Substance use disorder genetics projects in Thailand and in the US

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Work in Thailand, 2000-2020

- Opioid use disorder in a Northern Thailand Hill tribe population
- D43 international training grants
- Studies of substance use disorders in Bangkok and Chiang Mai

Contents lists available at ScienceDirect

Addictive Behaviors

Short Communication

Inter-rater reliability and concurrent validity of DSM-IV opioid dependence in a Hmong isolate using the Thai version of the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA)

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ARTICLE INFO

Keywords:
Opioid dependence
MINI
SSADDA
Reliability
Validity
Hmong

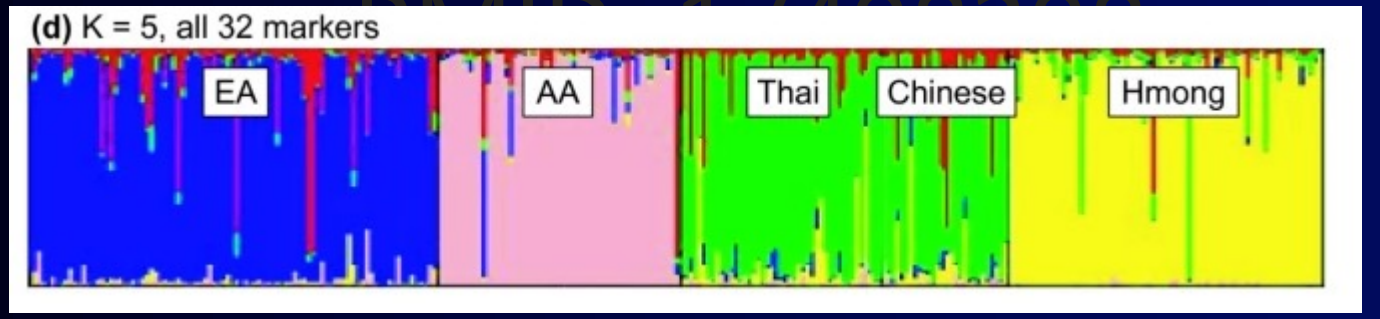
ABSTRACT

Because isolated populations offer relative genetic and environmental homogeneity, they are important resources for mapping genes for complex traits. Reliable and valid phenotypic characterization of the disease in the population studied is essential. We examined diagnostic reliability and concurrent validity of DSM-IV opioid dependence (OD) in a Hmong population in Thailand with historically high rates of opium (and heroin) use.

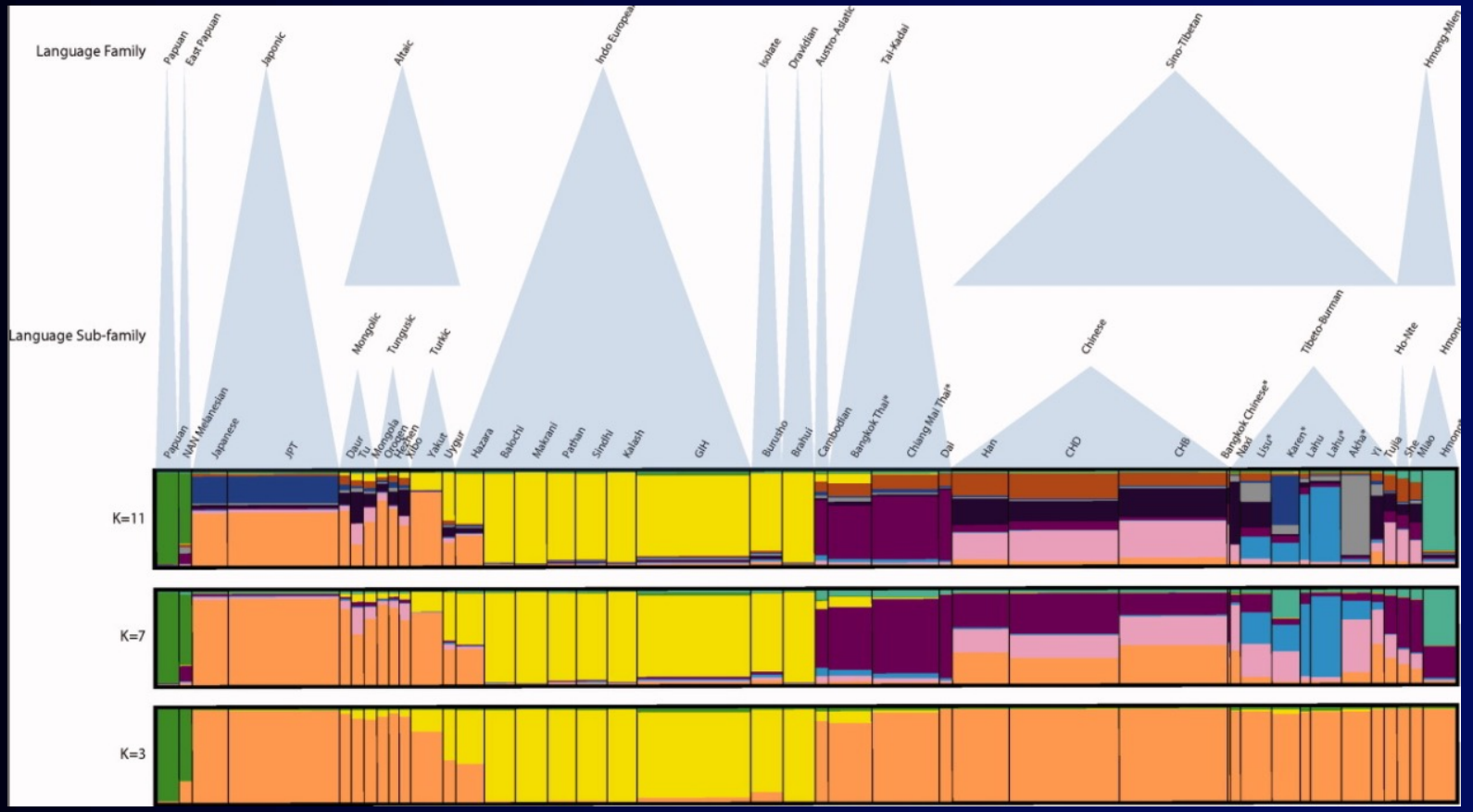
578 Thai-speaking Hmong individuals were assessed for lifetime OD, using Thai versions of both the Semi-Structured Assessment for Drug Dependence and Alcoholism (Thai SSADDA) and the Mini-Neuropsychiatric Interview (Thai MINI; adapted for lifetime diagnoses). In a subsample of 123 individuals, two raters interviewed each subject independently within a 2-week period. Chance-corrected agreement on the OD diagnosis was assessed between raters and instruments.

Results showed excellent agreement for the DSM-IV diagnosis of OD both for the SSADDA ($\kappa = 0.97$) and MINI ($\kappa = 1.00$) and between the SSADDA and MINI ($\kappa = 0.97$).

Consistent with reliability assessments of English versions, our data demonstrate high reliability for Thai versions of the SSADDA and MINI in the diagnosis of OD. The high concordance between instruments supports the concurrent validity of the diagnosis. Either interview provides reliable, valid OD diagnoses in Thai-speaking Hmong individuals.



PMID: 17498298
(2007)



PMID: 20979205
(2011)

Hill Tribe conclusions

- We ended up with participation from 4 of the 5 families… about 200 subjects in all
- But the fifth family was the one with the greatest concentration of OUD and – not coincidentally – the greatest involvement in trafficking
- We translated the SSADDA into Thai and established basic population genetics characteristic of Thai and minority Hill Tribe populations…
- And then we decided to continue our work in outbred populations, in Bangkok, and with a focus on methamphetamine dependence rather than opioid dependence

Work in Thailand, 2000-2020

- Opioid use disorder in a Northern Thailand Hill tribe population
- D43 international training grants: So far, 2x5yrs
- Just submitted a competing renewal application (July 2022)
- Studies of substance use disorders in Bangkok and Chiang Mai

Numerous trainees, several of whom are current key collaborators in Thailand

Drug and Alcohol Dependence 107 (2010) 196–201

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journal hom

Adolescent cannabis use incre

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Addiction

RESEARCH REPOR

Clinical feat
paranoia an
DBH-1021C

Rasmon Kalayasiri[1],
Robert T. Malison[3]

Department of Psychiatry, Faculty
Ministry of Public Health, Pathumt
Genetics of Cancer and Human I

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Drug

Risk factor
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Rasmon Kalayasiri[a], He
Ralitza Gueorguie
Lindsay Farrer

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Received 15 June 2005;

ORIGINAL RESEARCH

Sex Differences in Methamphetamine Use and Dependence in a Thai Treatment Center

Teerayuth Rungnirundorn, MD, Viroj Verachai, MD, Joel Gelernter, MD, Robert T. Malison, MD, and Rasmon Kalayasiri, MD

Background and Objective: Males and females who use methamphetamine (MA) differ in sociodemographics, MA diagnoses, comorbidities, and brain activity. The objective of this study was to investigate sex differences in the characteristics of MA use and dependence in patients at a Thai substance treatment center.

