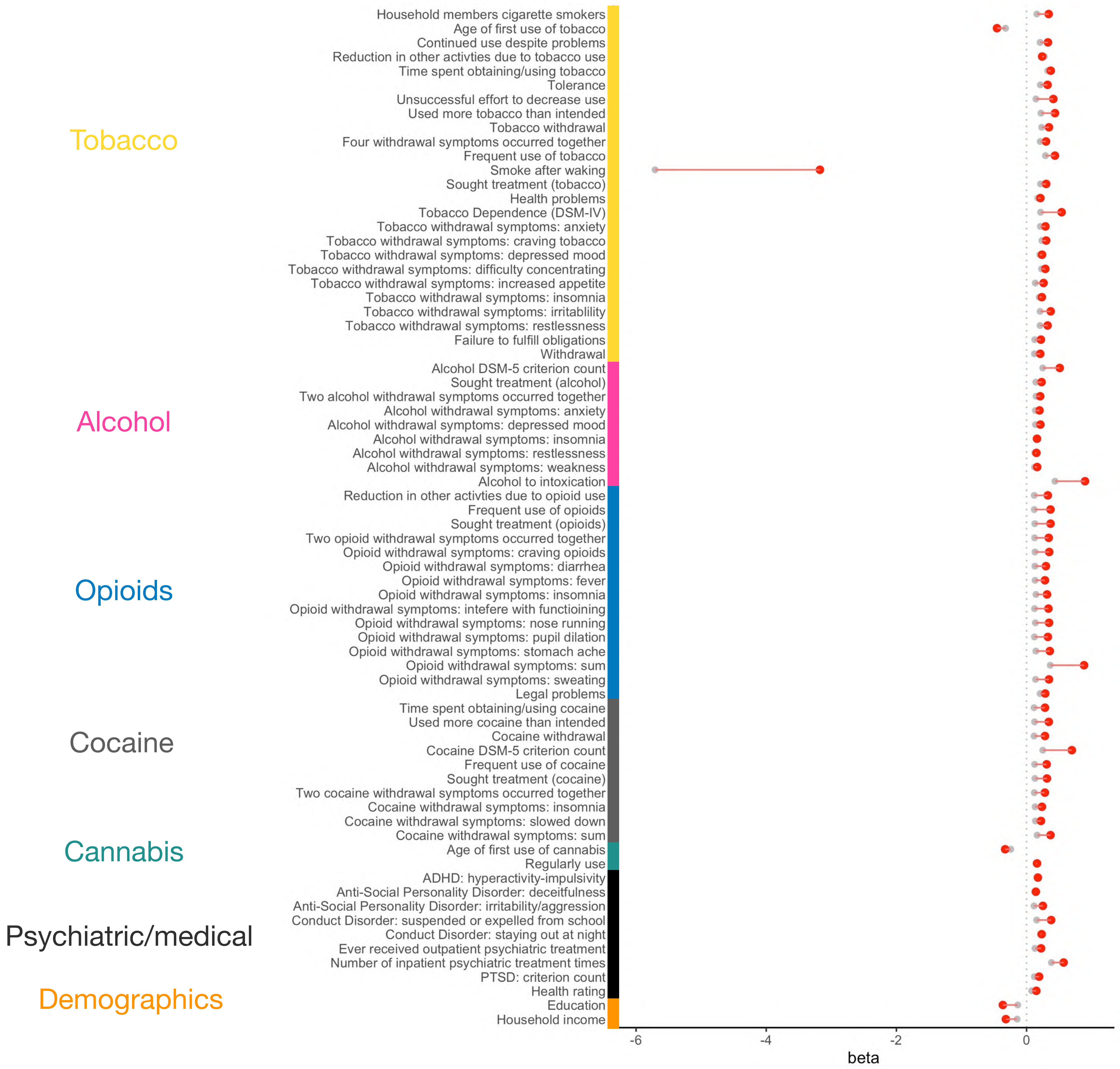
Sylvanus Toikumo

Rachel Kember

Toikumo*, Jennings* et al, *medRxiv*, 2023

How dissimilar are these results to those from prior smoking GWAS?

