What Genetics is Telling Us About Substance Use Disorders

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UC San Diego



MEDICAL CENTER



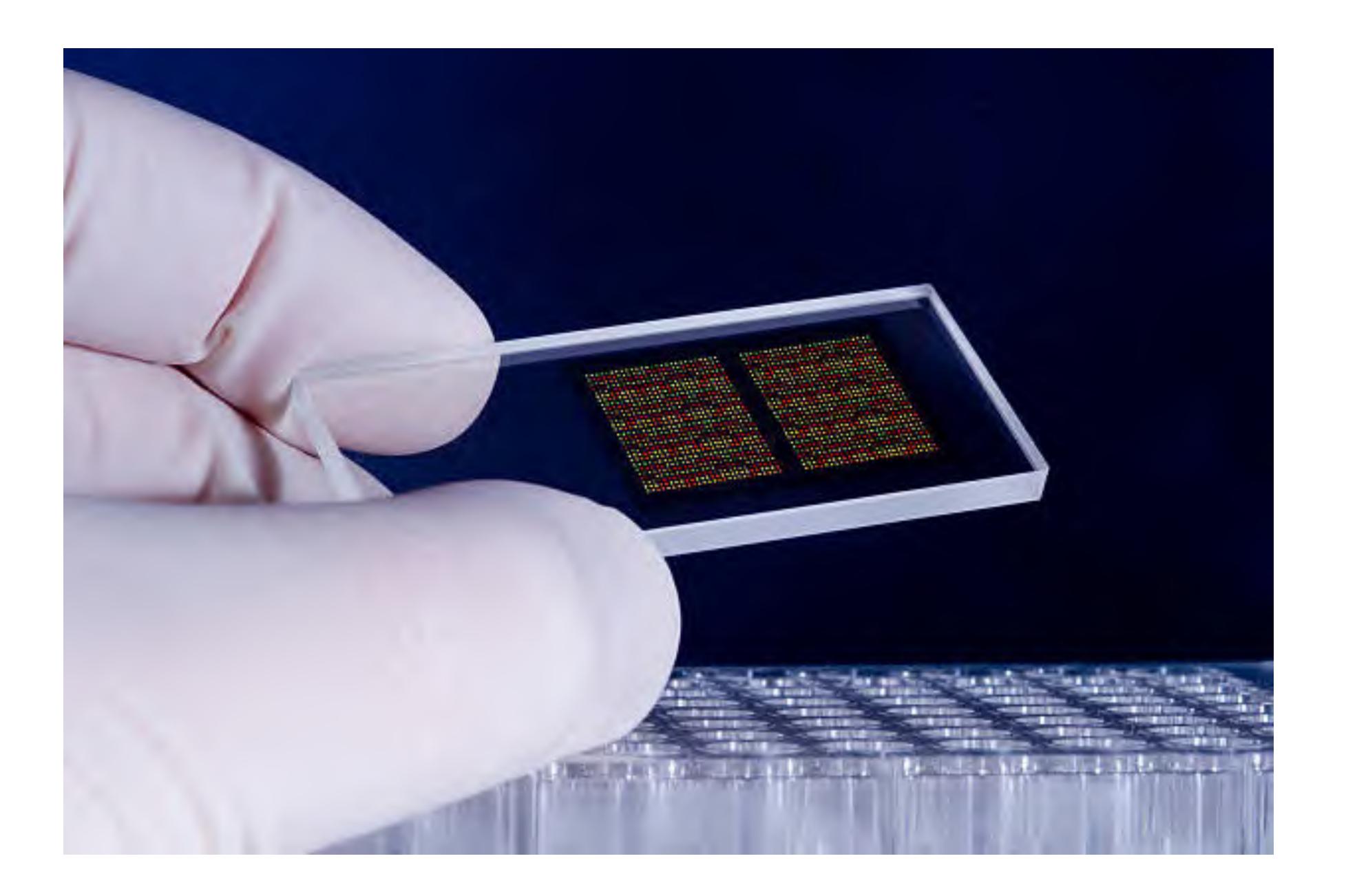
Substance use disorders are complex psychiatric conditions

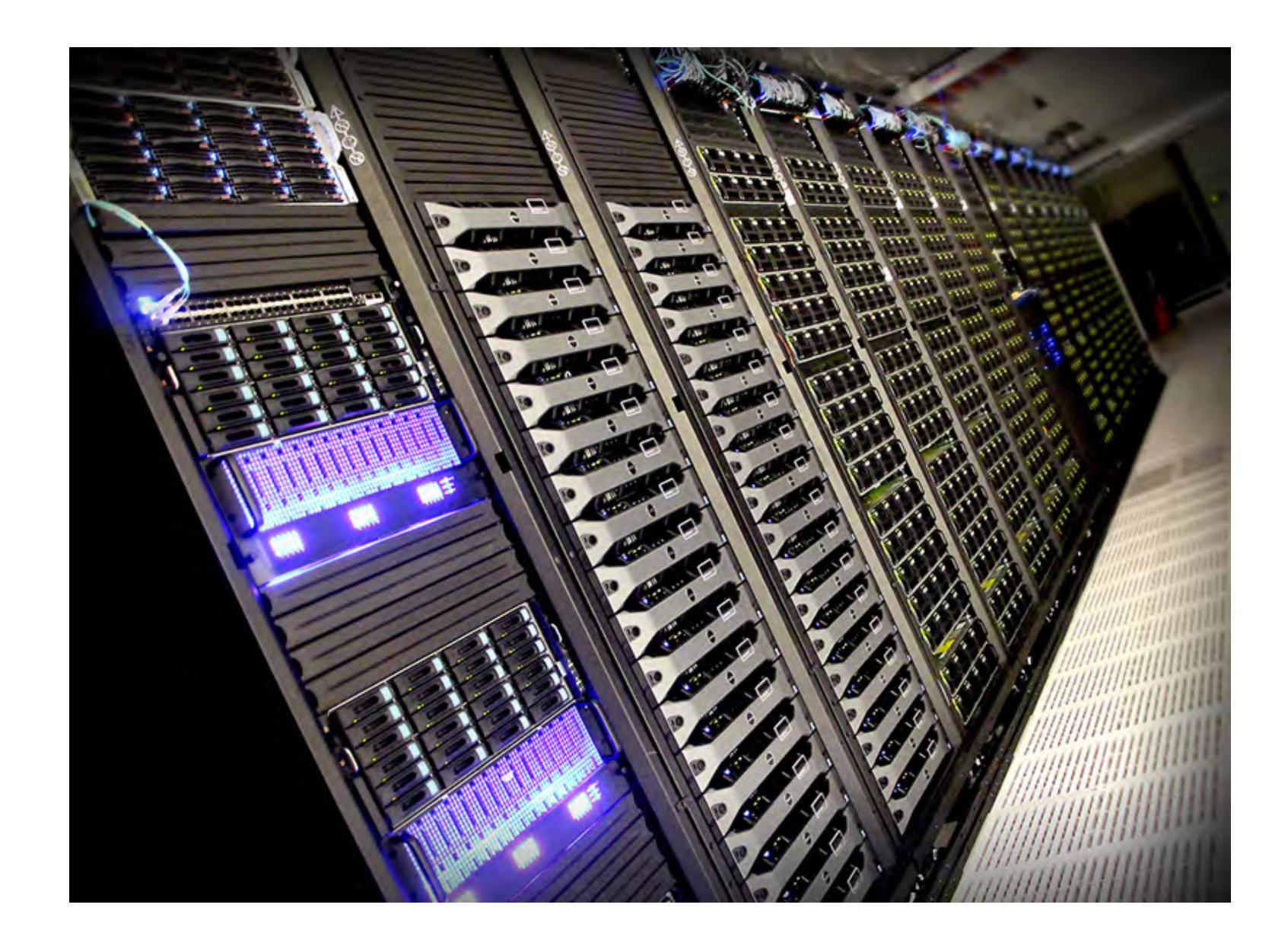
Substance use disorder genetics

Advances in human genetics

GWAS GWAS









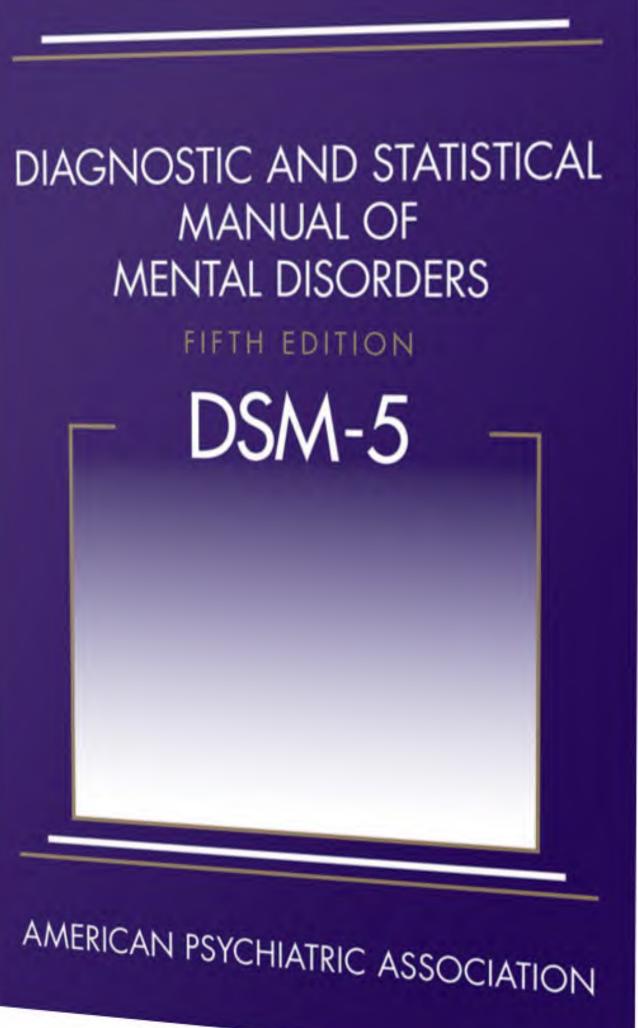
How do we MEASURE substance use disorders?





MANUAL OF FIFTH EDITION

DSM-5



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



Psychiatric Genomics Consortium

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



A GWAS of alcohol dependence Thalamus contextualizes PFC representations Network models of motor primitives



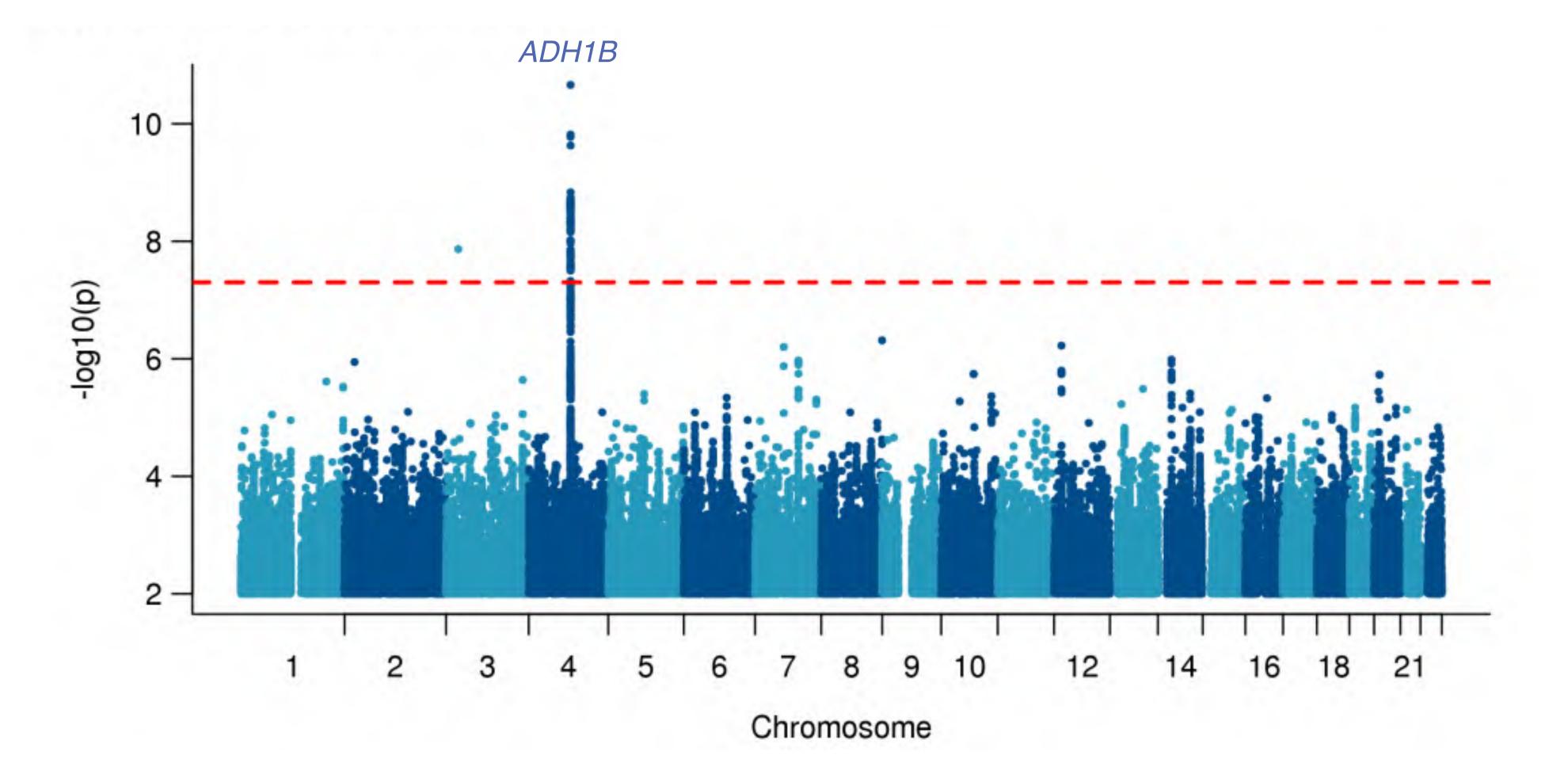
DECEMBER 2018 VOL 21 NO 12

neuroscience





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

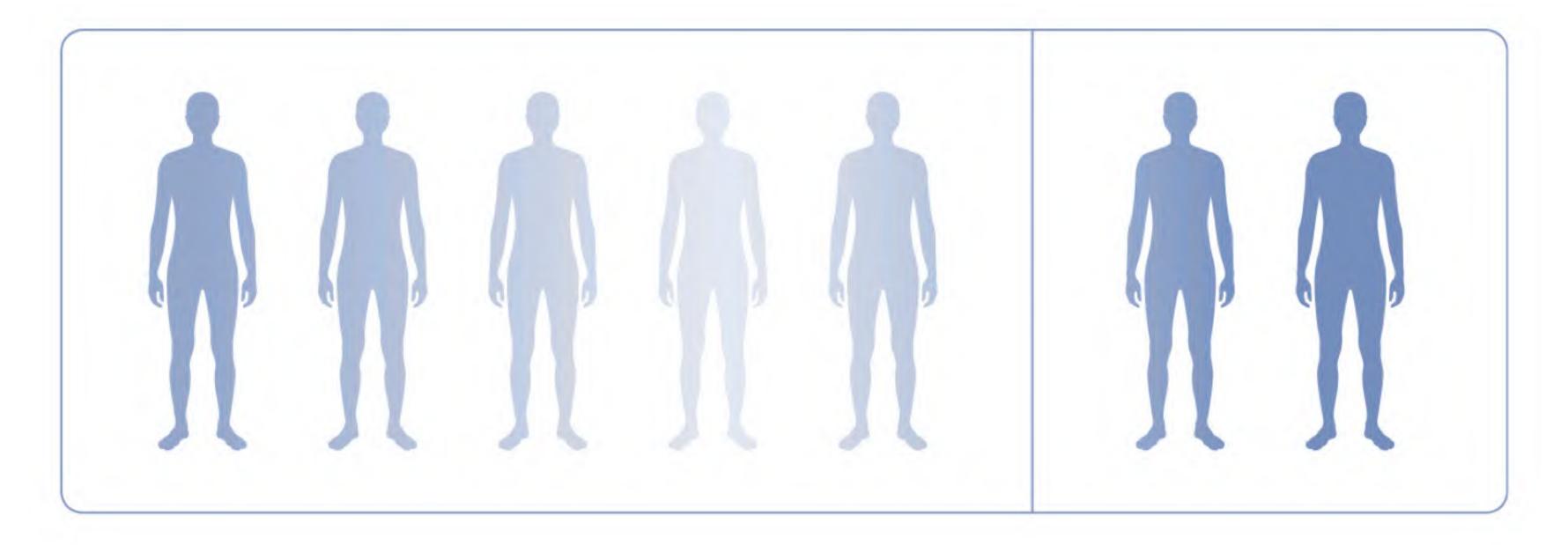


Walters et al PGC-Substance Use Disorder, Nature Neuroscience, 2018





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

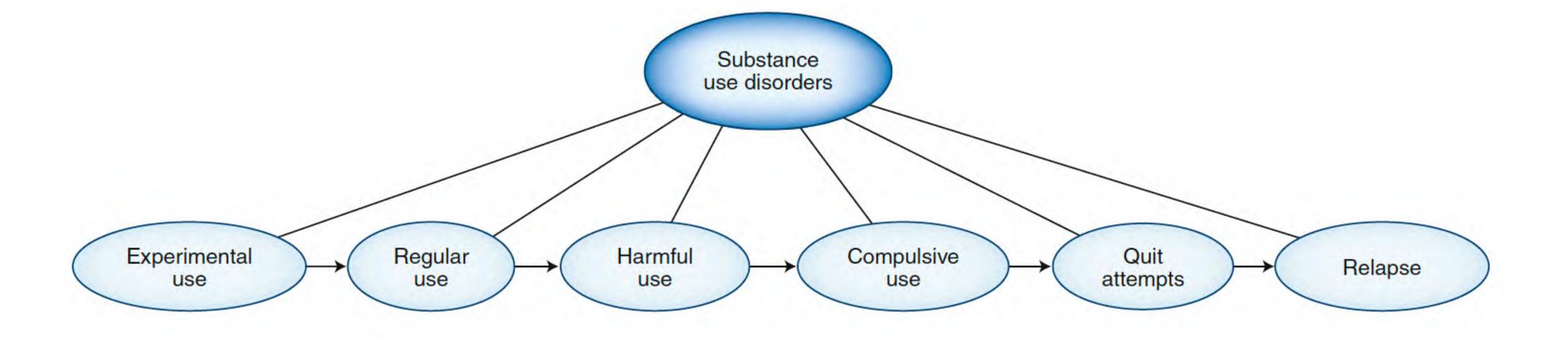


"controls"

"cases"



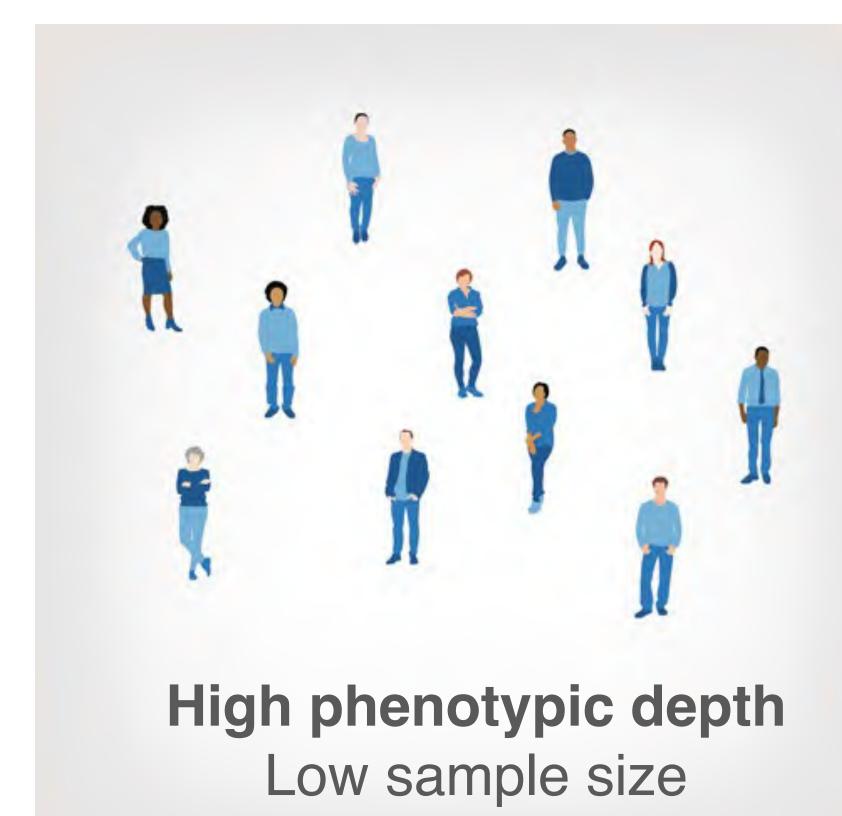
Substance use disorder can be dissected into symptoms