Methods: Demographic, MA use, and diagnostic data for 782 MA users were obtained by using the Semi-Structured Assessment for Drug Dependence and Alcoholism—Thai version. Categorical comparisons of males (n = 413, 53%) and females (n = 369, 47%) were made by chi-square test. Factors significantly differentiating men and women with respect to MA-dependence were identified by logistic regression analysis controlling for demographic, diagnostic, and MA use variables.

withdrawal-related hypersomnia (77.2% vs 64.8%; $\chi^2_1 = 14.5$, $P < 0.001$), fatigue (77.5% vs 70.3%; $\chi^2_1 = 5.2$, $P = 0.02$), and psychomotor retardation (64.5% vs 57.0%; $\chi^2_1 = 4.5$, $P = 0.03$). Similarly, females had heavier (eg, largest daily amount [$\chi^2_1 = 12.4$, $P < 0.001$), more frequent ($\chi^2_1 = 5.1$, $P = 0.02$]) and greater lifetime episodes of MA use ($\chi^2_1 = 24.1$, $P < 0.001$) than males. After controlling for such variables by logistic regression, being female remained a significant factor influencing the occurrence of MA-dependence (odds ratio [OR] 2.7, 95% confidence interval [CI] 1.8–4.1, $P < 0.001$). Shared associated factors (or comorbidities) for MA-dependence in both sexes included nicotine dependence (in males: OR 4.1, 95% CI 2.4–7.0, $P < 0.001$; and in females: OR 2.4, 95% CI 1.3–4.4, $P = 0.007$), greater lifetime episodes of MA use (in males: OR 3.5, 95% CI 1.9–6.4,

Work in Thailand, 2000-2020

- Opioid use disorder in a Northern Thailand Hill tribe population
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Thanyarak Hospital, 2001…

Also recruiting on our METH Genetics R01

R01: Genetics of Methamphetamine Dependence in a Thai Population

- Collect 2000 subjects in Bangkok, mostly Thanyarak – 1000 severely-affected cases, 1000 exposed controls
- Assess with full version of Thai SSADDA (Semi-structured Assessment of Drug Dependence and Alcoholism)
  - This is a very extensive assessment! Covers SUDs, major psychiatric traits, and medical hx
- Genomewide association study

SSADDA training in Bangkok

Yari Nunez, lead instructor

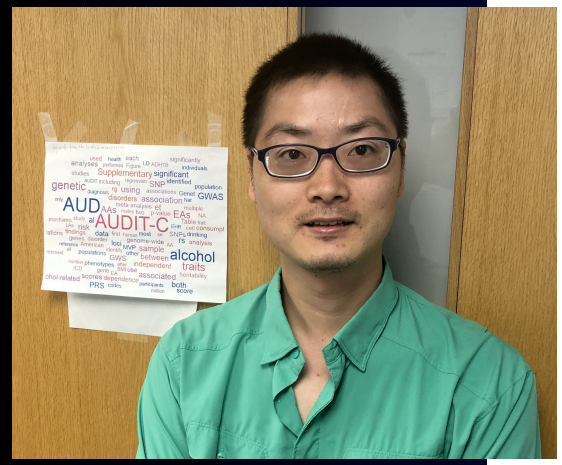
Fully assessed subjects recruited as of January 2022

Site	Cases	Controls	Total
Chulalongkorn (BKK)	2326	849	3175
Suan Prung (CNX)	291	1338	1629*
Total	**2617**	**2187**	**4804**

Why GWAS?

- Genomewide association study = GWAS
- GWAS is a method to search the entire genome for risk variants
- Hypothesis-free
- Findings robust
- Best application to find genes from complex traits
- GWAS results can be used to explore biology in detail

Alcohol trait GWAS – 2018



Genomewide Association Study of Alcohol Dependence and Related Traits in a Thai Population

Joel Gelernter, Hang Zhou, Yaira Z. Nuñez, Apiwat Mutirangura, Robert T. Malison, and Rasmon Kalayasiri

Background: Alcohol use (both quantity and dependence) is moderately heritable, and genomewide association studies (GWAS) have identified risk genes in European, African, and Asian populations. The most reproducibly identified risk genes affect alcohol metabolism. Well-known functional variants at the gene encoding alcohol dehydrogenase B and other alcohol dehydrogenases affect risk in European and African ancestry populations. Similarly, variants mapped to these same genes and a well-known null variant that maps to the gene that encodes aldehyde dehydrogenase 2 (*ALDH2*) also affect risk in various Asian populations. In this study, we completed the first GWAS for 3 traits related to alcohol use in a Thai population recruited initially for studies of methamphetamine dependence.

Methods: All subjects were evaluated with the Thai version of the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA). A total of 1,045 subjects were available for analysis. Three traits were analyzed: flushing, maximum number of alcoholic beverages consumed in any lifetime 24-hour period ("MAXDRINKS"), and DSM-IV alcohol dependence criterion count. We also conducted a pleiotropy analysis with major depression, the only other psychiatric trait where summary statistics from a large-scale Asian-population GWAS are available.

Results: All 3 traits showed genomewide significant association with variants near *ALDH2*, with significance ranging from 2.01×10^{-14} (for flushing; lead single nucleotide polymorphism (SNP) *PTPN11** rs143894582) to $p_{meta} = 5.80 \times 10^{-10}$ (for alcohol dependence criterion count; lead SNP rs149212747). These lead SNPs flank rs671 and span a region of over a megabase, illustrating the need for prior biological information in identifying the actual effect SNP, rs671. We also identified significant pleiotropy between major depression and flushing.

Conclusions: These results are consistent with prior findings in Asian populations and add new information regarding alcohol use-depression pleiotropy.

Key Words: Genomewide Association Study, *ALDH2*, Alcohol Dependence, Flushing Reaction, Depression.

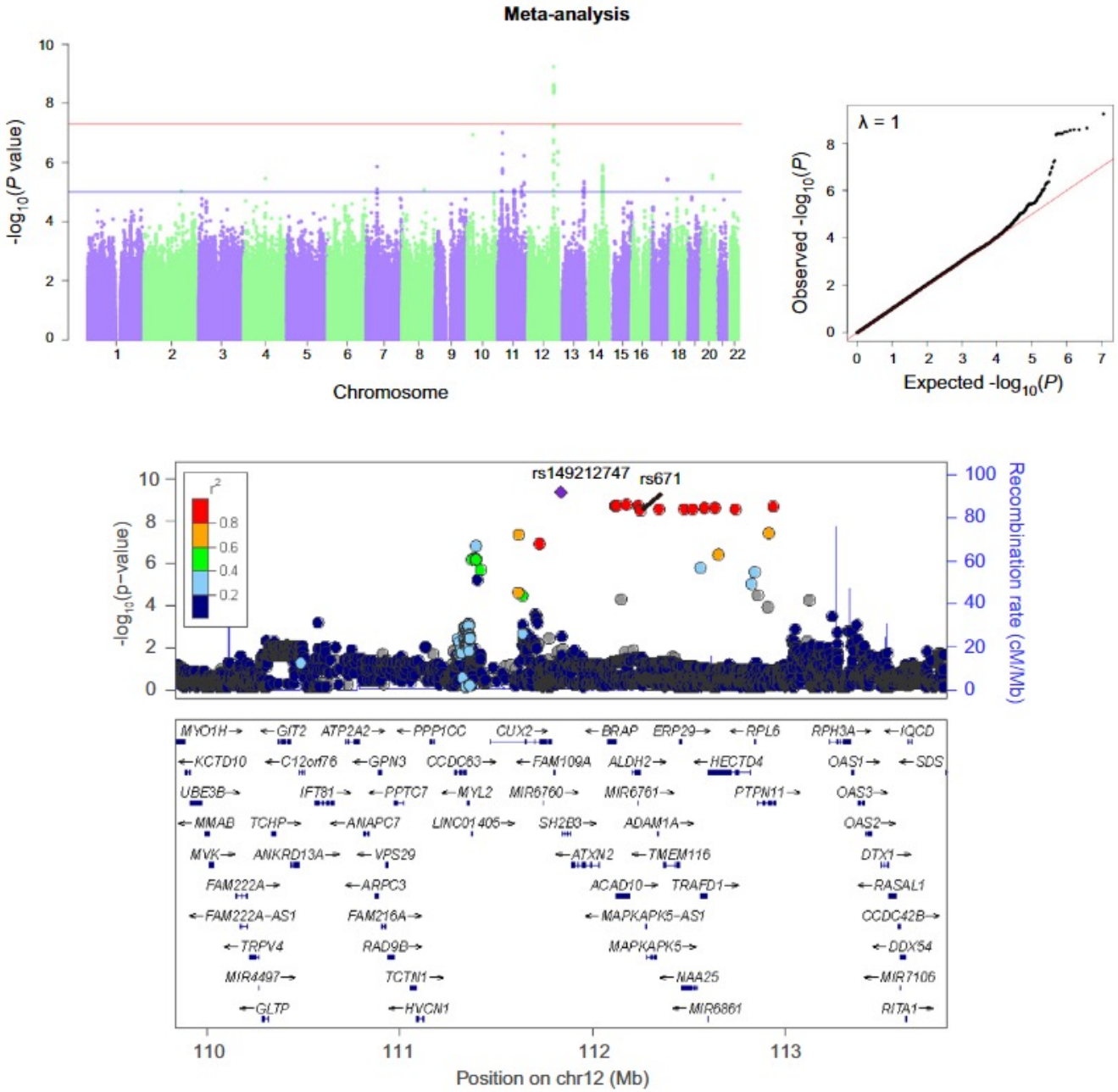
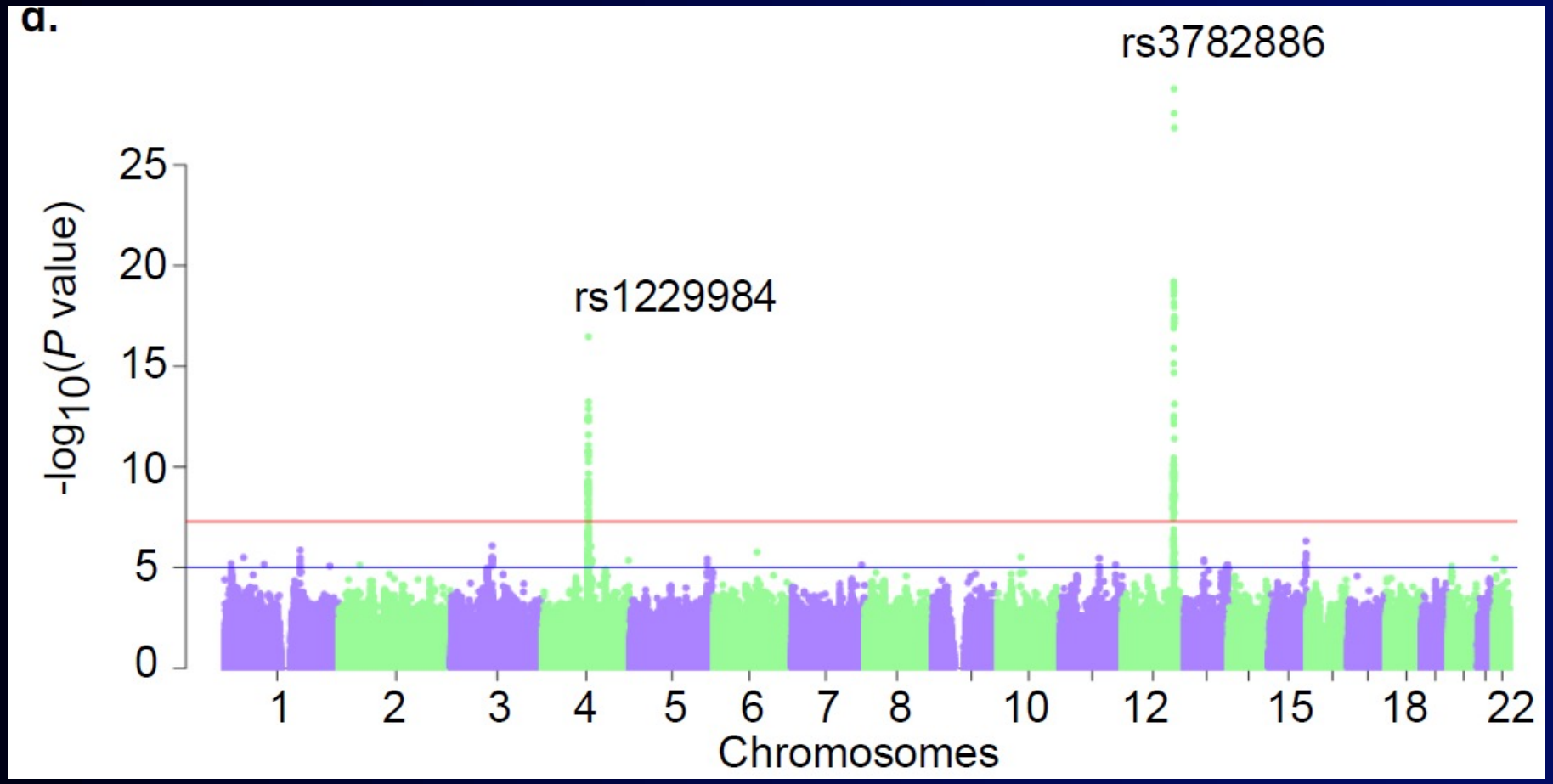