TUD PGS (in red) captures signal that is distinguishable from FTND PGS (in gray)



Toikumo*, Jennings* et al, *medRxiv*, 2023

Sylvanus Toikumo

Rachel Kember

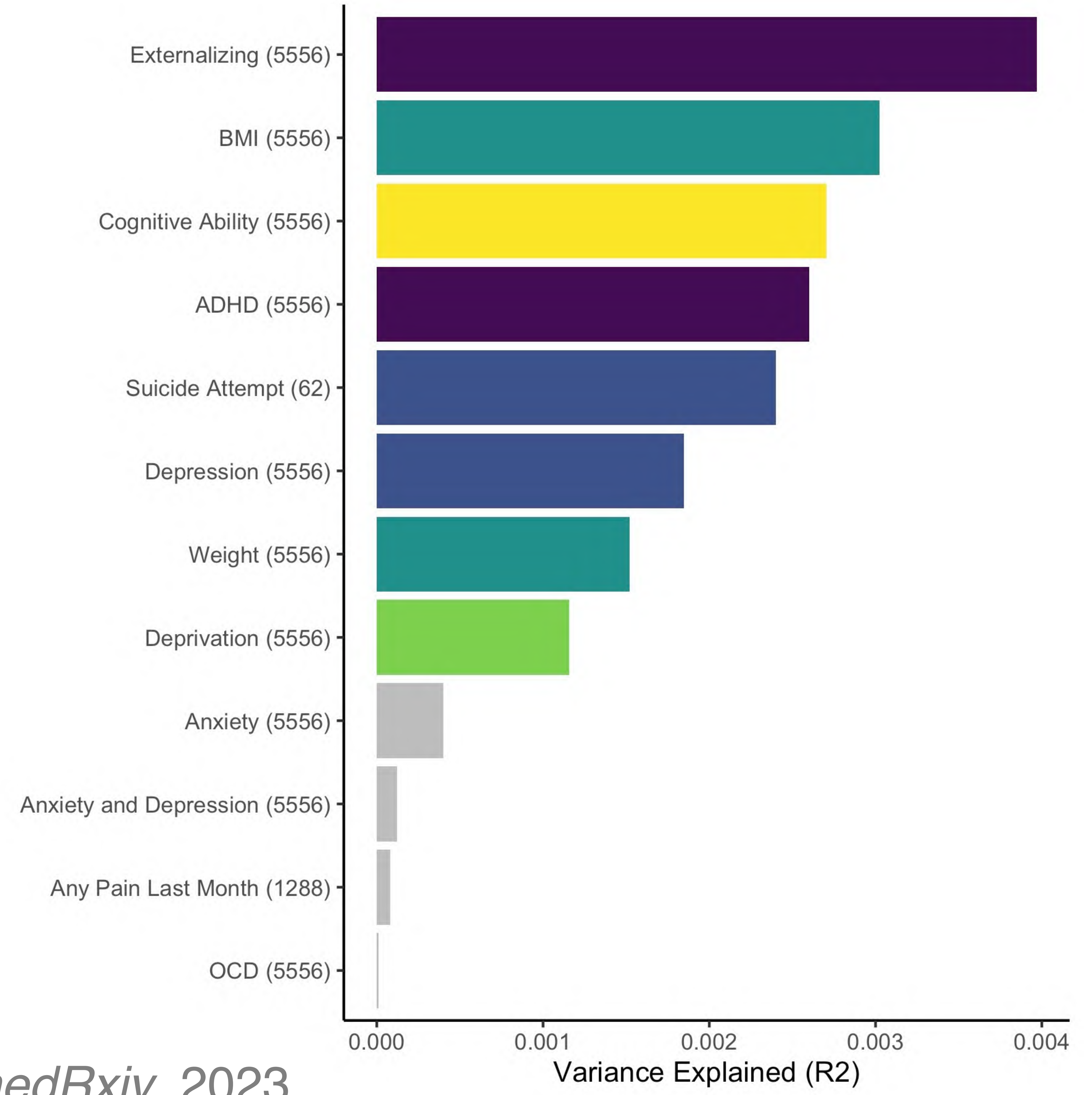
TUD PGS analysis in a young cohort

Children of 9-11 years of age (N=5,556 EUR) with negligible rates of prior nicotine exposure

Adolescent Brain Cognitive Development®

Teen Brains. Today's Science. Brighter Future.