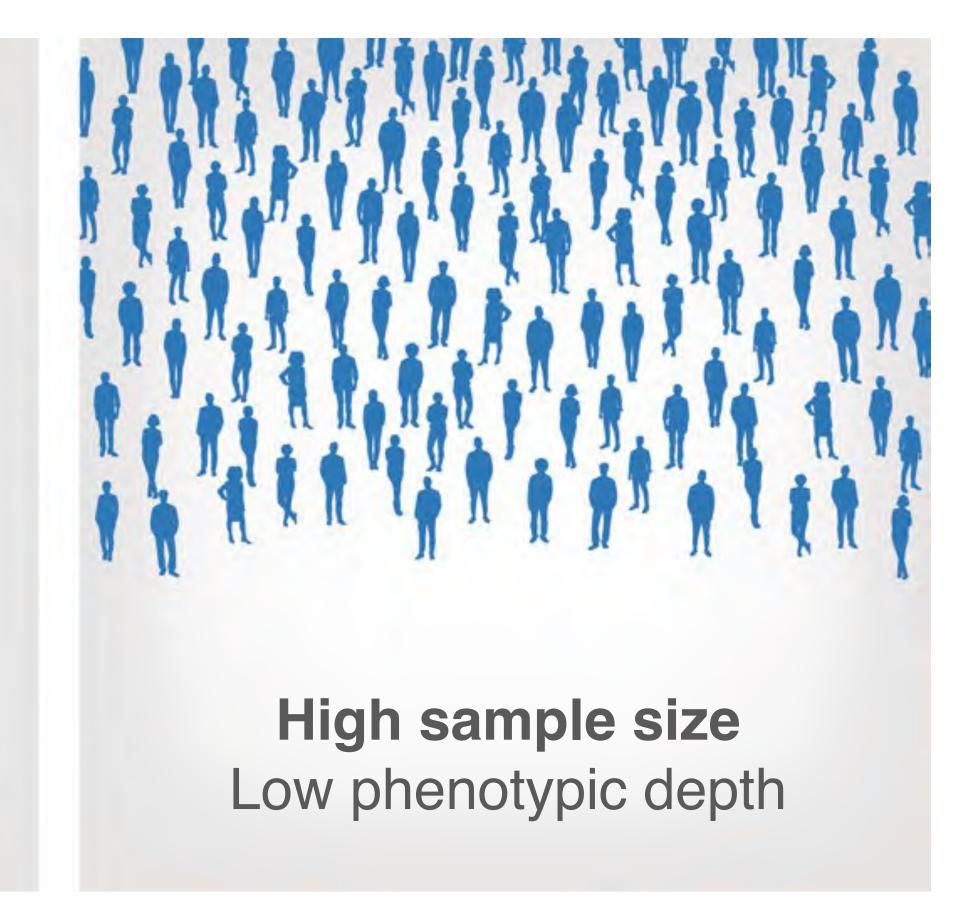




Continuous traits measured in the general population









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



Abraham Palmer







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

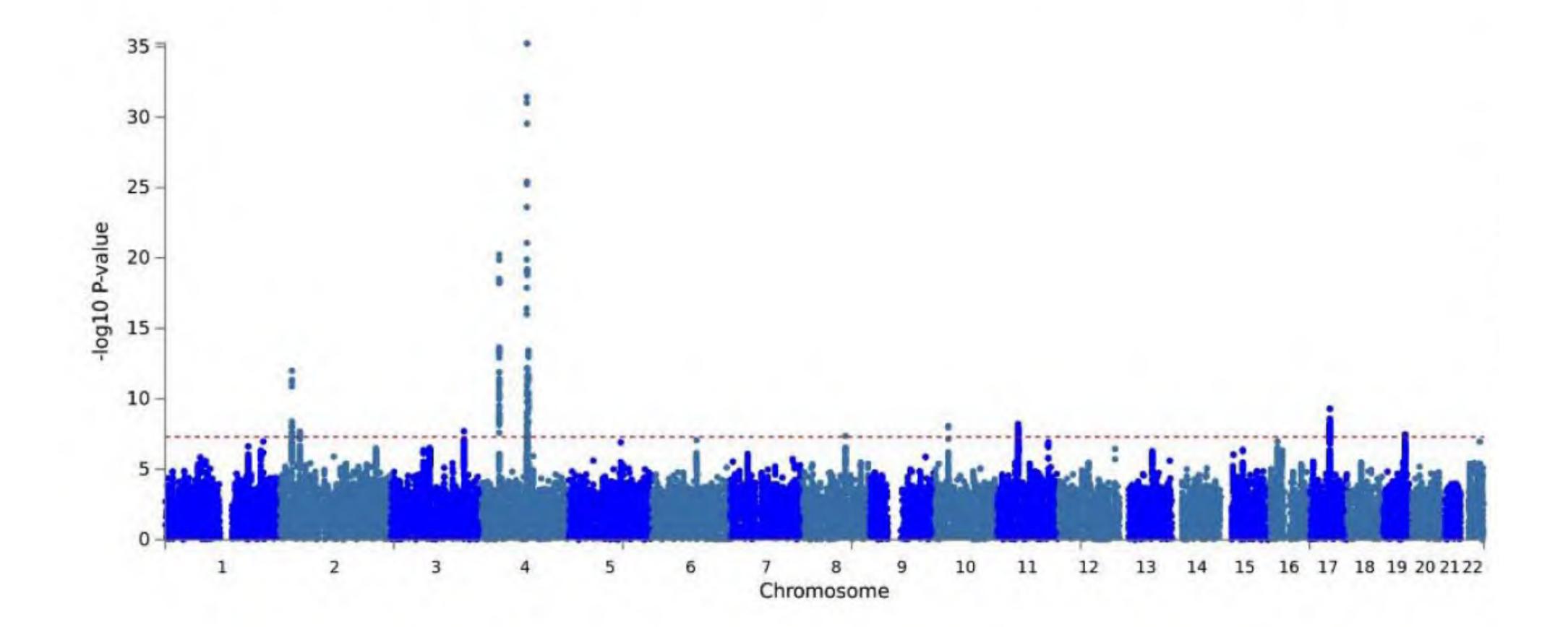




Toni Clarke



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



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



AUDIT captures aspects of alcohol use and misuse

Saunders et al, Addiction, 1993





1 How often do you have a drink containing alcohol?

2 How many drinks containing alcohol do you have on a typical day when you are drinking?

3 How often do you have six or more drinks on one occasion?

AUDIT-P

4 How often have you found that you were not able to stop drinking once you had started?

5 How often have you failed to do what was expected from you because of drinking?

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

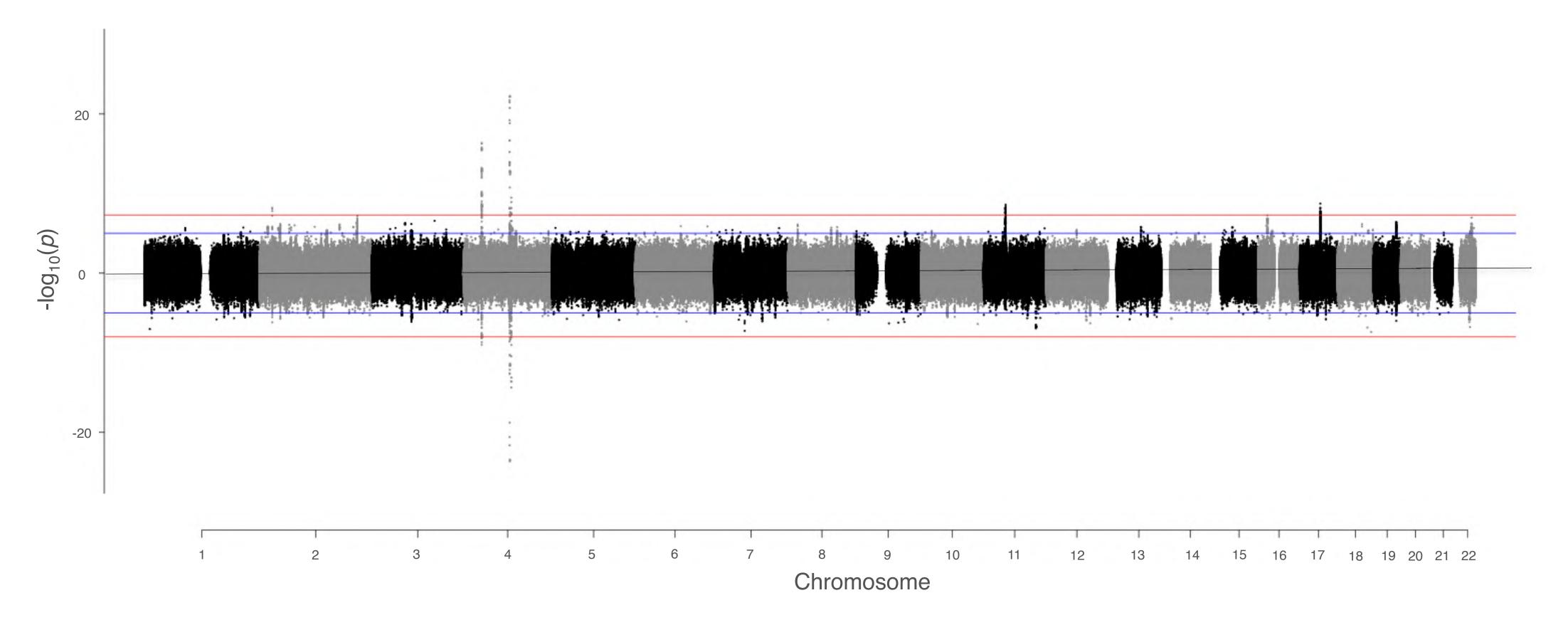


We performed separate GWAS for **AUDIT-C and AUDIT-P** in 121,604 UK Biobank participants

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



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

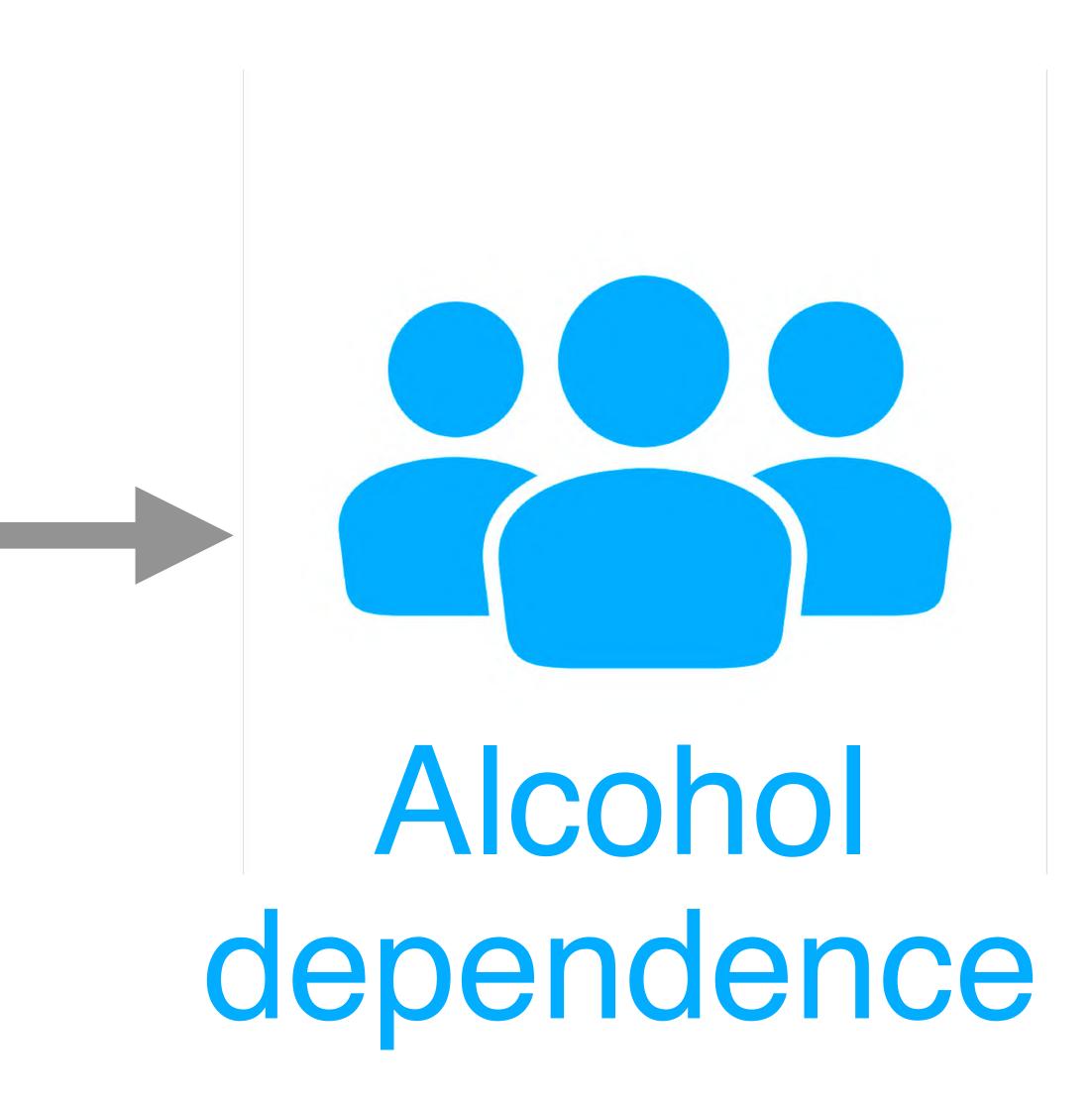


Sanchez-Roige et al, American Journal of Psychiatry, 2019



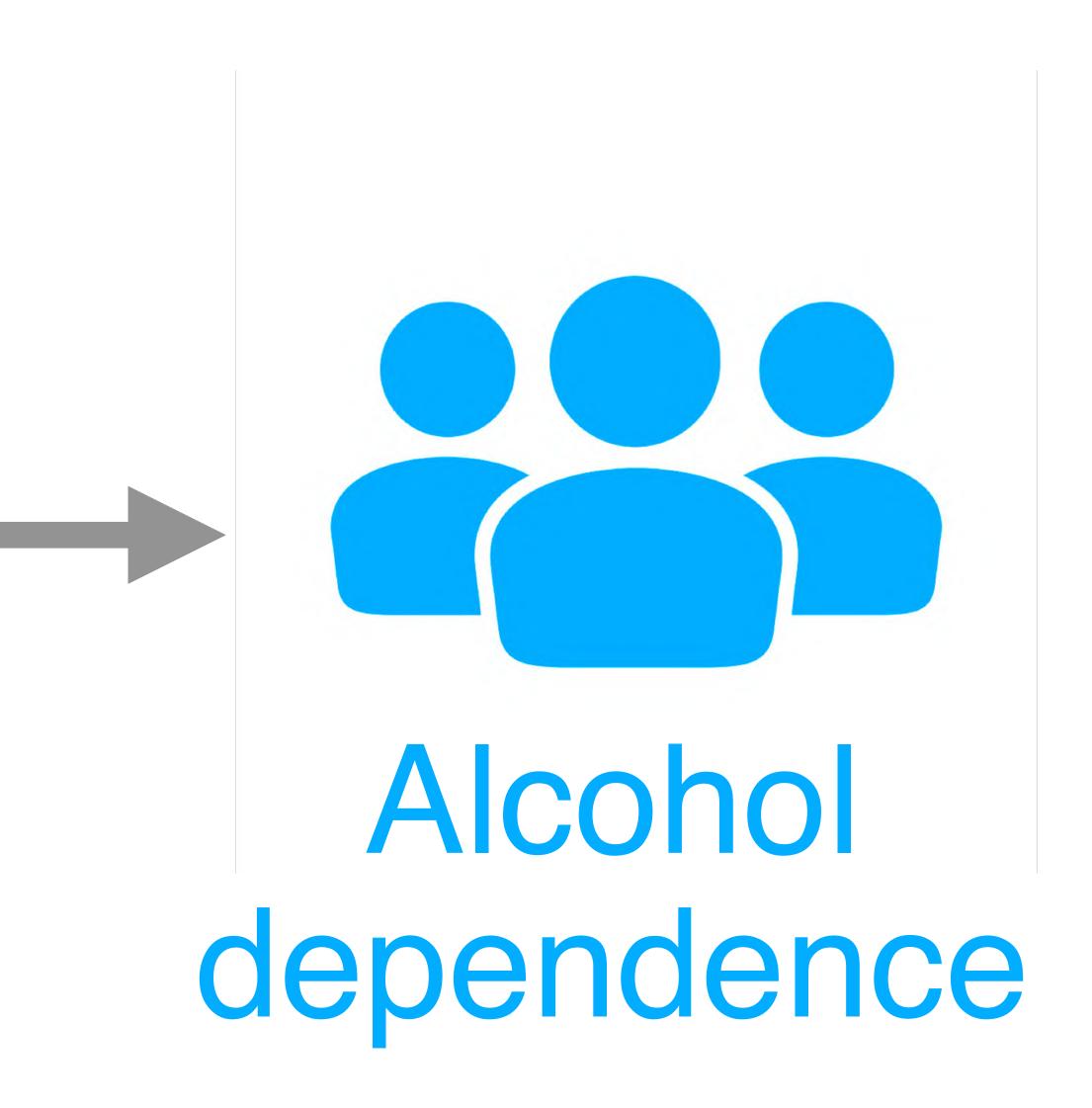
The genetic basis of alcohol consumption and problematic alcohol use is distinct







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

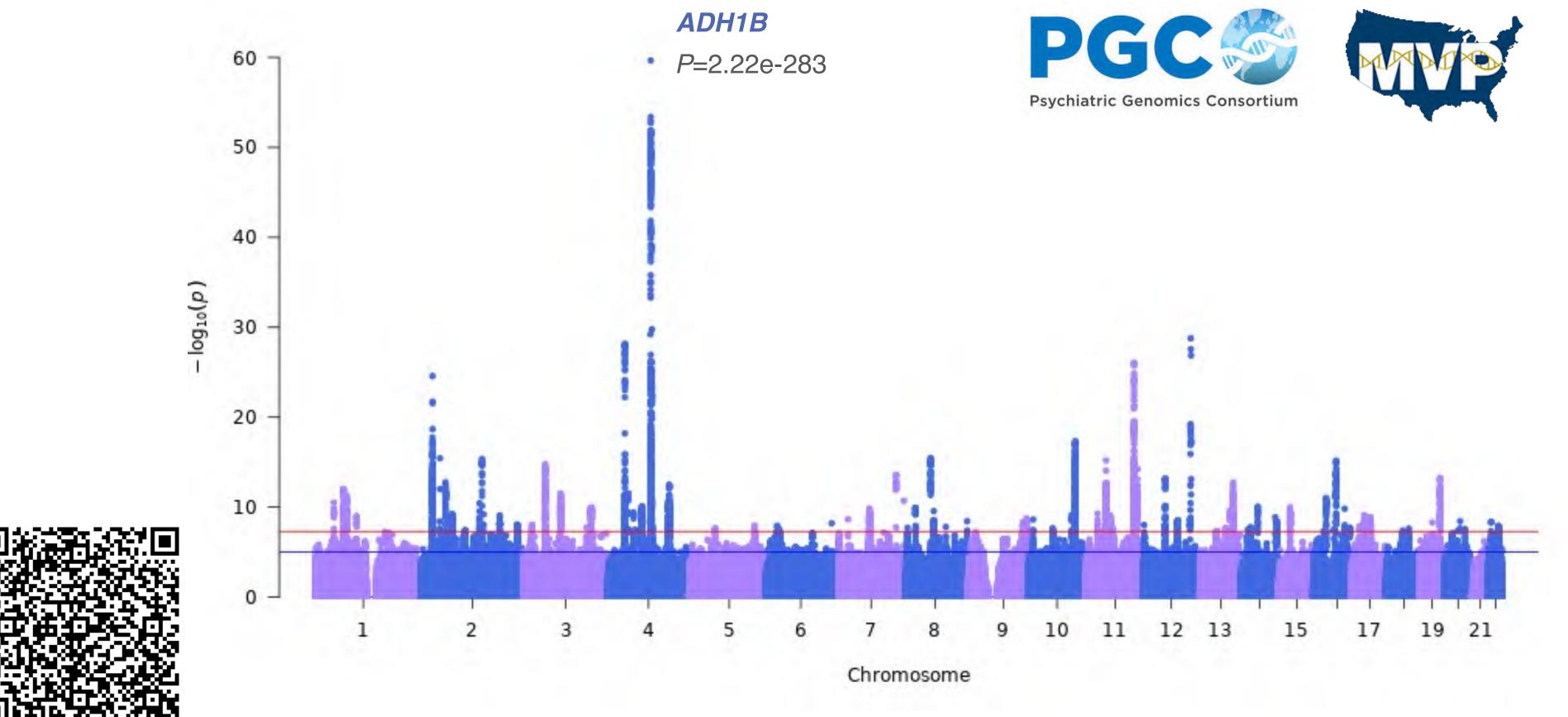


Walters et al PGC-Substance Use Disorder, *Nature Neuroscience*, 2018

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



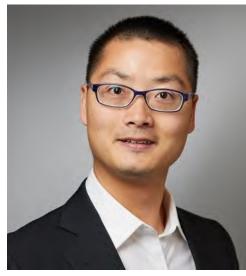
Link to blog article





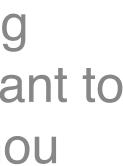


2018 Young Investigator Grant to Dr. Hang Zhou



Zhou et al, *medRxiv*, 2023











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



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

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!







23andMe®



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

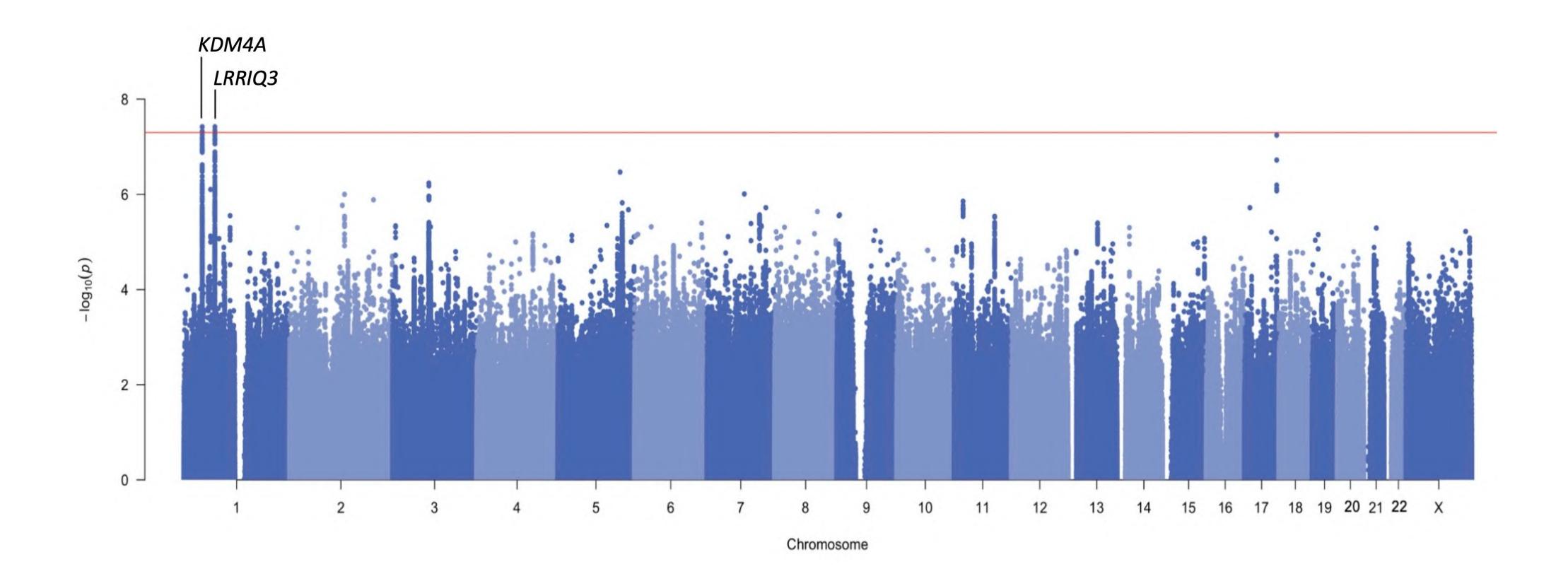


Abraham Palmer

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



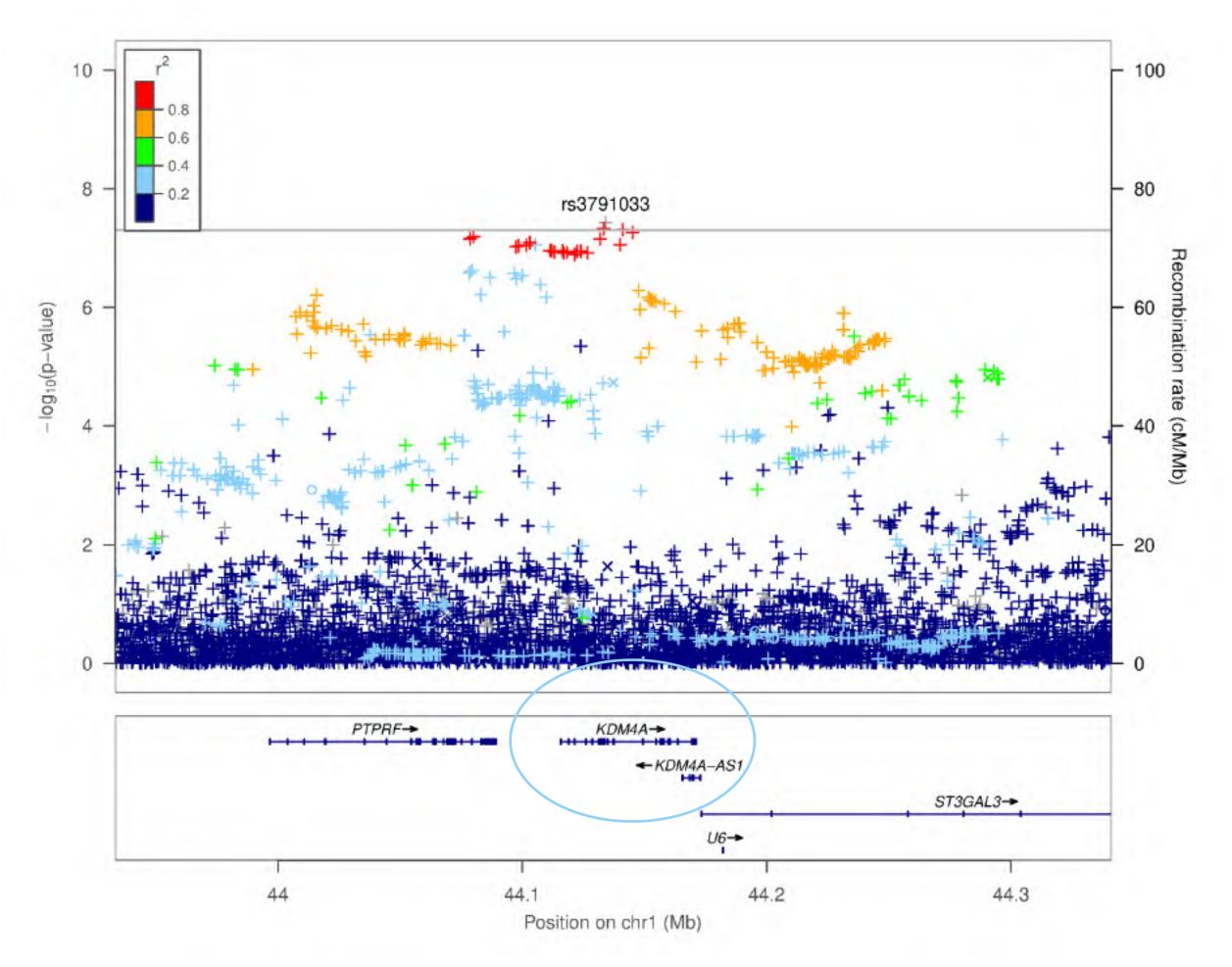
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Sanchez-Roige et al, *Molecular Psychiatry*, 2021