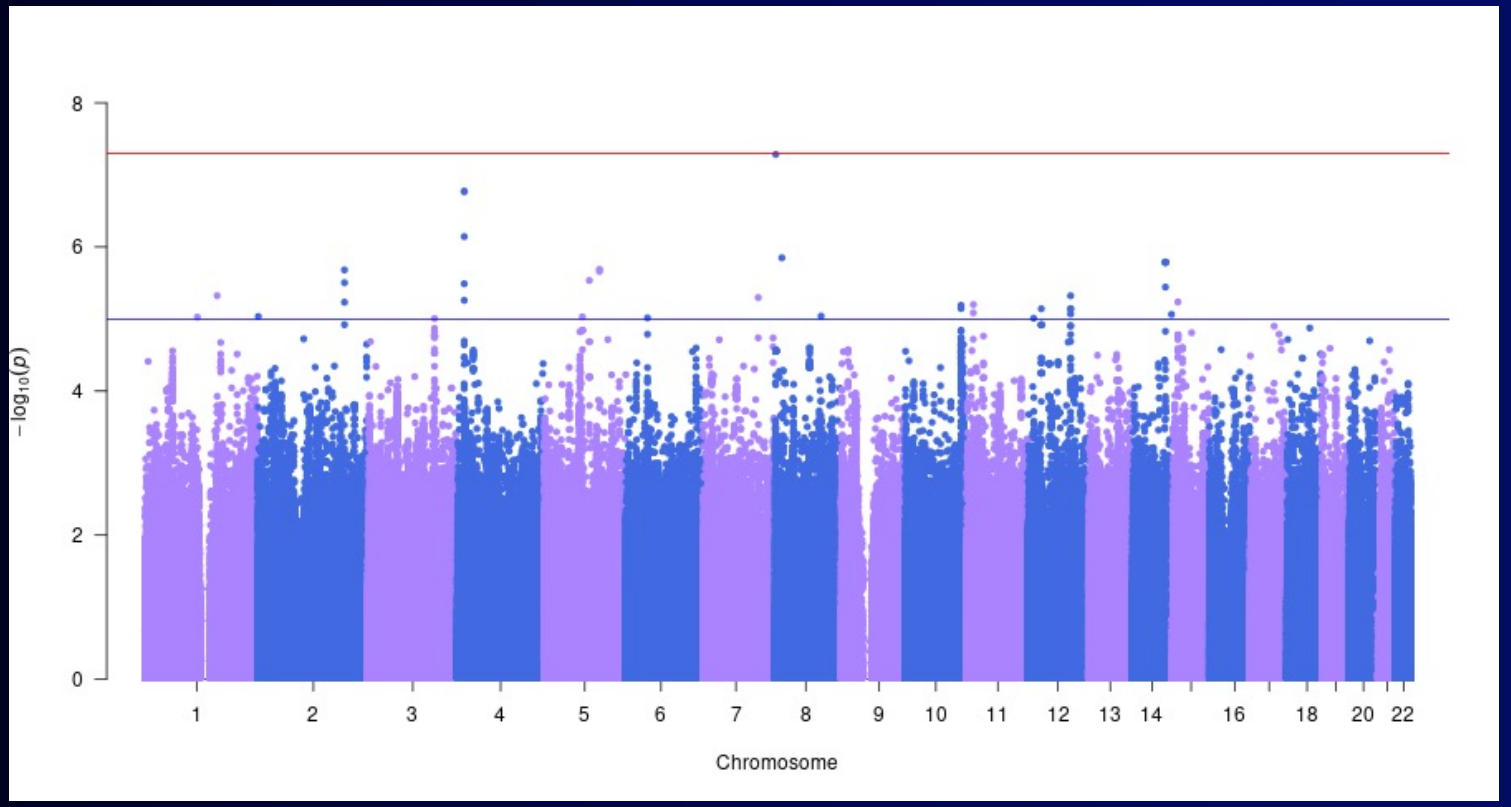
Fig. 2. Manhattan and QQ plots (above) and regional Manhattan plot (below) for alcohol dependence symptom criterion count (meta-analysis). (Results for the individual samples are shown separately in Fig. S5.) Regional Manhattan plot shows locations of the lead SNP (rs149212747) and functional variant rs671.

Zhou et al 2022 NPP: Largest-yet Asian AUD GWAS meta-analysis, including many new subjects from our Thai study



Methamphetamine dependence in Thailand – preliminary 2022 GWAS results

Lead SNP maps to *DLGAP2*, a gene with previously reported association to schizophrenia i*n an Asian sample*



Analysis: Hang Zhou (case=2466, control=2151, total=4617)

Entrez Gene Summary for DLGAP2 Gene

The product of this gene is a membrane-associated protein that may play a role in synapse organization and signalling in neuronal cells. This gene is biallelically expressed in the brain, however, only the paternal allele is expressed in the testis (PMID:18055845). Alternatively spliced transcript variants encoding different isoforms have been identified. [provided by RefSeq, Jun 2014]

Work in Thailand so far

- Most detailed work to date on population genetics of minority Thai populations
- Translation of two modern psychiatric assessment instruments into Thai – SSADDA and the MIND Biobank Instrument
- Largest Asian sample collected to date, ascertained carefully, and informative for substance use disorder genetics and first published SUD GWASs in that population
- Phenotype studies of methamphetamine dependence and psychosis in a deeply-phenotyped sample of >5000 subjects
- And most important, training of a cadre of outstanding independent researchers in Bangkok (Chulalongkorn Faculty of Medicine and Chiang Mai (Suan Prung Hospital) in psychiatric genetics and neuroimaging who continue to rpess forward with their research

Work in the Million Veteran Program sample: the MVP as a gene-mapping resource

- Large sample size (and still growing) - >825,000
- Good representation from non-Europeans
- Mostly male – about 93%; lower SES
- EHR, including some longitudinal repeated measures from EHR and data from self-report surveys
- Relatively old and sick (they have used VA health services) – 55% between 50-69 y/o

Some of these are clear advantages compared to other biobanks.

The Genetic Architecture of Cannabis Use Disorder

- An important secular trend: recently numerous state governments in the US have legalized both medical (mostly without demonstrated efficacy) and recreational use.
- Legalization results in increased cannabis use and dependence
- The consequences of this action are not being recognized
- And while the current administration has just proposed to gradually remove nicotine from tobacco products, there has been no analogous effort to remove THC from cannabis.

Cannabis-related phenot

- Cannabis related behaviors range from us
  "medicinally," to habitual use, to CanUD.
- There are substantial negative health outc
  cancers associated with inhaling products
  in cognitive capacity and motivation.
- Outcomes include decreased productivity
  intoxication.
- *The full range of risks and negative outcome*
  widely, which is surprising considering the w
  making cannabis readily available.
- Pleiotropy analysis and Mendelian random
  investigate genetic relationships with risk f
  outcomes to which CanUD might be causa
  such analyses was a goal of the present stu

WSJ NEWS EXCLUSIVE | WORK & LIFE

Positive Drug Tests Among U.S. Workers Hit Two-Decade High

Fewer employers tested applicants for marijuana last year than in 2020 as companies grappled with nationwide labor shortages

In the U.S., 18 states plus the District of Columbia have legalized recreational use of marijuana.

PHOTO: STEVE HELBER/ASSOCIATED PRESS

By Will Feuer Follow

Updated March 30, 2022 8:32 am ET

The percentage of working Americans testing positive for drugs hit a two-decade high last year, driven by an increase in positive marijuana tests, as businesses might have loosened screening policies amid nationwide labor shortages.

Of the more than six million general workforce urine tests that Quest Diagnostics Inc., one of the country's largest drug-testing laboratories, screened for marijuana last year, 3.9% came back positive, an increase of more than 8% from 2020, according to Quest's annual drug-testing index.

That figure is up 50% since 2017. Since then, the number of states that legalized marijuana for recreational use grew to 18 from eight, plus the District of Columbia.

