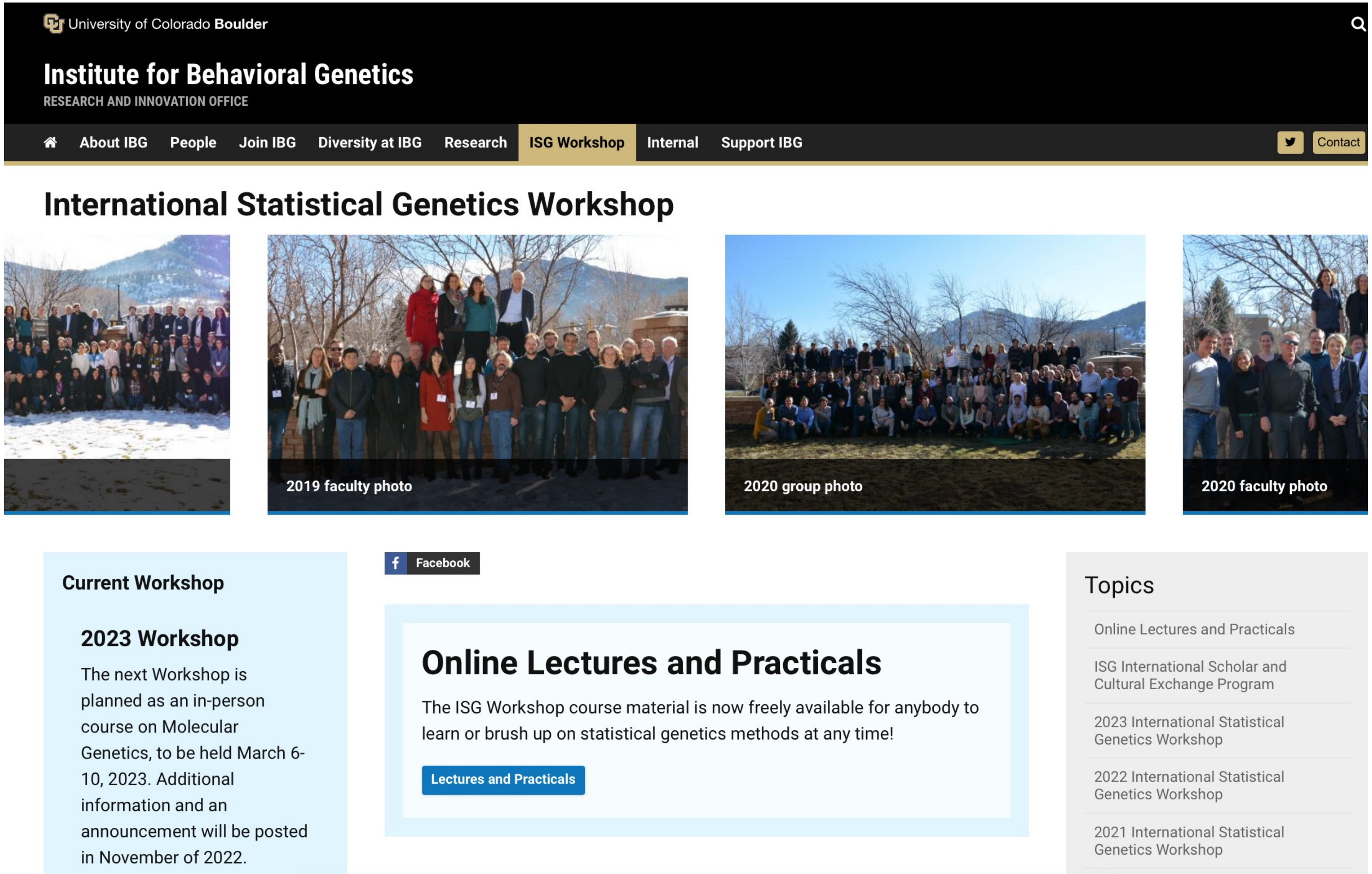
ISG 2023 Lightning Rounds



Institute for Behavioral Genetics

RESEARCH AND INNOVATION OFFICE

International Statistical Genetics Workshop

Current Workshop

2023 Workshop

The next Workshop is planned as an in-person course on Molecular Genetics, to be held March 6-10, 2023. Additional information and an announcement will be posted in November of 2022.

Online Lectures and Practicals

The ISG Workshop course material is now freely available for anybody to learn or brush up on statistical genetics methods at any time!

Topics

- Online Lectures and Practicals
- ISG International Scholar and Cultural Exchange Program
- 2023 International Statistical Genetics Workshop
- 2022 International Statistical Genetics Workshop
- 2021 International Statistical Genetics Workshop

Talks

- ❑ 3:35 Nick: Depression and Genetics of non-identical (DZ) twinning
- ❑ 3:42 Dorret: Multi-omics of MZ twinning
- ❑ 3:49 Loic: Reconciling linkage and association studies of height using 107,000 sibling pairs
- ❑ 3:56 Tim: Standardizing scalable representations and formats for the era of million-sample sequencing datasets
- ❑ 4:03 Liz: Including the wisdom of community and participant voices in genetically informative research: A Richmond story
- ❑ 4:10 Rohan: Applications of statistical genetics to substance use disorders & related behaviors
- ❑ 4:17 Sarah: The Equinox Conference
- ❑ 4:24 Abdel: Behavior <-> Genetics
- ❑ 4:31 Brittany Dissecting heterogeneity in depression
- ❑ 4:38 Mike: Detecting latent variable interactions
- ❑ 4:45 Matt: Behavioral genetics in the molecular age

Nick Martin

Two intriguing questions

(1) Why is depression prevalence 20% in females and 10% in males? (similar inequalities in almost every other complex trait)

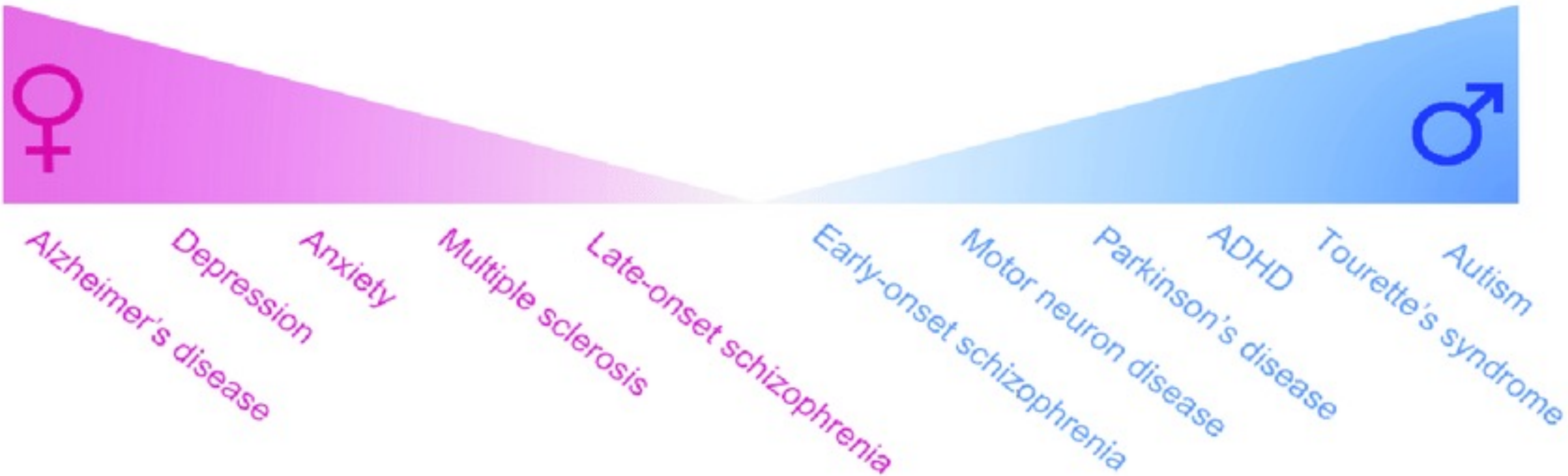
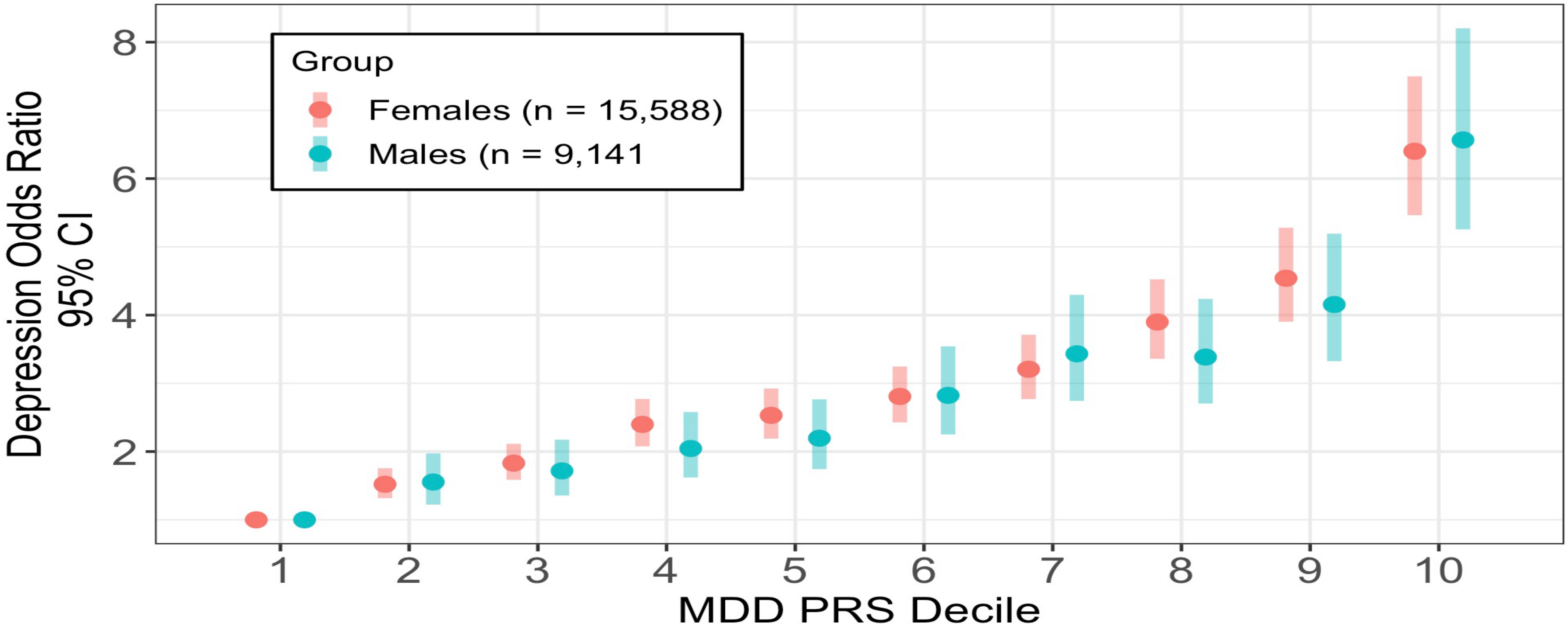


Figure 1. Sex differences in the prevalence of neurodegenerative and neuropsychiatric disorders.

Also applies to continuous traits e.g. height

How well does the MDD GWAS predict Depression caseness (DSM5)?

Prediction from PGC (Howard minus Oz, using SBayesR) into AGDS +QSkin



genetic correlation between the sexes not significantly different from one (rGmf= 0.90 s.e. 0.06; p = 0.096) ##

Am J Med Genet B Neuropsychiatr Genet. 2019 Sep; 180(6): 439–447

Some ideas

- Measurement invariance for the 9 MDD symptoms – do they have the same salience in females and males, early onset/ late onset? (Dorret)
- Need completely separate GWAS for females and males
  - Use sex- specific recombination map? (Sarah M)
  - Are betas the same in females and males? – test for SNP x sex interaction
  - Cross prediction into the other sex
- Is the sex prevalence difference confined to the reproductive years ? Interaction with sex hormone PRS

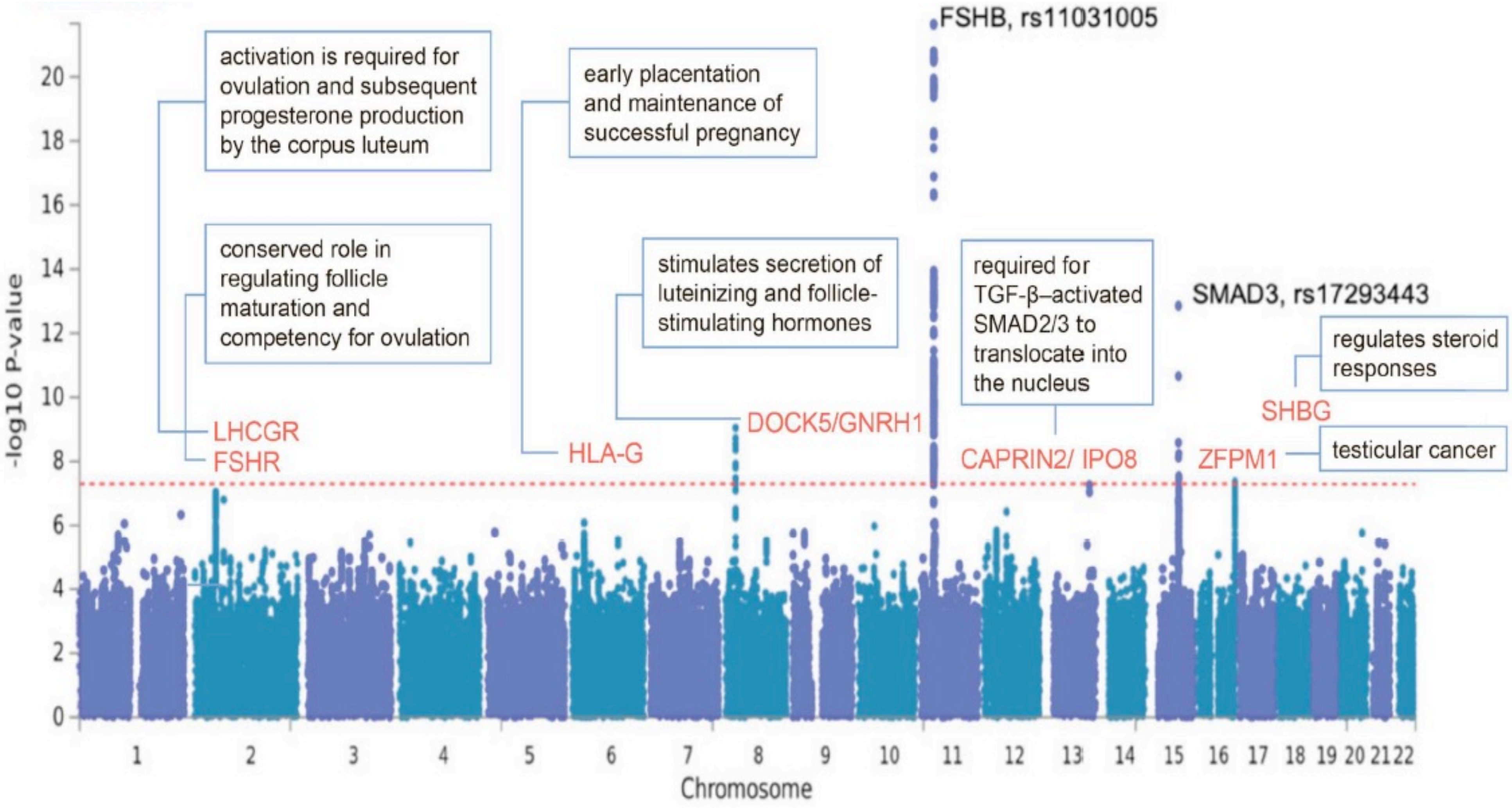
Two intriguing questions

(2) Genetics of [spontaneous] nonidentical (DZ) twinning:

why is frequency 20/1000 births in Africa and 2/1000 in east Asia – 10 fold difference!

[8/1000 in europeans]

New GWAS meta-analysis hits for DZ twinning – 8265 MoDZT cases, 264k controls



activation is required for ovulation and subsequent progesterone production by the corpus luteum

conserved role in regulating follicle maturation and competency for ovulation

early placentation and maintenance of successful pregnancy

stimulates secretion of luteinizing and follicle-stimulating hormones

required for TGF-β–activated SMAD2/3 to translocate into the nucleus

regulates steroid responses

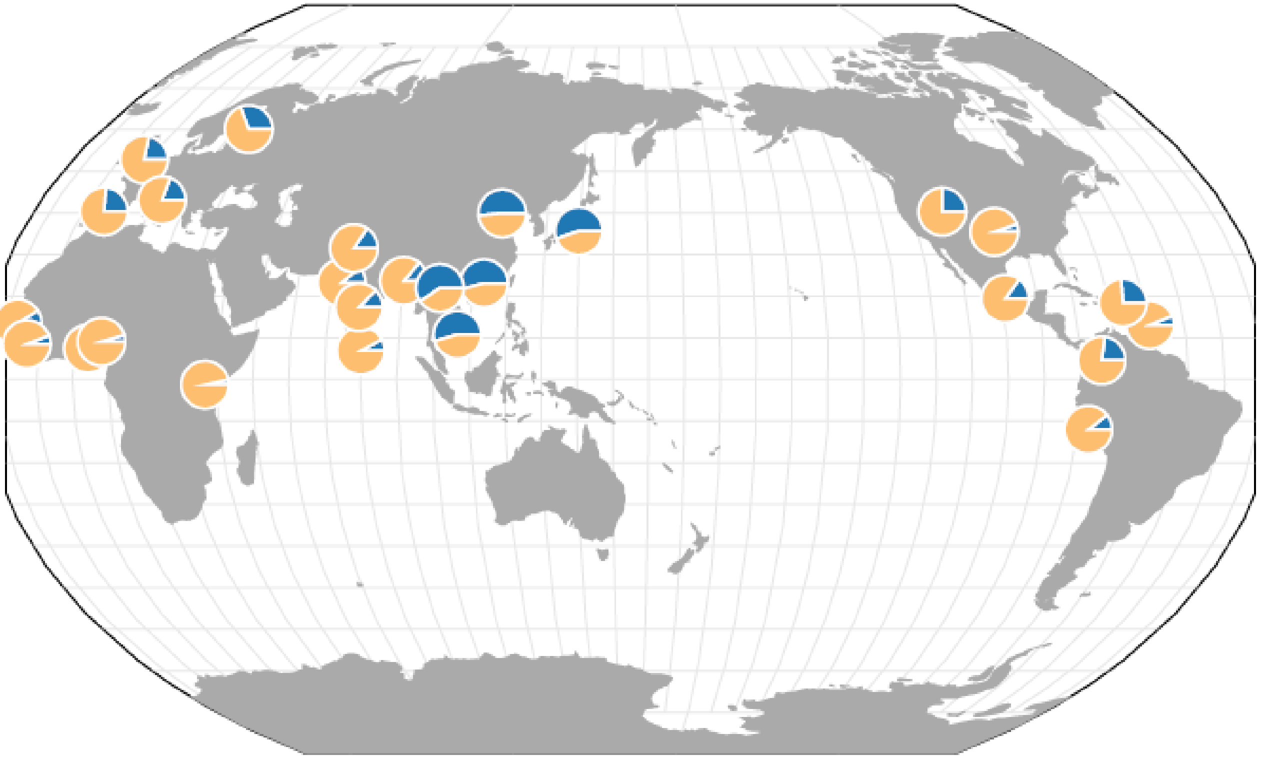
testicular cancer

Mothers of DZ twins	**8,265** cases, **264,567** controls
DZ twins	**26,252** cases, **417,433** controls