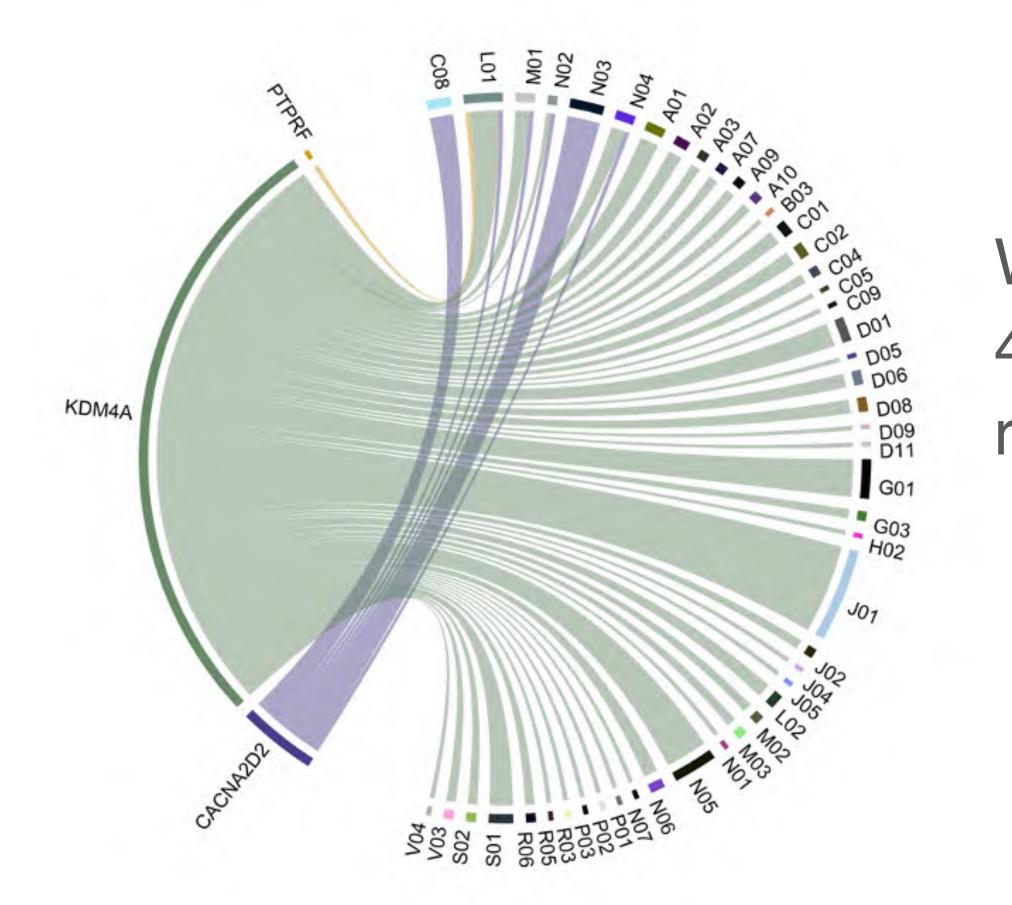
KDM4A, recently implicated in an independent opioid addiction GWAS



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Sanchez-Roige et al, Molecular Psychiatry, 2021





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

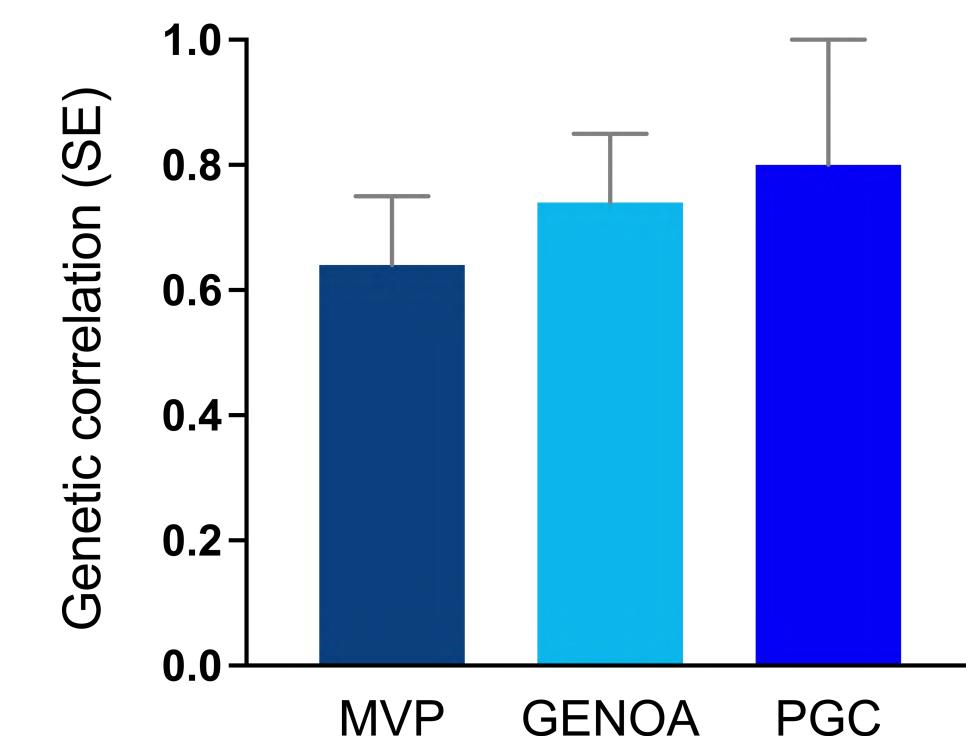
Chord diagram of genes significantly associated with POU and the Anatomical Therapeutic Chemical classifications of drugs

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





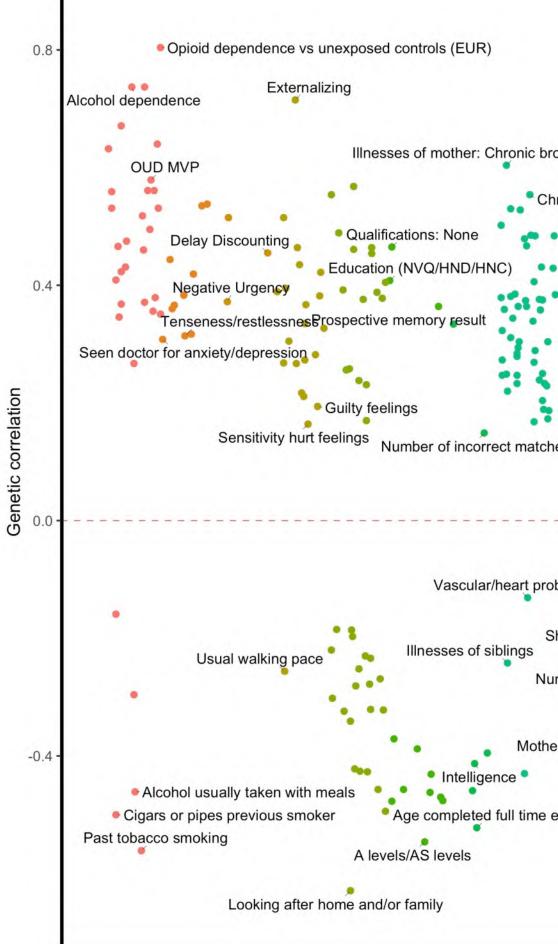
Strong genetic correlations with the largest available GWAS of OUD



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

GENOA PGC

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



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onchitis/emphysema		
ronic obstructive airwa Stillbirth, s Phenylalanine Glycoprotein acetyl	Pa spontaneous miscar Loose teeth s Dentures	ain relief medication (Ibuprofen) rriage or termination Weight change Pain relief medication (Paracetamol) Headacheeg fat percentage (right) n or discomfort Hip circumference Arm fat-free mass (left)
		Arm predicted mass (left)
blems		
Diet sugar nort-sightedness We	Sleep duration Medication for cho ears glasses or cont	olesterol, blood pressure or diabetes
nber of double bonds	in a fatty acid chair	n
	eath	oblems cation for pain relief, constipation, heartburn first live birth Age of first birth

ategory

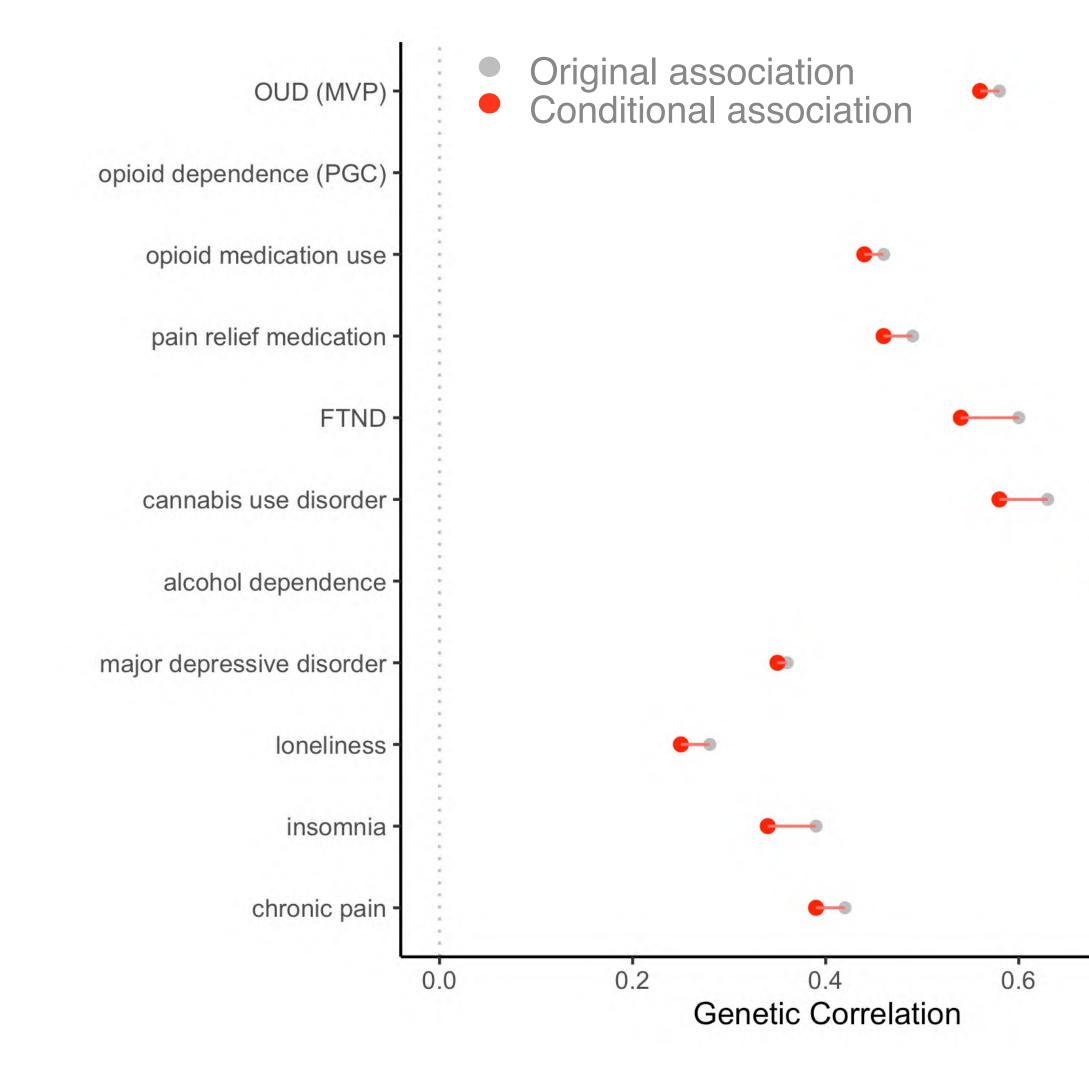
- substance use
- psychiatric
- impulsivity
- personality
- lifestyle
- education
- cognitive
- health
- Iongevity
- metabolic
- eyes
- teeth
- sleep pain
- reproductive
- medication
- anthropometric

Sanchez-Roige et al, Molecular Psychiatry, 2021



Is problematic opioid use simply a form of risky behavior?

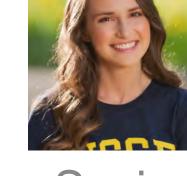
Although POU was genetically correlated with risk-taking ($r_a=0.35$), conditioning on risk had little impact on these genetic associations



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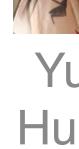


Jennings





Sevim Bianchi



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

0.8







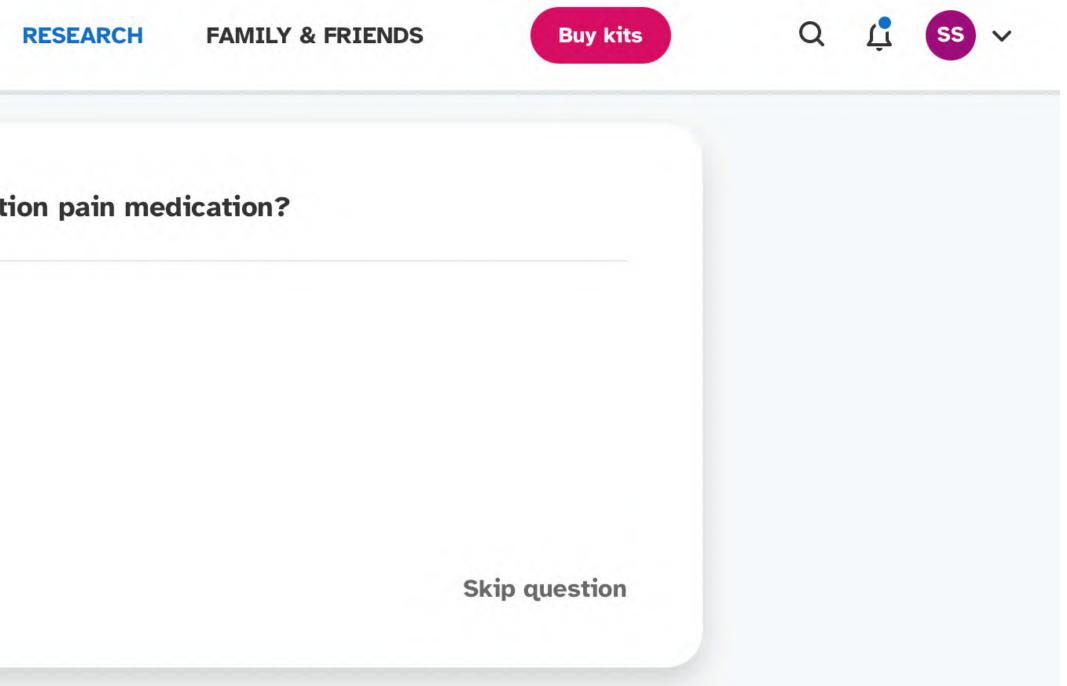
Opioid misuse as a cost-effective strategy to augment the power of studies directly examining OUD

The Prescription Opioid Genetics Study

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

23andMe	HOME	ANCESTRY	HEALTH & TRAITS	
		:: Have you	ever taken a prescrip	oti
		Yes No		
		NoI'm not su	ıre	

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

Lack of consideration when making decisions

Change in response criterion

Timing impairment

Personality disorders

Mania

Delay aversion

Motor

Impaired

to stop a

response

ability

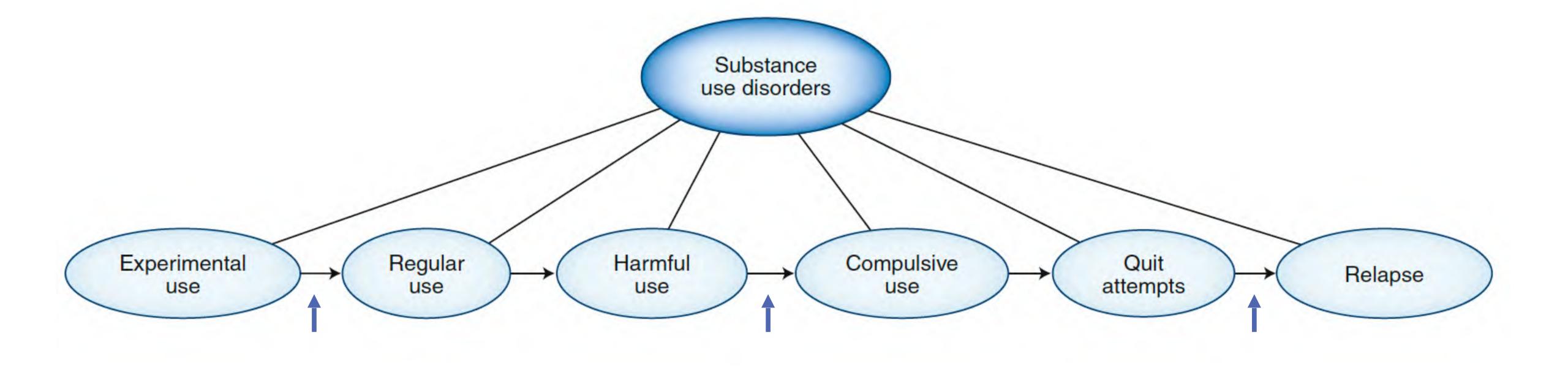
Eating disorders disinhibition

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

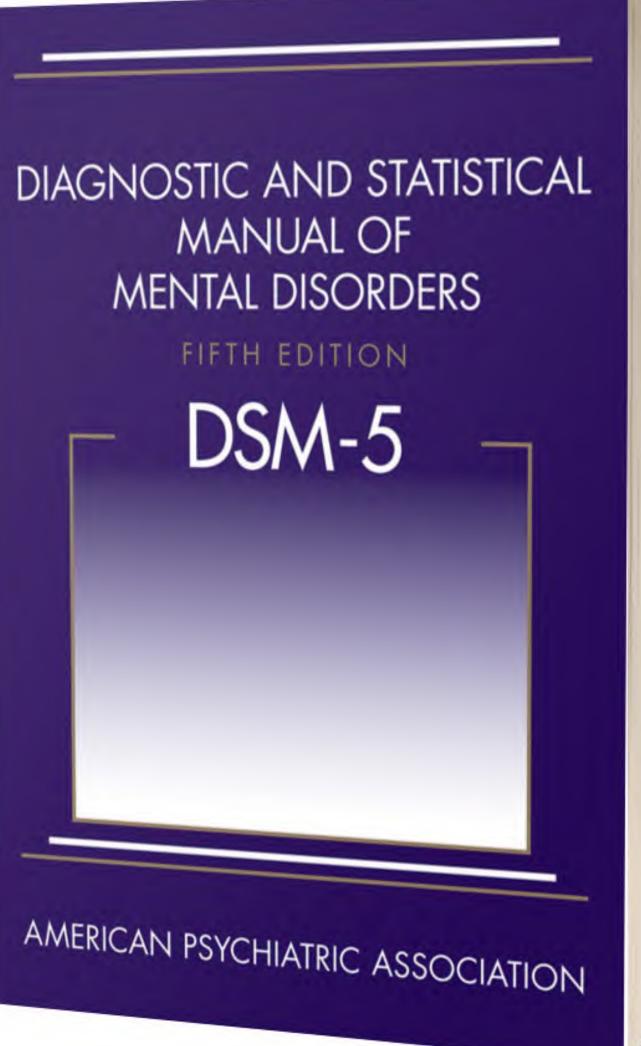


Impulsivity levels

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

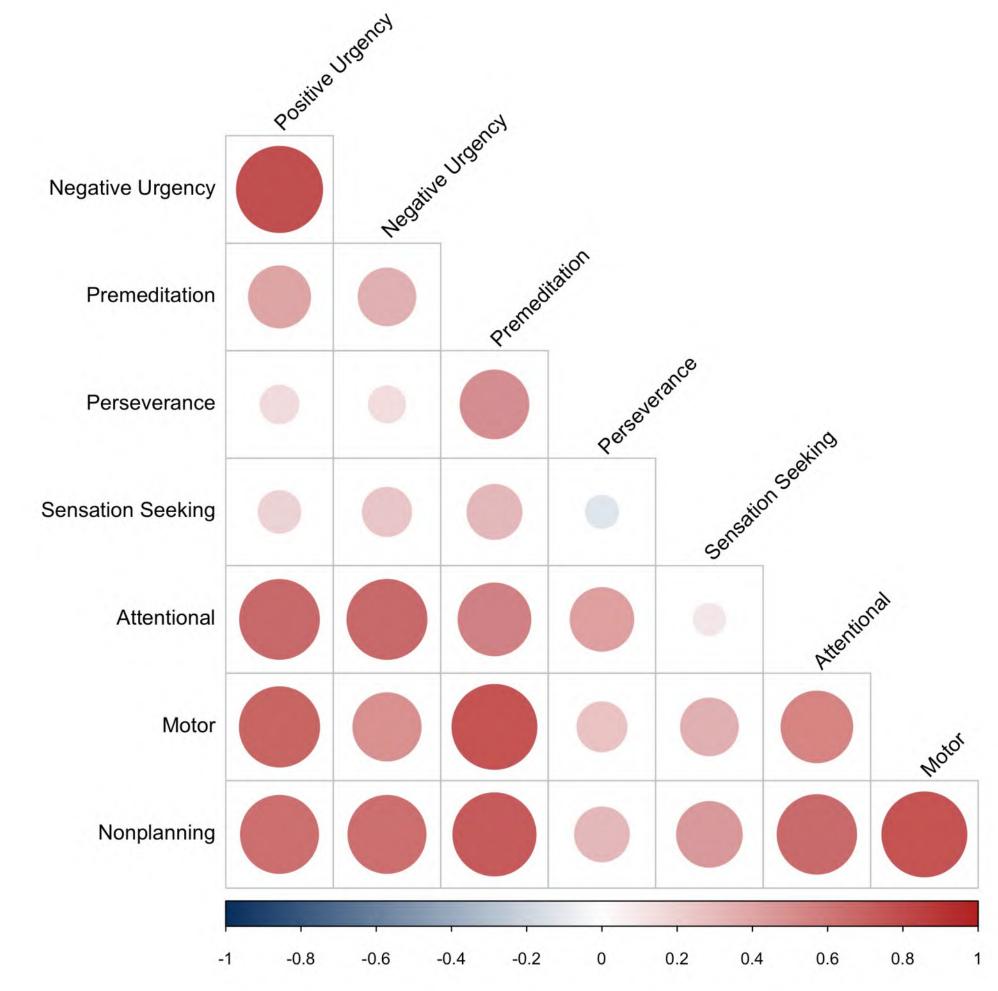
We collected 150,000 responses on 8 impulsive personality traits

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



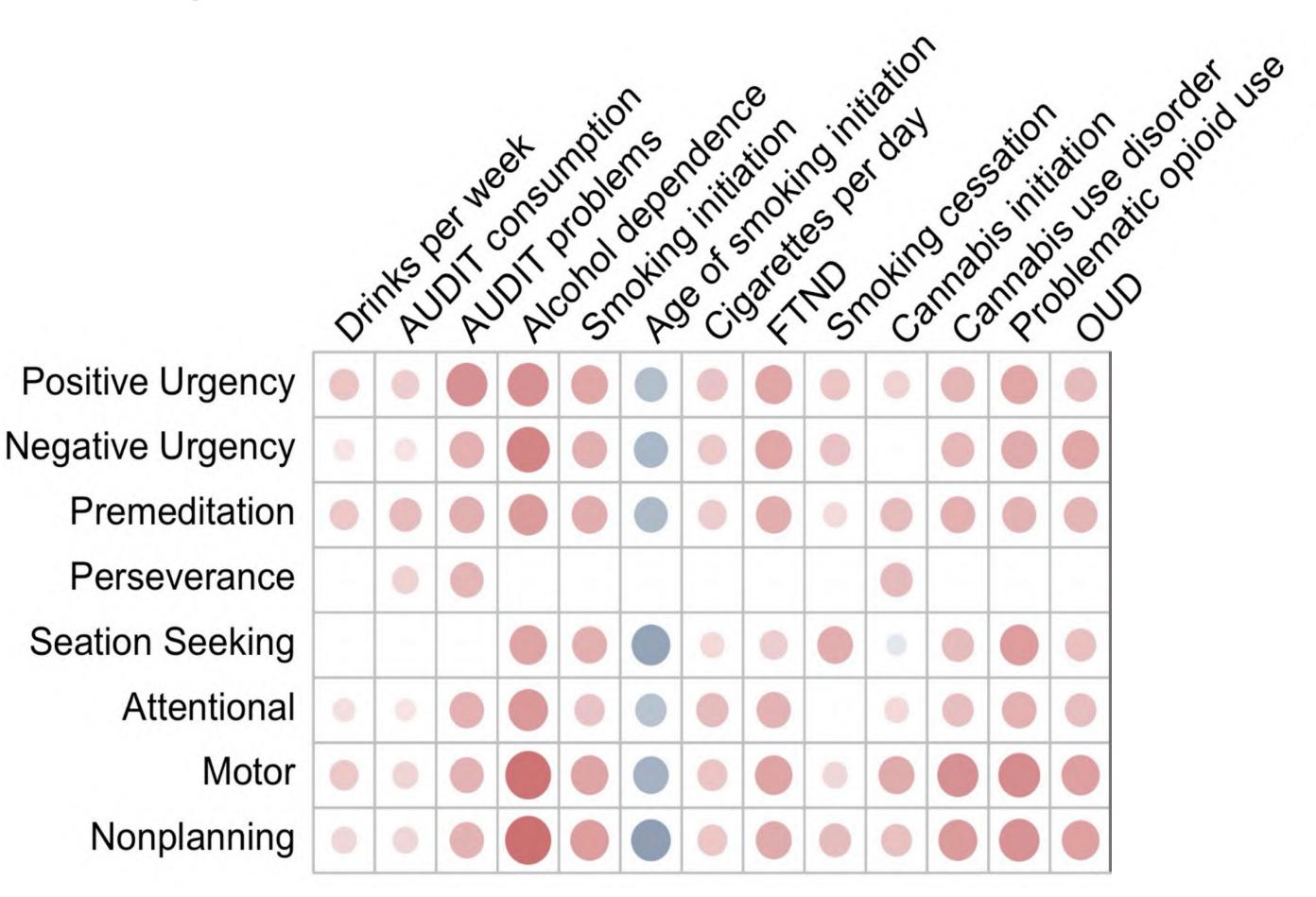
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Genetic correlations between impulsivity and substance use