Despite the increase in positivity last year, fewer companies tested their employees for THC, the substance in marijuana primarily

Prior work: Several GWAS; PGC GWAS was the largest

- Cannabis Use Disorder
  - Case control status based on ICD codes or DSM criteria for cannabis dependence OR cannabis abuse.
- 20 Samples
  - 20,916 cases, 36,316 controls

A large-scale genome-wide association study meta-analysis of cannabis use disorder

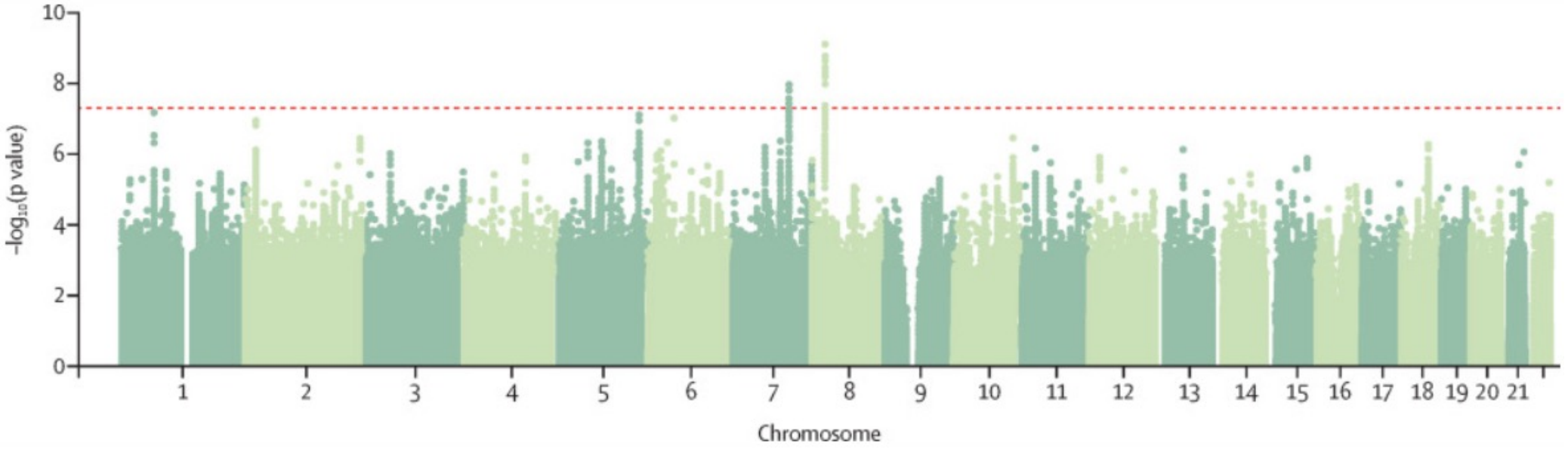
Emma C Johnson*, Ditte Demontis*, Thorgeir E Thorgeirsson*, Raymond K Walters, Renato Polimanti, Alexander S Hatoum, Sandra Sanchez-Roige, Sarah E Paul, Frank R Wendt, Toni-Kim Clarke, Dongbing Lai, Gunnar W Reginsson, Hang Zhou, June He, David A A Baranger, Daniel F Gudbjartsson, Robbee Wedow, Daniel E Adkins, Amy E Adkins, Jeffry Alexander, Silviu-Alin Bacanu, Tim B Bigdeli, Joseph Boden, Sandra A Brown, Kathleen K Bucholz, Jonas Bybjerg-Grauholm, Robin P Corley, Louisa Degenhardt, Danielle M Dick, Benjamin W Domingue, Louis Fox, Alison M Goate, Scott D Gordon, Laura M Hack, Dana B Hancock, Sarah M Hartz, Ian B Hickie, David M Hougaard, Kenneth Krauter, Penelope A Lind, Jeanette N McClintick, Matthew B McQueen, Jacquelyn L Meyers, Grant W Montgomery, Ole Mors, Preben B Mortensen, Merete Nordentoft, John F Pearson, Roseann E Peterson, Maureen D Reynolds, John P Rice, Valgerdur Runarsdottir, Nancy L Saccone, Richard Sherva, Judy L Silberg, Ralph E Tarter, Thorarinn Tyrfingsson, Tamara L Wall, Bradley T Webb, Thomas Werge, Leah Wetherill, Margaret J Wright, Stephanie Zellers, Mark J Adams, Laura J Bierut, Jason D Boardman,

PGC GWAS

CHRNA2 Gene - Cholinergic Receptor Nicotinic Alpha 2 Subunit

FOXP2 Gene - Forkhead Box P2

- Cannabis Use Disorder – 2 GWS loci, near *FOXP2* and *CHRNA2*



Johnson, Emma C., Ditte Demontis, Thorgeir E. Thorgeirsson, Raymond K. Walters, Renato Polimanti, Alexander S. Hatoum, Sandra Sanchez-Roige et al. "A large-scale genome-wide association study meta-analysis of cannabis use disorder." *The Lancet Psychiatry* 7, no. 12 (2020): 1032-1045.

The Million Veteran Program

- PGC study, 2 GWS loci from all the world's supply of cannabis use disorder subjects to that date; published in Lancet Psych (IF 27)
- …MVP provided the opportunity to approximately *double* the number of reported cannabis use disorder (CanUD) cases.

Current (MVP) Cannabis Use Disorder meta-analysis

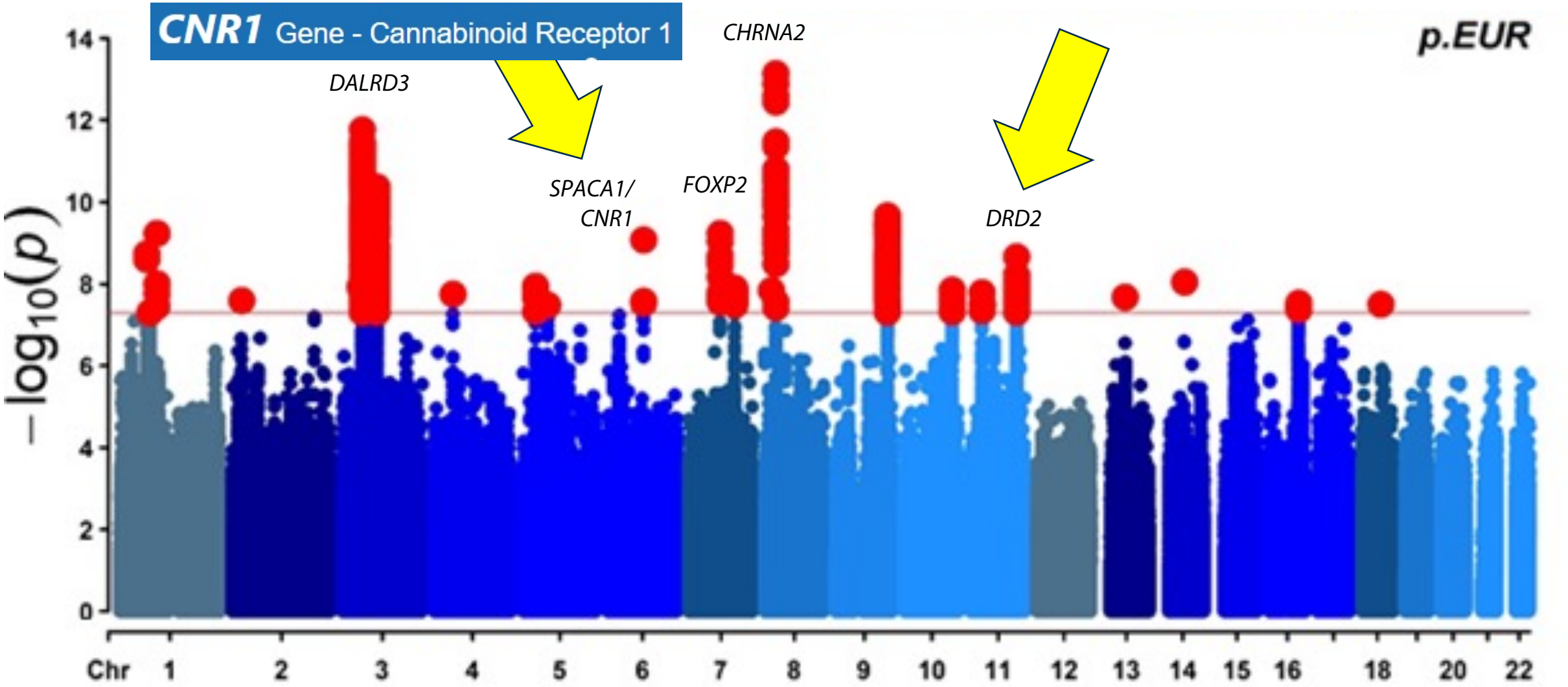
Levey et al – to be submitted soon

- New additions of an updated iPSYCH cohort, Yale Penn, MGH/Partners Biobank, and MVP.
- For meta with previous PGC analysis: Leave-one-out analysis for us, subtracting iPSYCH from the PGC sumstats.
- *A cannabis use disorders phenotype was derived from the VA electronic health records for the MVP portion of the analysis.*

Daniel F. Levey, Marco Galimberti, Joseph Deak, Frank Wendt, Arjun Bhattacharya, Dora Koller, Kelly Harrington, Rachel Quaden, Emma Johnson, Megan Cooke, Veera M. Rajagopal, Stefany L. L. Empke, Hang Zhou, Yaira Nunez, Henry R. Kranzler, Howard Edenberg, Arpana Agrawal, Jordan Smoller, Ditte Demontis, VA Million Veteran Program, J Michael Gaziano, Michael J Gandal, Renato Polimanti, Murray B. Stein, Joel Gelernter