Frequency of *GNRH1* SNP in world populations

note for G allele Africans>Europeans>East Asians

GNRH1 chr8:25280800 G/C

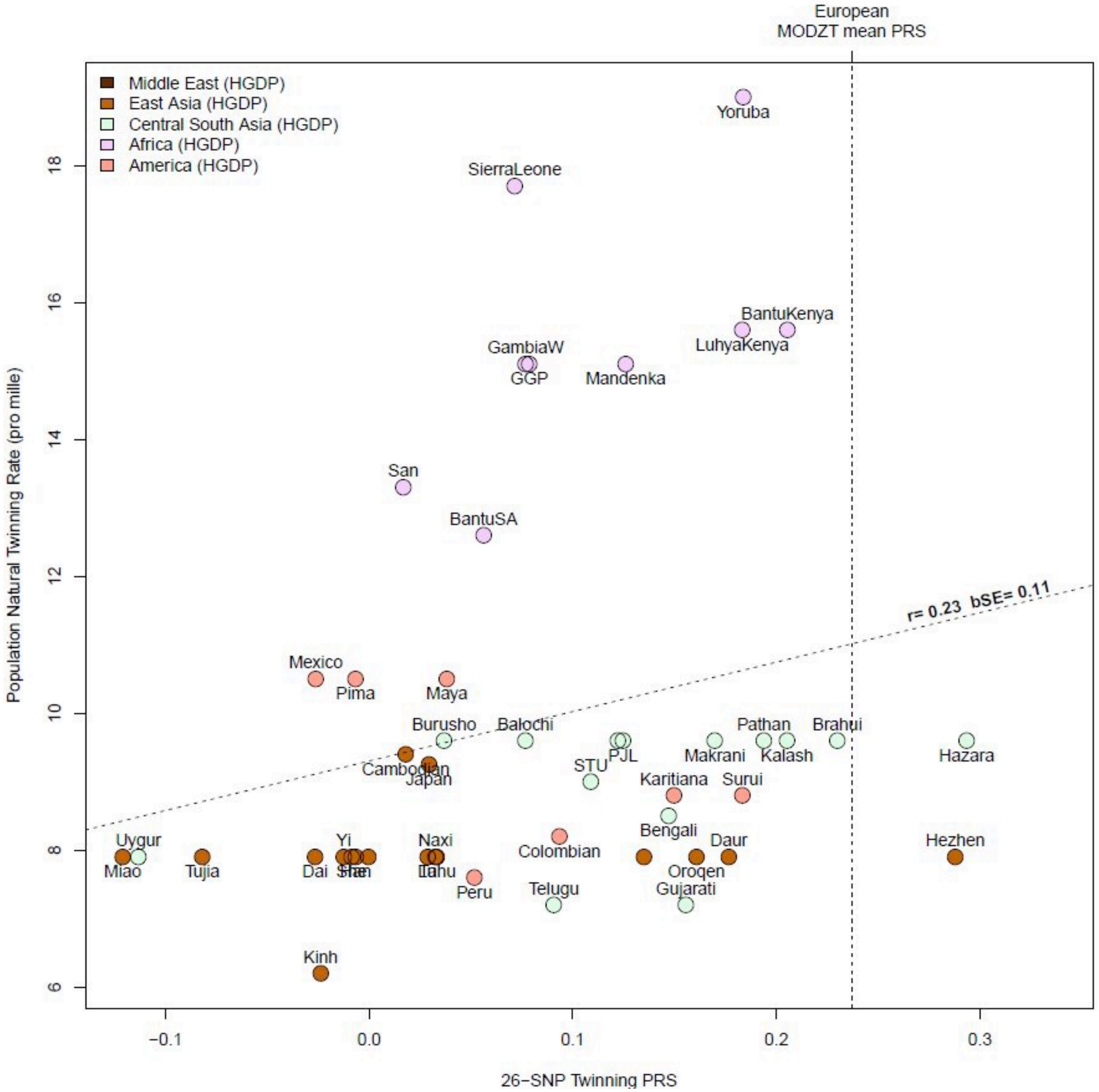


This SNP goes in the expected direction of ancestry frequencies in DZT - but others do not

Need to integrate across all significant DZT SNPs

See if we can explain Africans 20/k > europ 8/k > E Asians 2/k

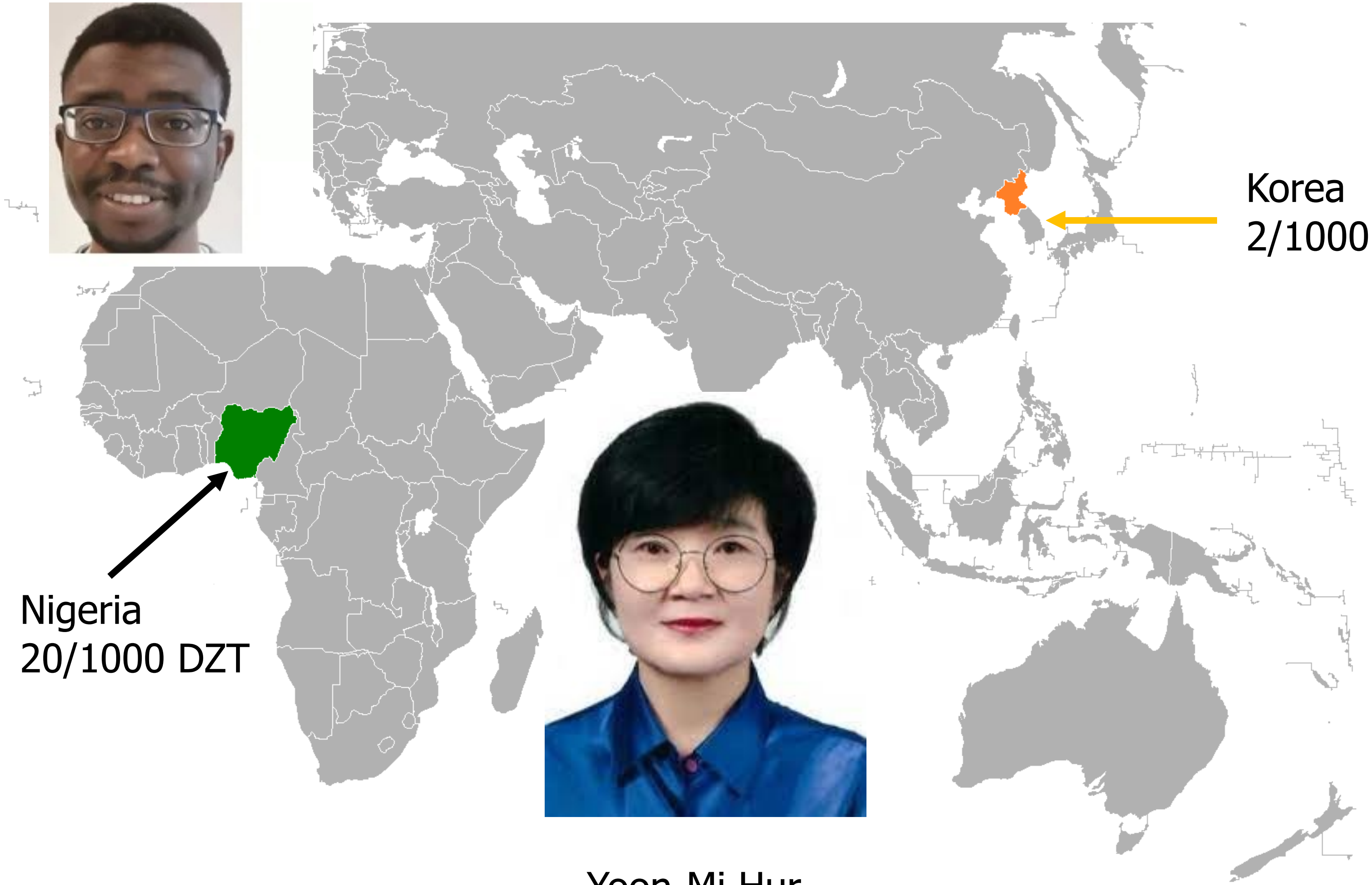
The correlation between population twinning rates from 47 non-European populations and predicted DZT PRS for each population based on European effect sizes of the 26 top SNPs



European PRS gives poor prediction of twinning rate in other ancestries. We need GWAS in Asia and Africa!

David Duffy

Plan to collect 1000 MoDZT and 1000 controls each in Korea and Nigeria



Olakunle Oginni

Korea
2/1000 DZT

Nigeria
20/1000 DZT

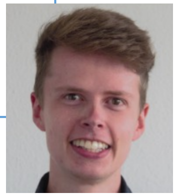
Yoon-Mi Hur

Collecting saliva samples from MoDZTs in Osogbo grammar school

Dorret Boomsma

Multi-omics of twinning

BIObanks Netherlands Internet Collaboration (BBMRI-BIONIC) -> MDD

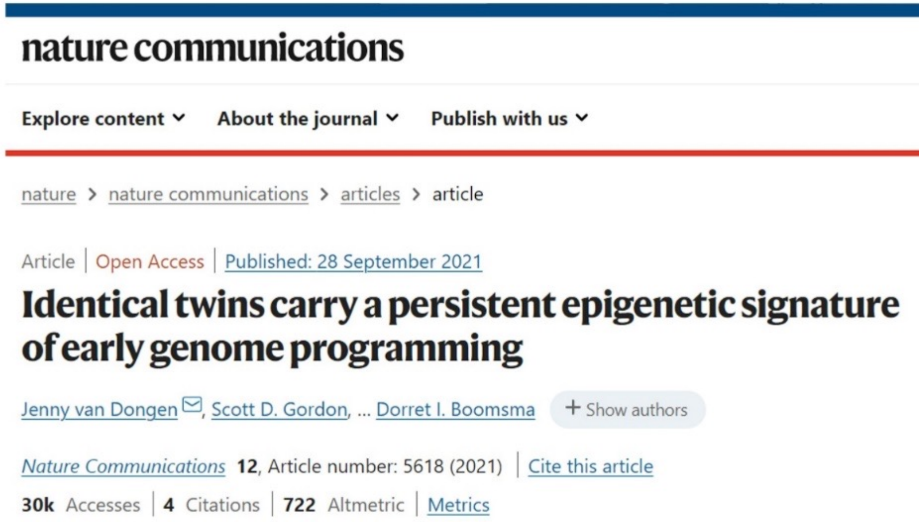


Open Data Infrastructure for Social Science and Economic Innovations (ODISSEI)

Longitudinal and Multi-omics of aggression /adhd

Microchimerism

nature
communications
LIFE AND BIOLOGICAL
SCIENCES
TOP 25
READ ARTICLES OF 2021
OFFICIAL AUTHOR



Article | Open Access | Published: 28 September 2021

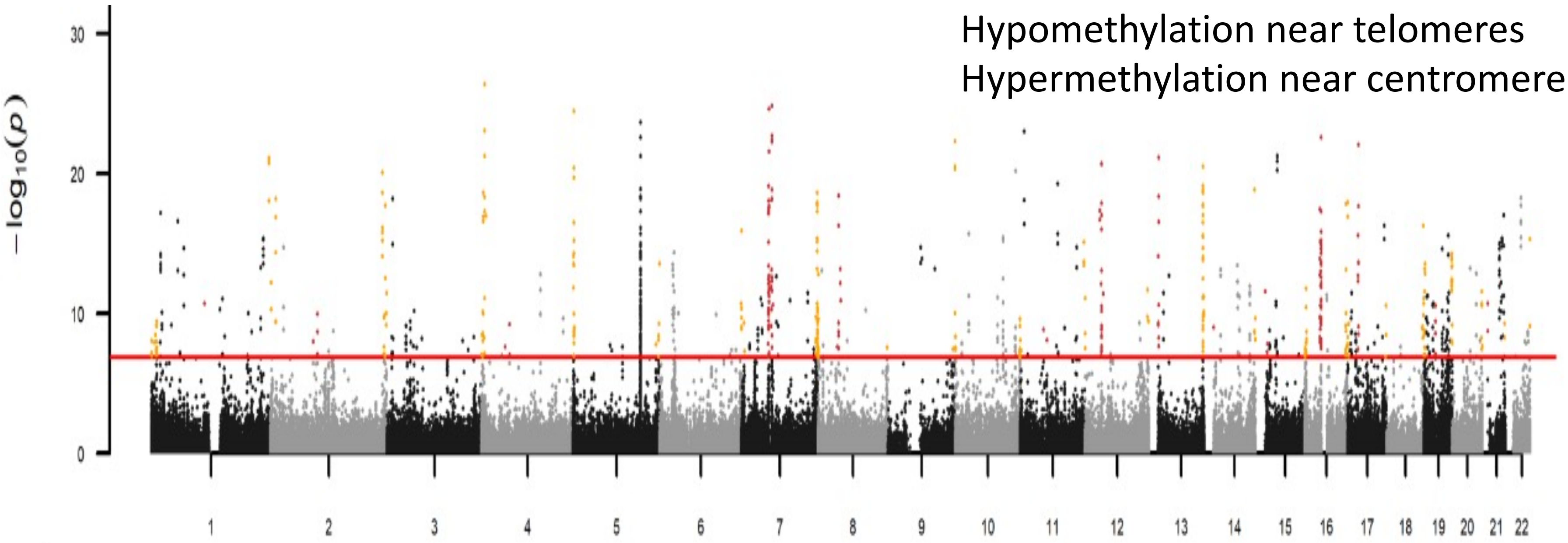
Identical twins carry a persistent epigenetic signature of early genome programming

Jenny van Dongen, Scott D. Gordon, ... Dorret I. Boomsma

Nature Communications **12**, Article number: 5618 (2021) | Cite this article

30k Accesses | **4** Citations | **722** Altmetric | Metrics

MZ twinning and differential DNA methylation

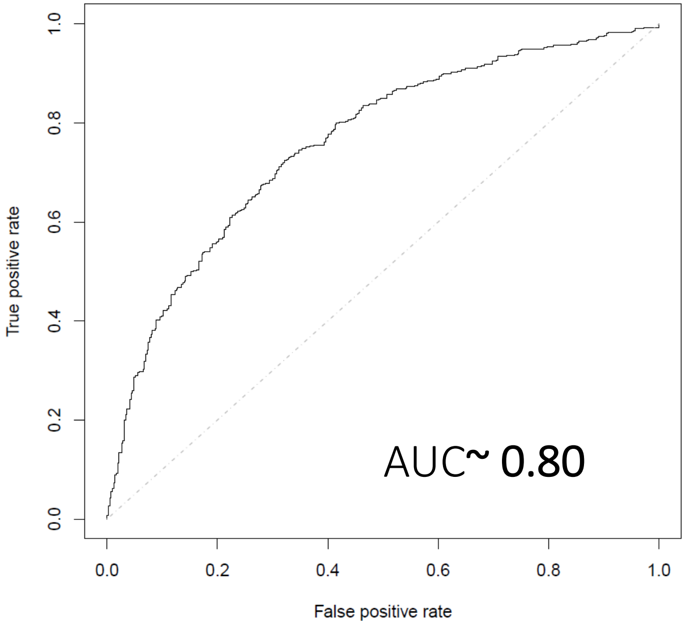


Hypomethylation near telomeres
Hypermethylation near centromeres

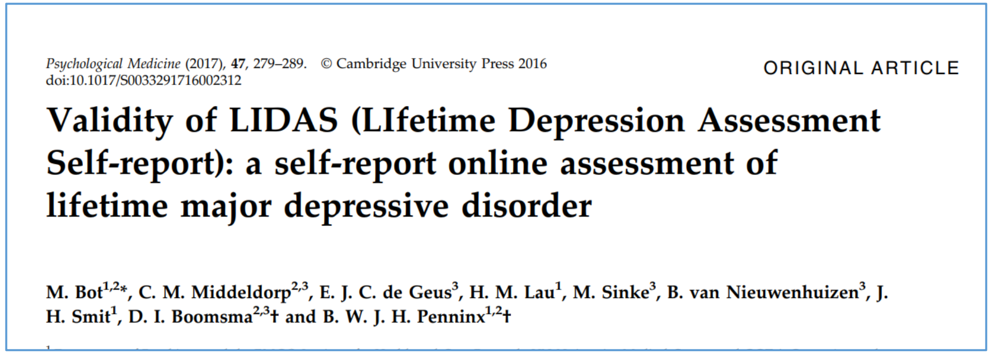
First molecular evidence for a signature for MZ twinning in humans

- A signature of MZ twinning event that persists, through many rounds of mitosis, to adult somatic tissues.
- Tool to examine link between MZ twinning and congenital disorders (e.g. imprinting disorders, Amyoplasia).
- Cause effect, or byproduct?
- New possibilities to examine **vanishing twin syndrome**

Beckwith-Wiedemann Syndrome



Diagnosis of MZ twinning using an epigenetic predictor

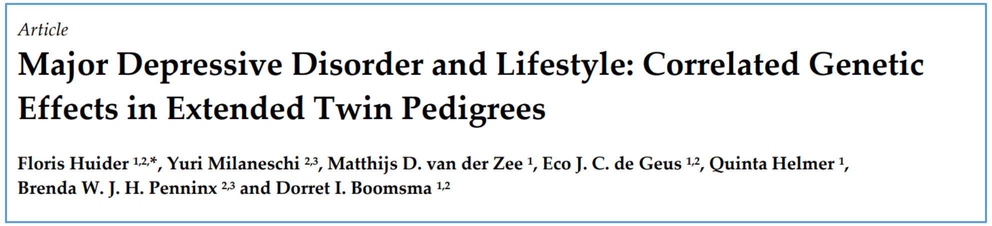


Psychological Medicine (2017), 47, 279–289. © Cambridge University Press 2016
doi:10.1017/S0033291716002312

ORIGINAL ARTICLE

Validity of LIDAS (LIfetime Depression Assessment Self-report): a self-report online assessment of lifetime major depressive disorder