Externalizing (a strong correlate of substance use) in children was amongst the strongest associations with TUD PGS



Emma Johnson

Alex Hatoum

Toikumo*, Jennings* et al, *medRxiv*, 2023

EHR are **powerful sources** for TUD genomics

Link to the preprint


www.h.hospital.com
H
HOSPITAL
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Patient Services
Find a Doctor
Our Centers
Contact Us
Search
Hotline Center
Online Services

“The genes have not read the DSM”

What is next?

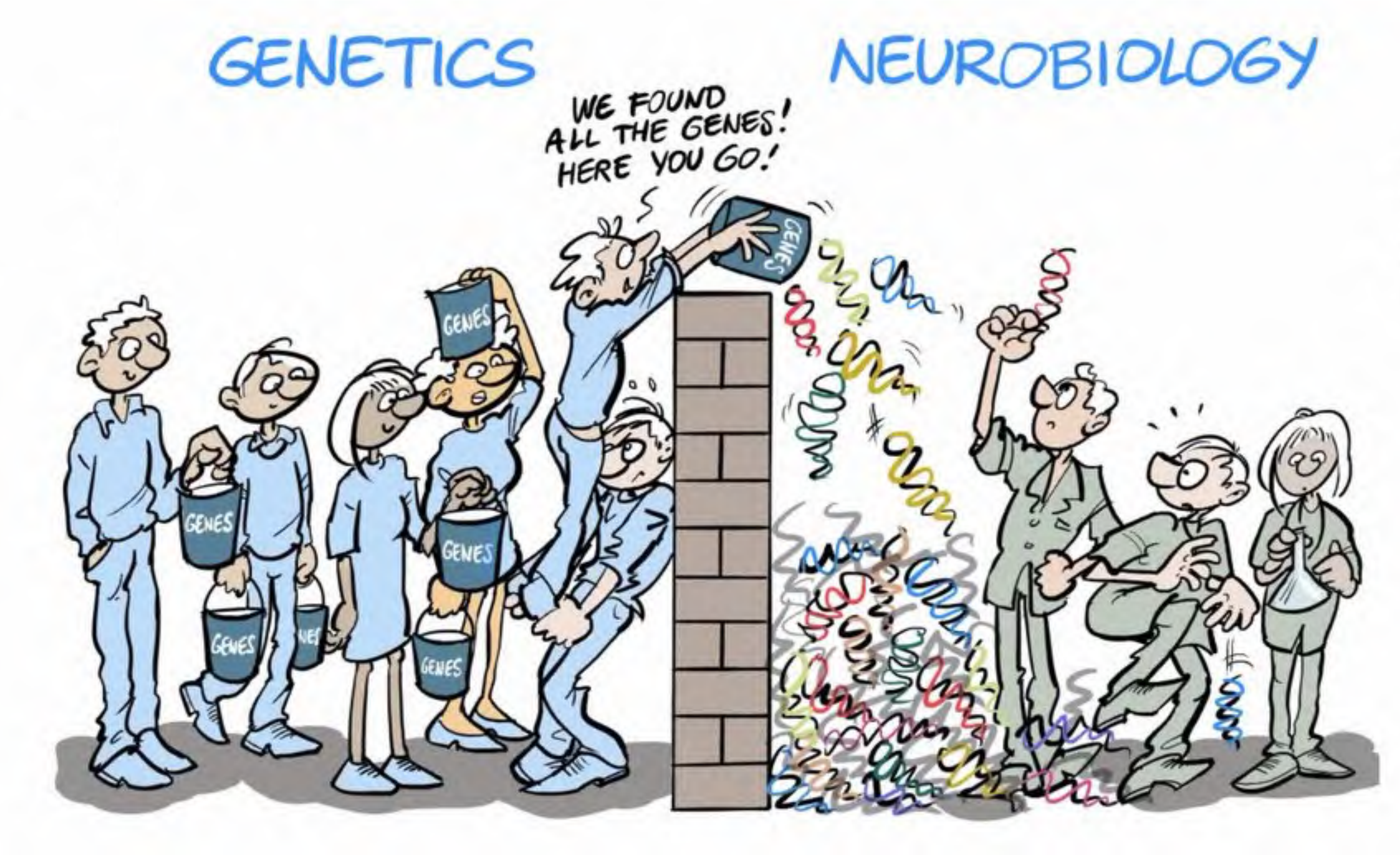
Hundreds of loci associated with substance use traits