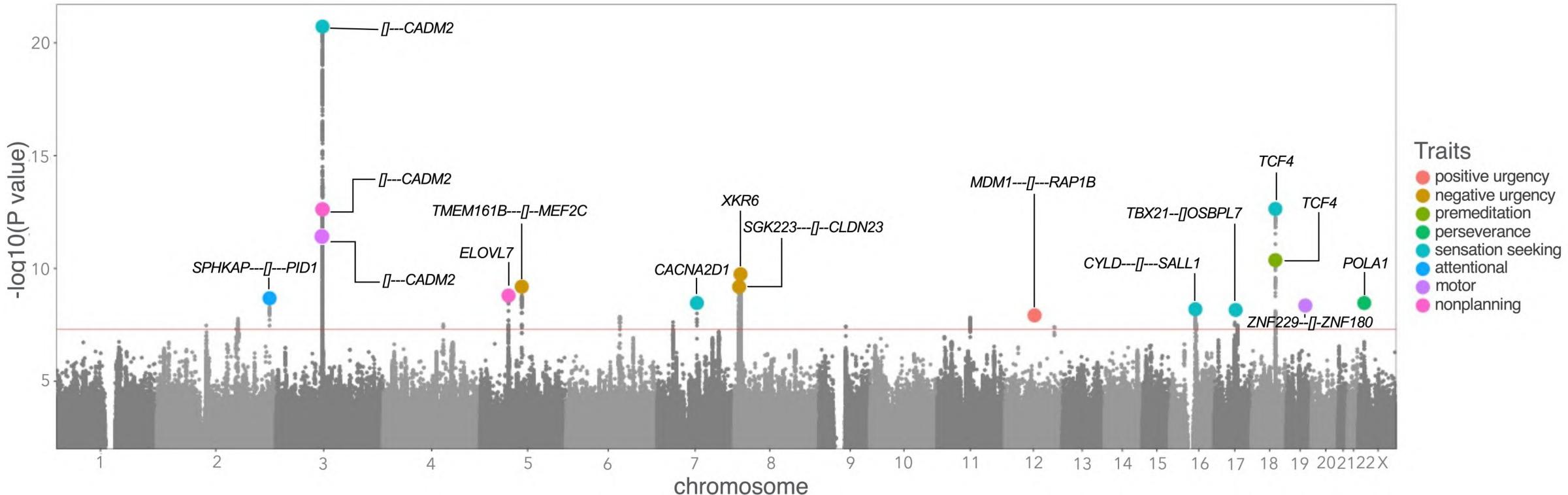
Genetic correlations between impulsivity and substance use and misuse



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

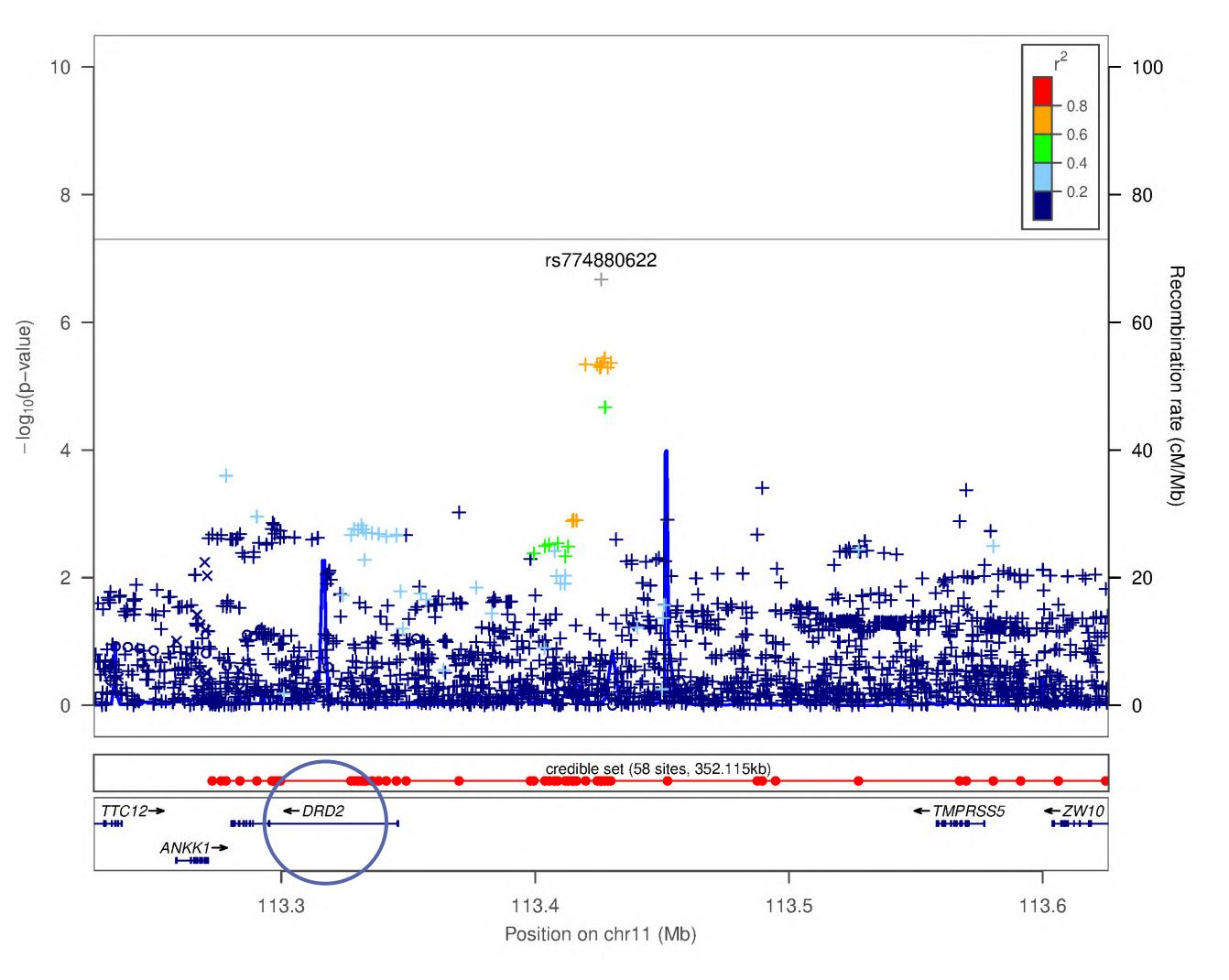


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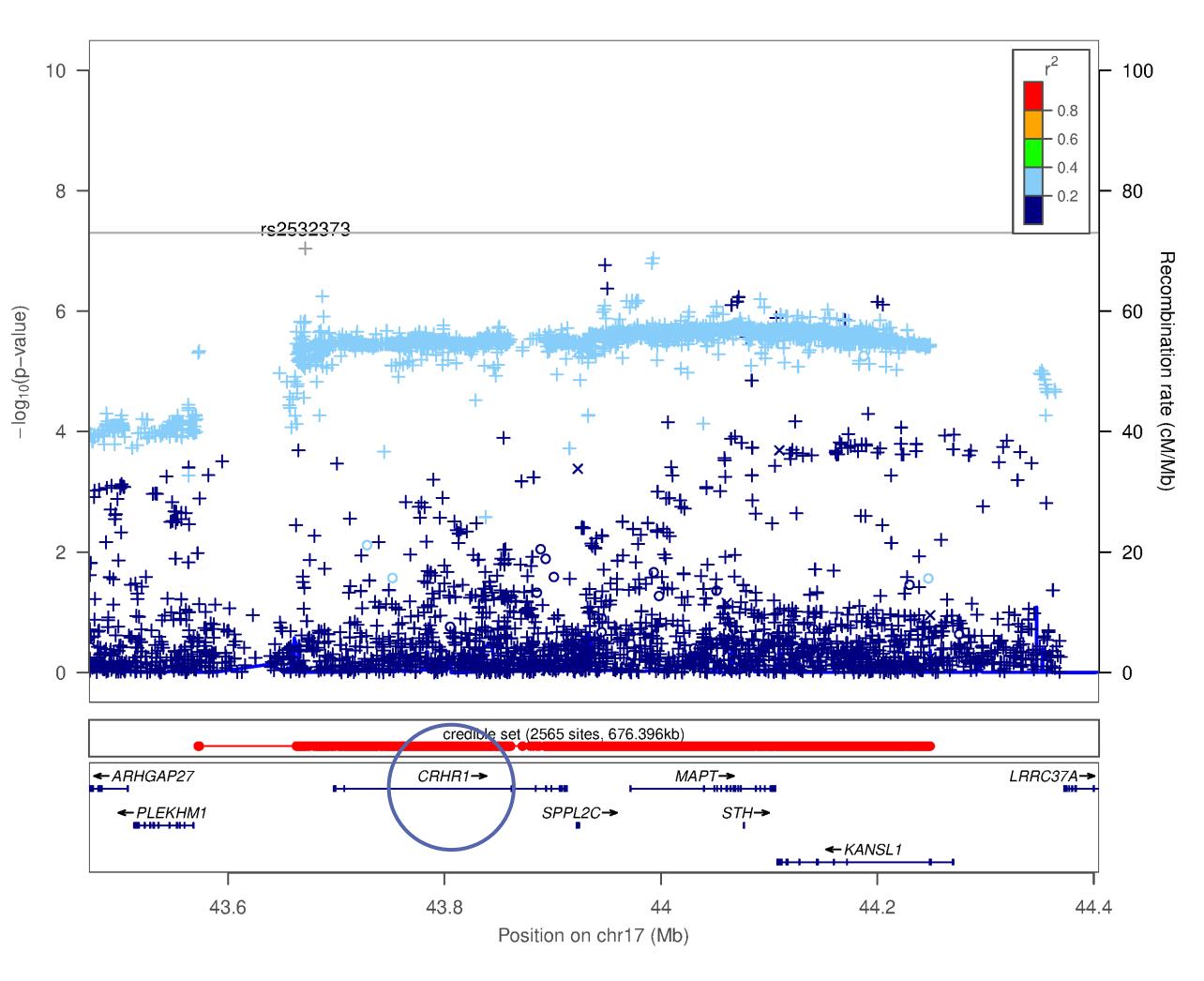
We noted a nominal association with rs774880622 (p=2.10E-07), near the Dopamine D2 receptor (DRD2) gene, and Premeditation



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

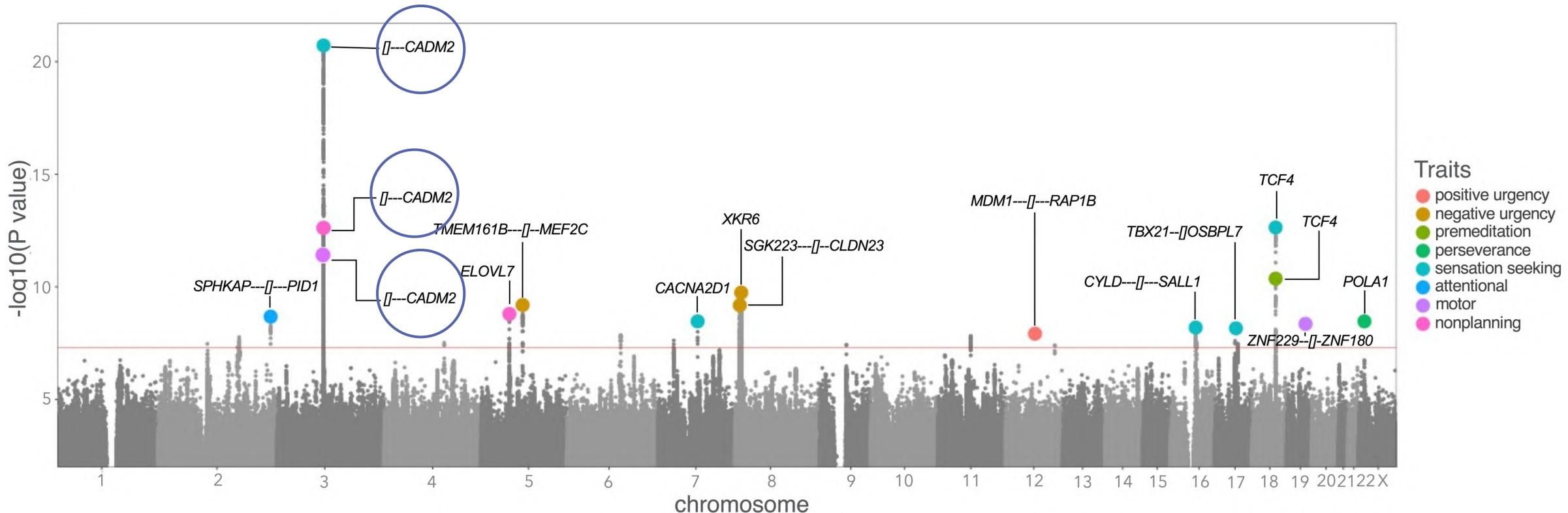


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One of the most consistent loci was located on chromosome 3, near the gene cell adhesion molecule 2 (CADM2)



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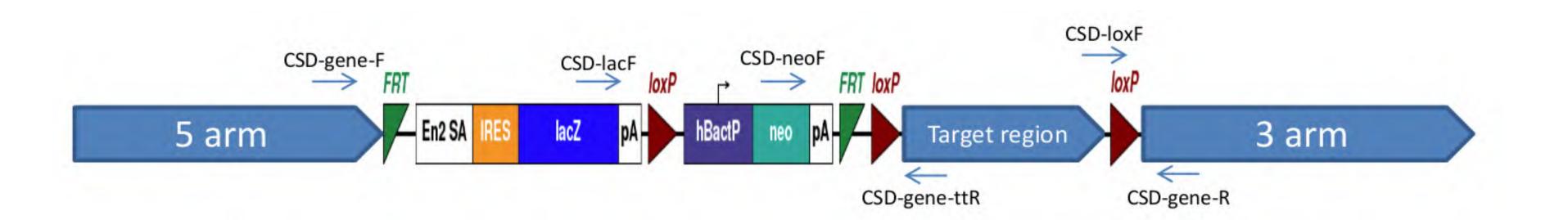
CADM2 has a profound effect on human behavior: ADHD, drug experimentation, alcohol and cannabis use, BMI, smoking, neuroticism, age at first sex, among others (see GWAS Catalog www.ebi.ac.uk/gwas/)

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



DISO PERSONALIT

···· RESEARCH ····

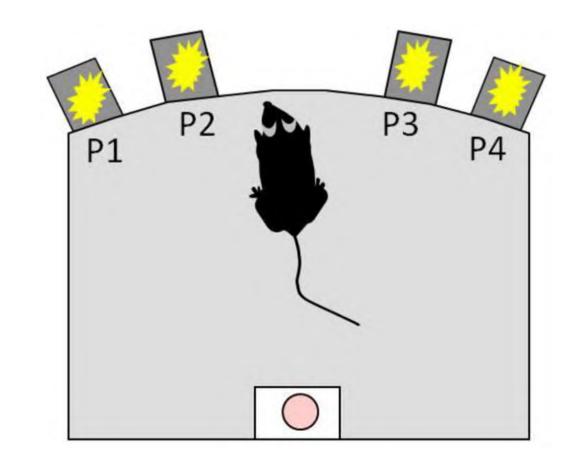


We produced mice that expressed a null allele Cadm2tm1a(KOMP)Mbp on an otherwise isogenic (inbred) background (C57BL/6N) under homogeneous environmental conditions



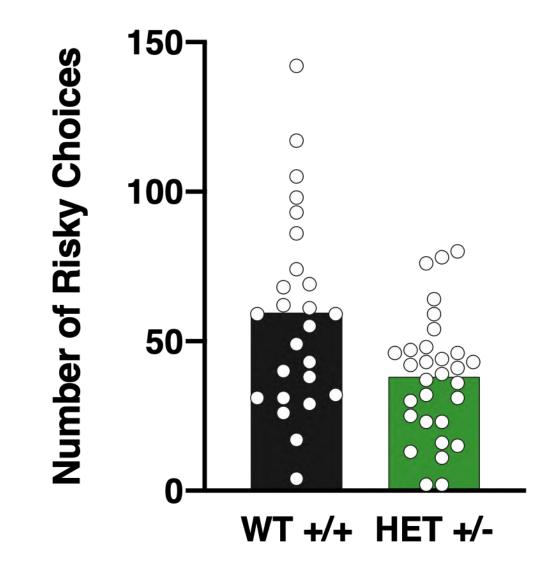


Decreased expression of *Cadm2* is associated with low risky responding in the mouse IOWA gambling task



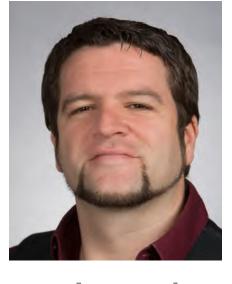
Mice had to choose between disadvantageous ("risky") options (higher reward but less often) vs advantageous options (lower reward, but more frequently)

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





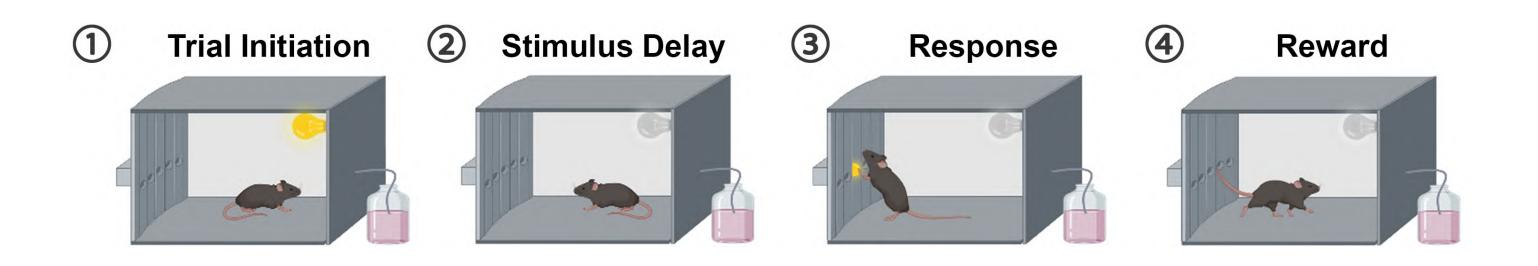
Lieke van der Werf



Jared Young

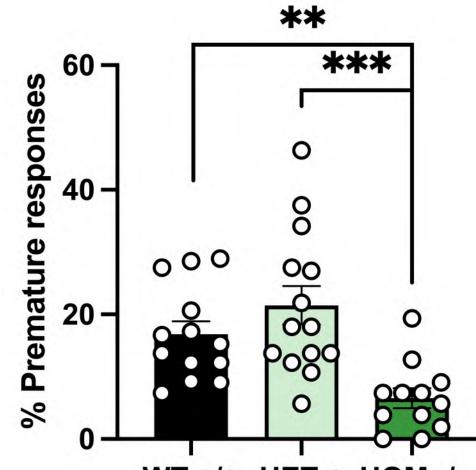


Decreased expression of *Cadm2* is associated with low motoric impulsivity in the 5-Choice Serial Reaction Time Task



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

Sanchez-Roige et al, Translational Psychiatry, 2023



WT +/+ HET + HOM -/-



Hayley Thorpe

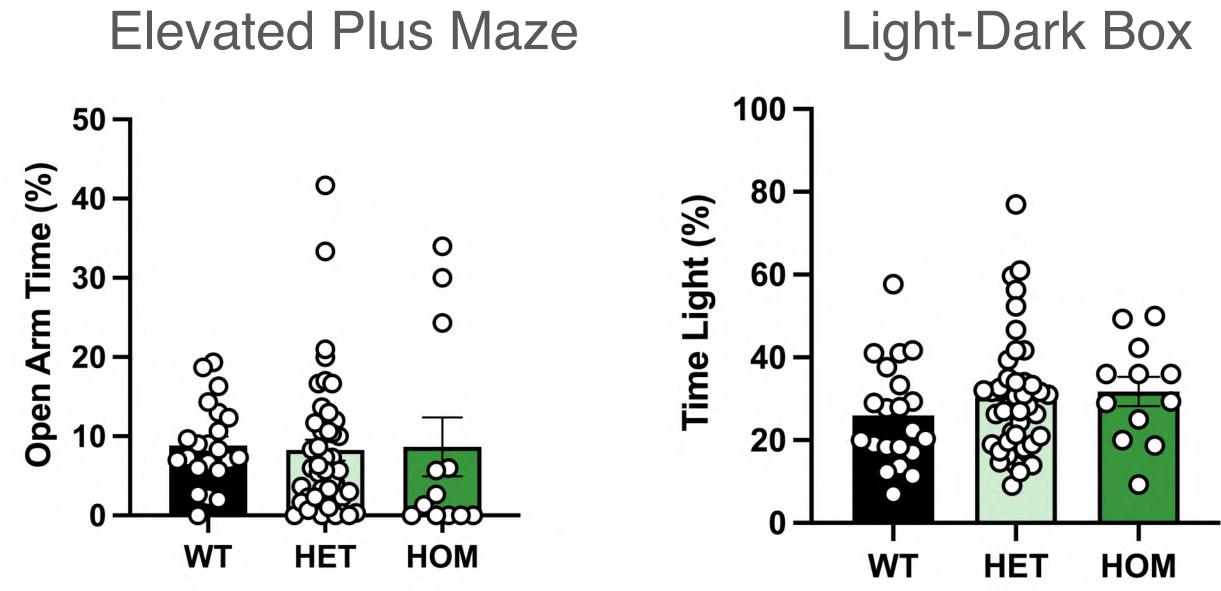


Jibran Khokhar

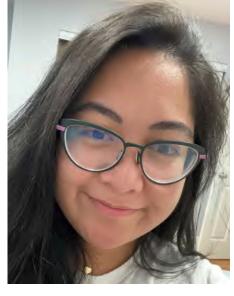




Decreased expression of Cadm2 was not associated with general anxiety-like behavior in mice



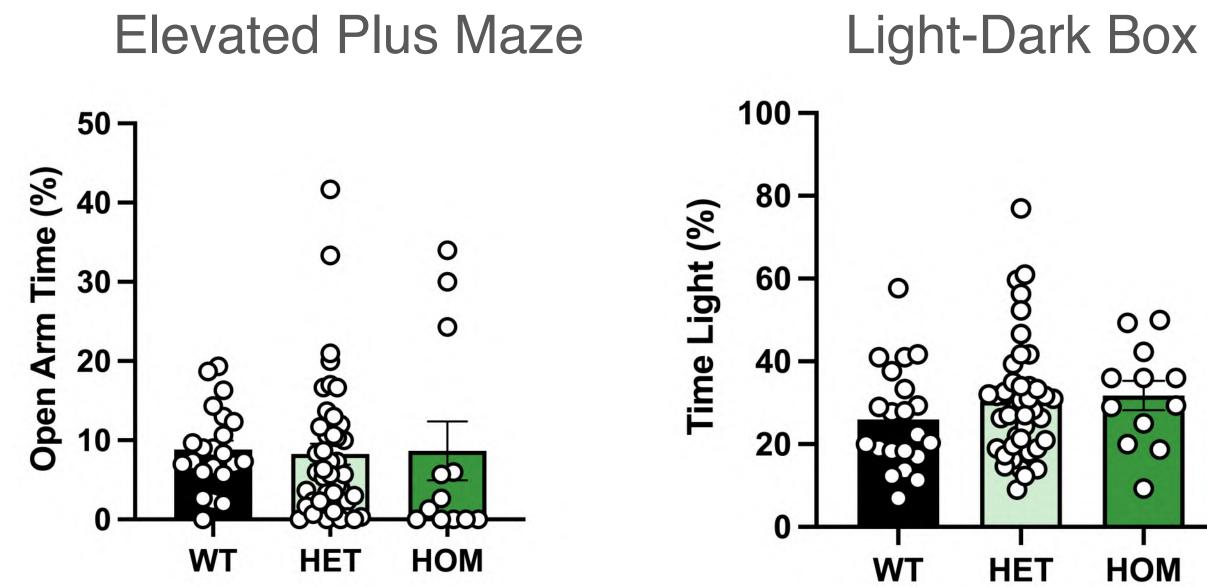
Sanchez-Roige et al, *Translational Psychiatry*, 2023