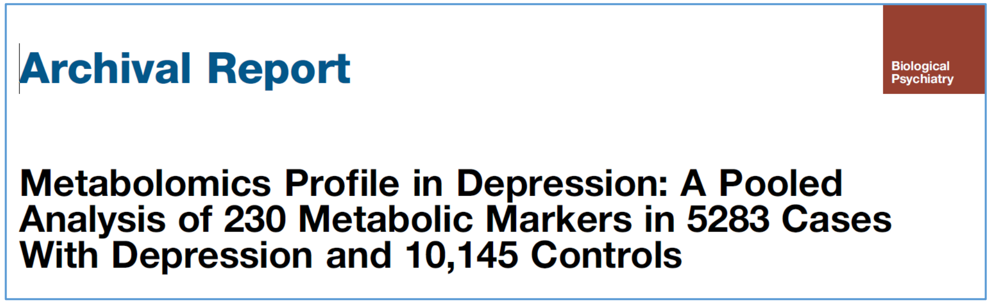
M. Bot[1,2]*, C. M. Middeldorp[2,3], E. J. C. de Geus[3], H. M. Lau[1], M. Sinke[3], B. van Nieuwenhuizen[3], J. H. Smit[1], D. I. Boomsma[2,3]† and B. W. J. H. Penninx[1,2]†



Article

Major Depressive Disorder and Lifestyle: Correlated Genetic Effects in Extended Twin Pedigrees

Floris Huider [1,2,]*, Yuri Milaneschi [2,3], Matthijs D. van der Zee [1], Eco J. C. de Geus [1,2], Quinta Helmer [1], Brenda W. J. H. Penninx [2,3] and Dorret I. Boomsma [1,2]



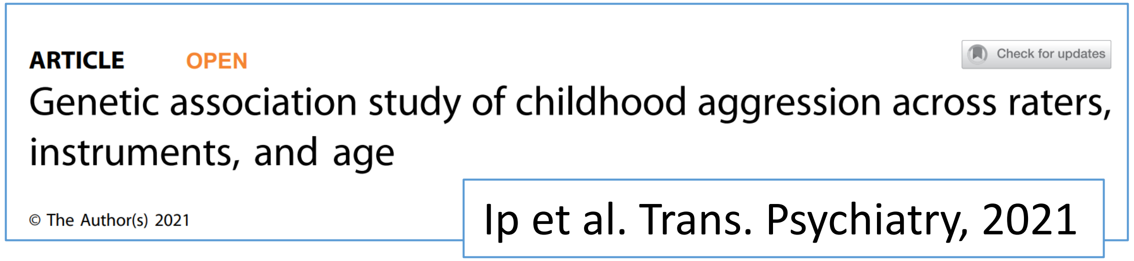
Archival Report

Biological Psychiatry

Metabolomics Profile in Depression: A Pooled Analysis of 230 Metabolic Markers in 5283 Cases With Depression and 10,145 Controls

BIObanks Netherlands Internet Collaboration (BIONIC)

- Goal: characterize the genetics of depression in the Netherlands.
- 13 Dutch cohorts, depression and genotype data at a central location.
- Phenotype data N = 100,000 / genotype data N = 70,000
- Collaboration with UK and Australia

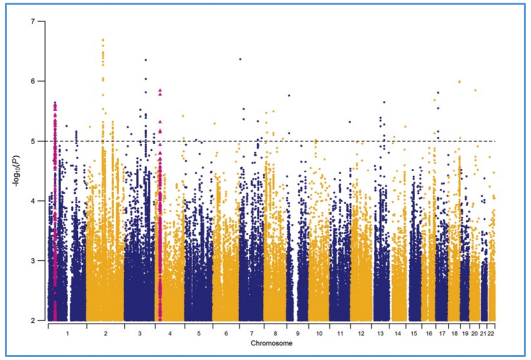


ARTICLE OPEN

Check for updates

Genetic association study of childhood aggression across raters, instruments, and age

Ip et al. Trans. Psychiatry, 2021



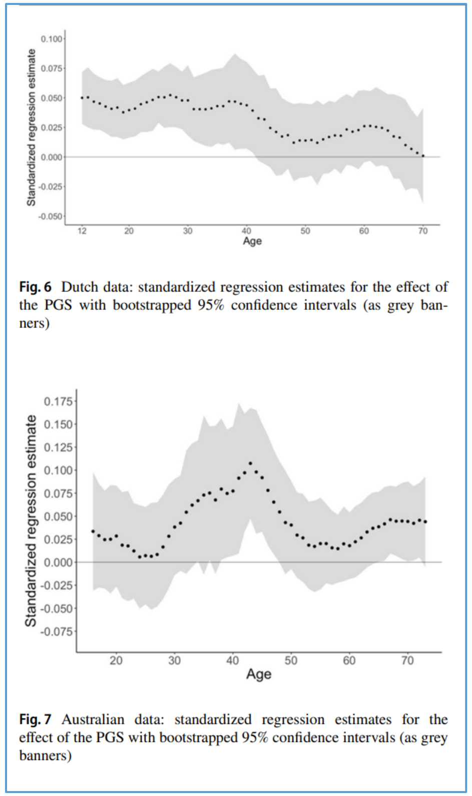
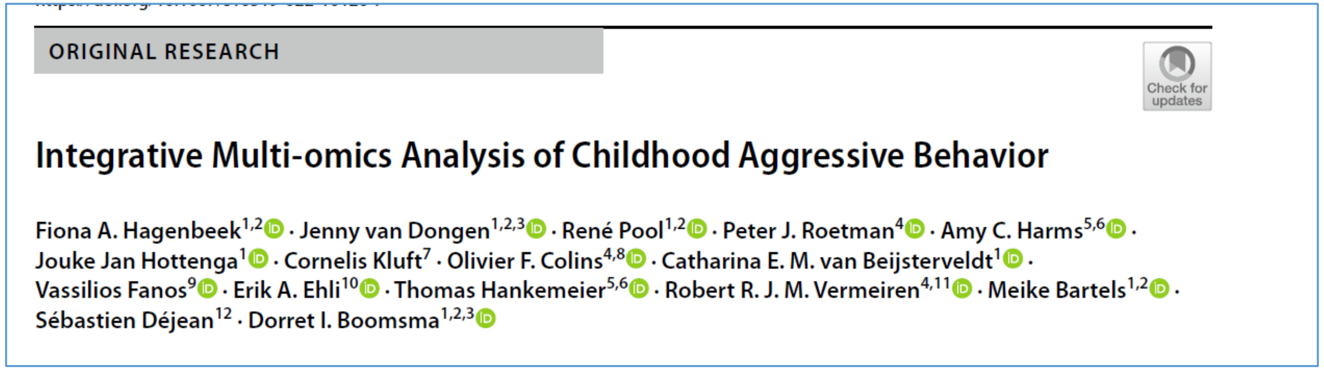


Fig. 6 Dutch data: standardized regression estimates for the effect of the PGS with bootstrapped 95% confidence intervals (as grey banners)

Fig. 7 Australian data: standardized regression estimates for the effect of the PGS with bootstrapped 95% confidence intervals (as grey banners)



ORIGINAL RESEARCH

Check for updates

Integrative Multi-omics Analysis of Childhood Aggressive Behavior

Fiona A. Hagenbeek[1,2] · Jenny van Dongen[1,2,3] · René Pool[1,2] · Peter J. Roetman[4] · Amy C. Harms[5,6] · Jouke Jan Hottenga[1] · Cornelis Kluft[7] · Olivier F. Colins[4,8] · Catharina E. M. van Beijsterveldt[1] · Vassilios Fanos[9] · Erik A. Ehli[10] · Thomas Hankemeier[5,6] · Robert R. J. M. Vermeiren[4,11] · Meike Bartels[1,2] · Sébastien Déjean[12] · Dorret I. Boomsma[1,2,3]

updates

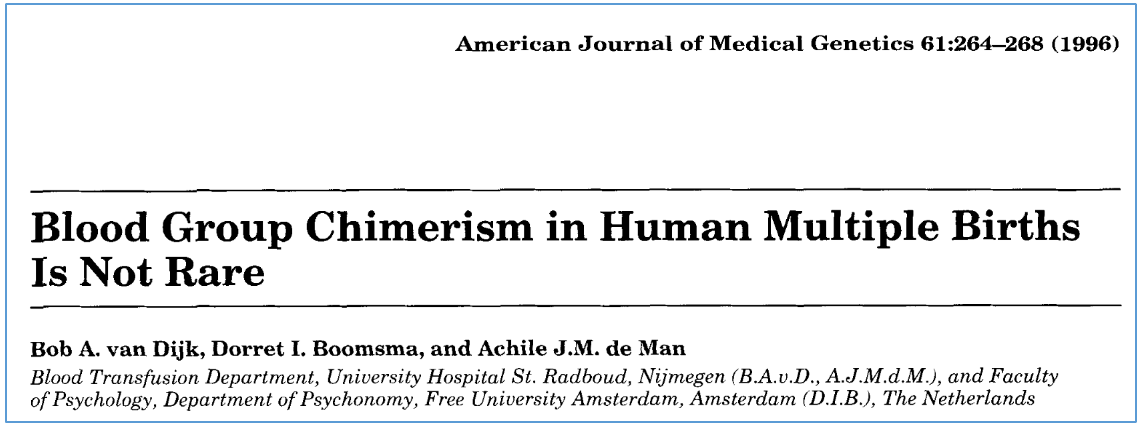
Continuity of Genetic Risk for Aggressive Behavior Across the Life-Course

Camiel M. van der Laan[1,2] · José J. Morosoli-García[3] · Steve G. A. van de Weijer[2] · Lucía Colodro-Conde[3] on behalf of the ACTION Consortium · Michelle K. Lupton[3] · Brittany L. Mitchell[3] · Kerrie McAloney[3] · Richard Parker[3] · Jane M. Burns[4] · Ian B. Hickie[5] · René Pool[1] · Jouke-Jan Hottenga[1] · Nicholas G. Martin[3] · Sarah E. Medland[3] · Michel G. Nivard[1] · Dorret I. Boomsma[1]

OSFPreprints: https://osf.io/rne4s/

Maximizing the Value of Twin Studies in Health and Behaviour

Hagenbeek, Hirzinger, Breunig, Bruins, Kuznetsov, Schut, Odintsova, Boomsma



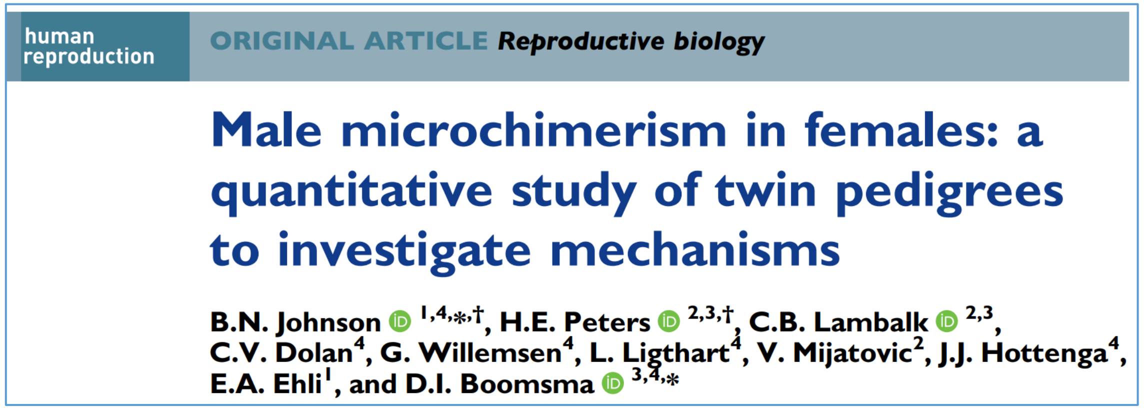
American Journal of Medical Genetics 61:264–268 (1996)

Blood Group Chimerism in Human Multiple Births Is Not Rare

Bob A. van Dijk, Dorret I. Boomsma, and Achile J.M. de Man

Blood Transfusion Department, University Hospital St. Radboud, Nijmegen (B.A.v.D., A.J.M.d.M.), and Faculty of Psychology, Department of Psychonomy, Free University Amsterdam, Amsterdam (D.I.B.), The Netherlands

8% prevalence of blood group chimerism in 552 dizygotic twin pairs and 24 triplet sets for multiple red cell blood group antigens.



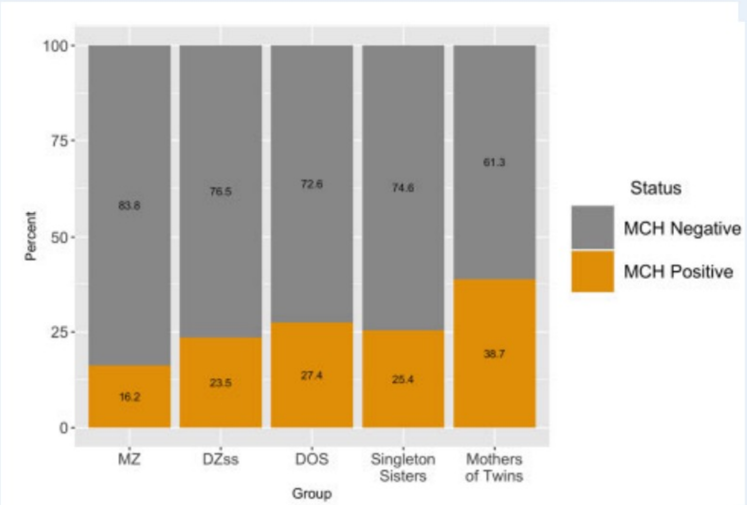
human reproduction

ORIGINAL ARTICLE ***Reproductive biology***

Male microchimerism in females: a quantitative study of twin pedigrees to investigate mechanisms

B.N. Johnson [1,4,*,†], H.E. Peters [2,3,†], C.B. Lambalk [2,3], C.V. Dolan[4], G. Willemsen[4], L. Ligthart[4], V. Mijatovic[2], J.J. Hottenga[4], E.A. Ehli[1], and D.I. Boomsma [3,4,*]

26.9% of women have having detectable male microchimerism in their peripheral blood samples



Prevalence of male microchimerism in women does not differ between MZ, DZ same-sex and DZ opposite-sex twins, sisters, mothers of twins.

(qPCR data for male genome equivalents by measure of DYS14 and b-globin targets)

Loic Yengo

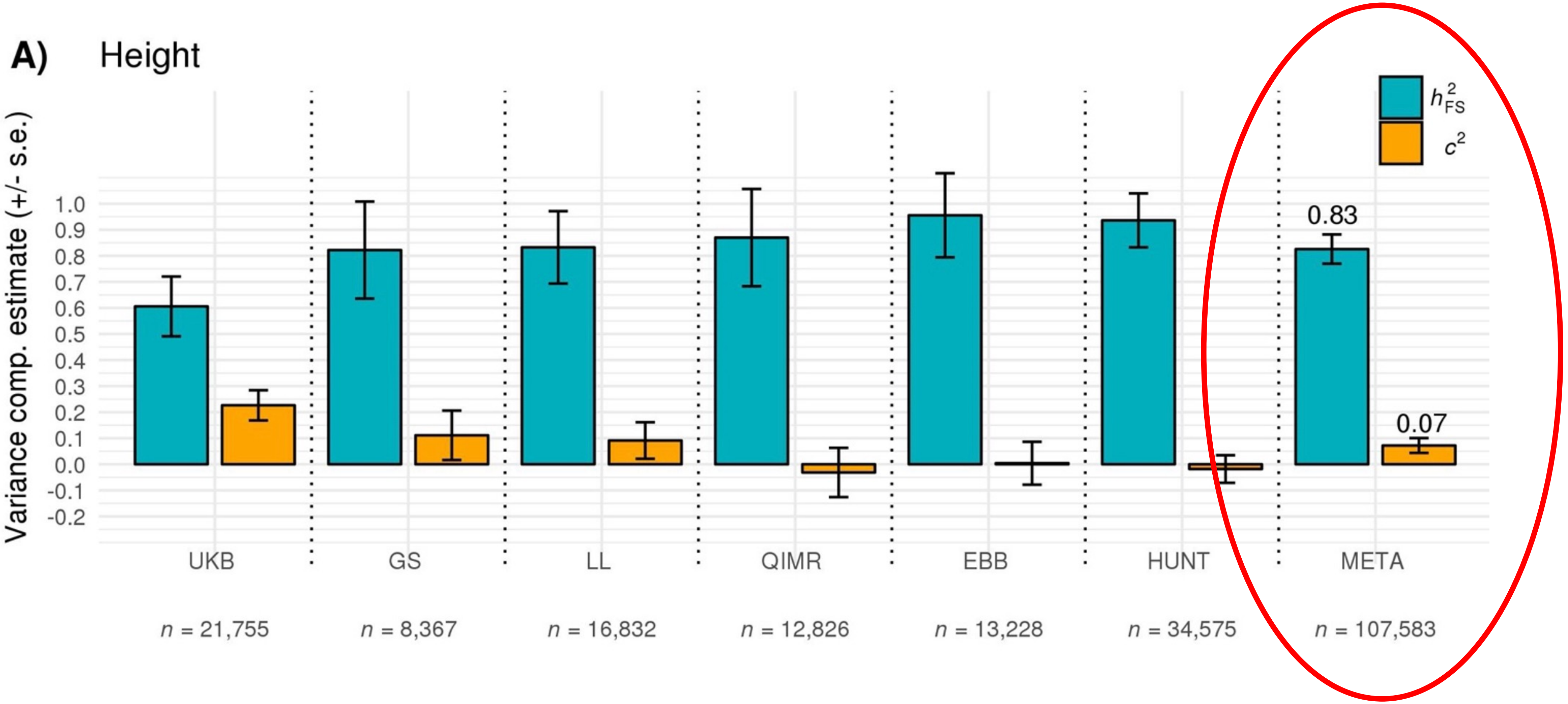
Julia Sidorenko et al.
(unpublished)

Peter Visscher

Reconciling linkage and Association Studies of height using 107,000 sibling pairs