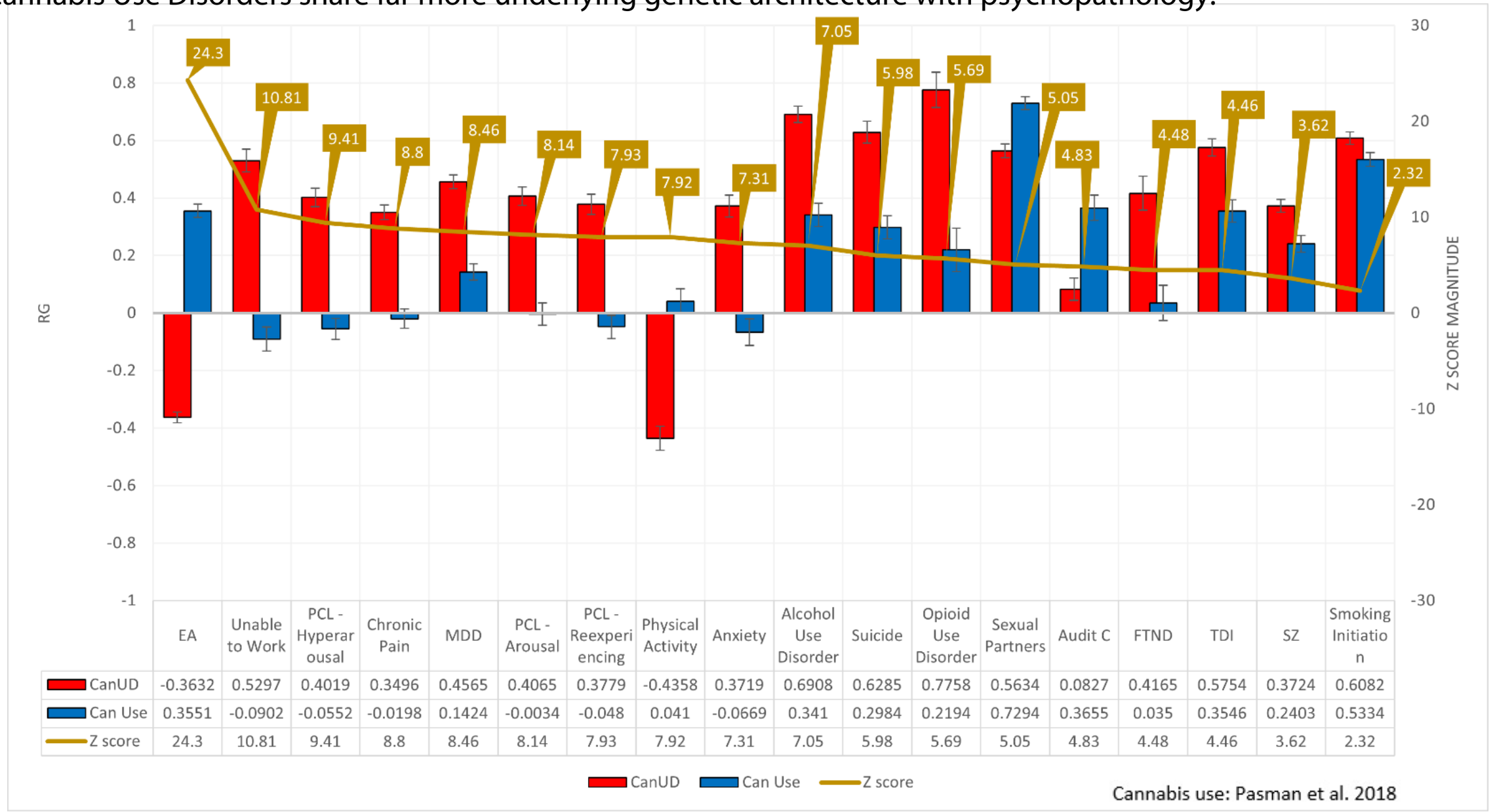
42,281 cases and 843,744 controls
22 Genomic risk loci
25 Independent lead SNPs

Lead SNP is near *CHRNA2*, identical to prior iPSYCH study
SNP near *FOXP2* remains GWS
20 additional novel loci



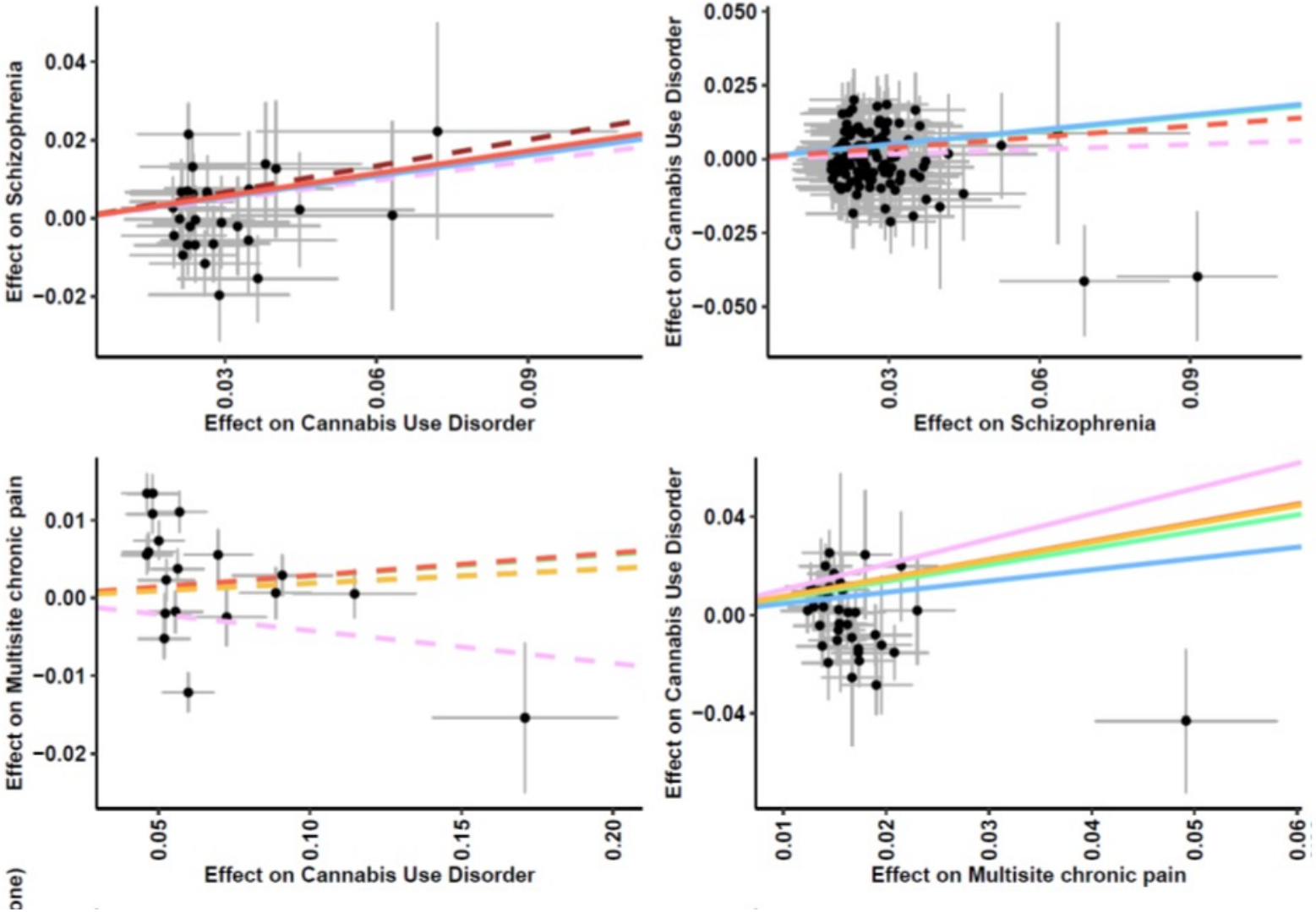
Comparison of genetic correlations between Cannabis Use (Blue) to Cannabis Use Disorders (Red) and other traits.

Cannabis Use Disorders share far more underlying genetic architecture with psychopathology.

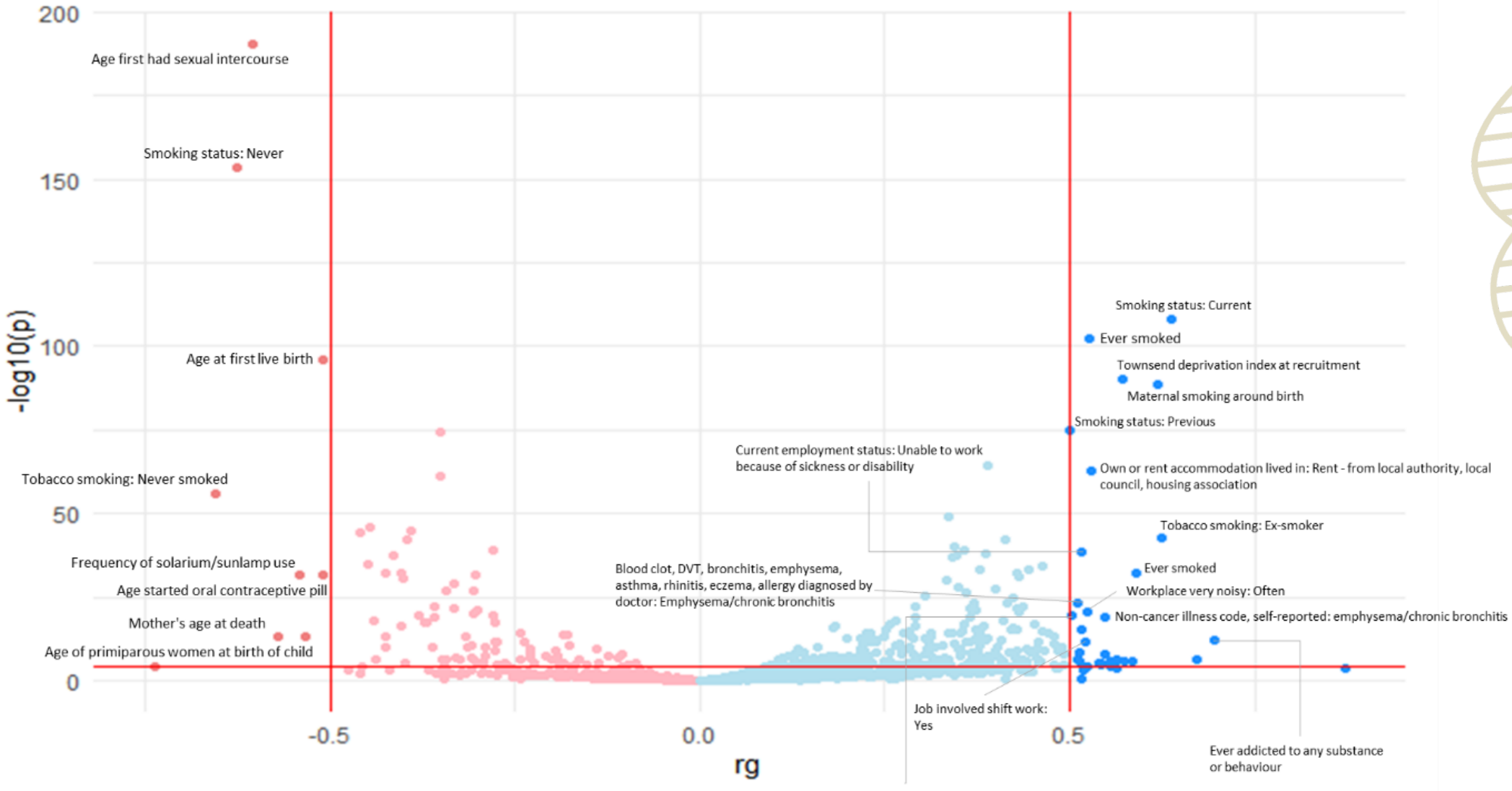


	EA	Unable to Work	PCL - Hyperarousal	Chronic Pain	MDD	PCL - Arousal	PCL - Reexperiencing	Physical Activity	Anxiety	Alcohol Use Disorder	Suicide	Opioid Use Disorder	Sexual Partners	Audit C	FTND	TDI	SZ	Smoking Initiation
CanUD	-0.3632	0.5297	0.4019	0.3496	0.4565	0.4065	0.3779	-0.4358	0.3719	0.6908	0.6285	0.7758	0.5634	0.0827	0.4165	0.5754	0.3724	0.6082
Can Use	0.3551	-0.0902	-0.0552	-0.0198	0.1424	-0.0034	-0.048	0.041	-0.0669	0.341	0.2984	0.2194	0.7294	0.3655	0.035	0.3546	0.2403	0.5334
Z score	24.3	10.81	9.41	8.8	8.46	8.14	7.93	7.92	7.31	7.05	5.98	5.69	5.05	4.83	4.48	4.46	3.62	2.32