Jazlene Mallari

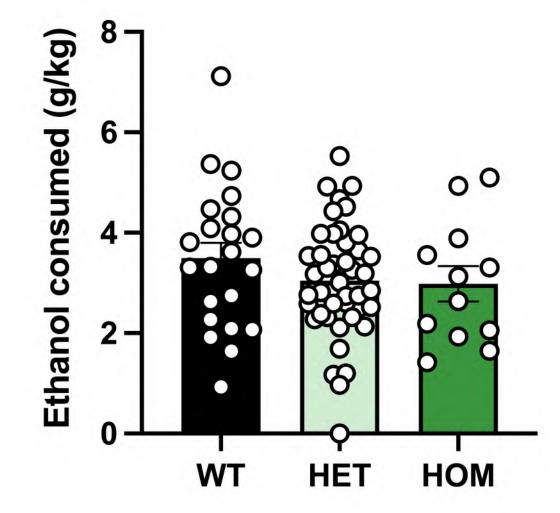


Decreased expression of Cadm2 was not associated with general anxiety-like behavior or ethanol consumption in mice



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

Drinking-in-the-dark paradigm





Jazlene Mallari





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!**



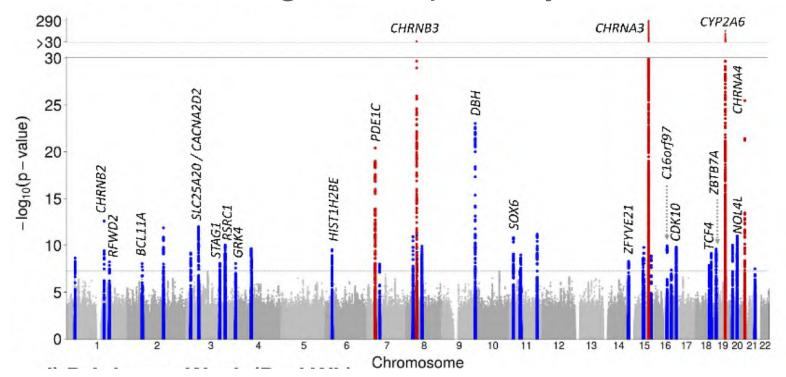
Sanchezroige@ucsd.edu

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

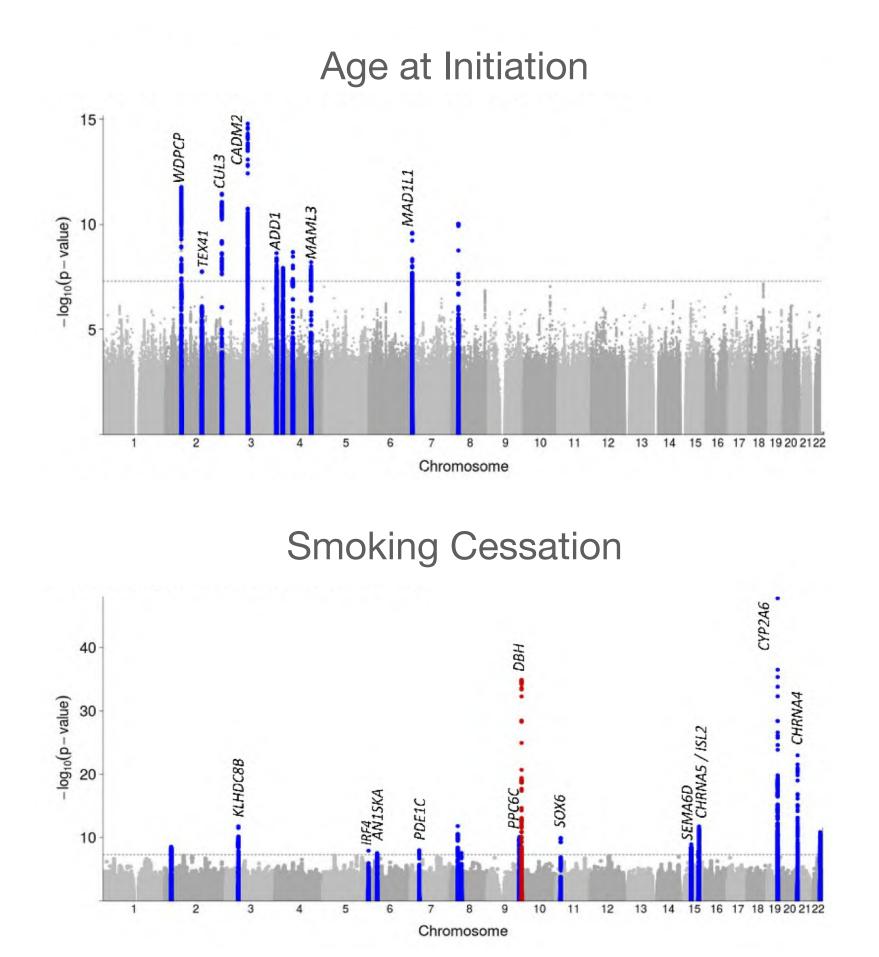
Big strides for understanding aspects of smoking behaviors via GWAS

Smoking Initiation THSD7E EED MAD3 ZCCHC1 40 - ADGRB2 RERE IGSF21 PHC2 FAT3 PHF21A ZNF804 DLX6-AS1 ST6GALNACE PDE4B (value) MAML -d)₀₁00 Chromosome

Cigarettes per Day



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

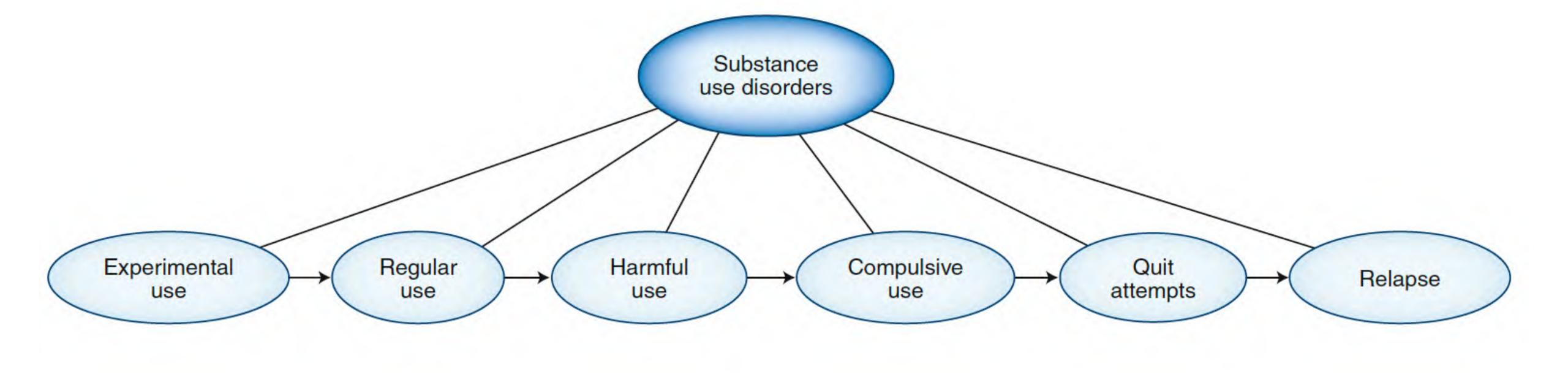




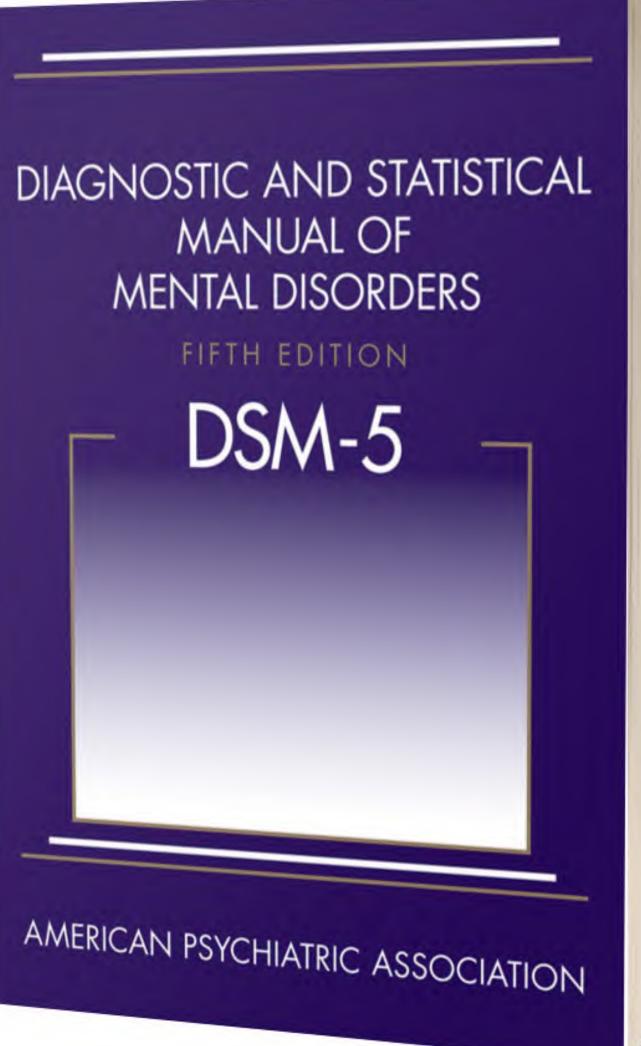
2,143 loci associated with tobacco use

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

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



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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

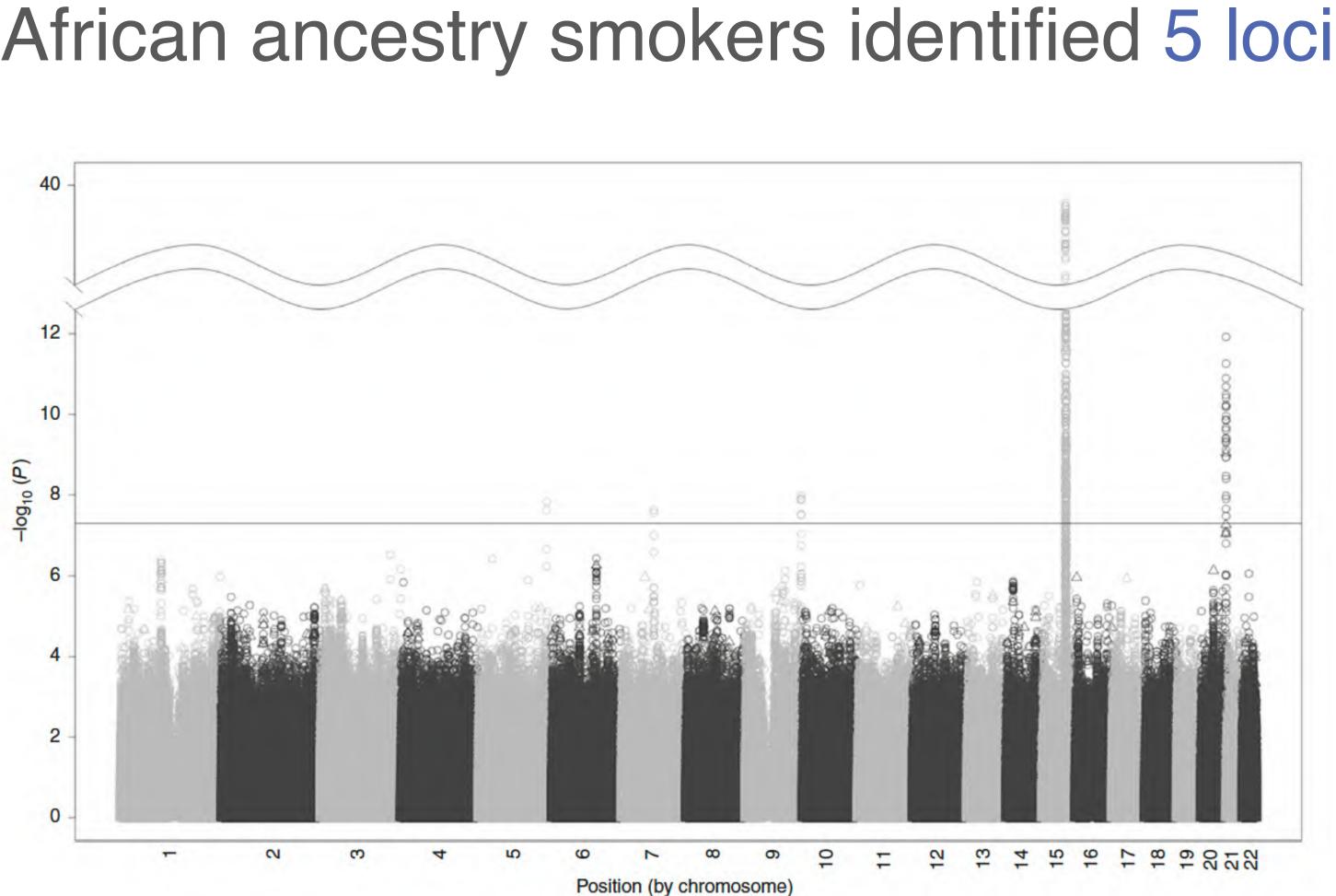
2. Cigarettes per day

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





PsycheMERGE

(Psych) Electronic Medical Record and GEnomics Network





Substance Use Disorder Workgroup



Vanessa Troiani



Mariela Jennings



Lea Davis



Niarchou



Hyunjoon Lee



Brandon Coombes



Yirui Hu



Lori Schirle



David Samuels



Renata Cupertino



Kritika Singh



Rick Crist





Travis Mallard



Jordan Smoller



Sylvanus Toikumo



Rachel Kember



Sevim Bianchi



Alvin Jeffery



Melissa Poulson



Colin Walsh



Laura Vilar-Ribo



Natasia Courchesne-Krak

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



Description Interest Interest

46,905 (EUR)



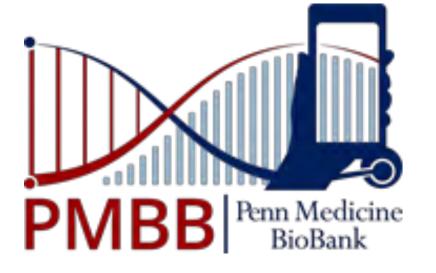




Mariela Sylvanus Hyunjoon Jennings Toikumo Lee

22,268 (EUR)







28,999 (EUR) 10,088 (AFR)

396,833 (EUR) 104,332 (AA) 44,365 (LA)

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



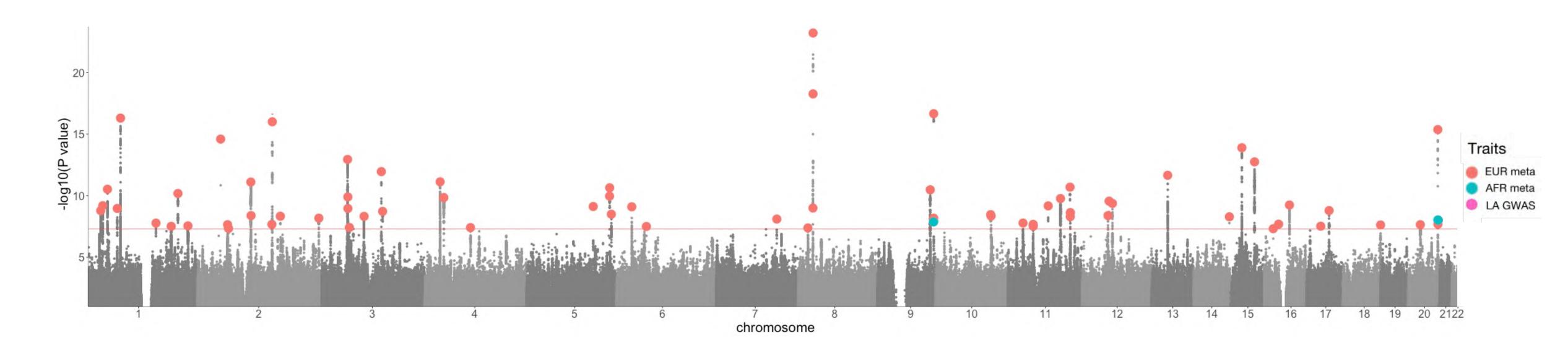
High genetic correlations across sites (mean $r_a = 0.74$, EUR; $r_a = 0.86$, AFR)

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)



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





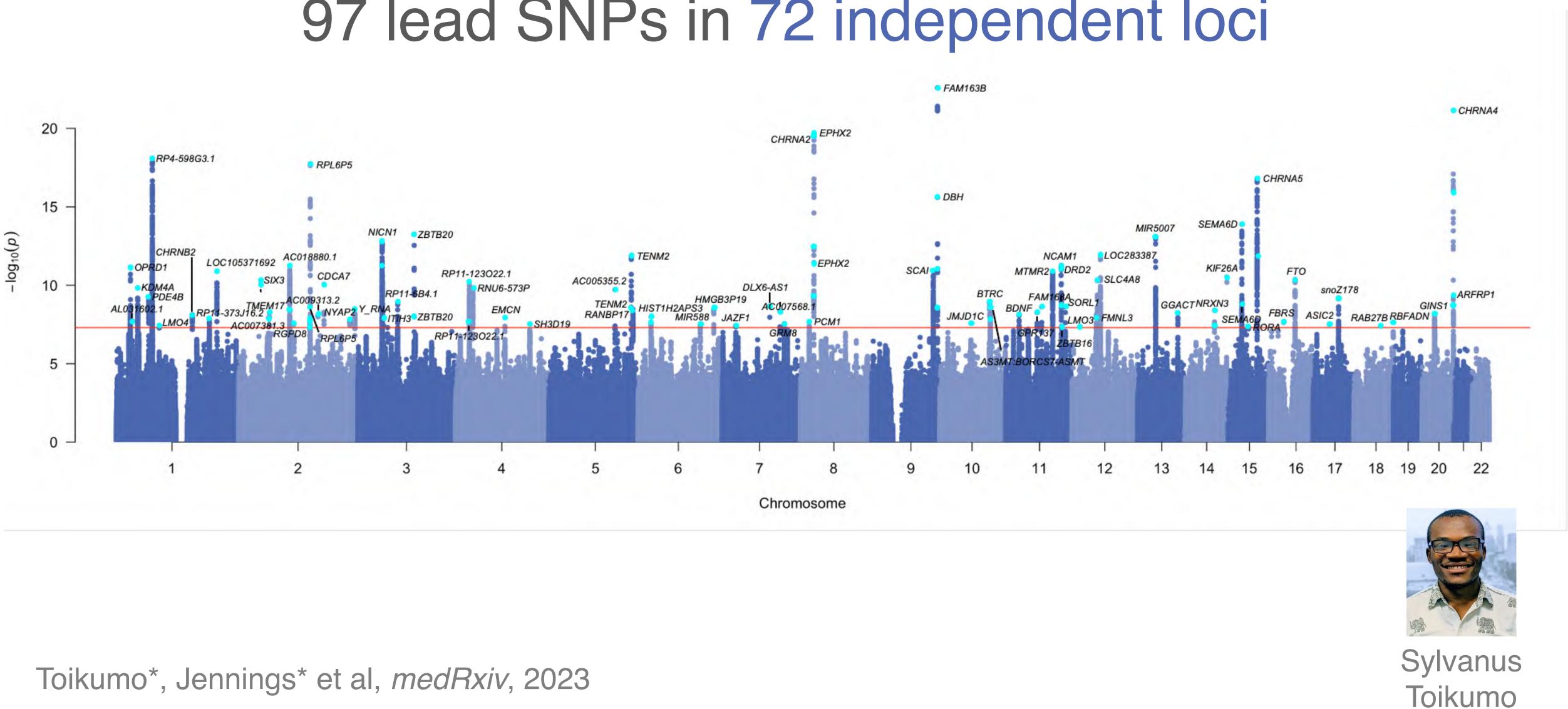
Mariela Sylvanus Hyunjoon Jennings Toikumo

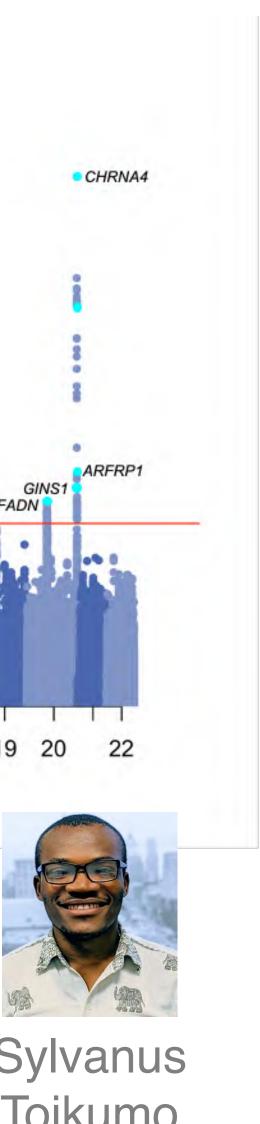


Lee



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





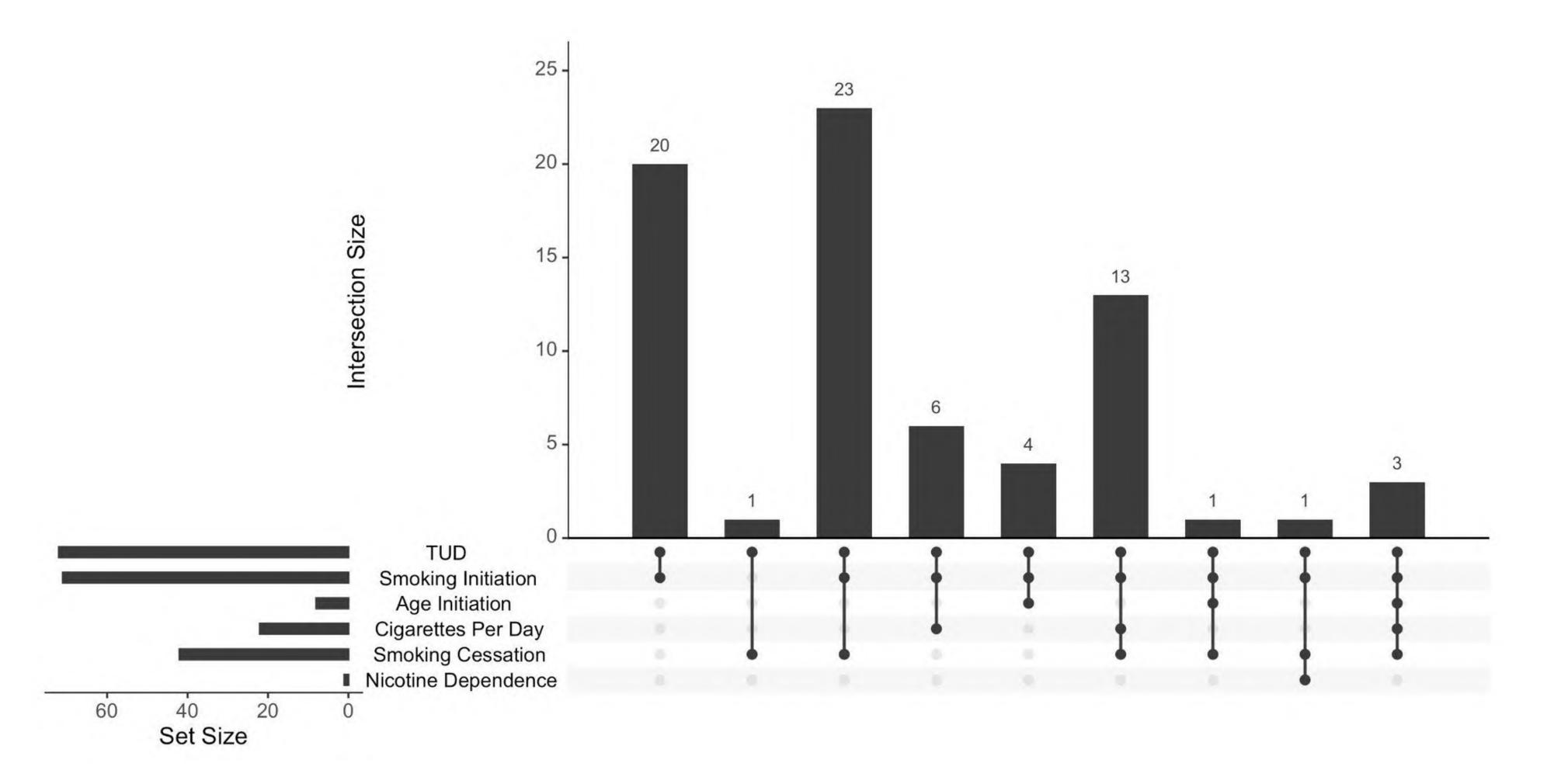
All GWS associations replicated the findings identified in the recent GSCAN study