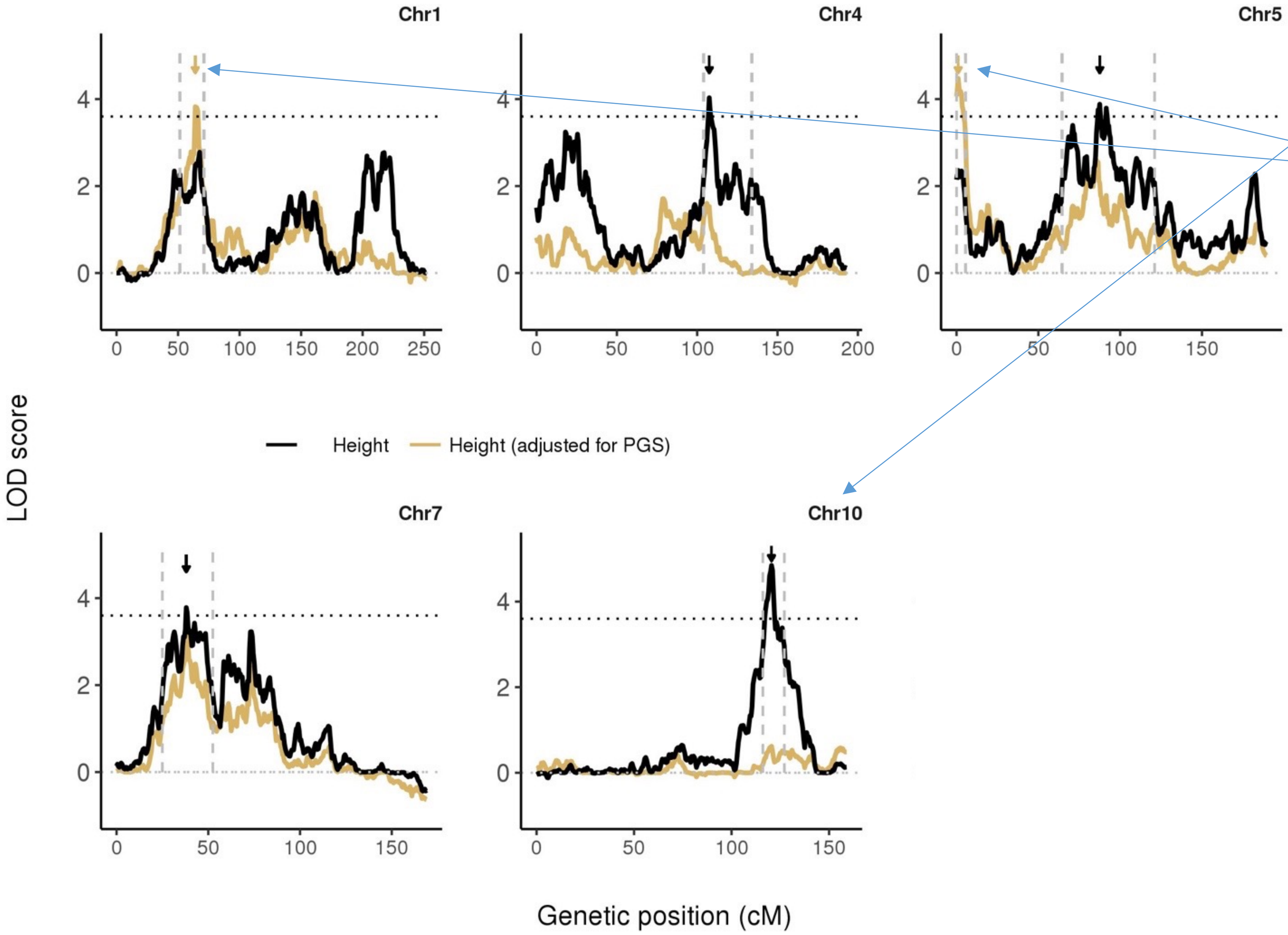
Loic Yengo, UQ

A “clean” estimate of h^2 for height



h^2 estimate are similar to pedigree-based between-families estimates

Linkage Peaks disappear fitting PGS

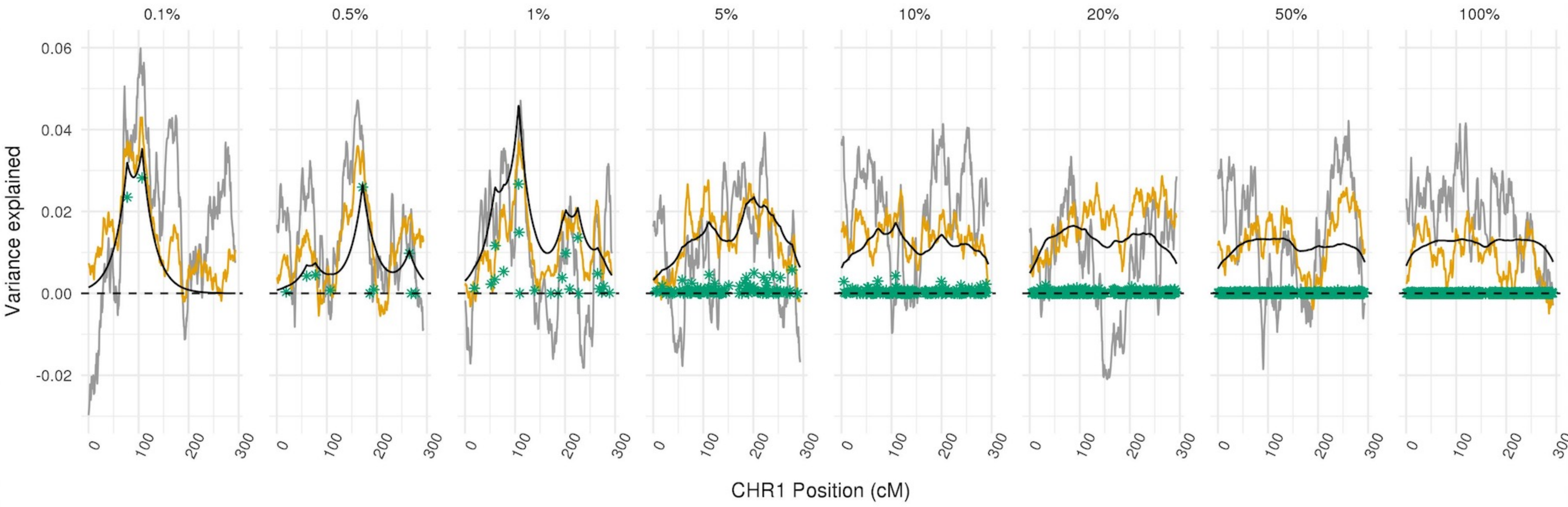


Peaks drop when fitting PGS

Detect new peaks too!

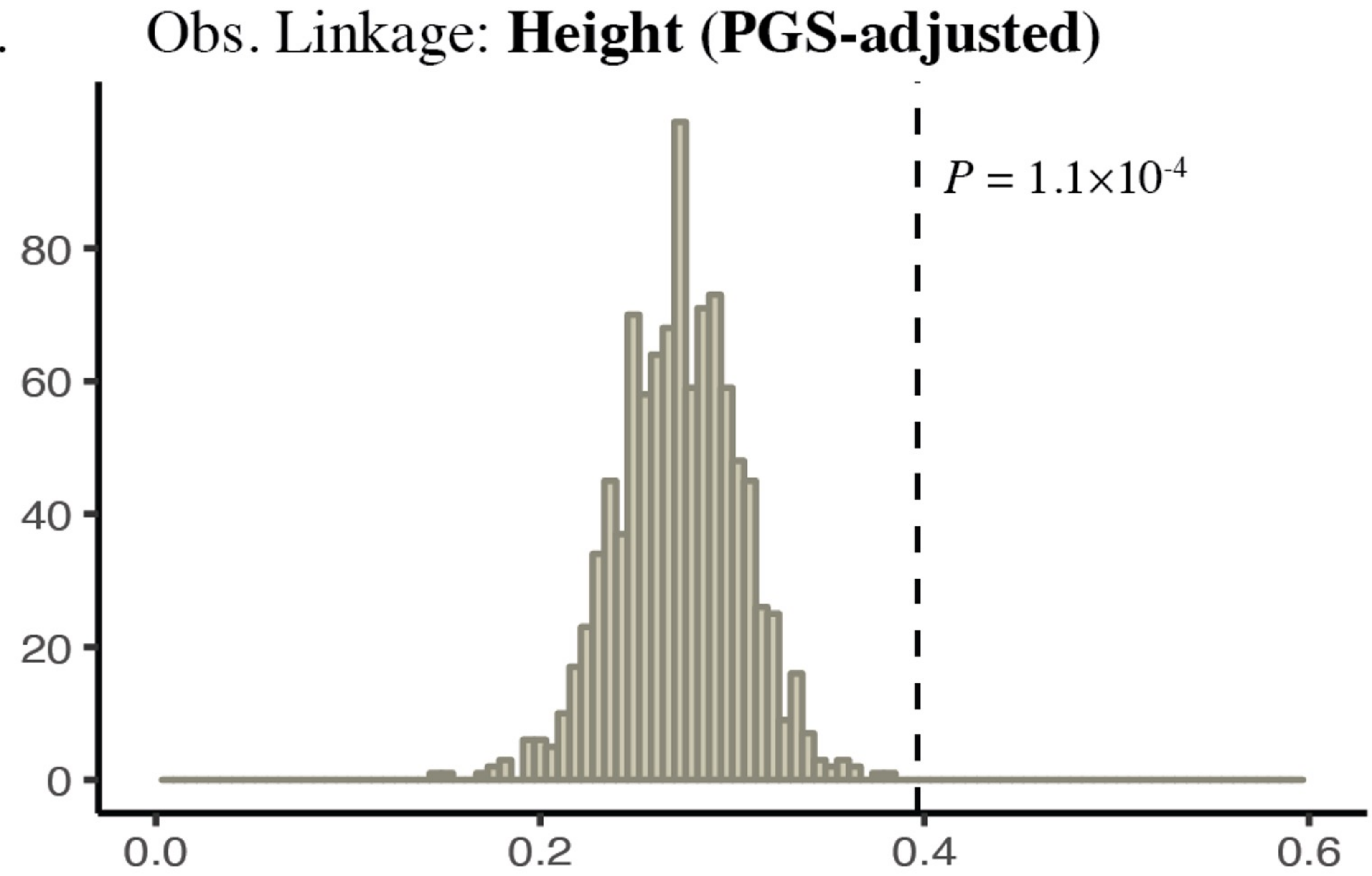
Measuring Colocalization of GWAS and linkage signals

(for locus k: $q^2(k) = SUM[2 * p_i * (1 - p_i) * b_i^2 * exp(-4 * L_i k)]$

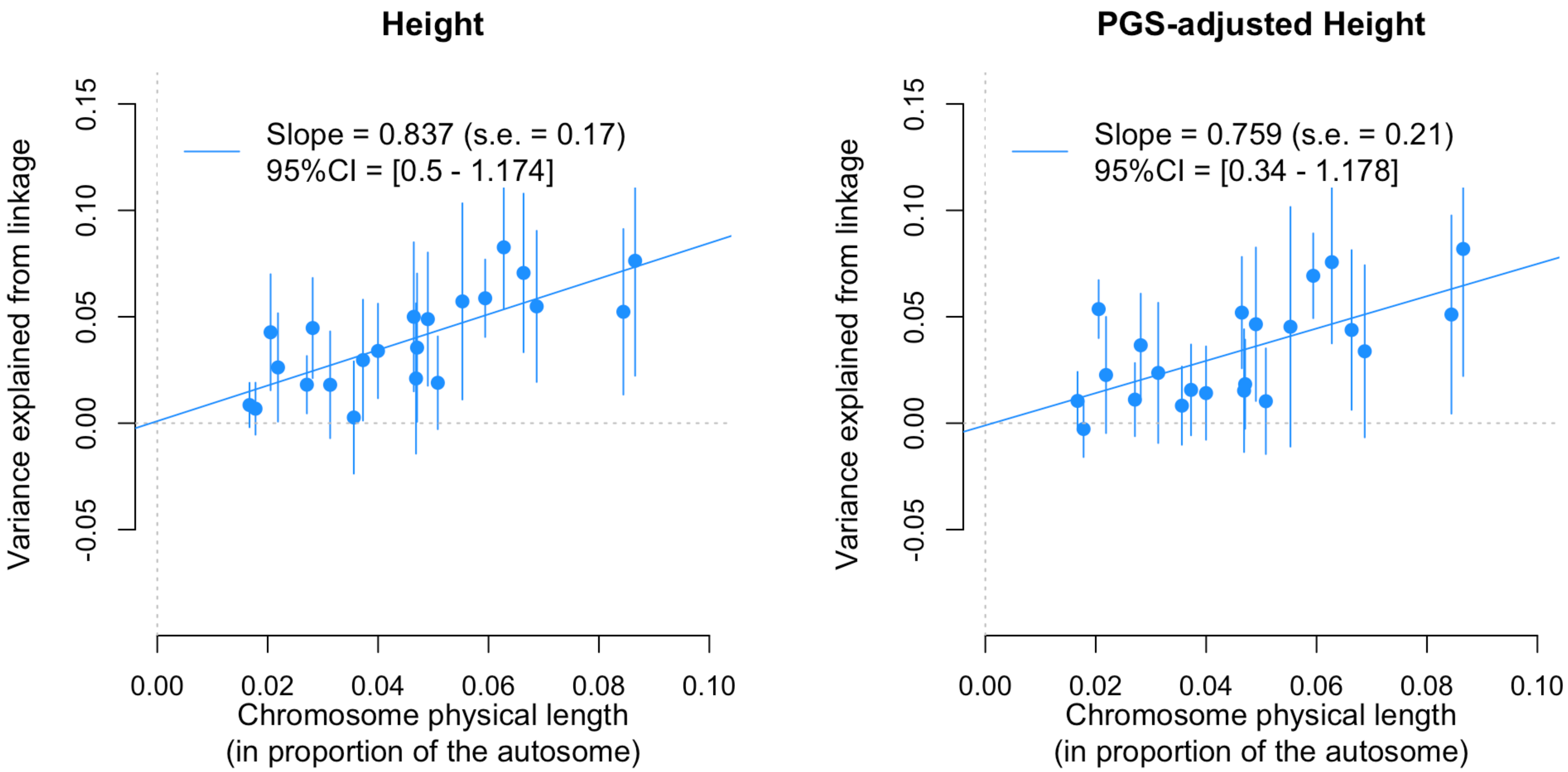


Dekkers & Dentine (1991)

Still-missing heritability colocalizes with GWAS hits



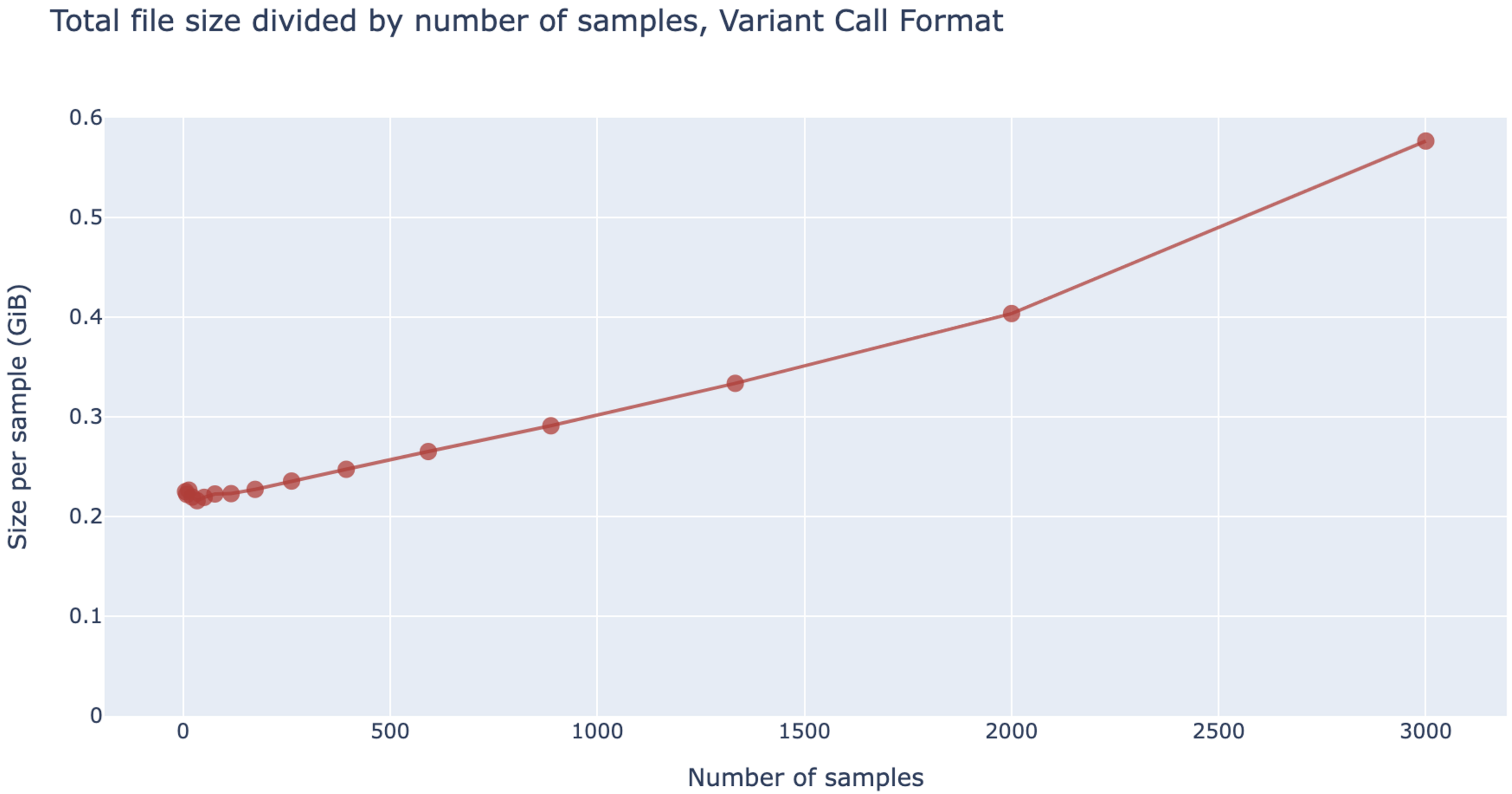
Still-missing heritability is polygenic



Tim Poterba

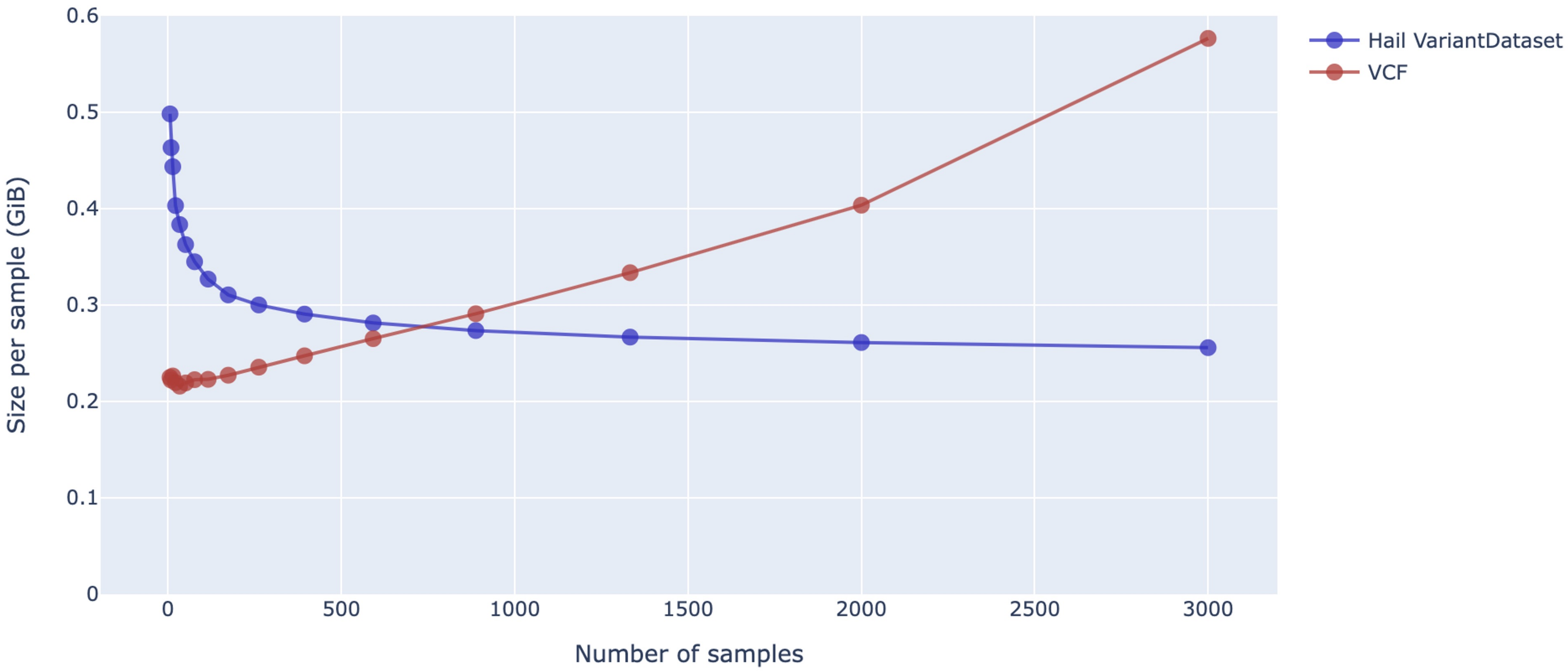
Standardizing scalable representations and formats for the era of million-sample sequencing datasets

Tim Poterba
Neale Lab, Broad Institute



Variant Call Format (VCF) - ubiquitous format for sequenced cohorts

The problem – VCF grows super-linearly in the number of samples, even though the amount of information grows linearly!