All of Us
RESEARCH PROGRAM

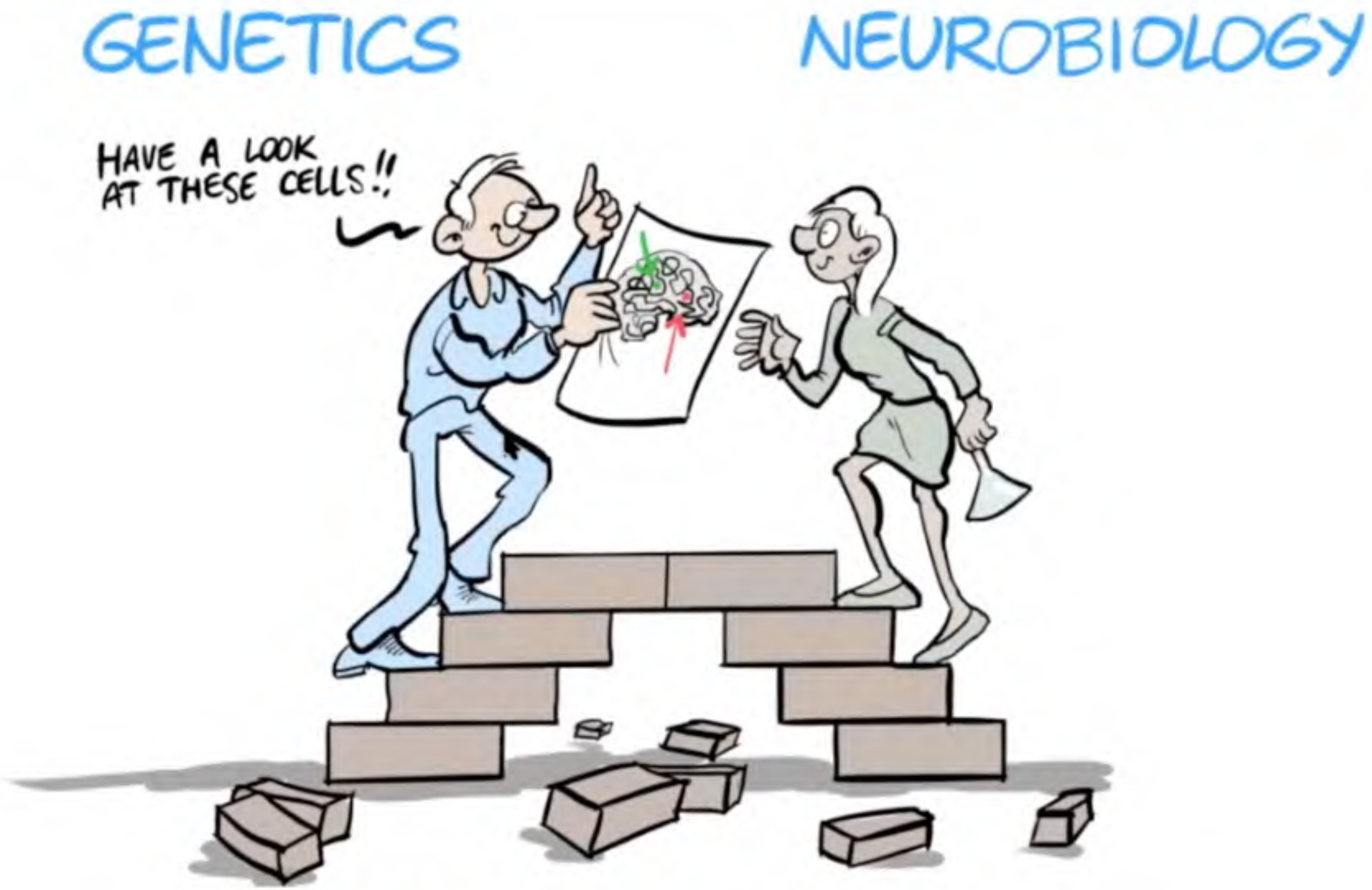
PsycheMERGE

(Psych) Electronic Medical Record
and GEnomics Network

The loci identified by GWAS of substance use disorders will continue to grow exponentially