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





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



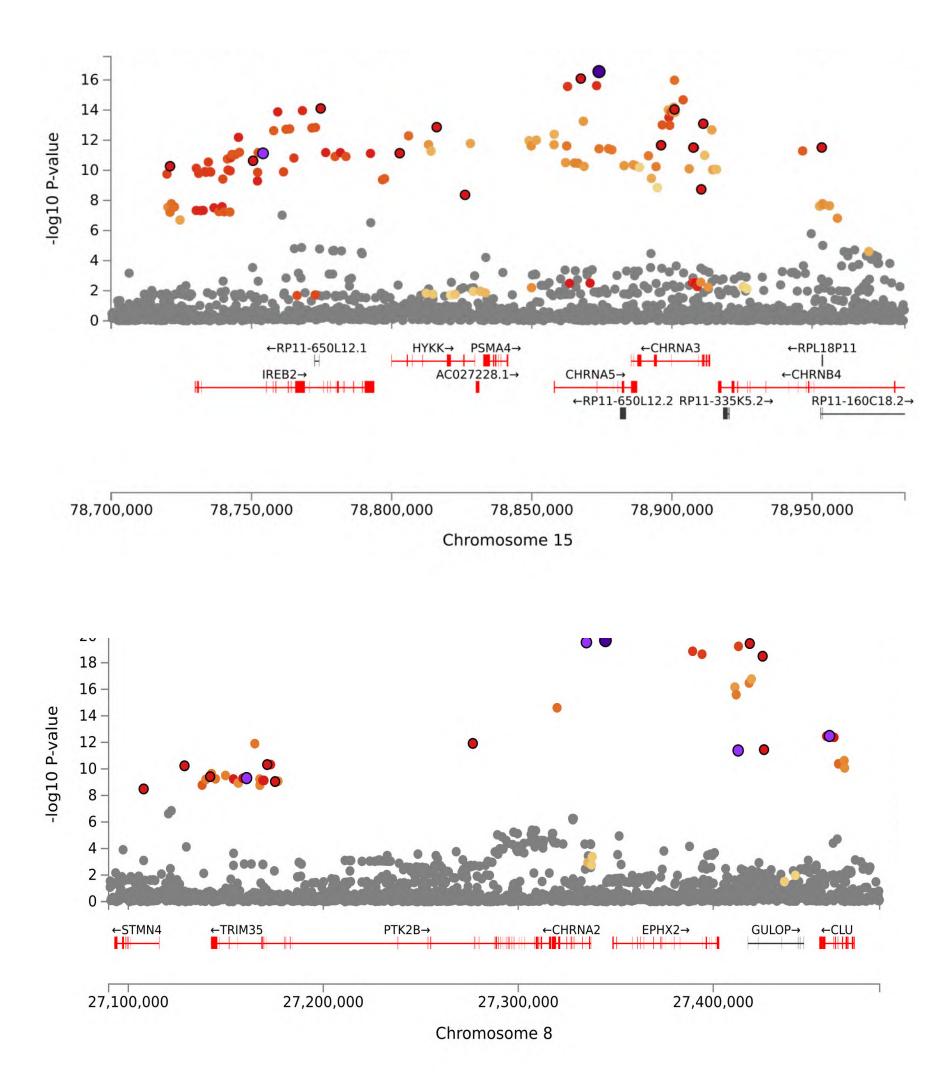
Toikumo*, Jennings* et al, *medRxiv*, 2023

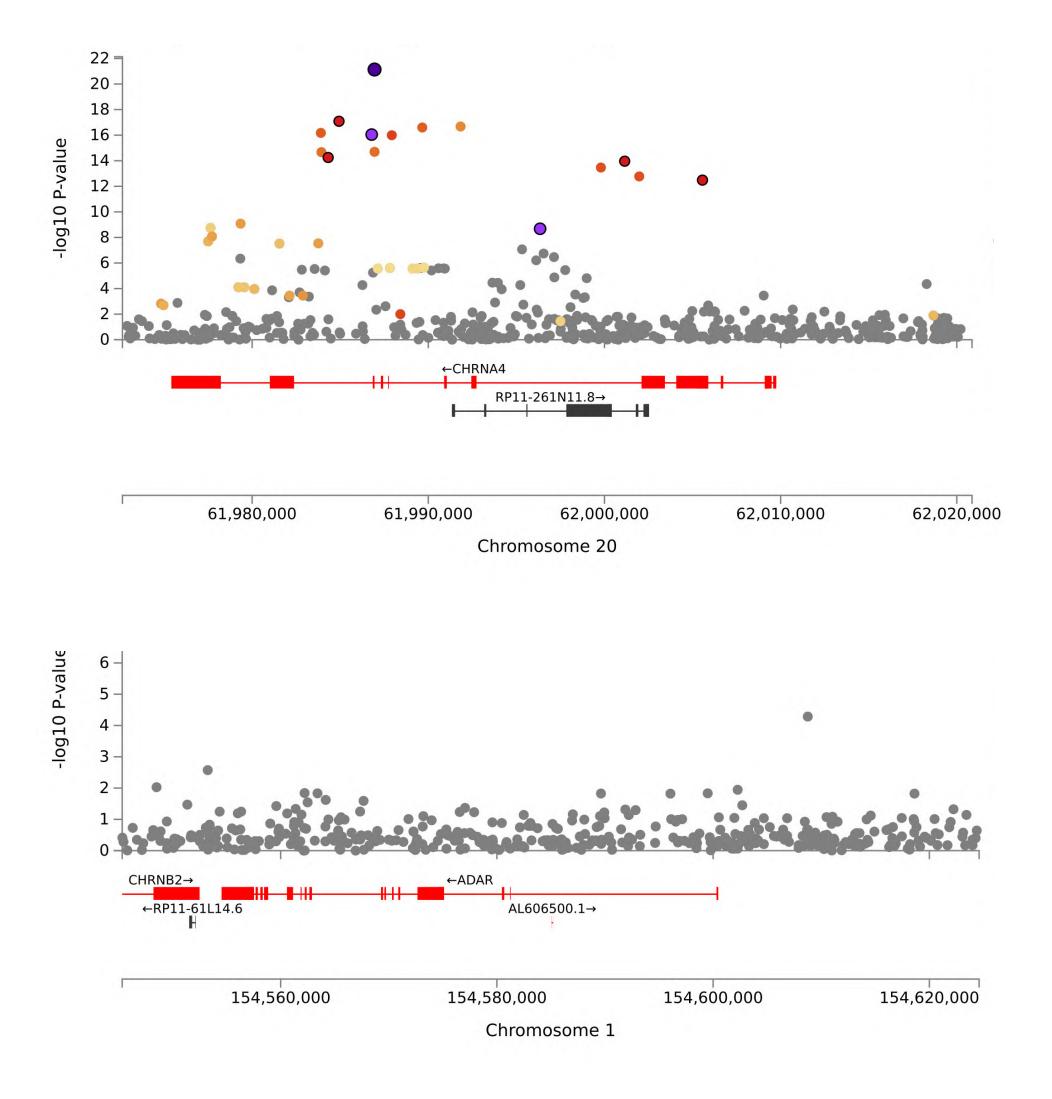


Associations with previous candidate genes with overwhelming biological evidence of involvement in tobacco use disorder



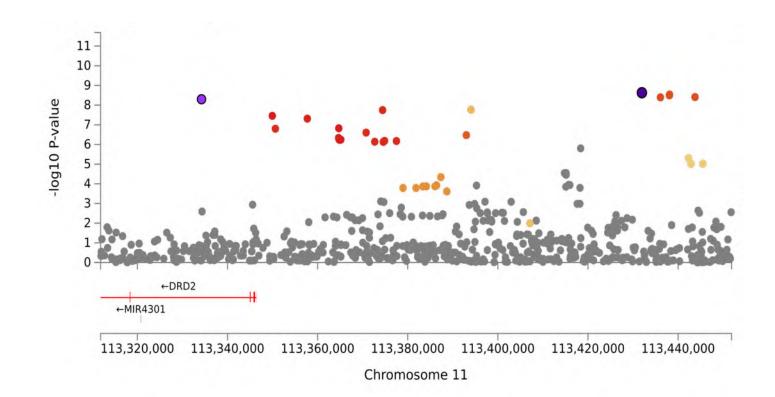
Corroborative support for the involvement of nicotinic acetylcholine receptor genes (CHRNA5-A3-B4, CHRNB2, CHRNA2, CHRNA4)



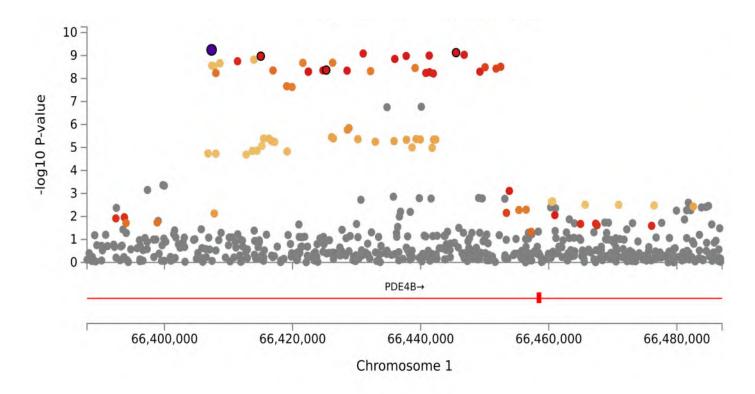




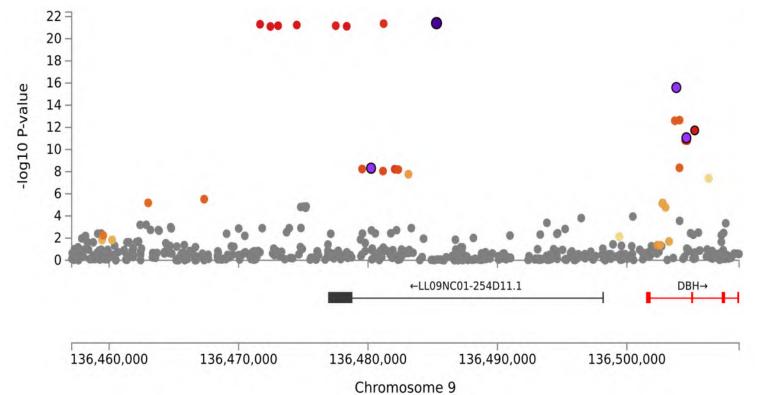
We identified associations with variants in several genes that modulate dopaminergic transmission

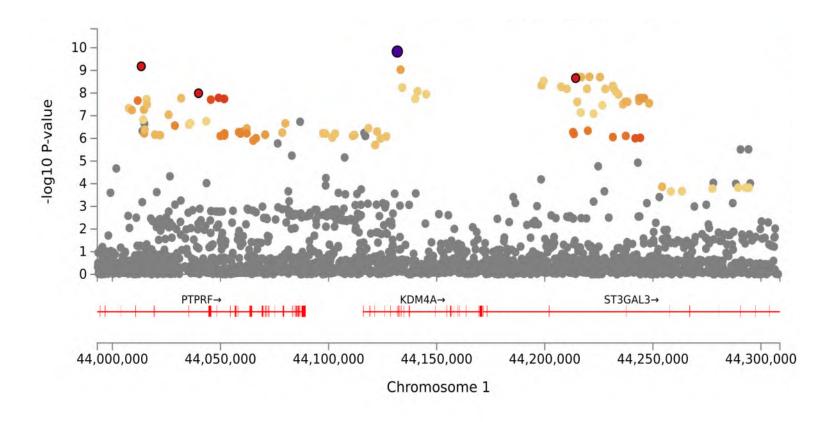


Dopamine Receptor D2 gene; dopaminergic transmission **DBH** encodes a dopamine β -hydroxylase enzyme is central to reward and reinforcement learning necessary to convert dopamine to norepinephrine



PDE4B has regulatory effects on dopaminergic pathways

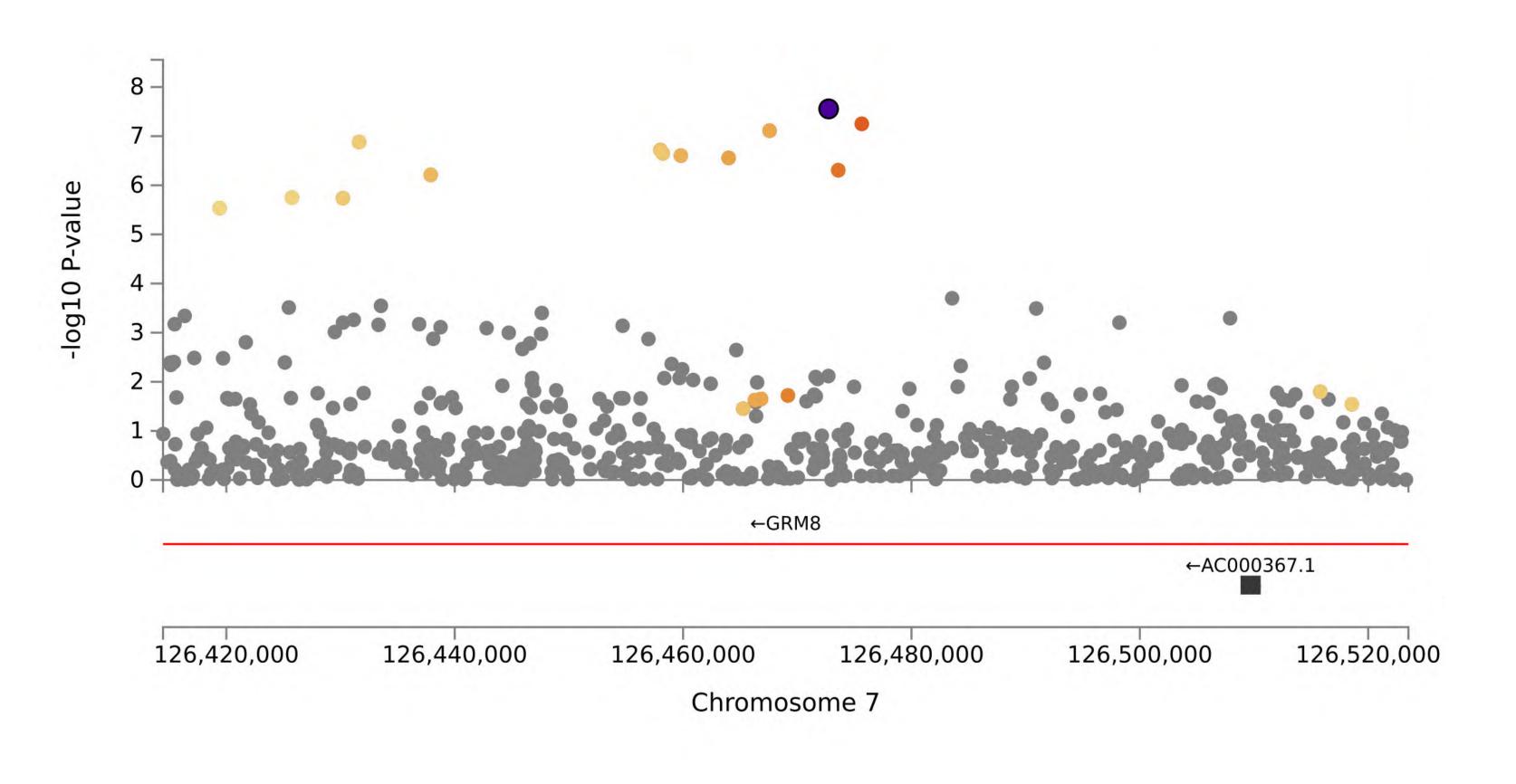




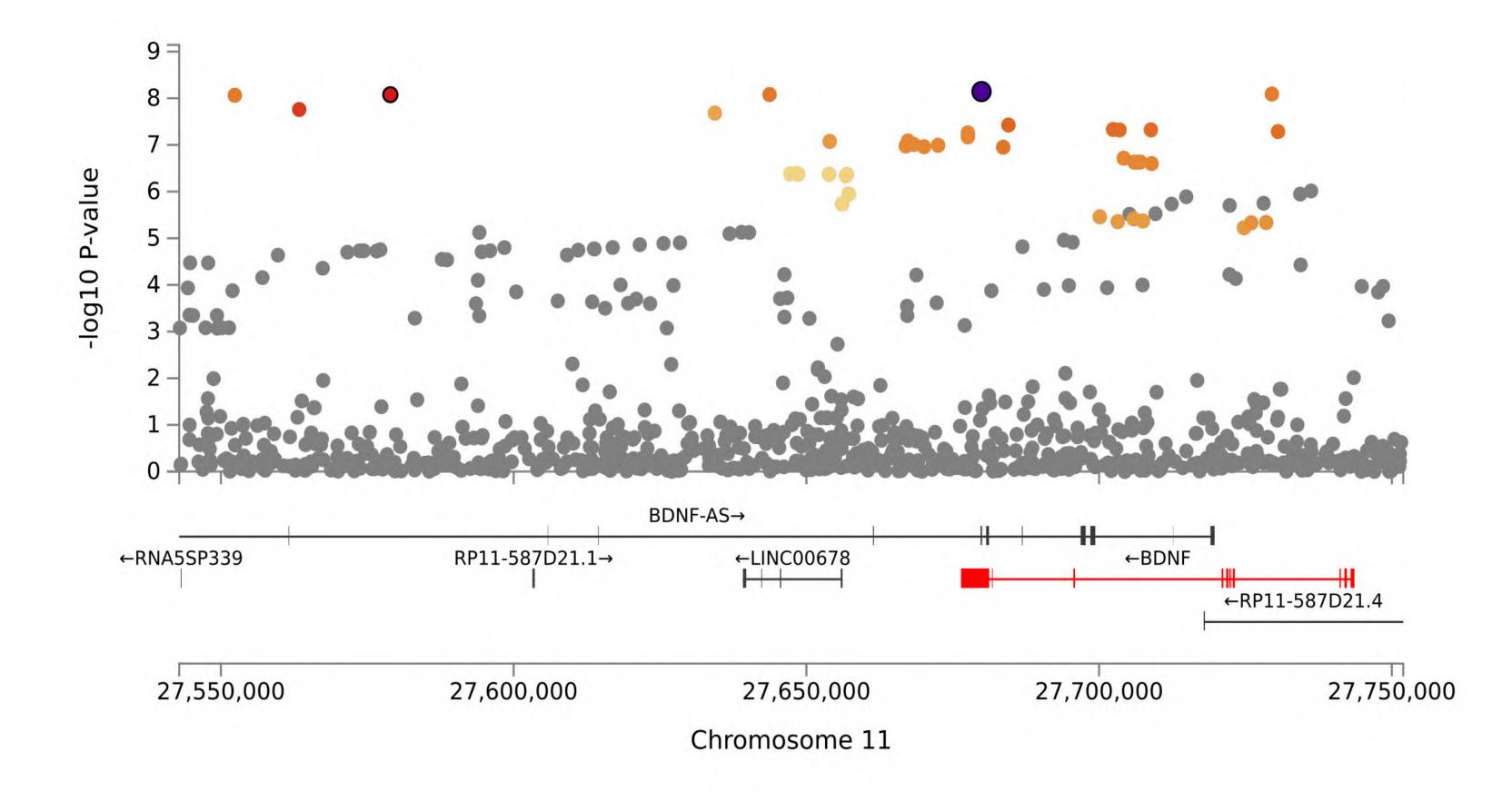
KDM4A has known interactions with dopamine agents