VariantDataset (VDS) - a data model that (+) scales linearly, (+) is losslessly mergeable, (+) can be merged!

How do we standardize a better representation?

Elizabeth Prom-Wormley

Including the Wisdom of Community and Participant Voices in Genetically Informative Research: A Richmond Story

Elizabeth Prom-Wormley MPH, PhD
Hermine Maes, PhD
Virginia Commonwealth University

Virginia Twin Study of Adolescent Behavioral Development + The Resist! Project

Data Collection

Mixed Methods Approach to establish an index of resistance factors (~120 twins)

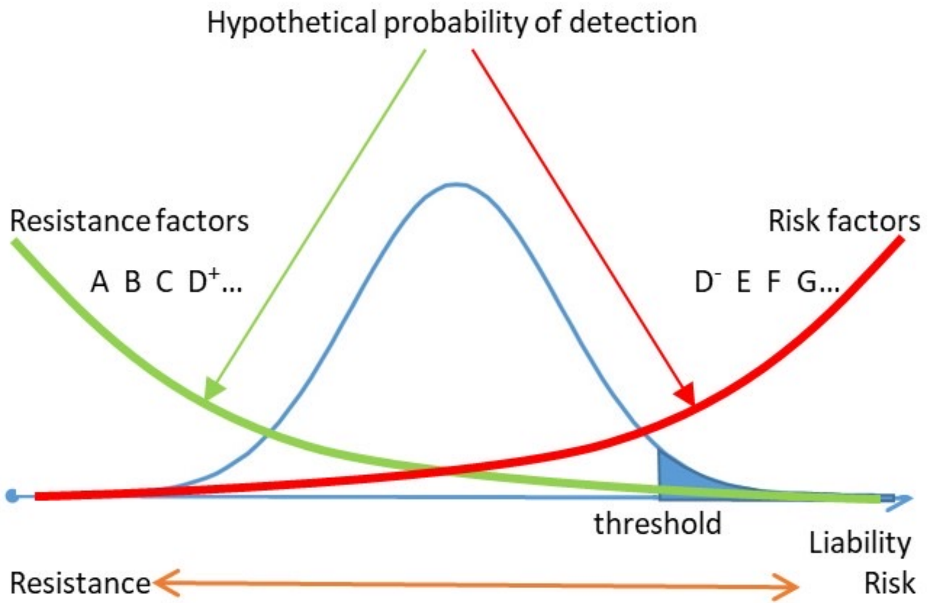
Secondary Data Analysis

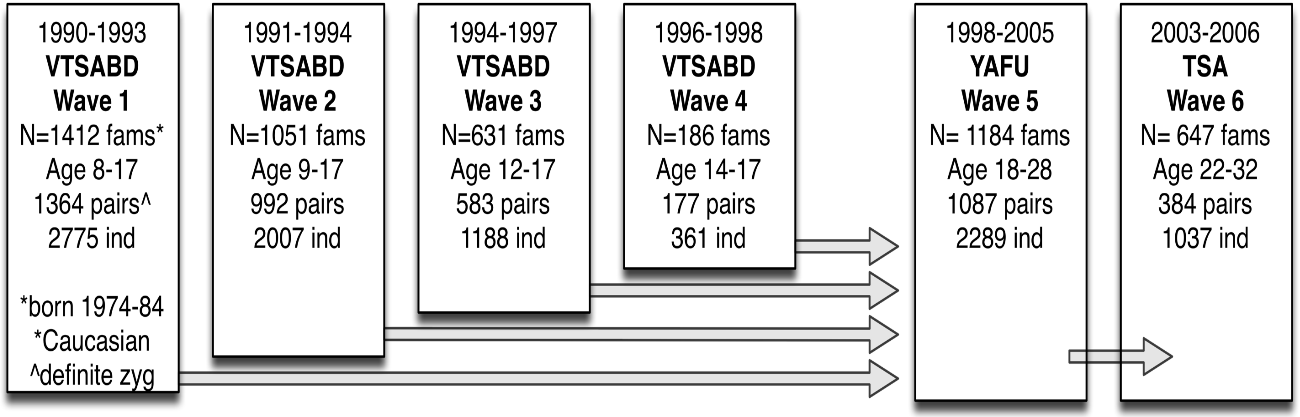
- Analyze collected variables to assess low-end of liability to substance use (resistance)
- Assess substance use trajectories of liability groups
- Conduct data mining of environmental factors to identify most important for resistance

Wave 7 Data Collection of VTSABD Twins

Resistance factors index*

Substance use behaviors, other behaviors





1990-1993 **VTSABD** **Wave 1**	1991-1994 **VTSABD** **Wave 2**	1994-1997 **VTSABD** **Wave 3**	1996-1998 **VTSABD** **Wave 4**	1998-2005 **YAFU** **Wave 5**	2003-2006 **TSA** **Wave 6**
N=1412 fams*	N=1051 fams	N=631 fams	N=186 fams	N= 1184 fams	N= 647 fams
Age 8-17	Age 9-17	Age 12-17	Age 14-17	Age 18-28	Age 22-32
1364 pairs^	992 pairs	583 pairs	177 pairs	1087 pairs	384 pairs
2775 ind	2007 ind	1188 ind	361 ind	2289 ind	1037 ind
*born 1974-84 *Caucasian ^definite zyg					

Why Do You Focus on Our Deficits?

2014

East End Residents
Alexis Edwards, PhD
Amy Popovich
Aquanetta Scott
Brandon Wormley
Brenda Kenney
Brittany McDermott
Cheryl Groce-Wright
Cynthia Newbille
Danita Gregory
De’Nisha Wilson
Dyanne Broidy
Faisal Ilyas
Gwen Corleigh Creighton
Helen Frye
Joanne Towles
Joseph Real
Katherine Crawford
Laleta Fritz
Michelle Wagner
Naomi Davis
Natalie Bareis
Patricia Willaford
Rhonda Perry-Acholes
Richard Seely
Shikitia Taylor
Stephanie Carrington
Tony Cornelious

Team RIA

- Dr. Omobukola Usidame
- Courtney Blondino
- James Clifford

VCU Office of Community Engagement

Richmond Memorial Health Foundation Engaging Richmond

Richmond Promise Neighborhoods- Community Action Network

7th District Health and Wellness Initiative

Richmond Health and Wellness Program

2020

Peter Paul Community Action Network

Richmond City Health District- Stephanie Carrington, Ivy Bell, Catherine Long

Planned Parenthood- LaNeda Wright

Faith Covenant Christian Fellowship Church- Justin Parkinson

Richmond City Public Schools, Office of Engagement

Darryl Williams, Erin Brown

VCU Health Hub at 25th- Natalie Pennywell, KJ Ricasata

5th Street Baptist Church

Church Hill Association

Neighborhood Resource Center

Survey Subcommittee

Candice Turner, Chanel Bea, Chimere Miles, Kim Young, Sherika Gillison-Chew

Team RIA (Research Inspiring Action)

Courtney Blondino, Kia Miles, Mariam Sankoh, Angela Liu, Syreen Goulamine, Anna Lee, Nora Mulroy, Jim Clifford, Brandon Wormley, Edith Prom, Trenece Wilson, Brittini Myrick, Alyson Vanlandingham, Heather Liffert, Maya Tucker, and the undergrad army

What’s the Benefit for Us?

Actions Requiring Minimum Effort

- Uplift the work of groups that do community-engaged research REGARDLESS of funding status
  - Consistently share skills, knowledge and resources without expectations

- Offer training for staff /community members who might be interested in learning more about research or research-related skills
  - Community Advisory Board
  - Community/Academia Research Fellows Program
  - Seminars/workshops (opportunities for trainees!)

- Incorporate publicly facing segments to research retreats/workshops or classic research products (e.g., flyers, blog posts) for ALL
  - Consult with community members AND compensate when possible
  - Community events

Thank You

Looking for a postdoctoral fellowship?

We’re hiring!

Elizabeth.Prom-Wormley@vcuhealth.org

Rohan Palmer

Applications of Statistical Genetics to Substance Use Disorders & Related Behaviors

EMORY

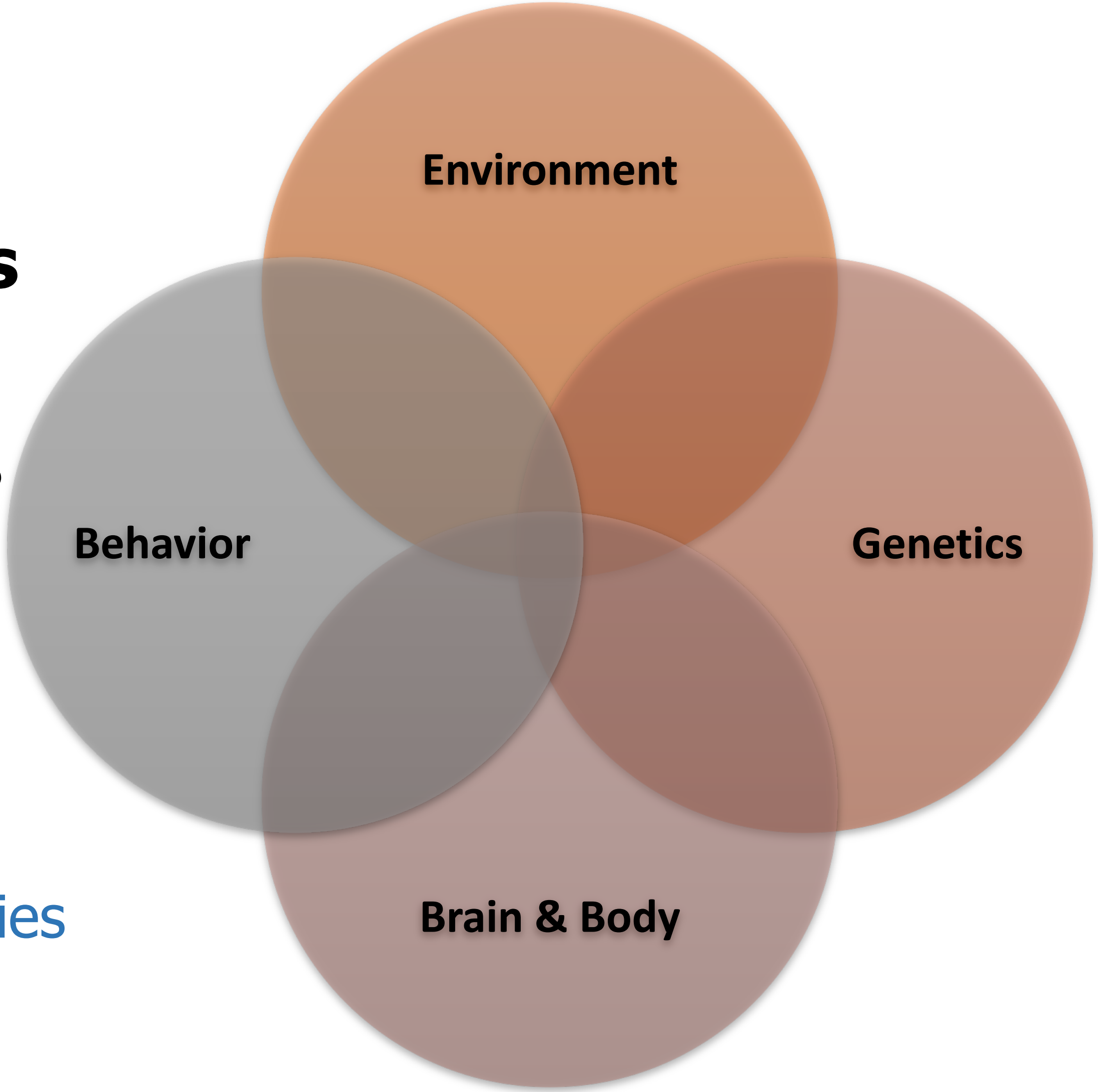
Rohan H C Palmer, PhD

Principal Investigator

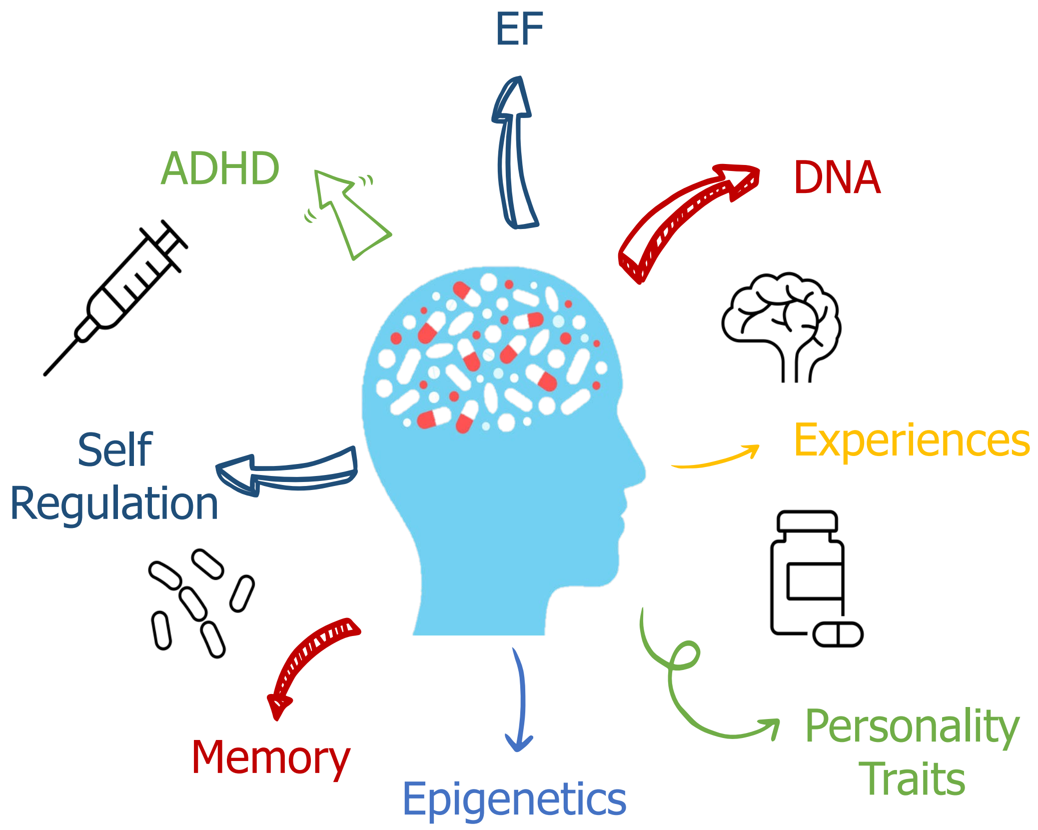
Associate Professor of Psychology

Research Goals

- **Identify mechanisms of risk for addiction and related behaviors using bio-behavioral approaches**
- **Enhance gene finding strategies for psychiatric genetics**
  - Data mining large populations
  - Phenotype refinement
  - Incorporation of knowledge across different omics' / species
  - Developing new translational technologies



The Many Facets of Drug Addiction



Addiction	- A chronically relapsing disorder
Characterizations	- Compulsion to seek and take a drug - Loss of control in limiting intake - Emergence of a negative emotional state (e.g. dysphoria, anxiety, irritability) when access to the drug is prevented

Approaches

Twins and Relatives

Population Registries

Comorbidity Studies

Longitudinal Studies

Quasi-Experimental Studies

Methods Development

Translational Studies

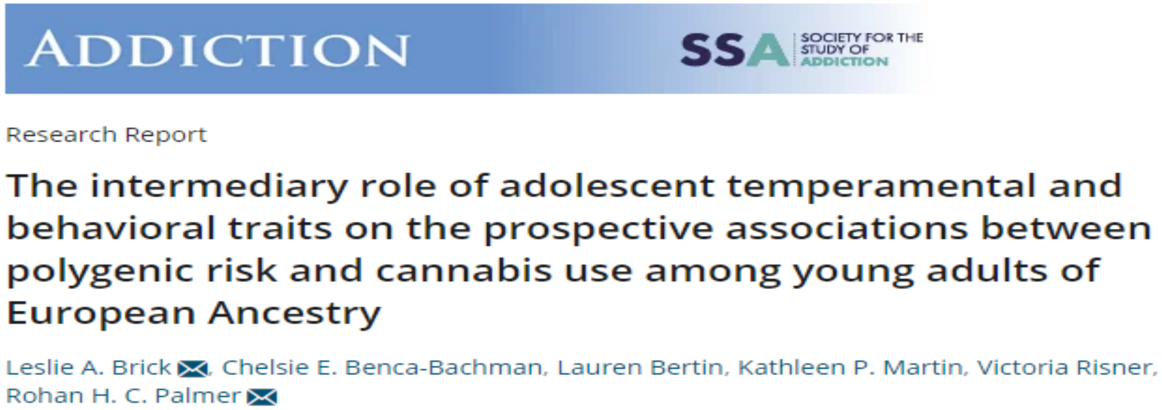
Understanding Drug Behaviors

Polygenic Applications to Addictive Behaviors

JOURNAL ARTICLE

Multi-Polygenic Analysis of Nicotine Dependence in Individuals of European Ancestry