Causal inference by MR. SCZ: bidirectional. Chronic pain: pain->CanUD only

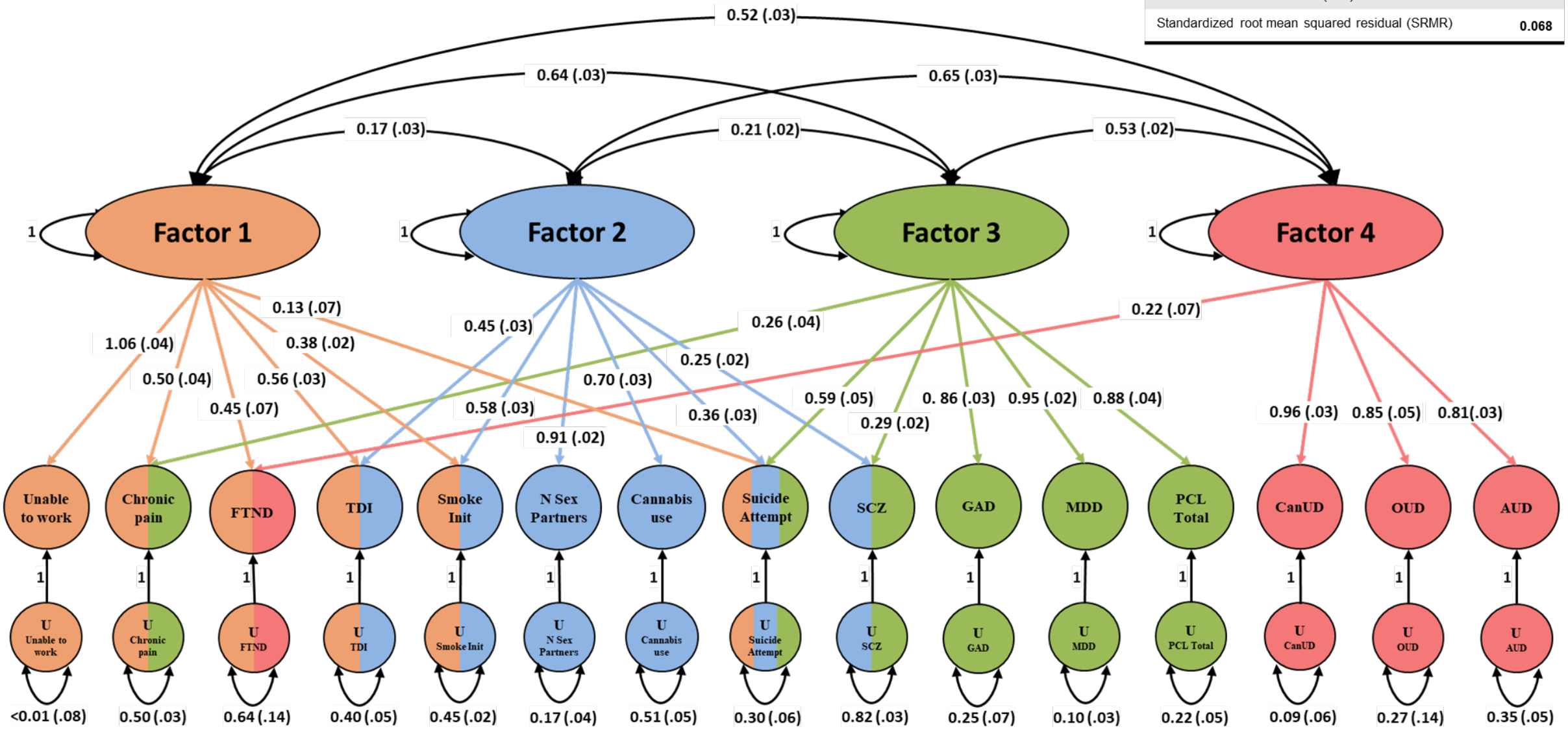


Multi-trait rG volcano plot calculated using 1335 traits



Joseph Deak

Confirmatory Factor Analysis (CFA) Model Fit	
Comparative fit index (CFI)	0.913
χ^2 (degrees of freedom)	1397.505
Akaike information criterion (AIC)	1483.505
Standardized root mean squared residual (SRMR)	0.068



Functional Impairment | Impulsivity/Risk Taking | Psychopathology | Substance Dependence

Conclusions

- Largest genetic study to date of Cannabis Use Disorders.
  - 22 loci (up from 2 discovered in the previous published study).
  - **New data from MVP more than doubles available cases for analysis!**

- Comparison of cannabis use and dependence
  - Cannabis use and cannabis dependence have different sets of correlations (Rg) with other traits (which mirrors what we showed previously with alcohol use disorder vs alcohol quantity/frequency traits).
  - Overlap with psychiatric illness – including PTSD -- substantially greater in those with CanUD.

- Context
  - Genomic structural equation model allows greater contextual understanding of GWASed traits.
  - Cannabis dependence fits a factor with other traits of dependence.

Yale University
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Renato Polimanti
Hang Zhou
Yaira Z. Nunez
Joseph Deak
Stefany L.L Empke
Marco Galimberti
Hongyu Zhao
Frank Wendt
Dora Koller
John Concato
Ning Sun

Vanderbilt University
Julia M. Sealock
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PGC-SUD group
Howard J. Edenberg
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Emma C. Johnson

PTSD, CanUD, SSRI Use

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Kelly Harrington
Rachel Quaden
Jordan Smoller

Yale University
School of Medicine

NIH
National Institutes of Health

And Many More
(please refer to publications)

The MVP for Gene Mapping in Psychiatric Traits

- **Genetics of SSRI Antidepressant Use and Implications for COVID19 Risk**

Many possible treatments for COVID19 were evaluated, starting from early in the pandemic

- Early treatment studies generally looked at drug repurposing
- Some considered fluvoxamine, a selective serotonin reuptake inhibitor (SSRI)
- It is also an activator of the sigma-1 receptor which decreases inflammation via reducing endoplasmic reticulum stress.
- Mouse model: fluvoxamine administration reduced mortality predominantly through sigma-1 activation.
- Leading to a key 2020 publication…

JAMA | Preliminary Communication

Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19
A Randomized Clinical Trial

JAMA. 2020;324(22):2292-2300. doi:10.1001/jama.2020.22760
Published online November 12, 2020.

Eric J. Lenze, MD; Caline Mattar, MD; Charles F. Zorumski, MD; Angela Stevens, BA; Julie Schweiger; Ginger E. Nicol, MD; J. Philip Miller, AB; Lei Yang, MPH, MSIS; Michael Yingling, MS; Michael S. Avidan, MBBCh; Angela M. Reiersen, MD, MPE

IMPORTANCE Coronavirus disease 2019 (COVID-19) may lead to serious illness as a result of an excessive immune response. Fluvoxamine may prevent clinical deterioration by stimulating the σ-1 receptor, which regulates cytokine production.

OBJECTIVE To determine whether fluvoxamine, given during mild COVID-19 illness, prevents clinical deterioration and decreases the severity of disease.

Visual Abstract
Editor's Note page 2300
Supplemental content

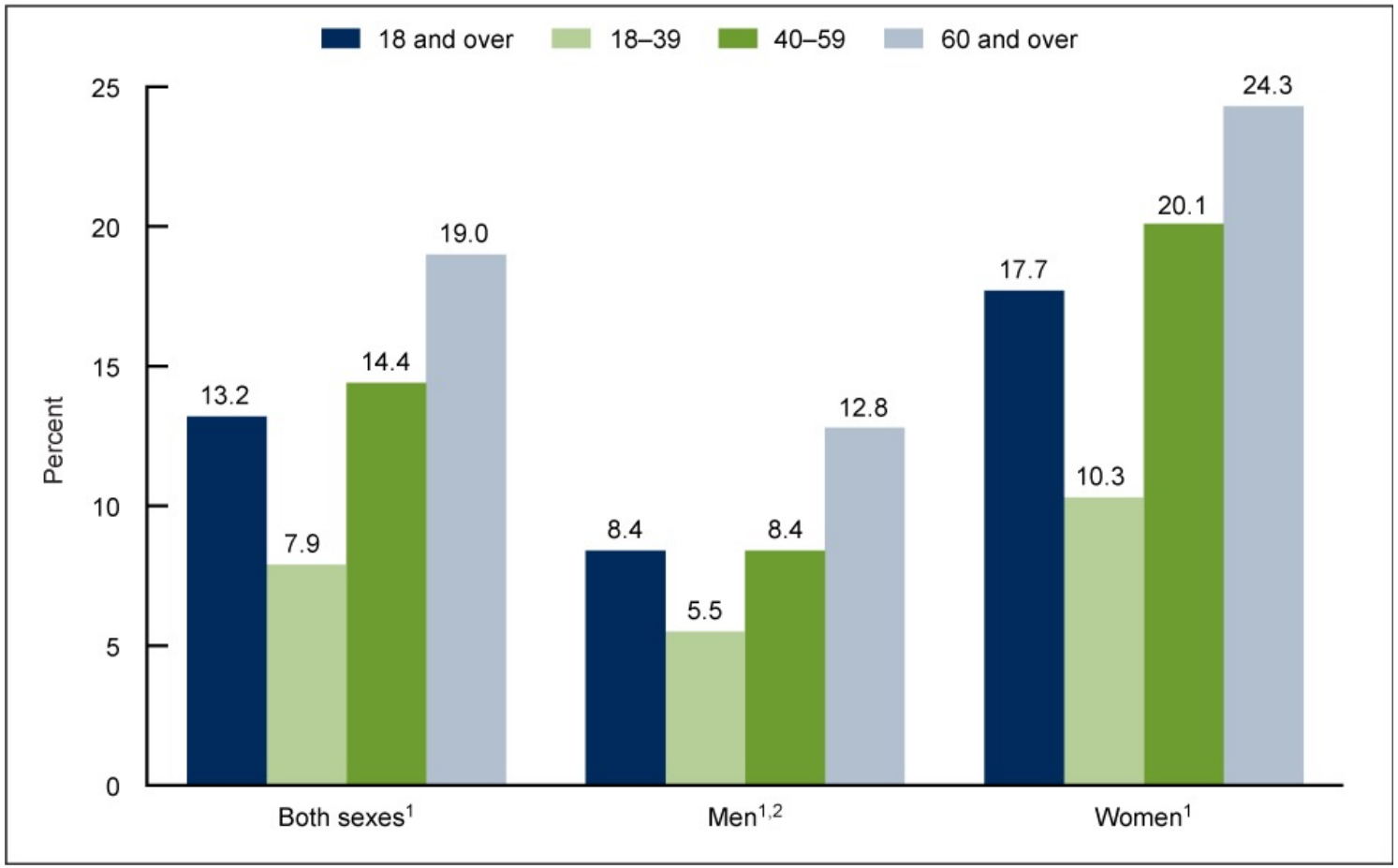
"In this preliminary study of adult outpatients with symptomatic COVID-19, patients treated with fluvoxamine, compared with placebo, had a lower likelihood of clinical deterioration over 15 days. However, the study is limited by a small sample size and short follow-up duration, and determination of clinical efficacy would require larger randomized trials with more definitive outcome measures."