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



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

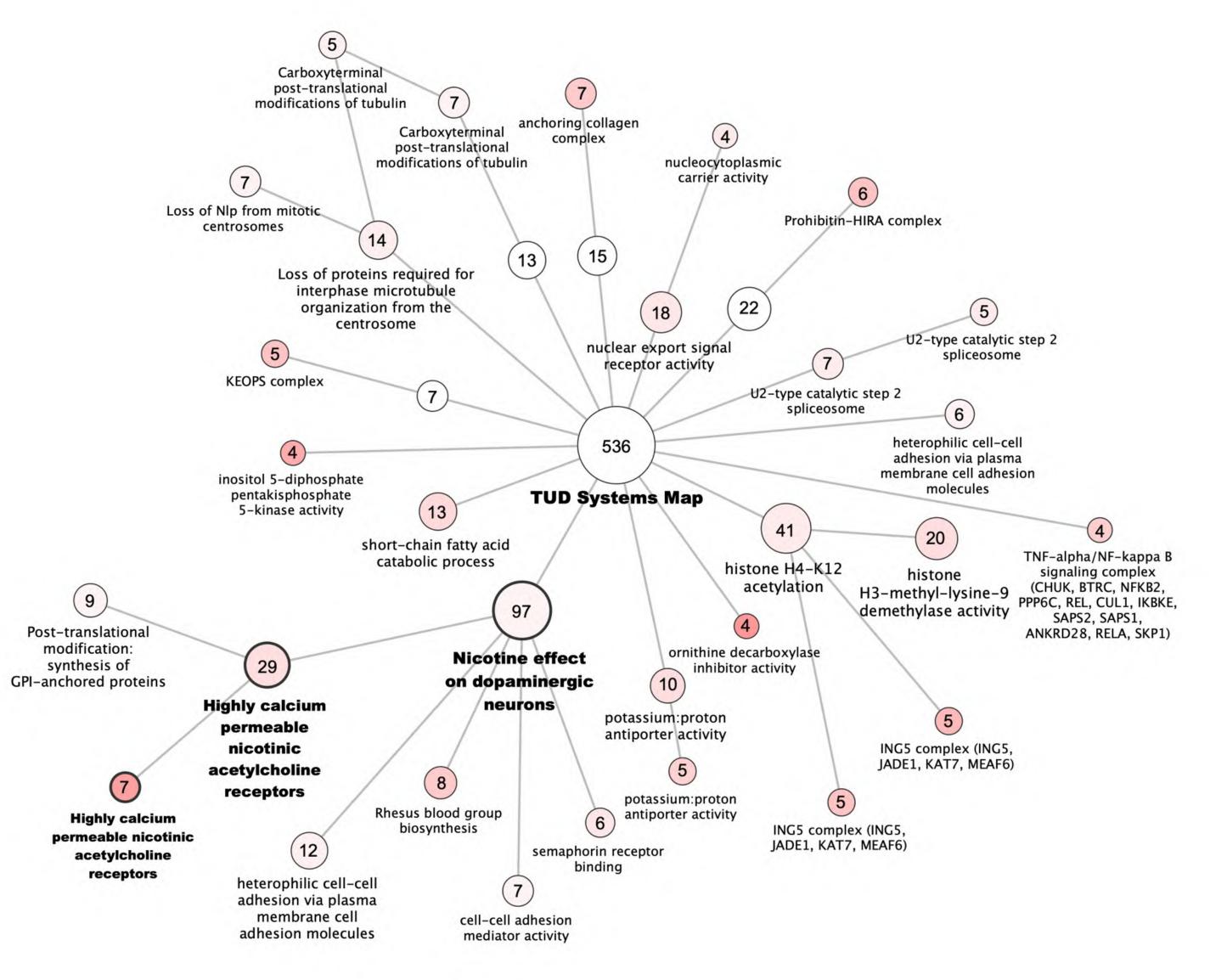




Mapping variants to genes identified 330 TUD risk genes



Pathways involved in cholinergic and dopamine transmission



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

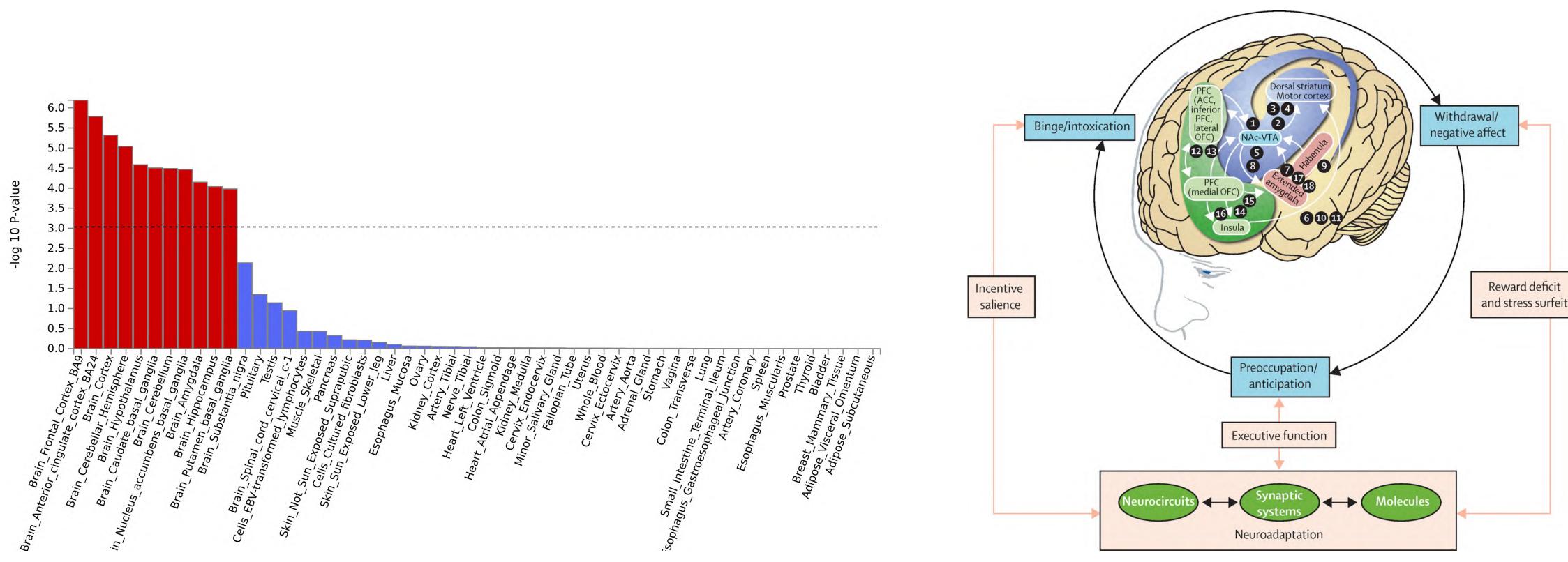


Brittany Leger





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



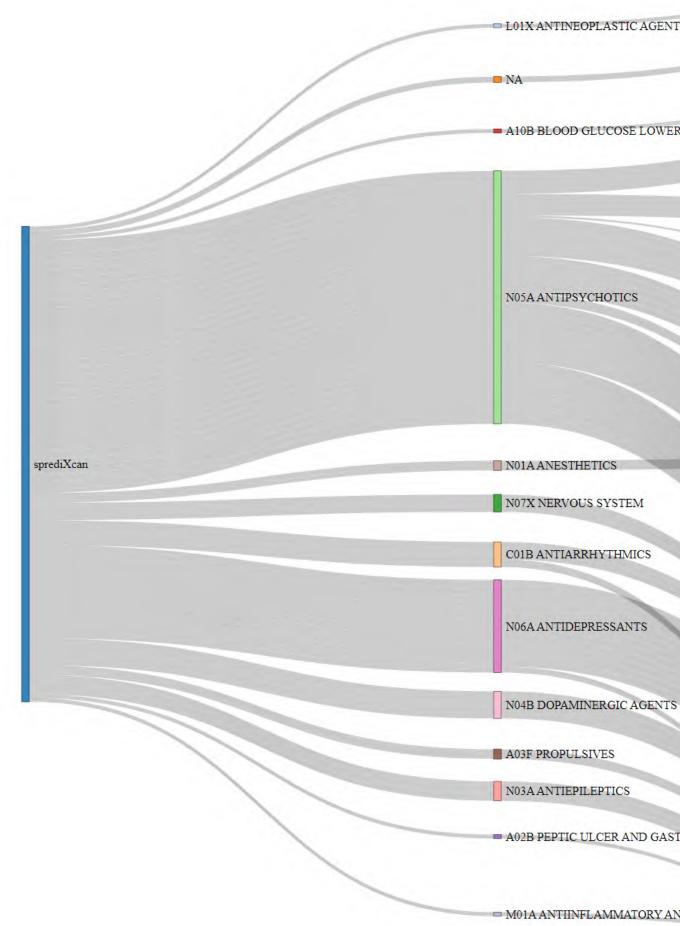
Toikumo*, Jennings* et al, *medRxiv*, 2023

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)



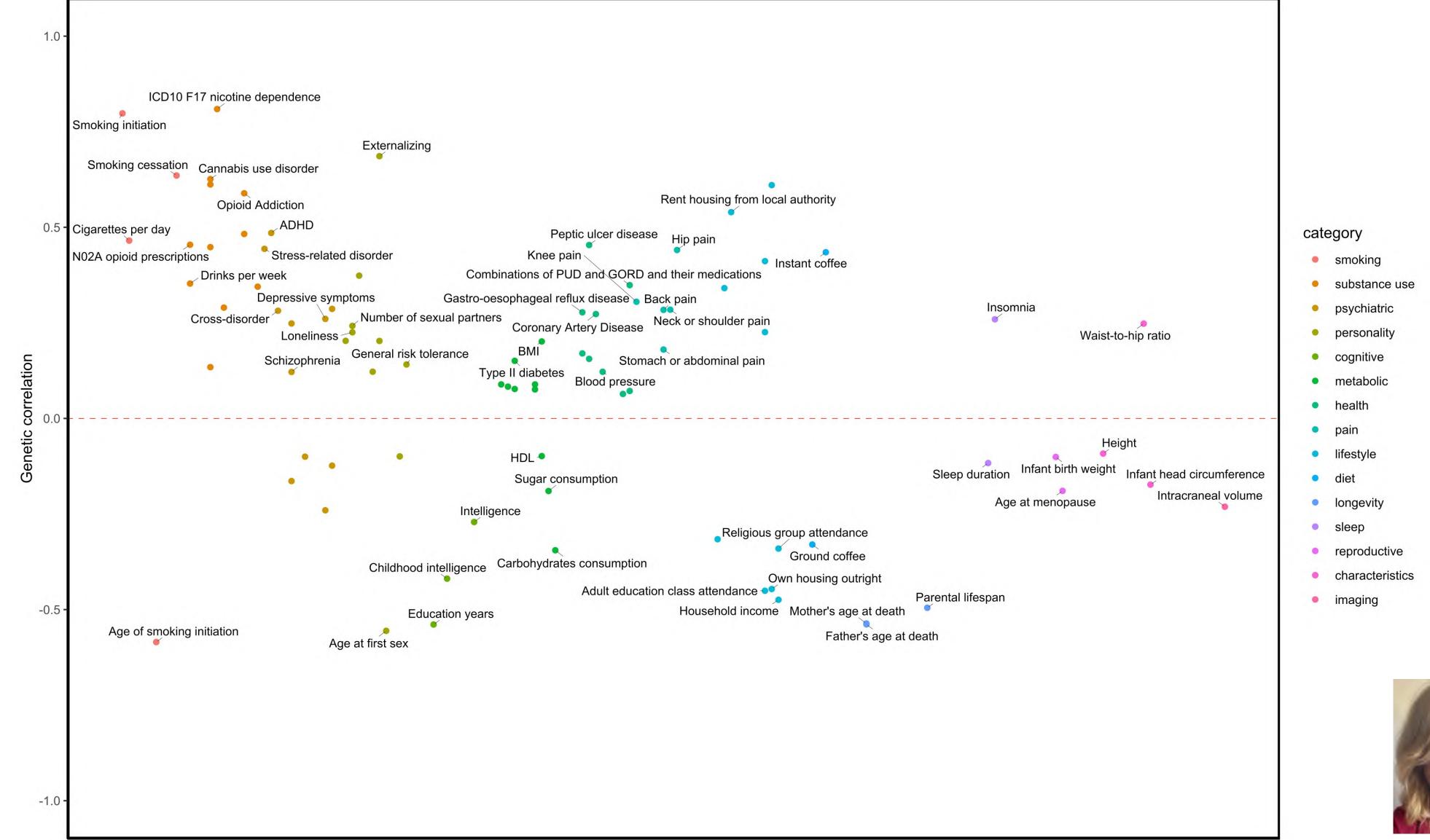
*Library of Integrated Network-Based Cellular Signatures (LINCS) database

		BARB1 BRD3
	olaparib	= BRD4 ACACB PRKAB
ENTS	□ i-bet-762	
		HTR1F
		ADRA1
	- metformin	HTR1E CALY
VERING	AH AMAM	DRD3
	pimozide	DRD4
		HTR2A
	HAT WARAN	HTR6
	iloperidone	DRD2
		HTR7
	- benperidol	DRD1
	A A A A A A A A A A A A A A A A A A A	ADRA11
		HTR1A
	risperidone	HTR5A
		ADRA20
		CHRM3
	levomepromazine	CHRM4
		DRD5
		HTR1D
	droperidol	ADRA2
		ADRA2
		HTR2C HRH2 KCNH2
	clozapine	KCNH2 HTR1B
		HRH4
		CHRM1
	AND	ADRB1 HTR3A KCNA7
		HIR2B
	loxapine	KCNH1 KCNH5
		KCNH5 KCNK1 KCNK6 SLC29A
	All and All All	KCNA5
	quinidine	KCNA5 ADRB2 SLC6A2
	doment doment	SLC6A3
VTS		
	amoxapine	
		E SABRB
		SCN5A GABRE
	propafenone	
ASTRO-OESOPHAGEAL REFLUX		- GABRO
	ropinirole	HTR4 SCN10A
	trimipramine	= SENIA
	metoclopramide	SEN3A
AND ANTIRHEUMATIC PRODUCTS	carbamazepine	E SCN/A
	omeprazole	ATP4A CLCN2



Ben Pham

Significant genetic correlations with 86 comorbid traits







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





Brandon Coombes



Joanna Biernacka

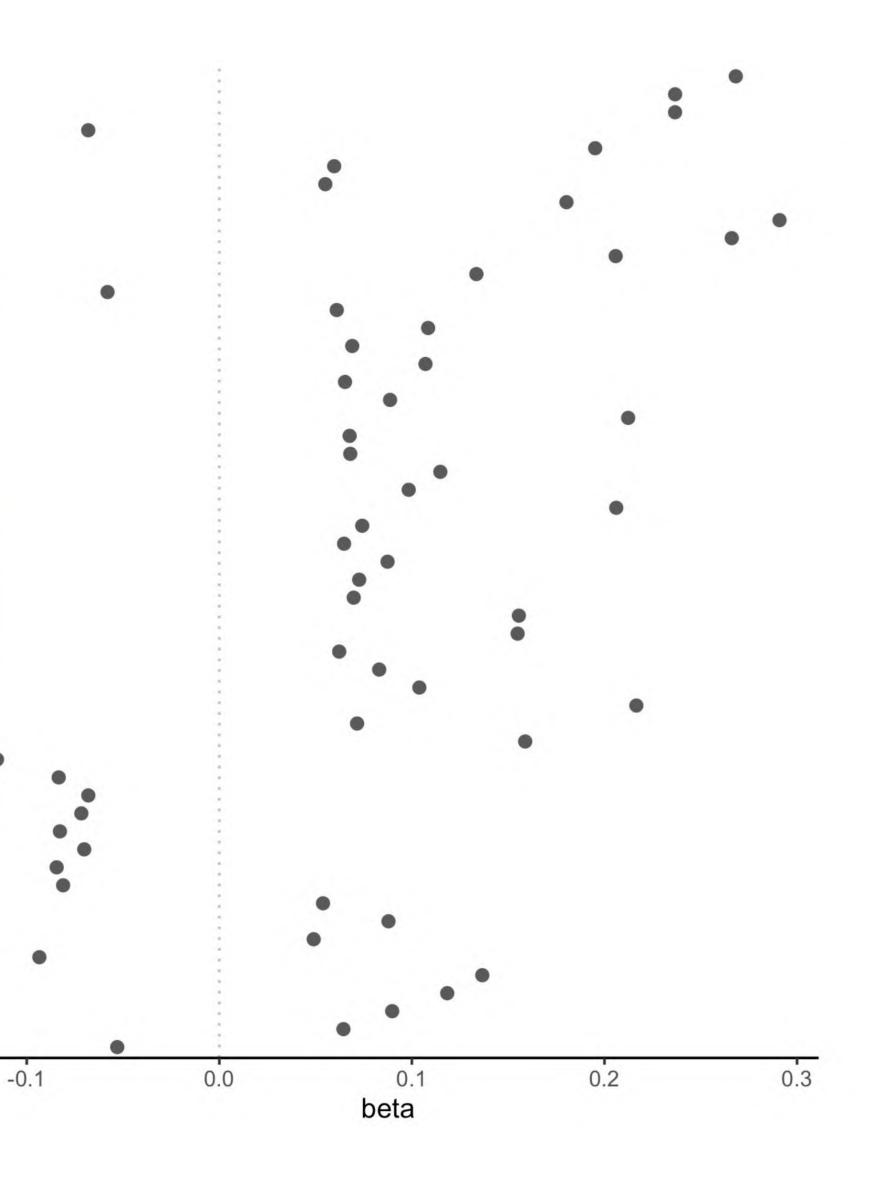




TUD PGS was associated with 54 medical conditions (selected traits below), including tobacco use disorder as defined by phecodes (European cohort)

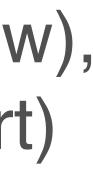
Teheese	
Tobacco	Tobacco use disorder Alcohol-related disorders
Alcohol	Alcoholism
D	Other mental disorder Substance addiction and disorders
Psychiatric	Depression Mood disorders
Respiratory	Chronic airway obstruction
	Emphysema Obstructive chronic bronchitis
	Chronic bronchitis
	Respiratory failure Acute upper respiratory infections Shortness of breath
Circulatory	Shortness of breath Respiratory failure, insufficiency, arrest
	Hypertension
	Hypertension Hypertensive chronic kidney disease Essential hypertension Hypertensive heart and/or renal disease
	Hypertensive heart and/or renal disease
	Abdominal aortic aneurysm Ischemic Heart Disease
	Coronary atherosclerosis Peripheral vascular disease
	Myocardial infarction
Endocrine/ Metabolic	Atherosclerosis of native arteries of the extremities Obesity
	Overweight, obesity and other hyperalimentation
	Disorders of fluid, electrolyte, and acid-base balance
	Electrolyte imbalance Disorders of magnesium metabolism
	Acidosis
	Type 2 diabetes Hypovolemia
	Acute renal failure
Genitourinary	End stage renal disease Renal failure
s.c	Chronic Kidney Disease, Stage IV Myopia
Sense organs	Disorders of refraction and accommodation
conce organo	Presbyopia Impacted cerumen
Neoplasms	Benjan neoplasm of skin
	Screening for malignant neoplasms of the skin Vascular hamartomas
	Nevus, non-neoplastic Diseases of esophagus
Digestive	Diseases of esophagus Other disorders of stomach and duodenum
	Esophagitis, GERD and related diseases Other tests
Medical	Asphyxia and hypoxemia Sepsis and SIRS
	Chronic pain
	Pain Disorder of skin and subcutaneous tissue

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

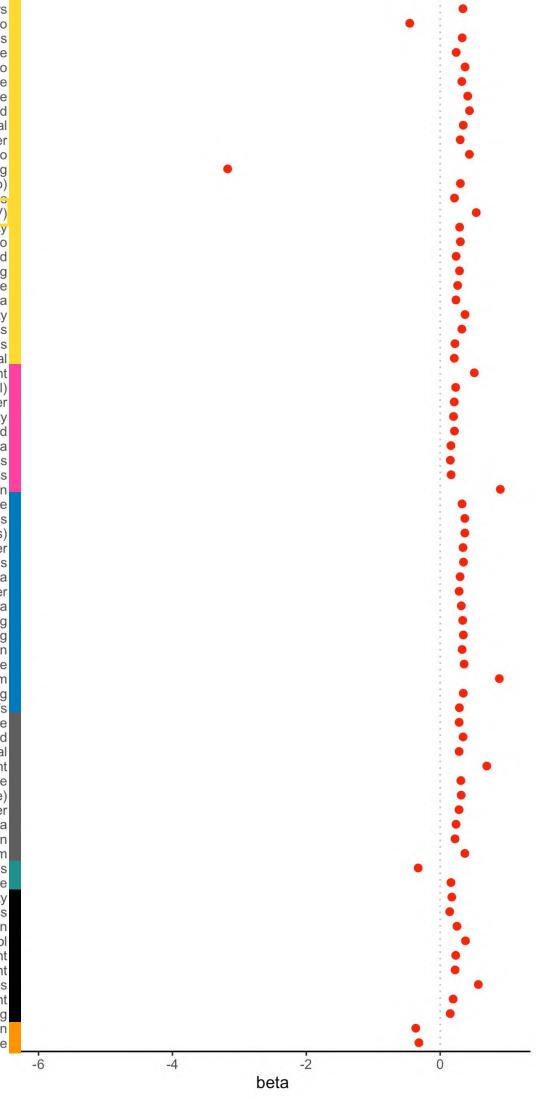


TUD Polygenic Score (PGS) PheWAS in >10k Yale-Penn individuals

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

	Housenoid members cigarette smoker
	Age of first use of tobacc
	Continued use despite problem
	Reduction in other activities due to tobacco us
	Time spent obtaining/using tobacc Toleranc
	Unsuccessful effort to decrease us
	Used more tobacco than intende
	Tobacco withdrawa
Tobacco	
TODUCCO	Four withdrawal symptoms occurred togethe
	Frequent use of tobacc Smoke after wakin
	Sought treatment (tobacco Health problem
	Tobacco Dependence (DSM-IV
	Tobacco withdrawai symptoms: anxiet Tobacco withdrawal symptoms: craving tobacc
	Tobacco withdrawal symptoms: depressed moo
	Tobacco withdrawal symptoms: difficulty concentratin Tobacco withdrawal symptoms: increased appetit
	Tobacco withdrawal symptoms: increased append Tobacco withdrawal symptoms: insomni
	Tobacco withdrawal symptoms: irritabilit
	Tobacco withdrawal symptoms: restlessnes
	Failure to fulfill obligation
	Withdrawa
	Alcohol DSM-5 criterion cour
	Sought treatment (alcoho
	Two alcohol withdrawal symptoms occurred togethe
Alcohol	Alcohol withdrawal symptoms: anxiet
AICOHOI	Alcohol withdrawal symptoms: depressed moo
	Alcohol withdrawal symptoms: insomni
	Alcohol withdrawal symptoms: restlessnes
	Alcohol withdrawal symptoms: weaknes
	Alcohol to intoxicatio
	Reduction in other activities due to opioid us
	Frequent use of opioid
	Sought treatment (opioids
	Two opioid withdrawal symptoms occurred togethe
	Opioid withdrawal symptoms: craving opioid
	Opioid withdrawal symptoms: diarrhe
Opioids	Opioid withdrawal symptoms: feve
Opiolas	Opioid withdrawal symptoms: insomni
	Opioid withdrawal symptoms: intefere with functioinin
	Opioid withdrawal symptoms: nose runnin
	Opioid withdrawal symptoms: pupil dilatio
	Opioid withdrawal symptoms: stomach ach
	Opioid withdrawal symptoms: sur
	Opioid withdrawal symptoms: sweatin
	Legal problem
	Time spent obtaining/using cocain
	Used more cocaine than intende
Cocaine	Cocaine withdrawa
Cocame	Cocaine DSM-5 criterion cour
	Frequent use of cocain
	Sought treatment (cocaine
	Two cocaine withdrawal symptoms occurred togethe
	Cocaine withdrawal symptoms: insomni
	Cocaine withdrawal symptoms: slowed dow
	Cocaine withdrawal symptoms: sur
Cannabis	Age of first use of cannabi
Carriabio	Regularly us
	ADHD: hyperactivity-impulsivit
	Anti-Social Personality Disorder: deceitfulnes
	Anti-Social Personality Disorder: irritability/aggressio
	Conduct Disorder: suspended or expelled from school
Psychiatric/medical	Conduct Disorder: staying out at nigh
	Ever received outpatient psychiatric treatment
	Number of inpatient psychiatric treatment time
	PTSD: criterion cour
Domographico	Health ratin
Demographics	Educatio
č i	Household incom

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

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





Sylvanus Toikumo

Rachel Kember

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)

Household members cigarette smokers Age of first use of tobacco Continued use despite problems Reduction in other activties due to tobacco use Time spent obtaining/using tobacco Tolerance

Unsuccessful effort to decrease use Used more tobacco than intended Tobacco withdrawal Four withdrawal symptoms occurred together Frequent use of tobacco Smoke after waking Sought treatment (tobacco) Health problems Tobacco Dependence (DSM-IV) Tobacco withdrawal symptoms: anxiety Tobacco withdrawal symptoms: craving tobacco Tobacco withdrawal symptoms: depressed mood Tobacco withdrawal symptoms: difficulty concentrating Tobacco withdrawal symptoms: increased appetite Tobacco withdrawal symptoms: insomnia Tobacco withdrawal symptoms: irritablility Tobacco withdrawal symptoms: restlessness Failure to fulfill obligations

Two alcohol withdrawal symptoms occurred together Alcohol withdrawal symptoms: anxiety Alcohol withdrawal symptoms: depressed mood Alcohol withdrawal symptoms: insomnia Alcohol withdrawal symptoms: restlessness Alcohol withdrawal symptoms: weakness Reduction in other activties due to opioid use Two opioid withdrawal symptoms occurred together Opioid withdrawal symptoms: craving opioids Opioid withdrawal symptoms: diarrhea Opioid withdrawal symptoms: fever Opioid withdrawal symptoms: insomnia Opioid withdrawal symptoms: intefere with functioining Opioid withdrawal symptoms: nose running Opioid withdrawal symptoms: pupil dilation Opioid withdrawal symptoms: stomach ache Opioid withdrawal symptoms: sum Opioid withdrawal symptoms: sweating

> Time spent obtaining/using cocaine Used more cocaine than intended

Two cocaine withdrawal symptoms occurred together Cocaine withdrawal symptoms: insomnia Cocaine withdrawal symptoms: slowed down Cocaine withdrawal symptoms: sum

ADHD: hyperactivity-impulsivity Anti-Social Personality Disorder: deceitfulness Anti-Social Personality Disorder: irritability/aggression order: suspended or expelled from scho Conduct Disorder: staying out at night Ever received outpatient psychiatric treatment Number of inpatient psychiatric treatment times

Household income

Alcohol

Tobacco

Opioids

Cocaine

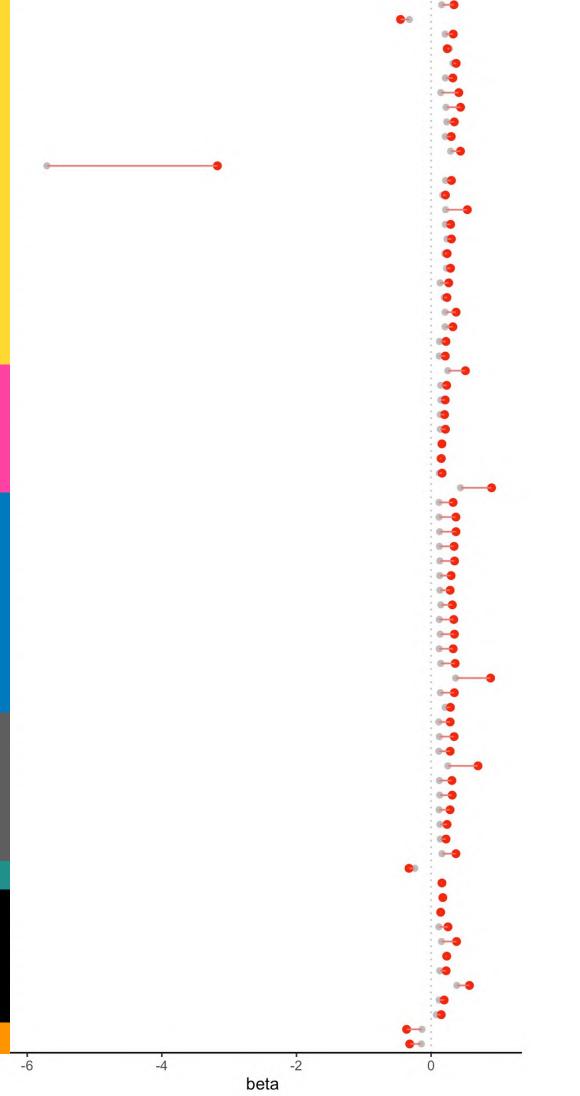
Cannabis

Psychiatric/medical

Demographics

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

Withdrawal Alcohol DSM-5 criterion count Sought treatment (alcohol) Alcohol to intoxication Frequent use of opioids Sought treatment (opioids) Legal problems Cocaine withdrawal Cocaine DSM-5 criterion count Frequent use of cocaine Sought treatment (cocaine) Age of first use of cannabis Regularly use PTSD: criterion count Health rating Education