Victoria A Risner, BS, Chelsie E Benca-Bachman, PhD, Lauren Bertin, MA, Alicia K Smith, PhD, Jaakko Kaprio, PhD, John E McGeary, PhD, Elissa Chesler, PhD, Valerie S Knopik, PhD, Naomi P Friedman, Rohan H C Palmer, PhD



ADDICTION

SSA SOCIETY FOR THE STUDY OF ADDICTION

Research Report

The intermediary role of adolescent temperamental and behavioral traits on the prospective associations between polygenic risk and cannabis use among young adults of European Ancestry

Leslie A. Brick, Chelsie E. Benca-Bachman, Lauren Bertin, Kathleen P. Martin, Victoria Risner, Rohan H. C. Palmer

R01DA042742 [Palmer]

Genetic Studies in Substance Use Disorder

Original Article

Shared additive genetic variation for alcohol dependence among subjects of African and European ancestry

Leslie A. Brick, Matthew C. Keller, Valerie S. Knopik, John E. McGeary, Rohan H.C. Palmer ✉

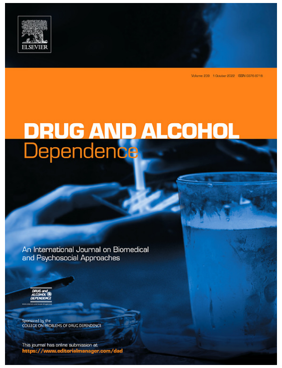
First published: 27 November 2017 | https://doi.org/10.1111/adb.12578

Opioid Use Disorder and Alternative mRNA Splicing in Reward Circuitry

by Spencer B. Huggett [1] ✉, Ami S. Ikeda [1] ✉, John E. McGeary [2] ✉, Karla R. Kaun [3] ✉ and Rohan H. C. Palmer [1,*] ✉

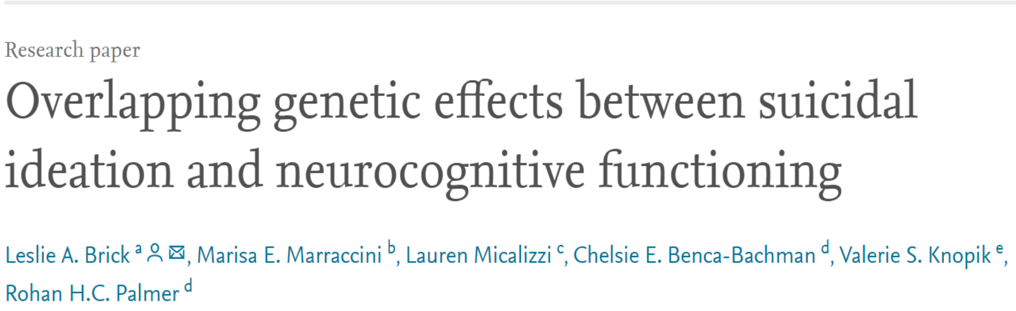
The etiology of DSM-5 alcohol use disorder: Evidence of shared and non-shared additive genetic effects

Rohan H.C. Palmer [a] ✉, Leslie A. Brick [b, c], Yi-Ling Chou [d], Arpana Agrawal [d], John E. McGeary [b, c, e], Andrew C. Heath [d], Laura Bierut [d], Matthew C. Keller [f], Eric Johnson [g], Sarah M. Hartz [d], Marc A. Schuckit [h], Valerie S. Knopik [i]



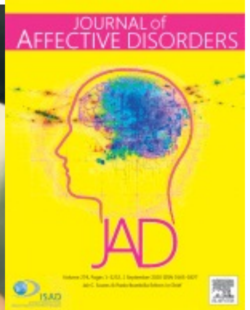
K01AA021113 [Palmer]
DP1DA042103 [Palmer]

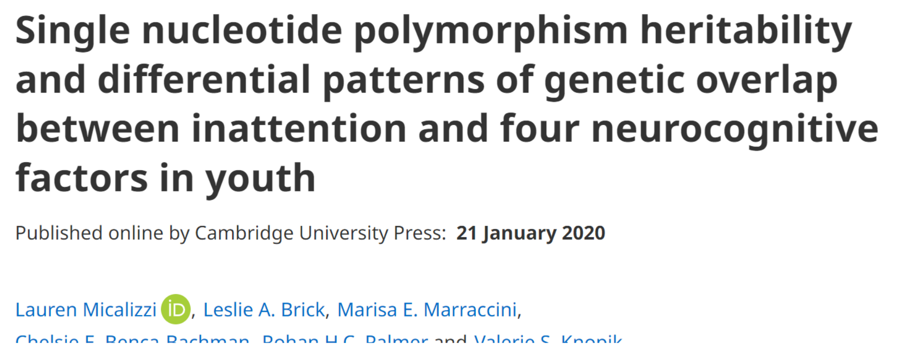
Genetic Studies of Cognition & Psychopathology


Research paper

Overlapping genetic effects between suicidal ideation and neurocognitive functioning

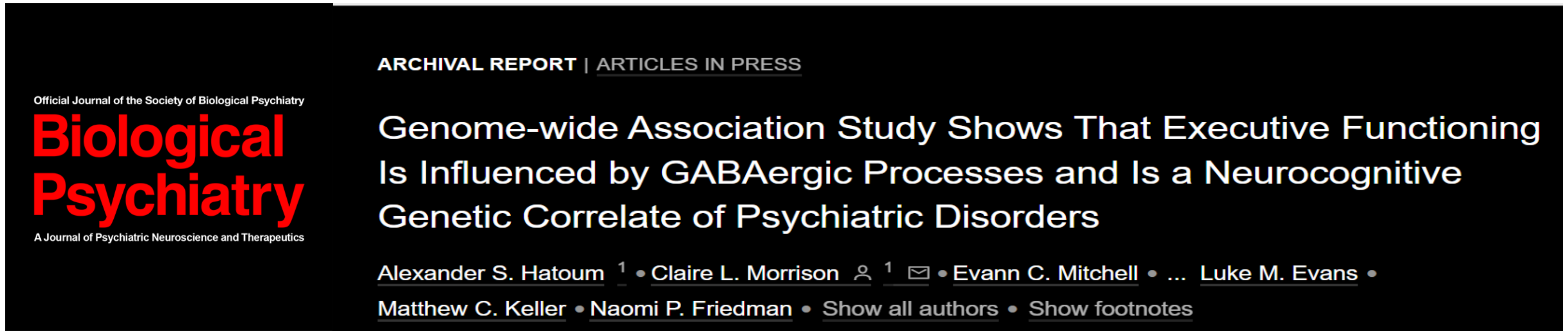
Leslie A. Brick [a], Marisa E. Marraccini [b], Lauren Micalizzi [c], Chelsie E. Benca-Bachman [d], Valerie S. Knopik [e], Rohan H.C. Palmer [d]




Single nucleotide polymorphism heritability and differential patterns of genetic overlap between inattention and four neurocognitive factors in youth

Published online by Cambridge University Press: **21 January 2020**

Lauren Micalizzi, Leslie A. Brick, Marisa E. Marraccini,
Chelsie E. Benca-Bachman, Rohan H.C. Palmer and Valerie S. Knopik


Official Journal of the Society of Biological Psychiatry

Biological Psychiatry

A Journal of Psychiatric Neuroscience and Therapeutics

ARCHIVAL REPORT | ARTICLES IN PRESS

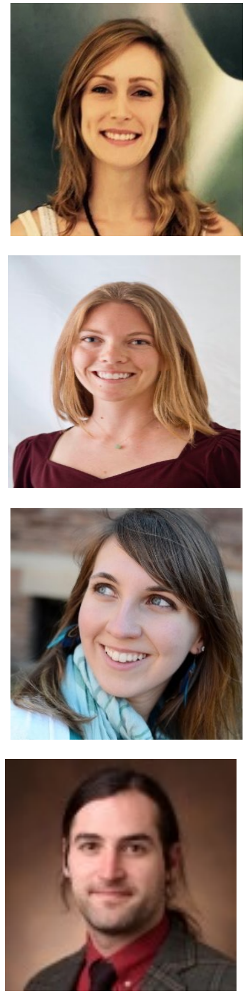
Genome-wide Association Study Shows That Executive Functioning Is Influenced by GABAergic Processes and Is a Neurocognitive Genetic Correlate of Psychiatric Disorders

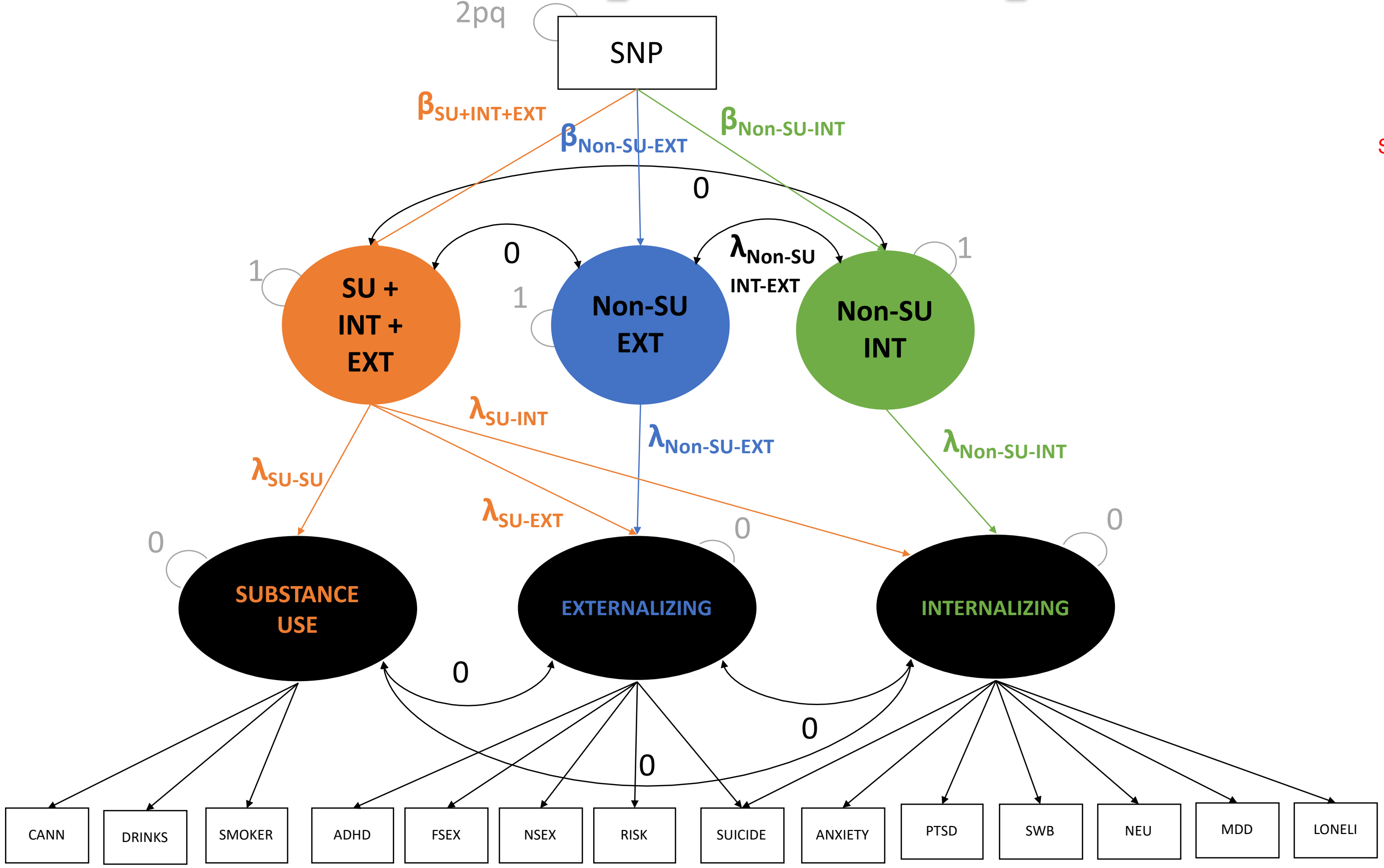
Alexander S. Hatoum [1] • Claire L. Morrison [1] • Evann C. Mitchell • ... Luke M. Evans • Matthew C. Keller • Naomi P. Friedman • Show all authors • Show footnotes

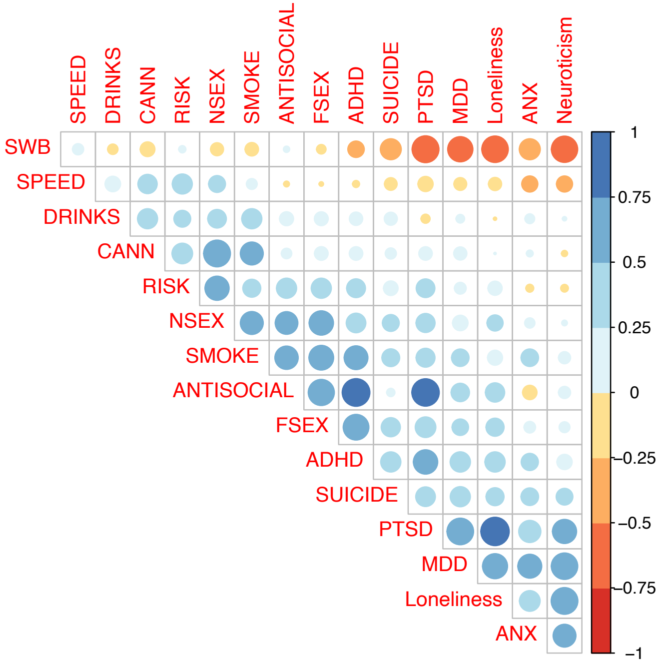
R01DA042742 [Palmer]

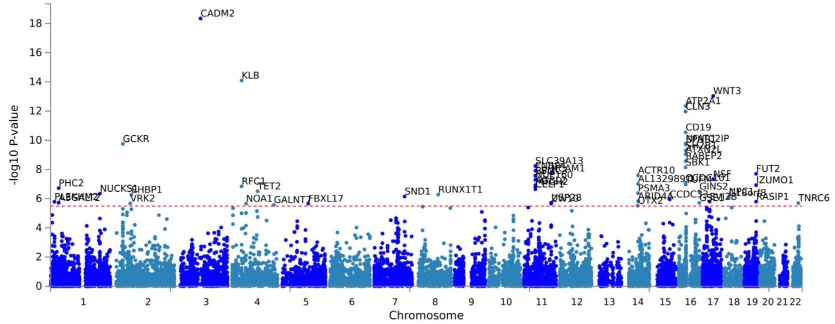
Ongoing works

Genetics Study of PolySubstance Use







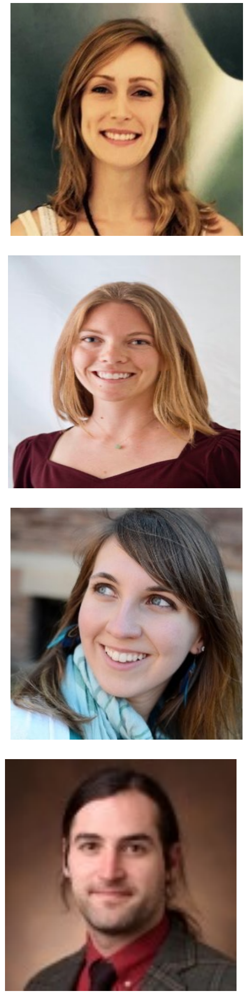


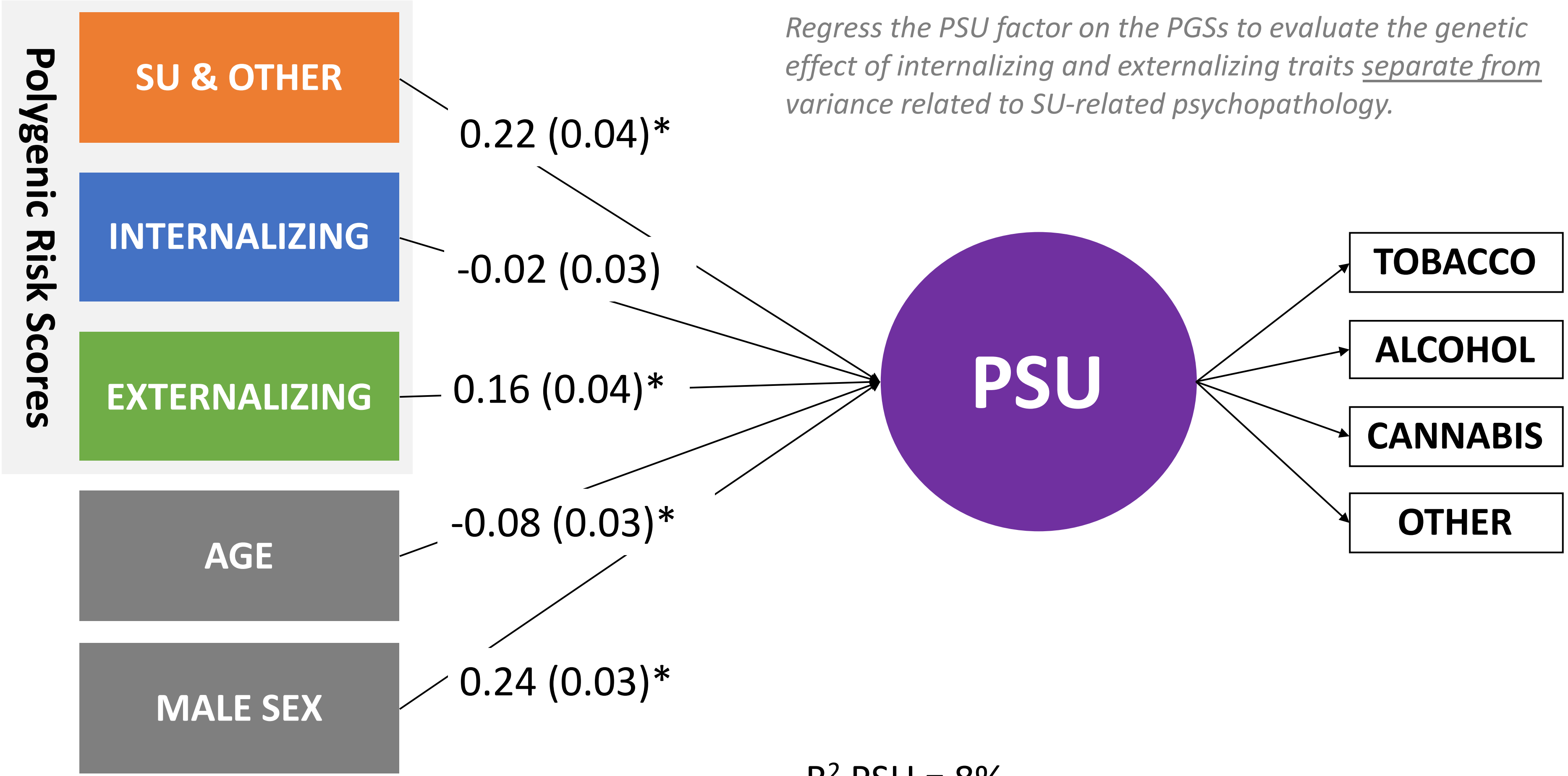
414 hits

$h^2 = 0.48\ (0.02)$

R01DA042742 [Palmer]

PGSs predict Polydrug Use in AddHealth





Polygenic Risk Scores

SU & OTHER — 0.22 (0.04)*

INTERNALIZING — -0.02 (0.03)

EXTERNALIZING — 0.16 (0.04)*

AGE — -0.08 (0.03)*

MALE SEX — 0.24 (0.03)*

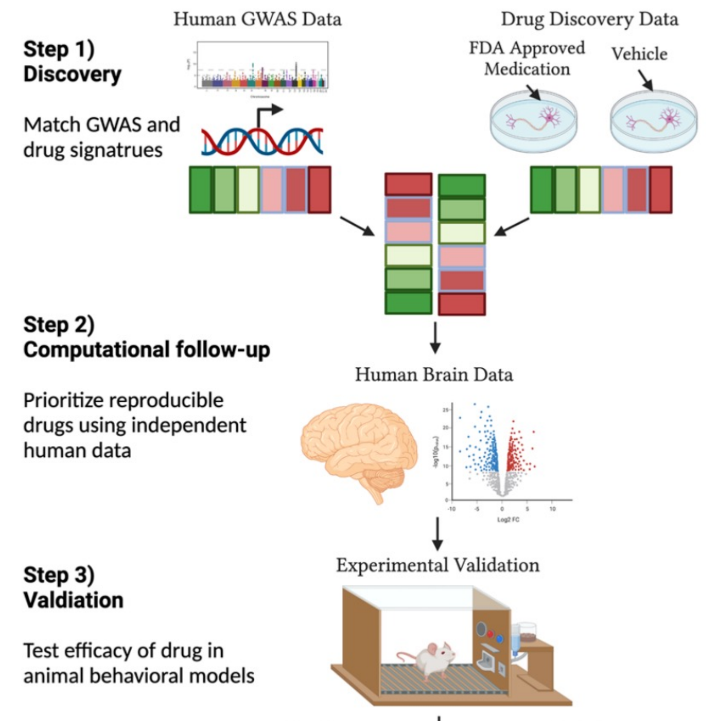
PSU → TOBACCO, ALCOHOL, CANNABIS, OTHER

Regress the PSU factor on the PGSs to evaluate the genetic effect of internalizing and externalizing traits <u>separate from</u> variance related to SU-related psychopathology.