From Lenze et al (2020):

- "lung damage from COVID-19 was related to an excessive inflammatory response, prompting numerous trials of immunomodulatory drugs….
- A potential mechanism for immune modulation is σ-1 receptor (S1R) agonism.
- The S1R is an endoplasmic reticulum chaperone protein with various cellular functions, including regulation of cytokine production through its interaction with the endoplasmic reticulum stress sensor inositol-requiring enzyme1α (IRE1). Previous studies have shown that fluvoxamine,a selective serotonin reuptake inhibitor (SSRI)with high affinity for the S1R, reduced damaging aspects of the inflammatory response during sepsis through the S1R-IRE1 pathway, and decreased shock in murine sepsis models.
- Fluvoxamine is a strong S1R agonist, is highly lipophilic, and has rapid intracellular uptake."
- *Study demonstrated that fluvoxamine, as early treatment in individuals with COVID-19 illness, prevented clinical deterioration.*

Antidepressants are used very widely (US CDC data, 2020)

Figure 1. Percentage of adults aged 18 and over who used antidepressant medication over past 30 days, by age and sex: United States, 2015–2018



[1]Significant increasing trend by age.
[2]Significantly lower than women in the same age group.
NOTE: Access data table for Figure 1 at: https://www.cdc.gov/nchs/data/databriefs/db377-tables-508.pdf#1.
SOURCE: National Center for Health Statistics, National Health and Nutrition Examination Survey, 2015–2018.

Late 2021: Some SSRIs are effective COVID19 treatments

- The antidepressants fluvoxamine and fluoxetine have been shown to prevent hospitalization and other severe outcomes for COVID19, and these effects may extend to other selective serotonin reuptake inhibitors (SSRI) medications.
- With the wide use of SSRIs, we can ask: what data are available readily, to increase our understanding of this relationship?
- We could think about SSRI use *per se*, or SSRI use *as a genetic trait*.
- One way to understand the SSRI-COVID19 relationship is via querying the underlying genetic relationships, including assessing causality via Mendelian randomization.

Selective Serotonin Reuptake Inhibitor (SSRI) Use GWAS

- We undertook GWAS analyses of the trait of SSRI use in the Million Veteran Program (MVP) sample. The analysis in EUR included 177,494 cases (who had received SSRI prescriptions) and 268,353 controls (who had not).
  - Any SSRI prescription recorded in the inpatient or outpatient EHR for fluvoxamine, fluoxetine, sertraline, escitalopram, paroxetine, or citalopram recorded as a case.

- This resulted in discovery of 26 independent genomewide risk loci.

- SSRIs are most commonly used for depression, and therefore we might have expected similar discovery to what was seen for that trait, but there were more risk loci for SSRI use, contrary to expectations. However, the Rg with depression (in UK Biobank, UKB) was 0.80; the Rg with citalopram (another SSRI) use was 0.89. Other UKB traits with Rgs >0.7 with SSRI use included headache, use of amitriptyline (a non-SSRI antidepressant), and inability to work due to disability.

- Associated SNPs mapped (for example) to *DRD2* (lead locus), *NRXN1*, and *MAD1L1*.

EUR	Status	N	Effective
MVP	Case	177494	427331
445847	Control	268353	

No	uniqID	rsID	chr	pos	p	nSNPs	nGWASSNPs	
1	1:37169665:C:T	rs218985	1	37169665	2.66E-08	263	110	***FTLP18***
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19	11:112852611:G:T	rs1940726	11	112852611	2.89E-08	597	311	***NCAM1***
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22	14:103256961:A:G	rs56101042	14	103256961	7.53E-10	287	159	***TRAF3***
23	15:91426560:A:G	rs4702	15	91426560	1.52E-09	62	24	***FURIN***
24	17:35146499:C:T	rs145626091	17	35146499	4.91E-08	93	21	***RP11-445F12.1***
25	17:66079619:C:T	rs62084747	17	66079619	3.40E-09	578	355	***KPNA2***
26	18:35156177:A:G	rs7243428	18	35156177	1.16E-08	220	107	***CELF4***
27	18:50824885:C:G	rs11082975	18	50824885	2.86E-10	1578	762	***DCC***
28	19:45392254:C:T	rs6857	19	45392254	2.71E-08	85	47	***CTB-129P6.4***

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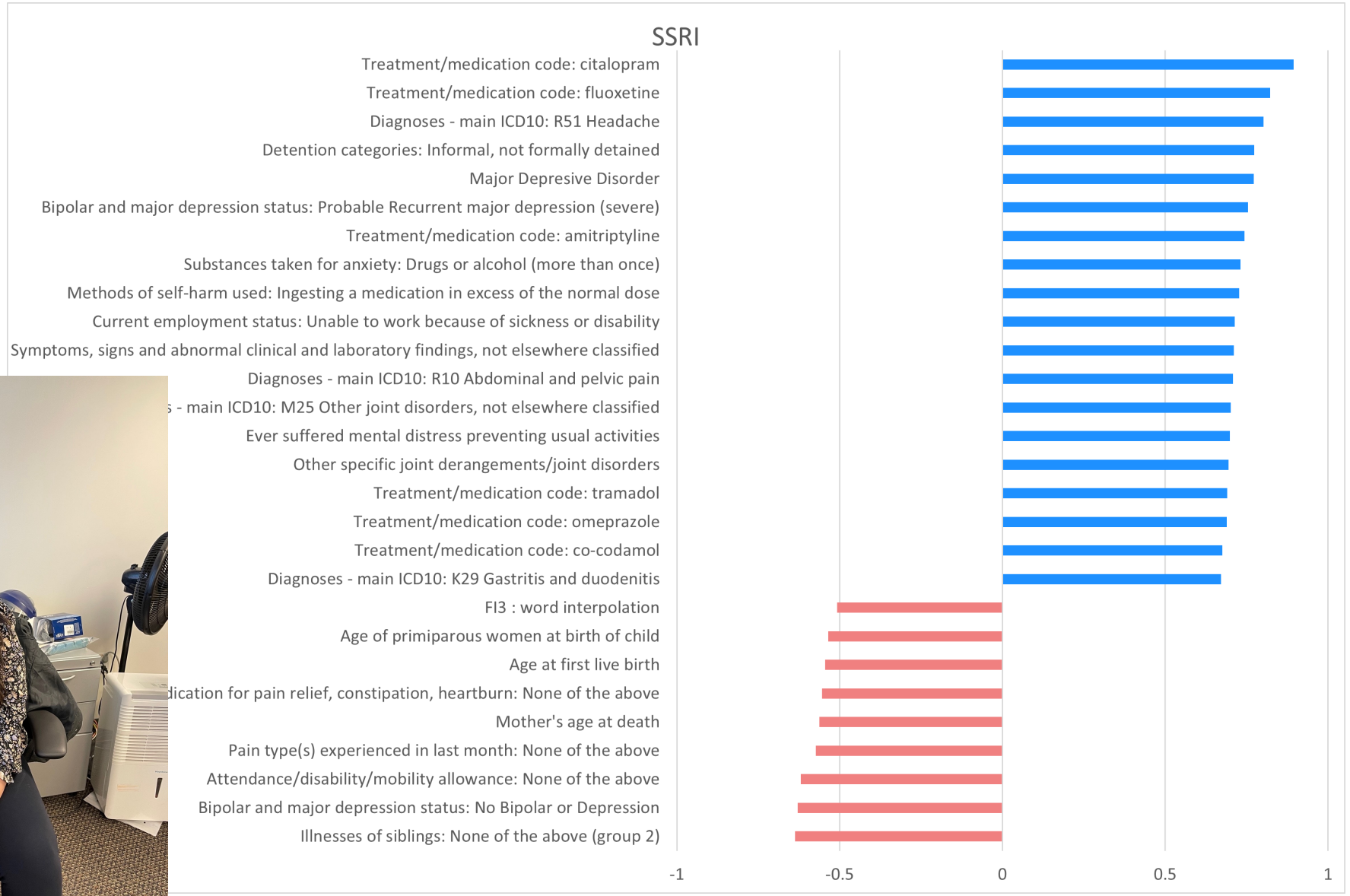