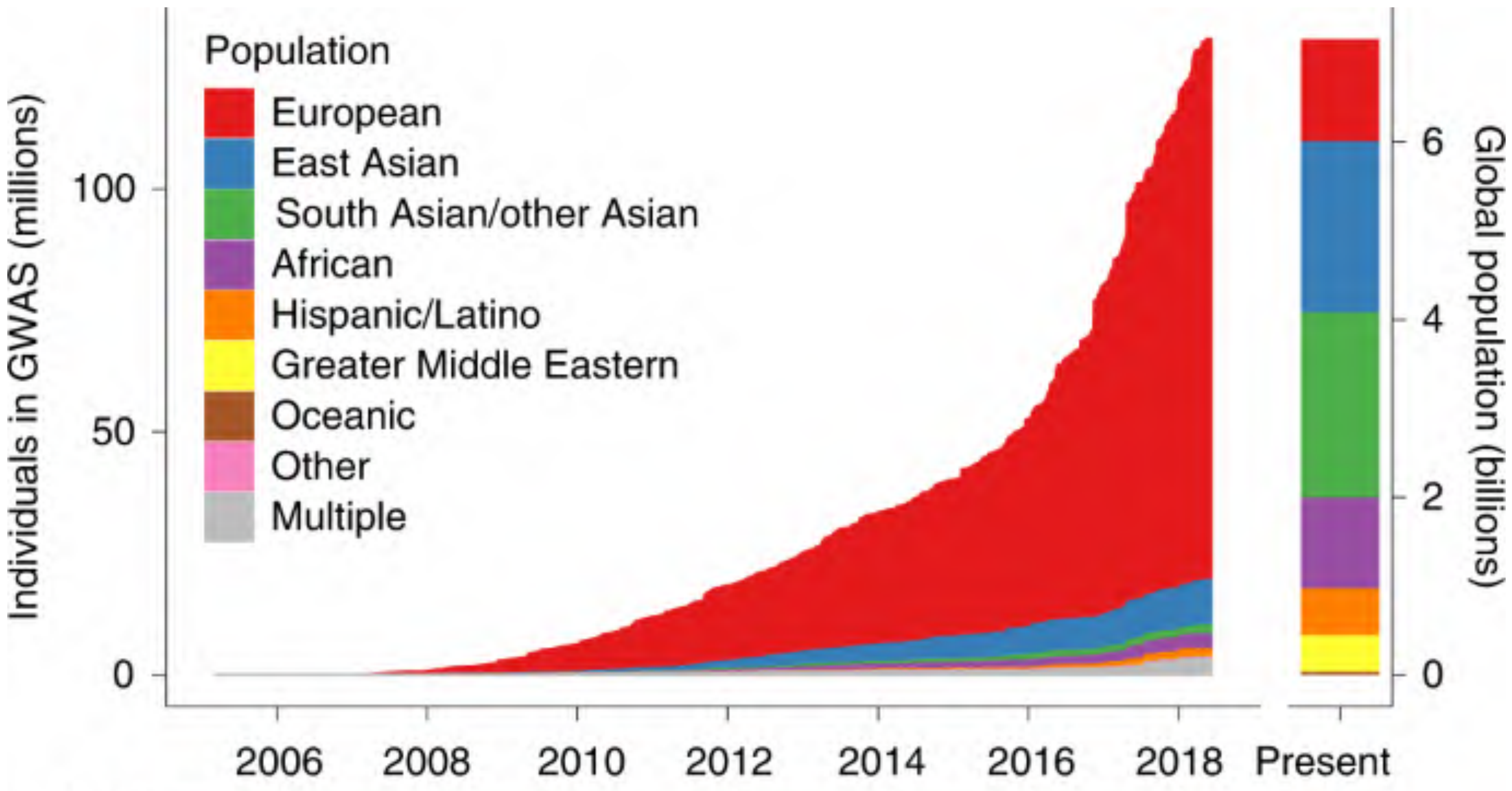


Credit: Danielle Posthuma, Tom and @BRAINSCAPES1



Credit: Danielle Posthuma, Tom and @BRAINSCAPES1