R^2 PSU = 8%

$\chi^2(17)=89.77$, $p<0.001$, CFI=0.89, RMSEA=0.03

R01DA042742 [Palmer]



Step 1)
Discovery

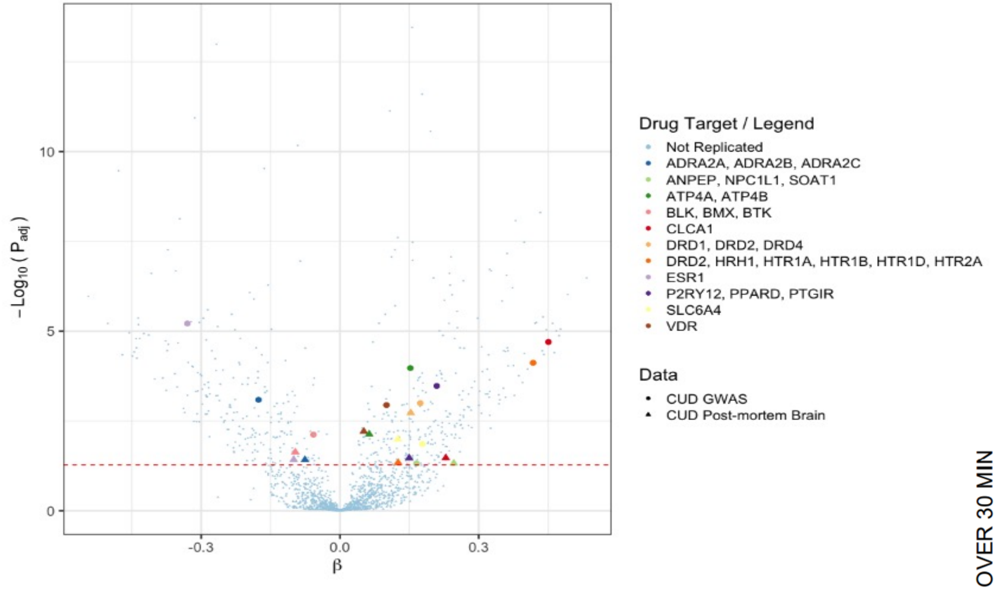
Match GWAS and drug signatrues

Step 2)
Computational follow-up

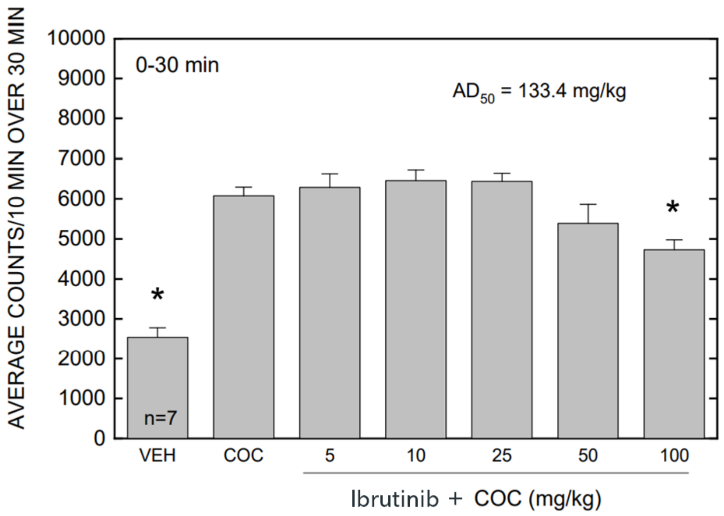
Prioritize reproducible drugs using independent human data

Step 3)
Valdiation

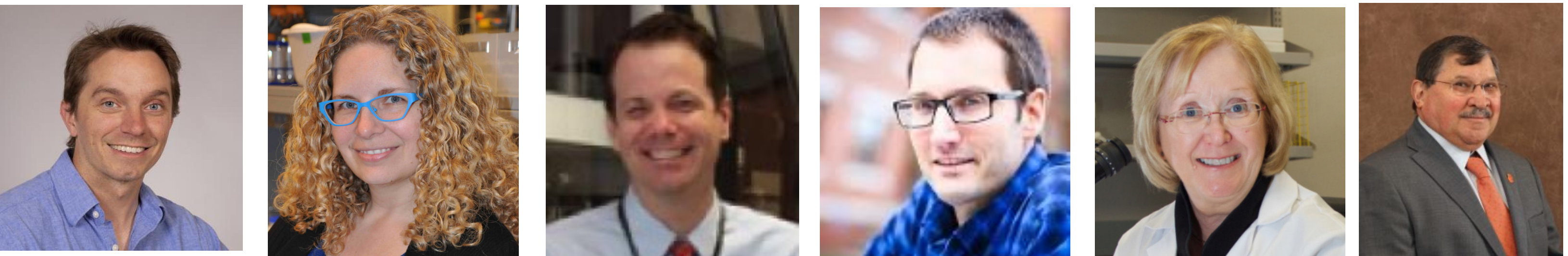
Test efficacy of drug in animal behavioral models



Ibrutinib attenuates cocaine locomotor behavior



THERAPIES FOR COCAINE & OPIOID ADDICTION



DP1DA042103 [Palmer]

Accepting postdoctoral trainees

- **Contact Rohan.Palmer@Emory.edu**

Sarah Medland

THE EQUINOX CONFERENCE

Statistical Genetics – Genetic Epidemiology – Behaviour Genetics

21 September

Free – Accessible – Open – Supportive – Inclusive

http://equinoxconference.org/

How Does it work?

- 23.5 hours of science
- Continuous zoom call
- All presenters scheduled to talk during their usual waking hours
- Join when you can – watch a recording later

Abstracts are open to…

- People who are currently finding it difficult to travel to attend in-person conferences
  - For any reason
- People whose work is so cross disciplinary that it is hard to find a 'home'

EVERY ONE <u>is</u> WELCOME to ATTEND!

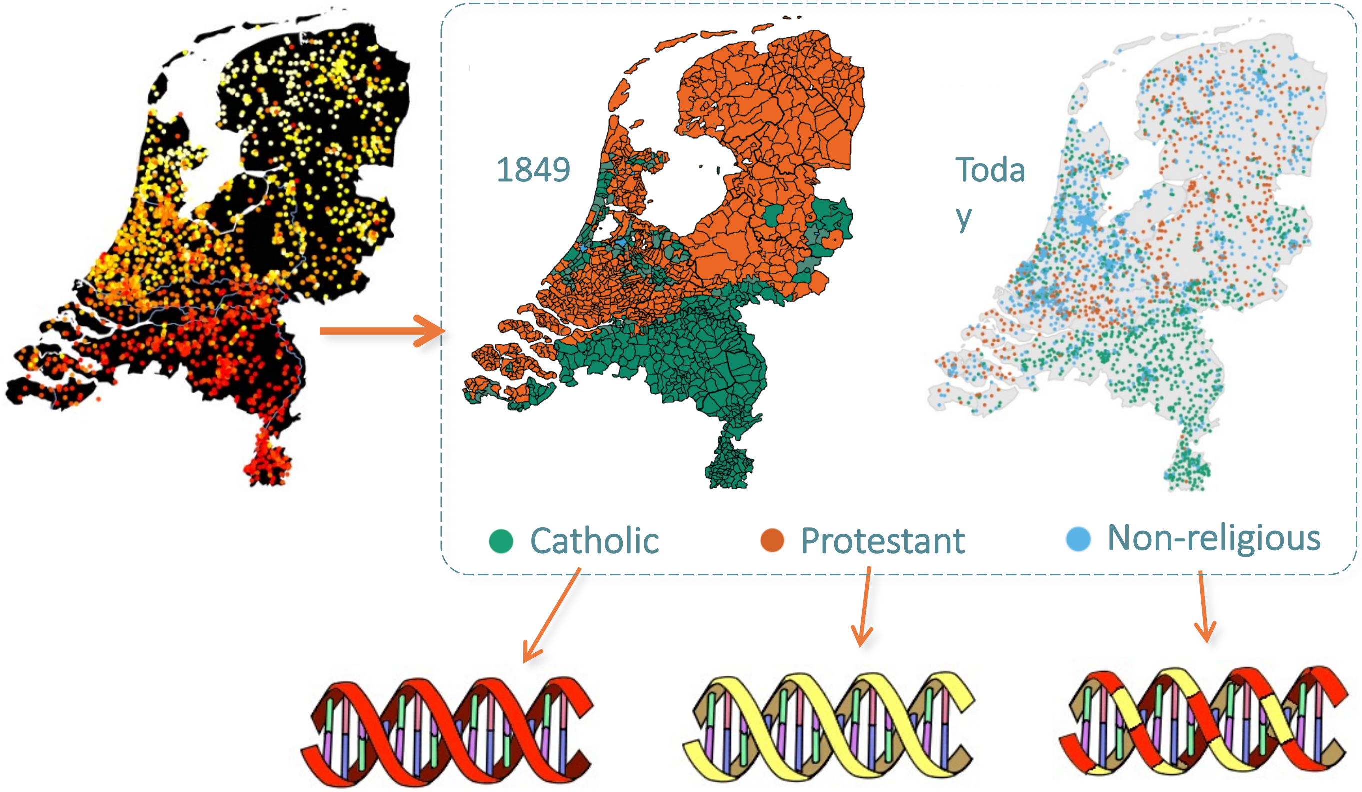
Abdel Abdellaoui

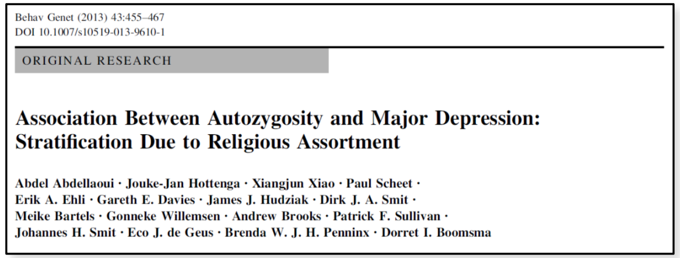
BEHAVIOR ↔ GENETICS

ABDEL ABDELLAOUI

a.abdellaoui@amsterdamumc.nl

dr_appi
e

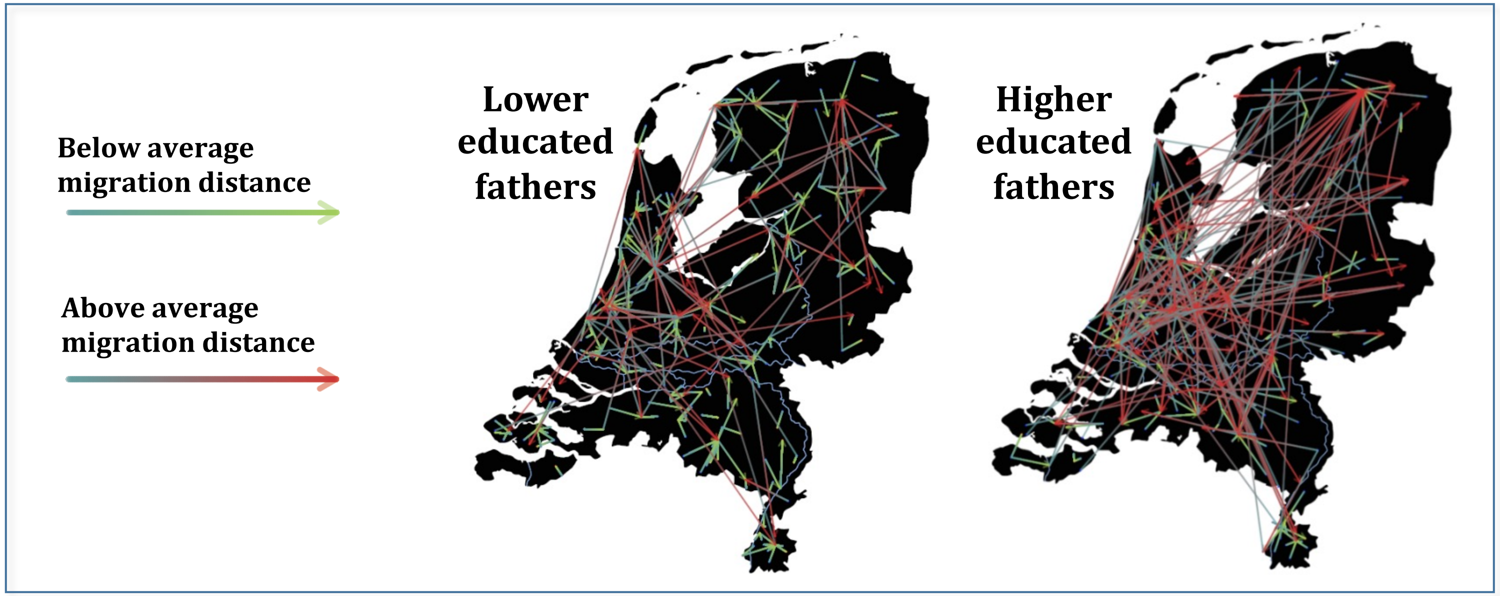



Behav Genet (2013) 43:455–467
DOI 10.1007/s10519-013-9610-1

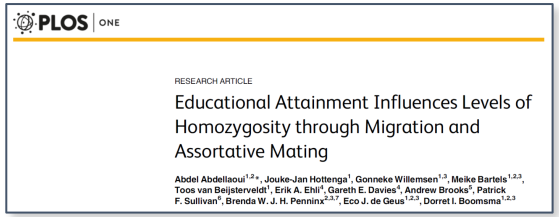
ORIGINAL RESEARCH

Association Between Autozygosity and Major Depression: Stratification Due to Religious Assortment

Abdel Abdellaoui · Jouke-Jan Hottenga · Xiangjun Xiao · Paul Scheet ·
Erik A. Ehli · Gareth E. Davies · James J. Hudziak · Dirk J. A. Smit ·
Meike Bartels · Gonneke Willemsen · Andrew Brooks · Patrick F. Sullivan ·
Johannes H. Smit · Eco J. de Geus · Brenda W. J. H. Penninx · Dorret I. Boomsma



- Educational attainment was significantly associated with F_{roh} (inbreeding)
- But parental education was *much* more significantly associated with F_{roh}
- Why?
  - Higher educated parents **migrated** significantly more often and greater distances
  - There is strong **assortative mating** for educational attainment