Reference data from UKBiobank

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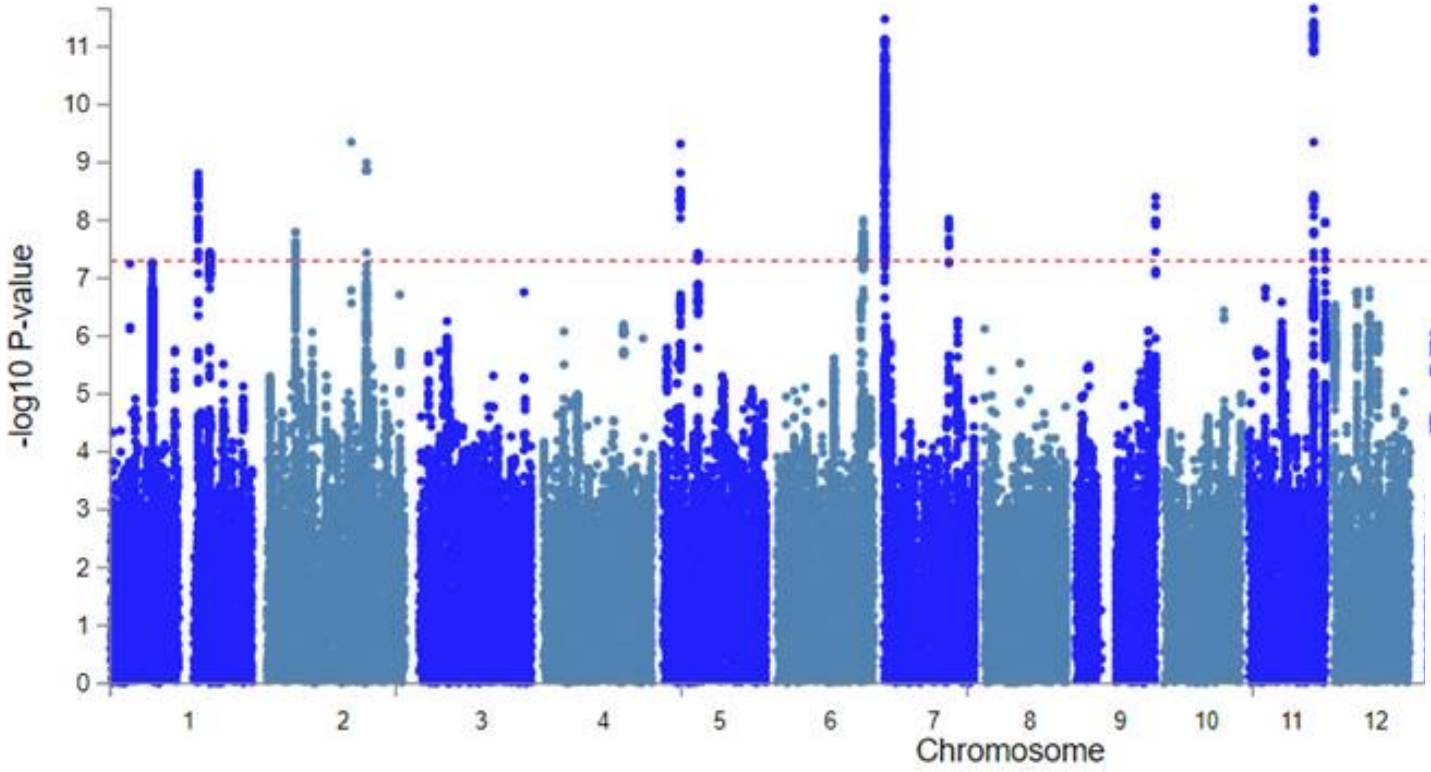
- Associated SNPs mapped (for example) to *DRD2* (lead locus), *NRXN1*, and *MAD1L1*.

Depression GWAS – 16 independent risk loci (MVP EUR)



nature neuroscience
ARTICLES
https://doi.org/10.1038/s41593-021-00860-2
Check for updates

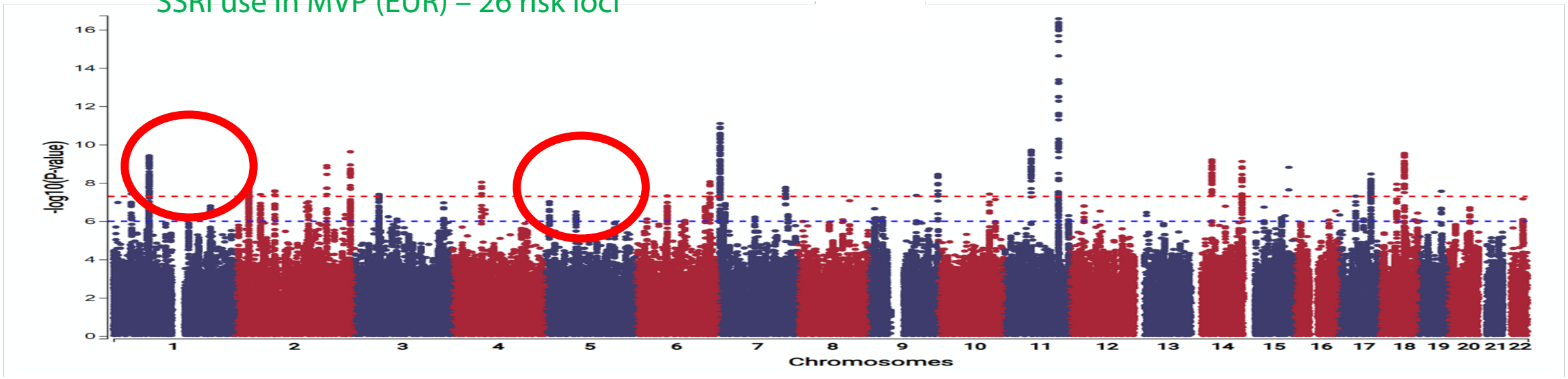
Bi-ancestral depression GWAS in the Million Veteran Program and meta-analysis in >1.2 million individuals highlight new therapeutic directions

Daniel F. Levey[1,2,15], Murray B. Stein[3,4,15]✉, Frank R. Wendt[1,2], Gita A. Pathak[1,2], Hang Zhou[1,2], Mihaela Aslan[5,6], Rachel Quaden[7], Kelly M. Harrington[7,8], Yaira Z. Nuñez[1,2], Cassie Overstreet[1,2], Krishnan Radhakrishnan[5,9], Gerard Sanacora[10,11], Andrew M. McIntosh[12], Jingchunzi Shi[13], Suyash S. Shringarpure[13], 23andMe Research Team*, the Million Veteran Program*, John Concato[5,14], Renato Polimanti[1,2] and Joel Gelernter[1,2]✉

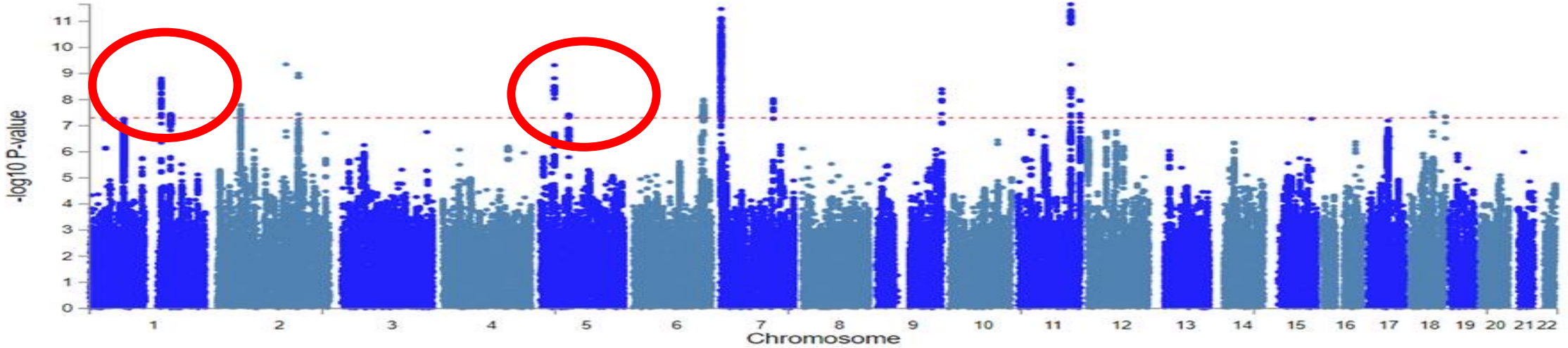
Major depressive disorder is the most common neuropsychiatric disorder, affecting 11% of veterans. Here we report results of a large meta-analysis of depression using data from the Million Veteran Program, 23andMe, UK Biobank and FinnGen, including individuals of European ancestry ($n = 1,154,267$; 340,591 cases) and African ancestry ($n = 59,600$; 25,843 cases). Transcriptome-wide association study analyses revealed significant associations with expression of *NEGR1* in the hypothalamus and *DRD2* in the nucleus accumbens, among others. We fine-mapped 178 genomic risk loci, and we identified likely pathogenicity in these variants and overlapping gene expression for 17 genes from our transcriptome-wide association study, including *TRAF3*. Finally, we were able to show substantial replications of our findings in a large independent cohort ($n = 1,342,778$) provided by 23andMe. This study sheds light on the genetic architecture of depression and provides new insight into the interrelatedness of complex psychiatric traits.

MVP.Depression vs SSRI - rG									
rG	se	z	P	h2_obs	h2_obs_se	h2_int	h2_int_se	gcov_int	gcov_int_se
0.9692	0.0186	52.1223	0	0.0479	0.0023	1.0484	0.0114	0.4844	0.0079

SSRI use in MVP (EUR) – 26 risk loci



MDD in MVP (EUR) – 16 risk loci



SSRI GWAS: 177,494 cases and 268,353 controls

MDD GWAS: 151,974 cases and 226,640 controls

Mendelian Randomization: SSRI use and COVID19 hospitalization

Hospitalized covid vs. population

Exposure	Outcome	Method	nspns	b	se	pval
SSRI	Covid	MR Egger	124	0.04	0.13	0.77
SSRI	Covid	Weighted median	124	0.145	0.057	0.01
SSRI	Covid	Inverse variance weighted	124	0.204	0.039	$1.4x10^{-7}$
SSRI	Covid	Simple mode	124	0.44	0.17	0.009

Conclusions

- SSRI use provides a strong GWAS signal, stronger even than major depression. We were therefore able to uncover some underlying biology.
- SSRIs are used for a range of psychiatric traits – depression, OCD, PMDD, anxiety, PTSD, etc etc… they have favorable therapeutic indices
- We thought SSRI use might predict better COVID19 outcomes, but we observed the opposite
  - Due to high correlation with depression (which increases COVID19 risk)?
  - Or the fact that we were measuring lifetime SSRI use, when what we really care about is use at the time of COVID infection?
  - (And what about Rg with other medication-use traits?)
- Clinical studies with large samples needed – in progress in the VA

Dr Robert T Malison 1959-2020