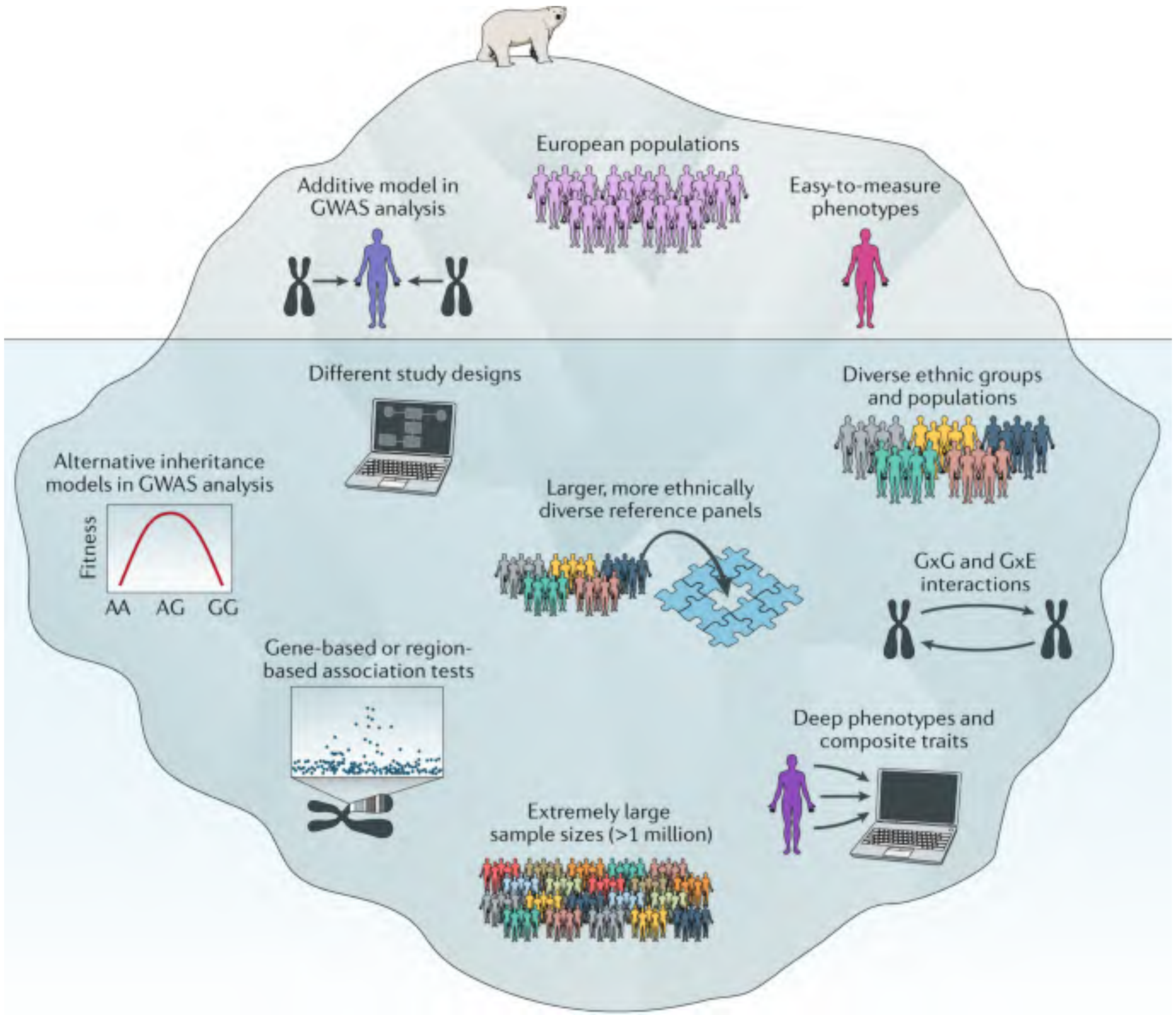
~79% of all GWAS participants are of European descent despite making up only 16% of the global population