Sylvanus Toikumo

Kember



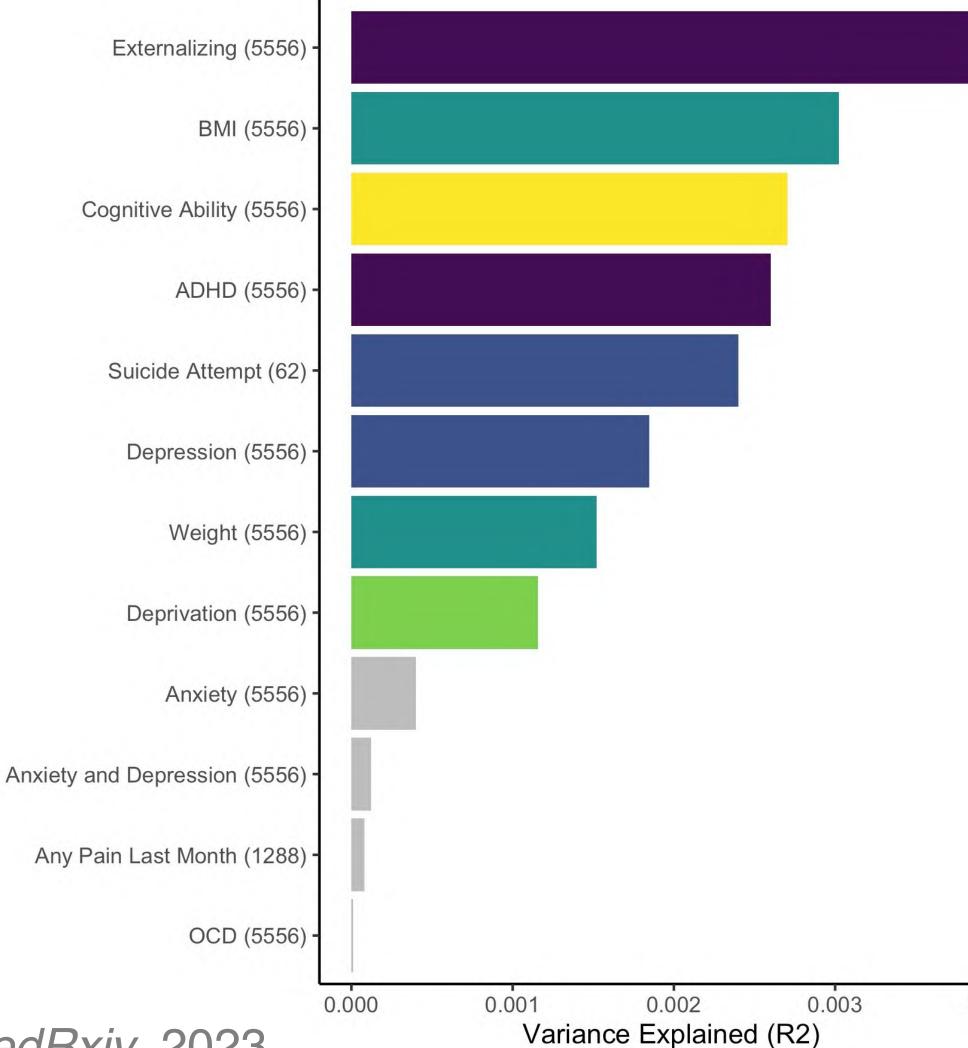
TUD PGS analysis in a young cohort

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



OCD (5556) · Toikumo*, Jennings* et al, *medRxiv*, 2023





Emma Johnson



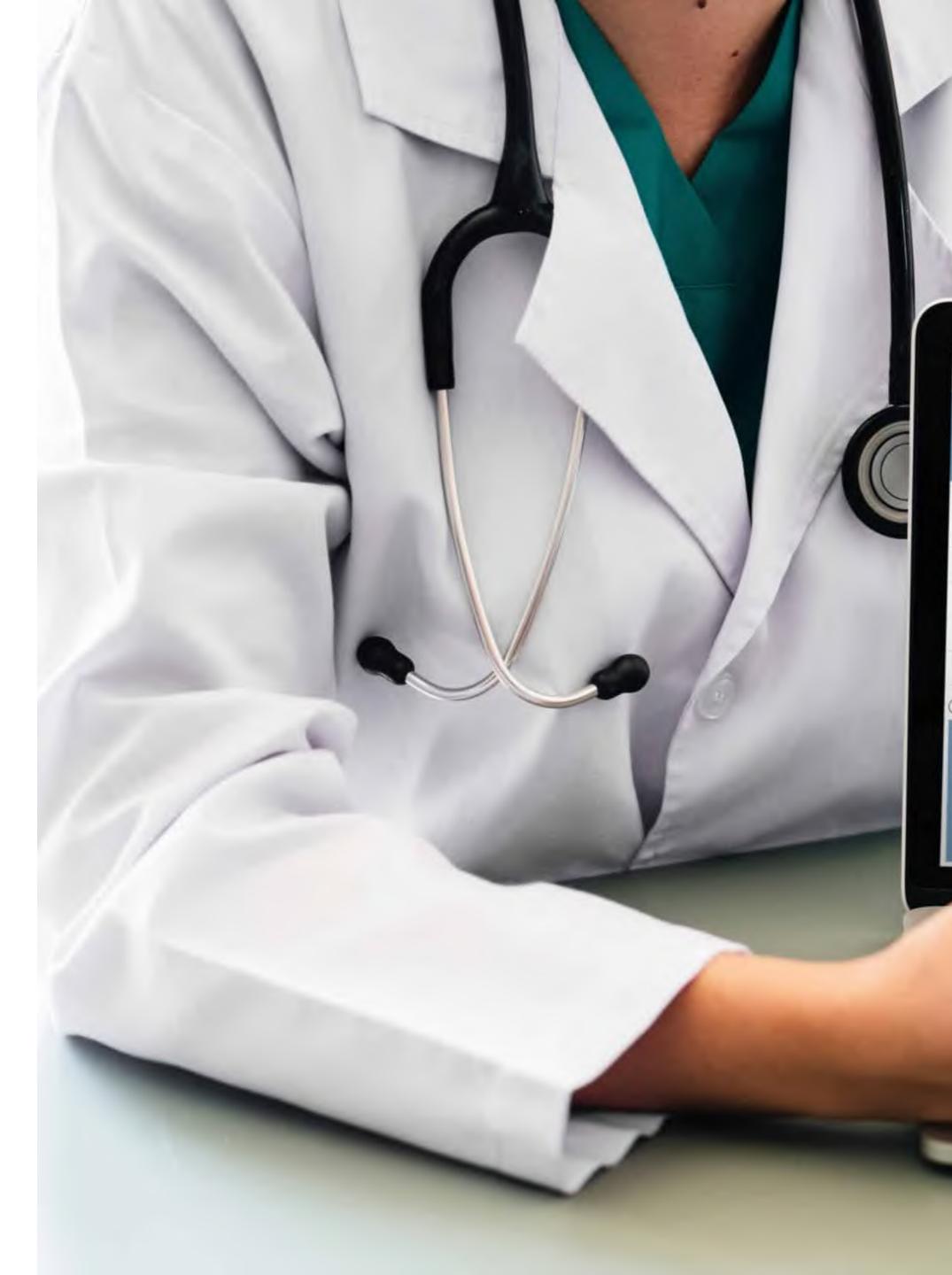
Alex Hatoum

EHR are powerful sources for TUD genomics



Link to the preprint





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"The genes have not read the DSM"



Hundreds of loci associated with substance use traits

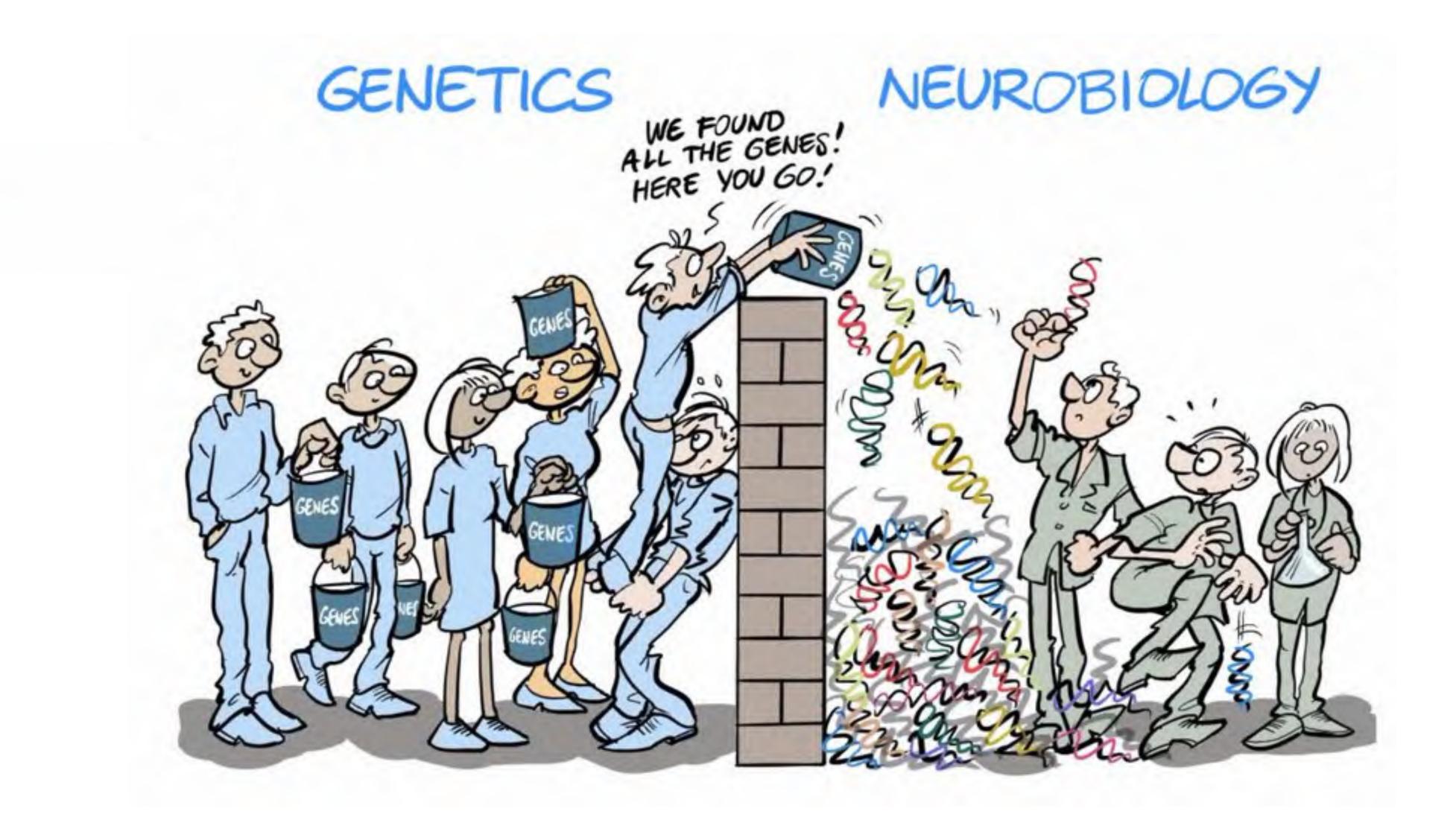


PsycheMERGE

(Psych) Electronic Medical Record and GEnomics Network

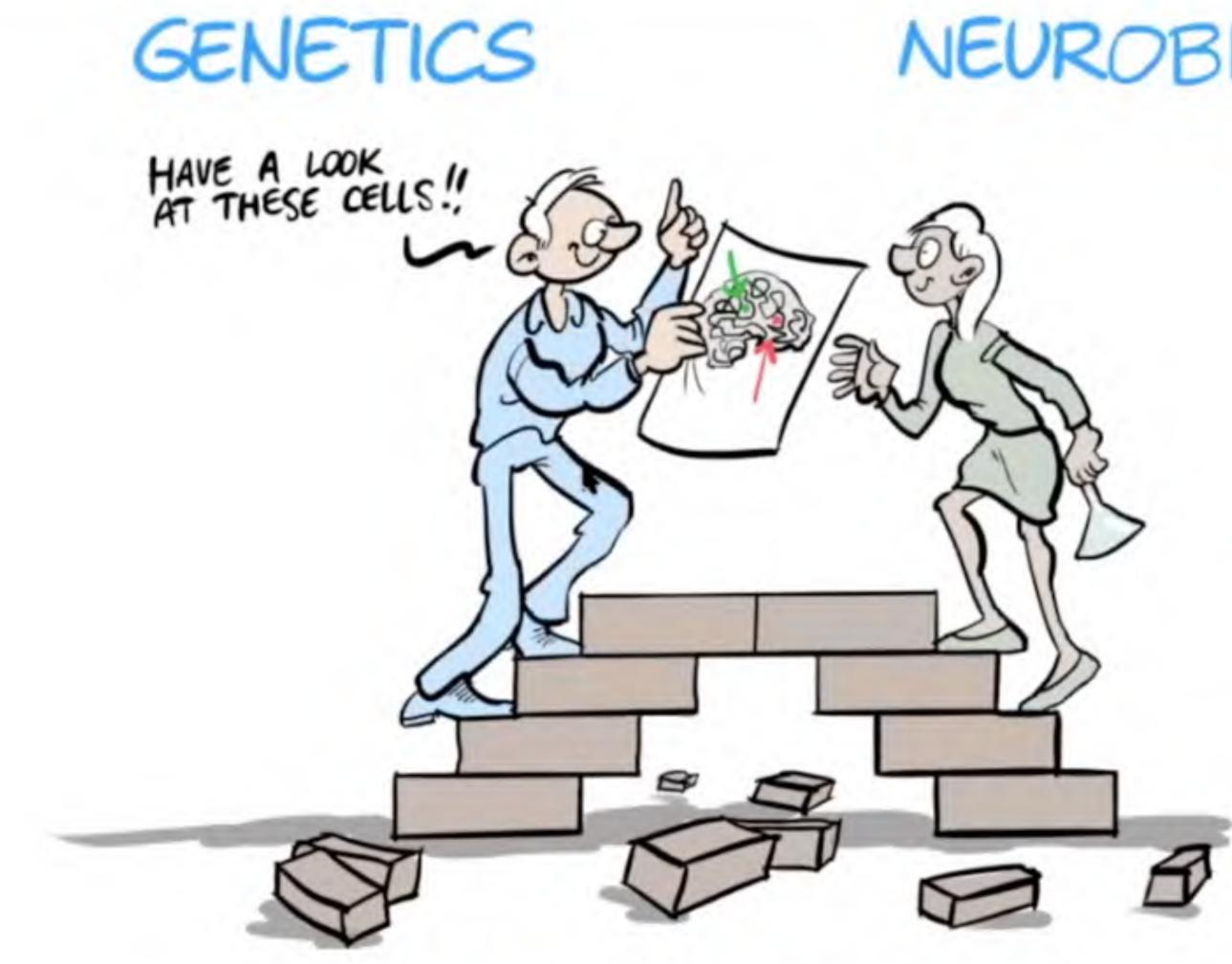


The loci identified by GWAS of substance use disorders will continue to grow exponentially



Credit: Danielle Posthuma, Tom and @BRAINSCAPES1

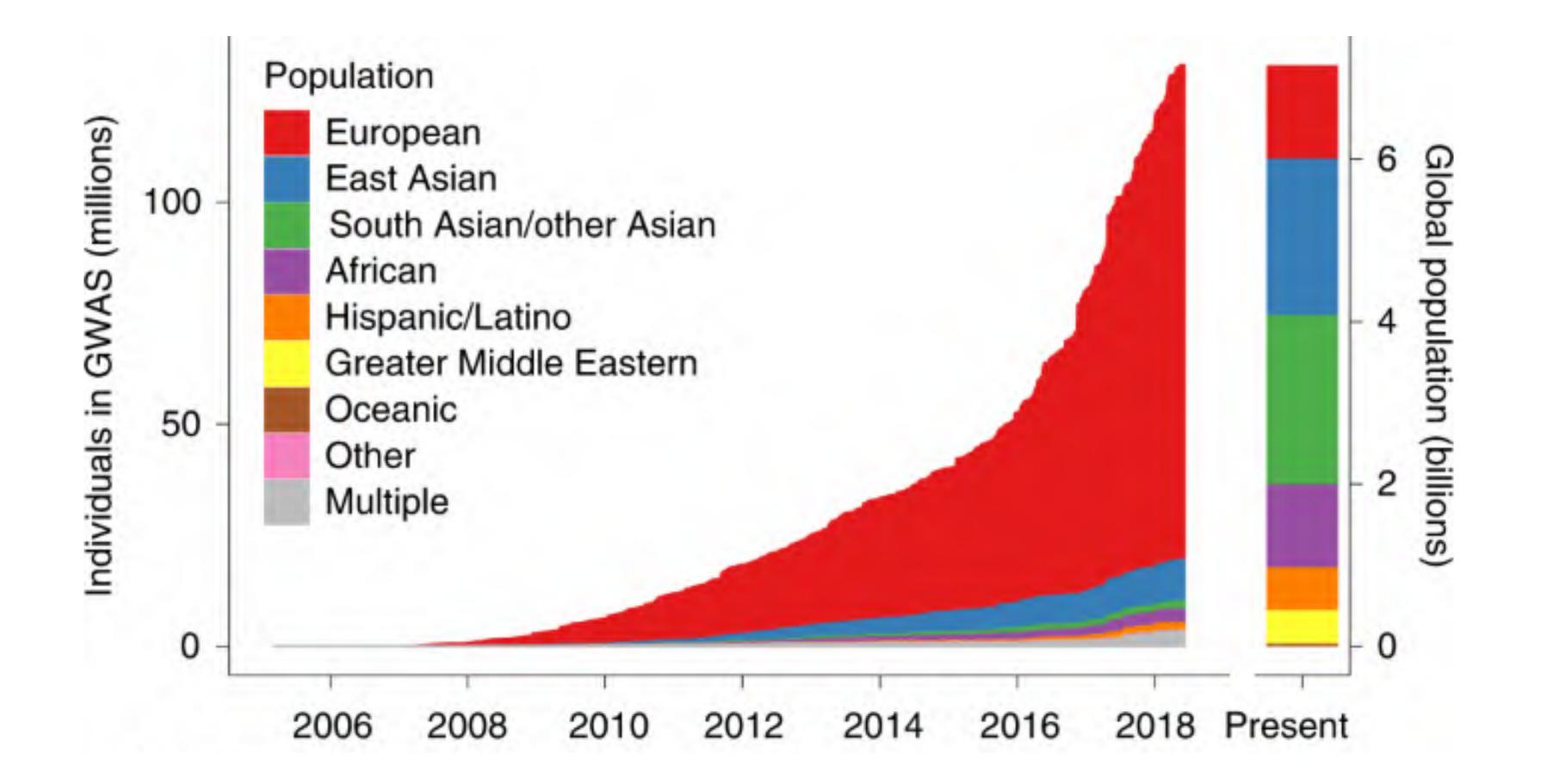






Credit: Danielle Posthuma, Tom and @BRAINSCAPES1

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



Martin et al, *Nature Genetics*, 2019

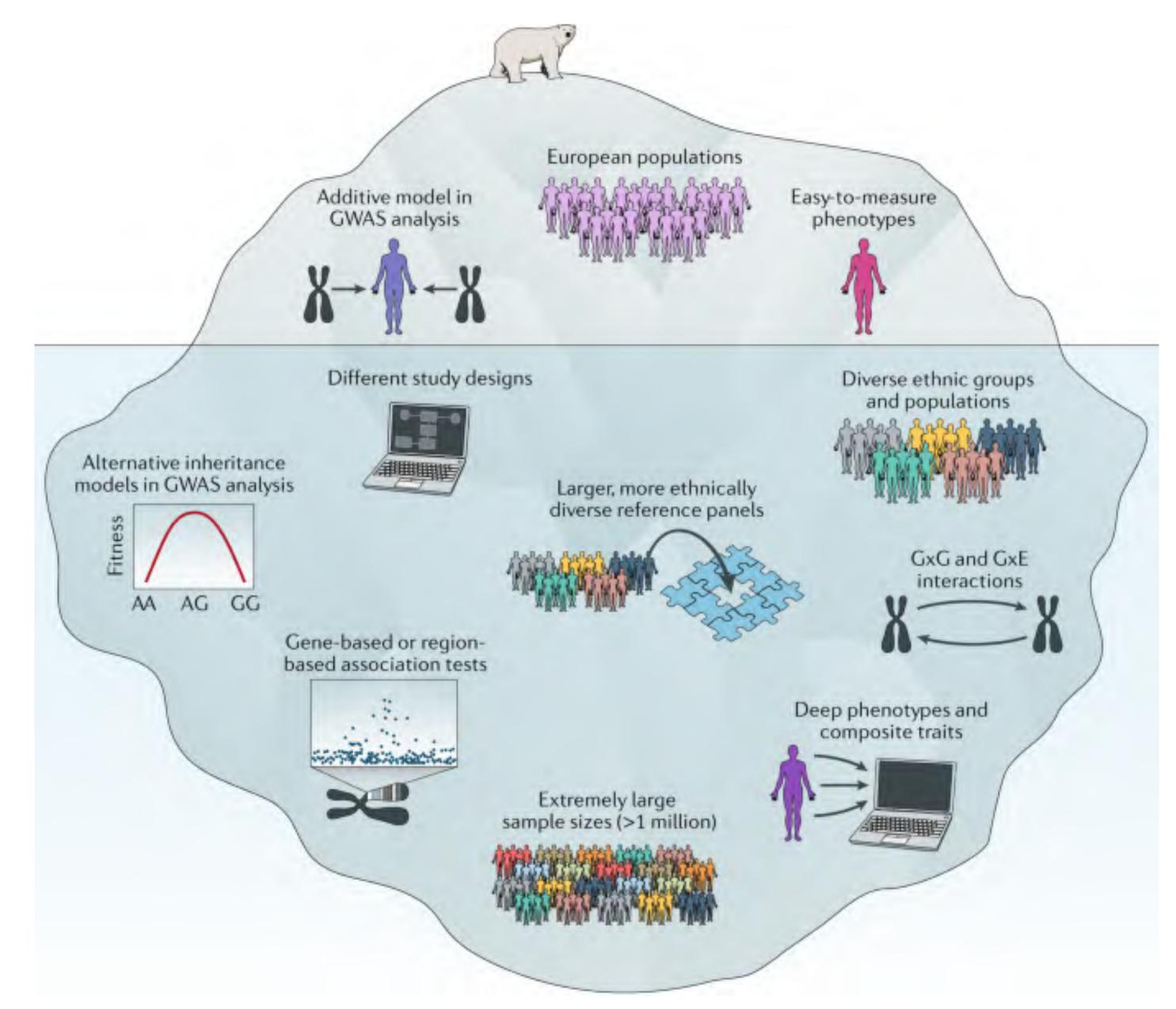






Latin American Genomics Consortium





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



Sarah Elson



Pierre Fontanillas



Dana Hancock

Ke Xu



Justice



Arpana Agrawal

ΝH 23andMe **National Institute** on Drug Abuse **Psychiatric Genomics Consortium**



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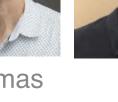


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Maria

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Travis Mallard



Jordan Smoller



Sylvanus Toikumo



Rachel Kember

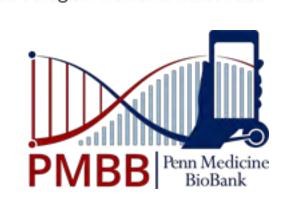
Hank Kanzler

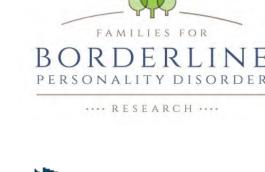






























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