Martin et al, *Nature Genetics*, 2019

LAGC

Latin American
Genomics Consortium

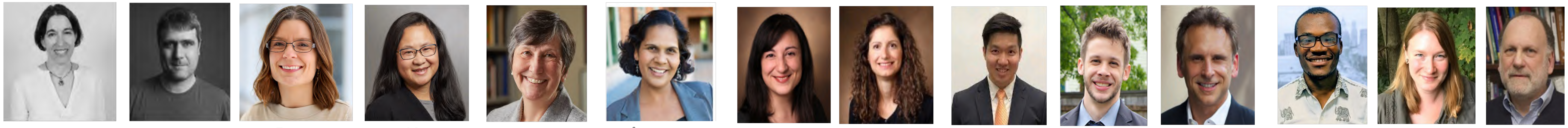


Tam et al, *Nature Review Genetics*, 2019

If you want to go fast, go alone
If you want to go far, go together

Collaborative Effort

Abraham Palmer | Mariela Jennings | Sevim Bianchi | Yuye Huang | Jazlene Mallari | Hayley Thorpe | Jibran Khokhar | Jared Young | Thomas Biederer | Ben Pham | Toni Clarke | James MacKillop | Harriet de Wit | *Cadm2* mice



Sarah Elson | Pierre Fontanillas | Dana Hancock | Ke Xu | Amy Justice | Arpana Agrawal | Lea Davis | Maria Niarchou | Hyunjoon Lee | Travis Mallard | Jordan Smoller | Sylvanus Toikumo | Rachel Kember | Hank Kanzler

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NIH National Institute on Drug Abuse

TOBACCO-RELATED DISEASE RESEARCH PROGRAM

BRAIN & BEHAVIOR RESEARCH FOUNDATION Awarding NARSAD Grants

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THE EXTERNALIZING CONSORTIUM

UNIVERSITY OF CALIFORNIA SAN DIEGO

PGC Psychiatric Genomics Consortium

BioVU VANDERBILT UNIVERSITY MEDICAL CENTER

Mass General Brigham

biobank uk

PMBB Penn Medicine BioBank

MVP

PsycheMERGE

We would like to thank the research participants and employees of 23andMe, Inc. (Michelle Agee, Babak Alipanahi, Adam Auton, Robert K. Bell, Katarzyna Bryc, Sarah L. Elson, Pierre Fontanillas, Nicholas A. Furlotte, David A. Hinds, Karen E. Huber, Aaron Kleinman, Nadia K. Litterman, Jey C. McCreight, Matthew H. McIntyre, Joanna L. Mountain, Elizabeth S. Noblin, Carrie A.M. Northover, Steven J. Pitts, J. Fah Sathirapongsasuti, Olga V. Sazonova, Janie F. Shelton, Suyash Shringarpure, Chao Tian, Joyce Y. Tung, Vladimir Vacic, and Catherine H. Wilson) for making this work possible.

FAMILIES FOR
BORDERLINE
PERSONALITY DISORDER
RESEARCH

BRAIN &
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RESEARCH FOUNDATION
Awarding **NARSAD** Grants

sanchezroige@ucsd.edu