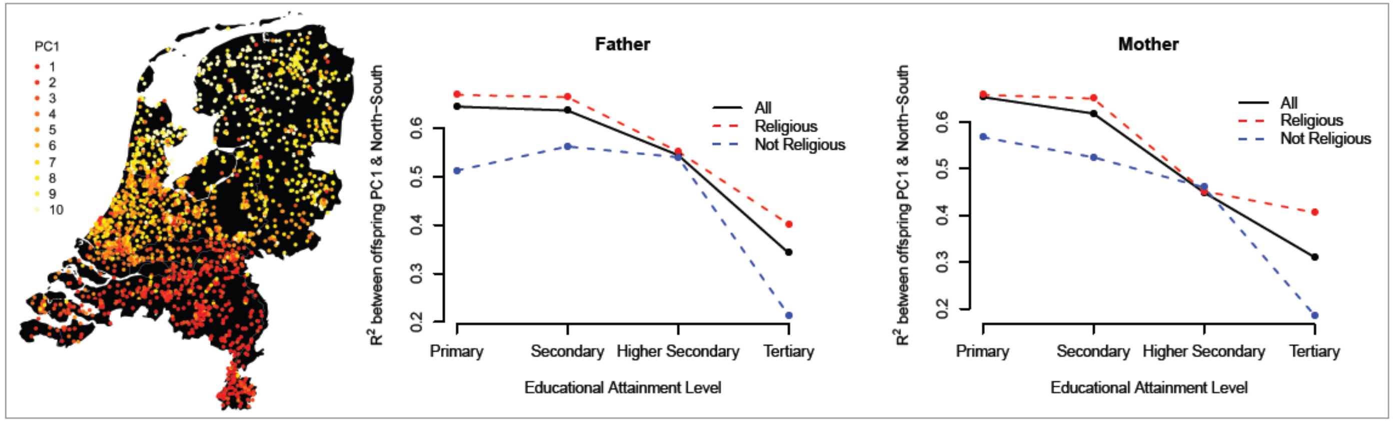

PLOS | ONE

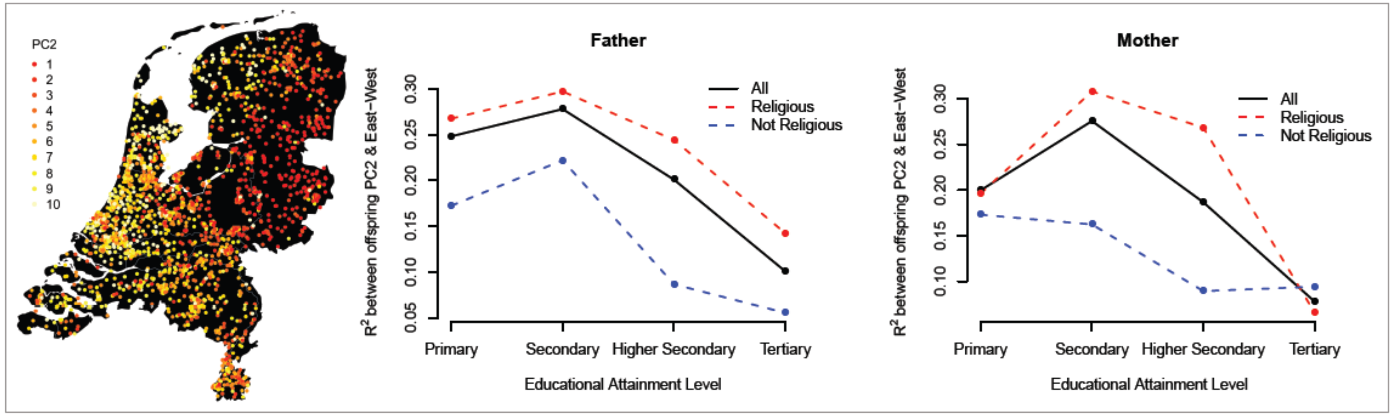
RESEARCH ARTICLE

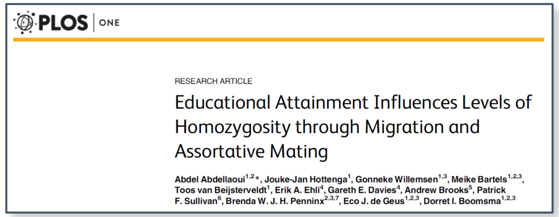
Educational Attainment Influences Levels of Homozygosity through Migration and Assortative Mating

Abdel Abdellaoui[1,2]*, Jouke-Jan Hottenga[1], Gonneke Willemsen[1,3], Meike Bartels[1,2,3], Toos van Beijsterveldt[1], Erik A. Ehli[4], Gareth E. Davies[4], Andrew Brooks[5], Patrick F. Sullivan[6], Brenda W. J. H. Penninx[2,3,7], Eco J. de Geus[1,2,3], Dorret I. Boomsma[1,2,3]

Correlation between offspring ancestry and geography significantly decreased as parental education increased






PLOS | ONE

RESEARCH ARTICLE

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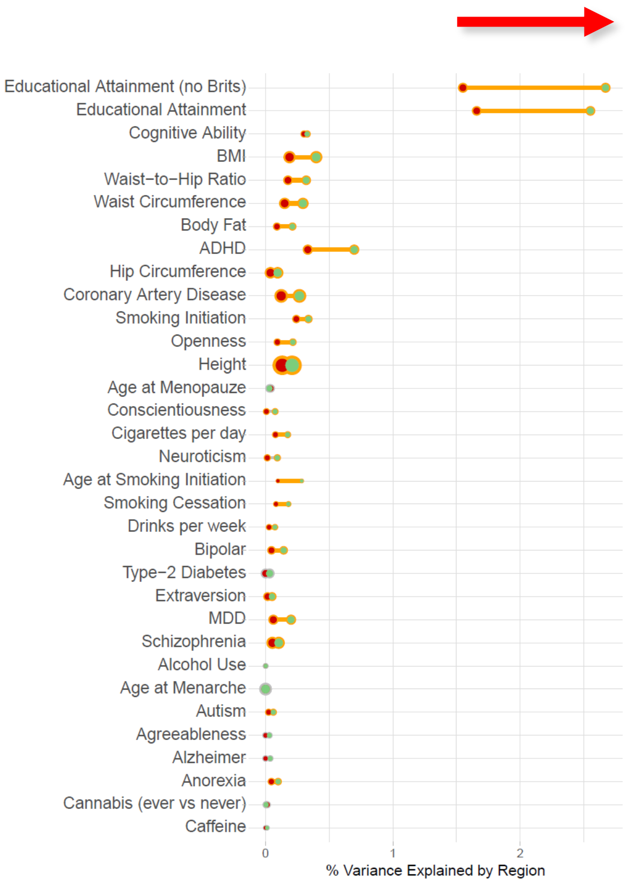
Polygenic Scores



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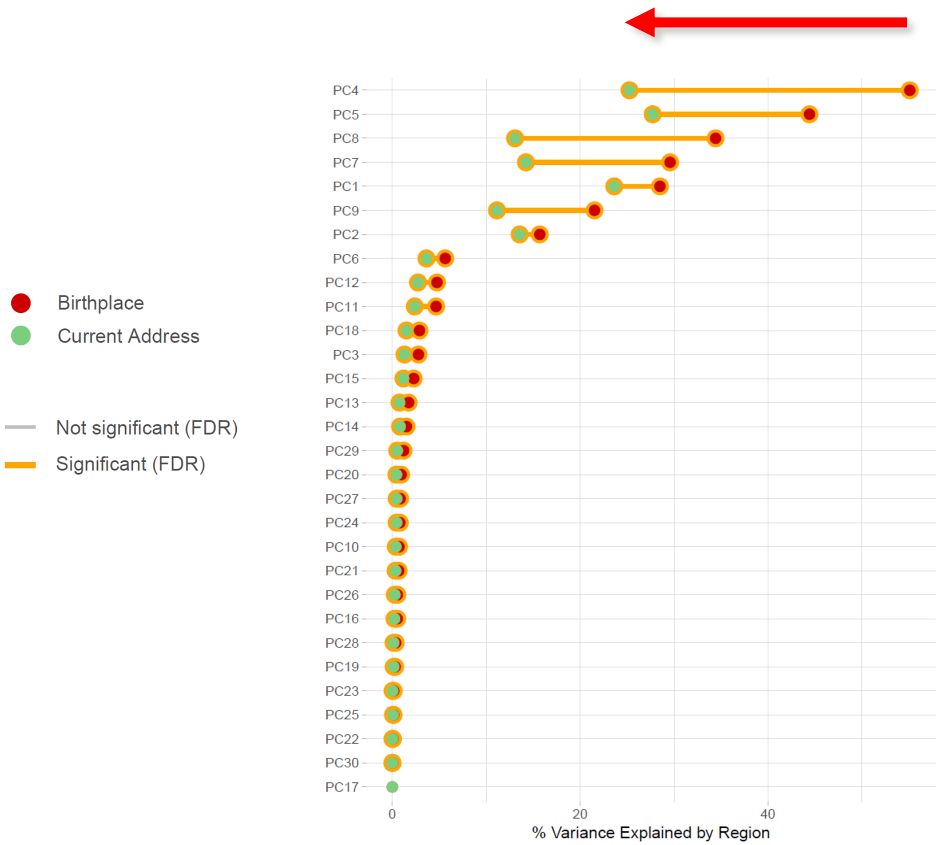


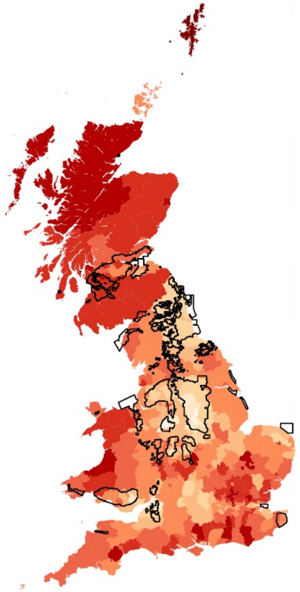
ARTICLES

https://doi.org/10.1038/s41562-019-0757-5

nature human behaviour

Genetic correlates of social stratification in Great Britain

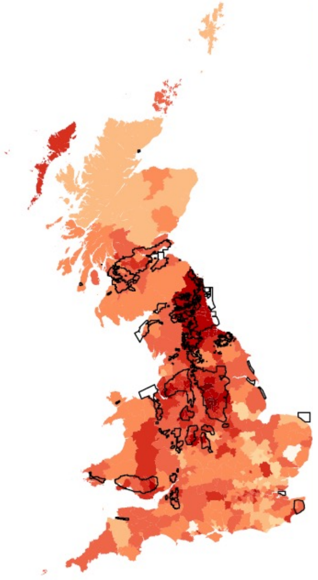
Abdel Abdellaoui[1*], David Hugh-Jones[2], Loic Yengo[3], Kathryn E. Kemper[3], Michel G. Nivard[4], Laura Veul[1], Yan Holtz[3], Brendan P. Zietsch[5], Timothy M. Frayling[6], Naomi R. Wray[3,7], Jian Yang[3,7], Karin J. H. Verweij[1] and Peter M. Visscher[3,7*]



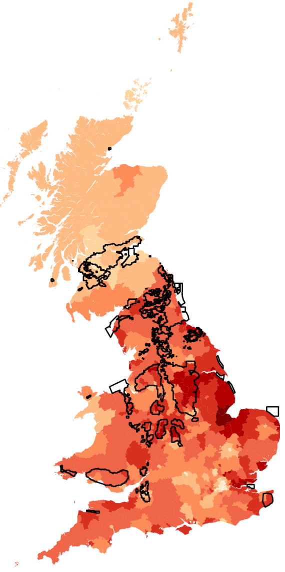
Educational Attainment Polygenic Score

(*EA3, without British cohorts*)

Townsend Index
(measure of economic deprivation)



Overall Health



Brexit
(Leave Votes)

ARTICLES
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Genetic correlates of social stratification in Great Britain

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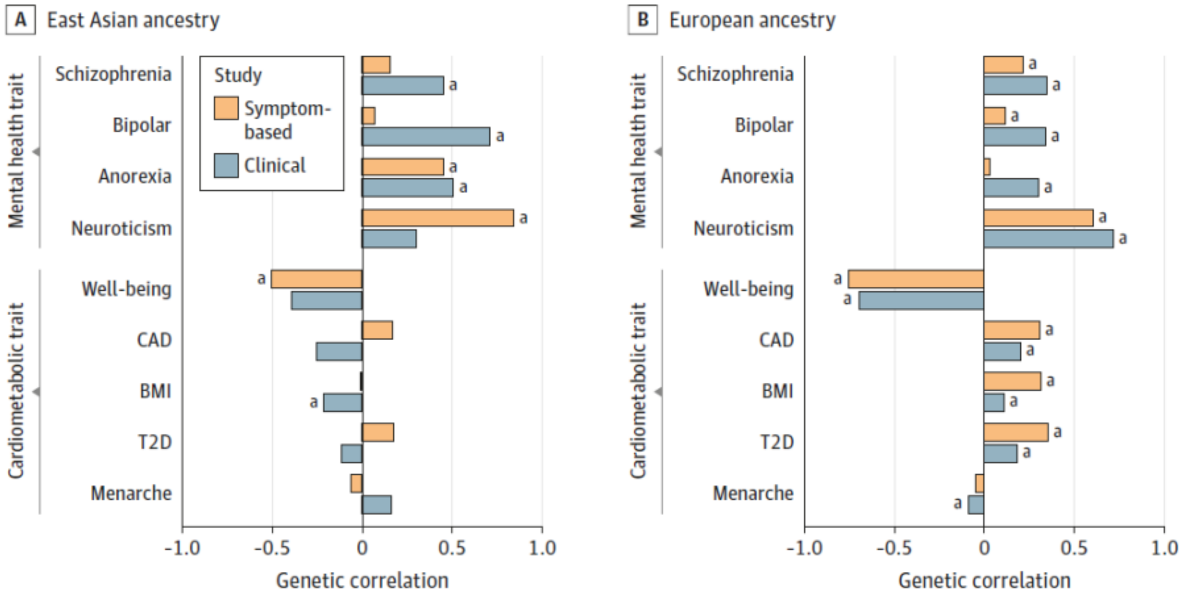
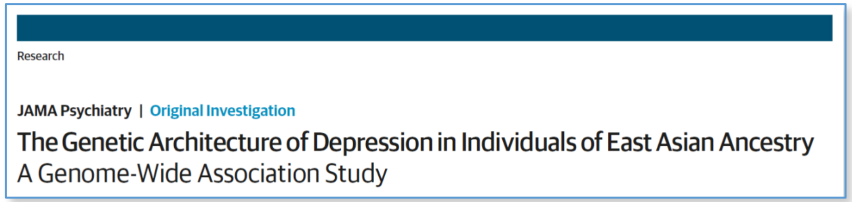
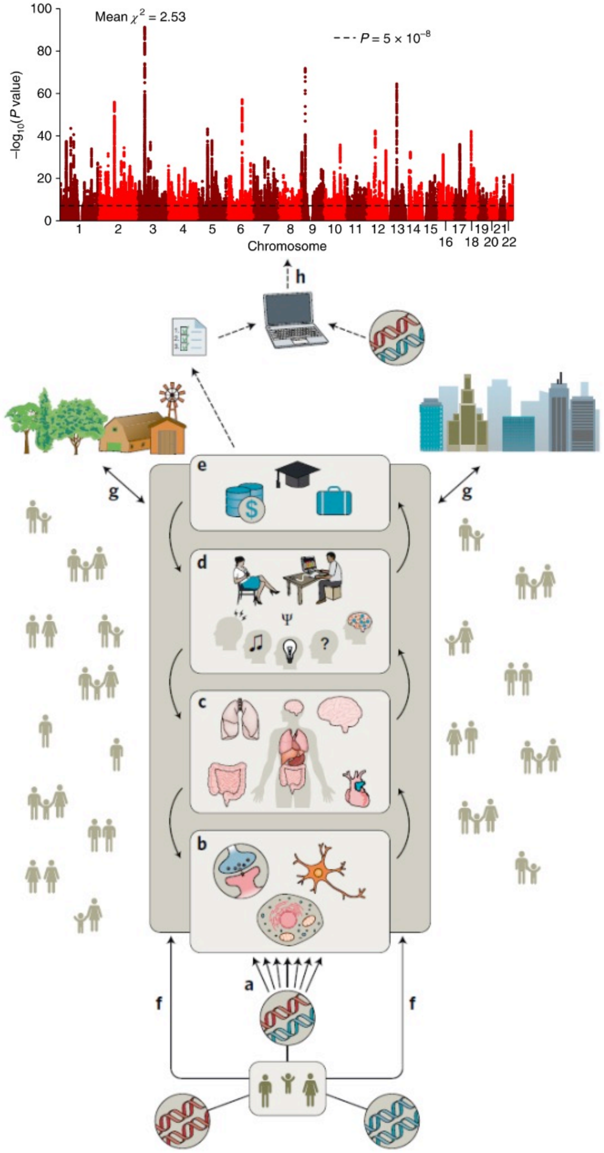
Figure 3. Genetic Correlations for Clinical and Symptom-Based Depression With Cardiometabolic and Mental Health Traits

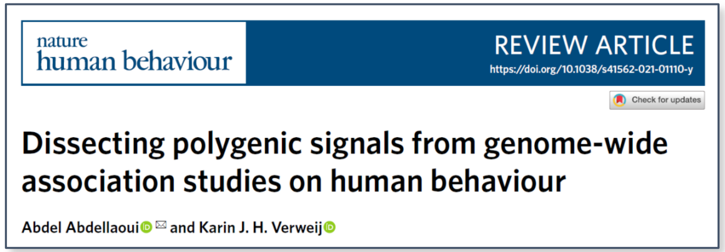



Research

JAMA Psychiatry | Original Investigation

The Genetic Architecture of Depression in Individuals of East Asian Ancestry
A Genome-Wide Association Study




nature
human behaviour

REVIEW ARTICLE

https://doi.org/10.1038/s41562-021-01110-y

Check for updates

Dissecting polygenic signals from genome-wide association studies on human behaviour

Abdel Abdellaoui and Karin J. H. Verweij

Brittany Mitchell

Dissecting heterogeneity in depression

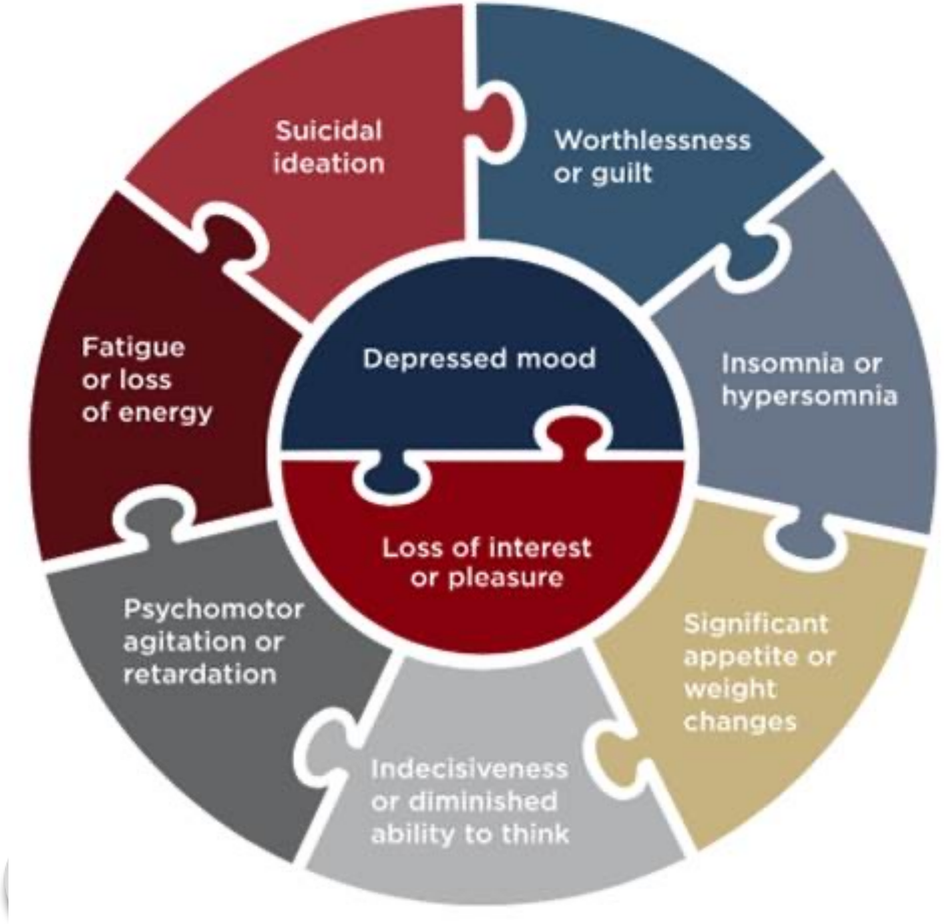
BRITTANY MITCHELL

QIMR Berghofer
Medical Research Institute

Australian Genetics of Depression Study

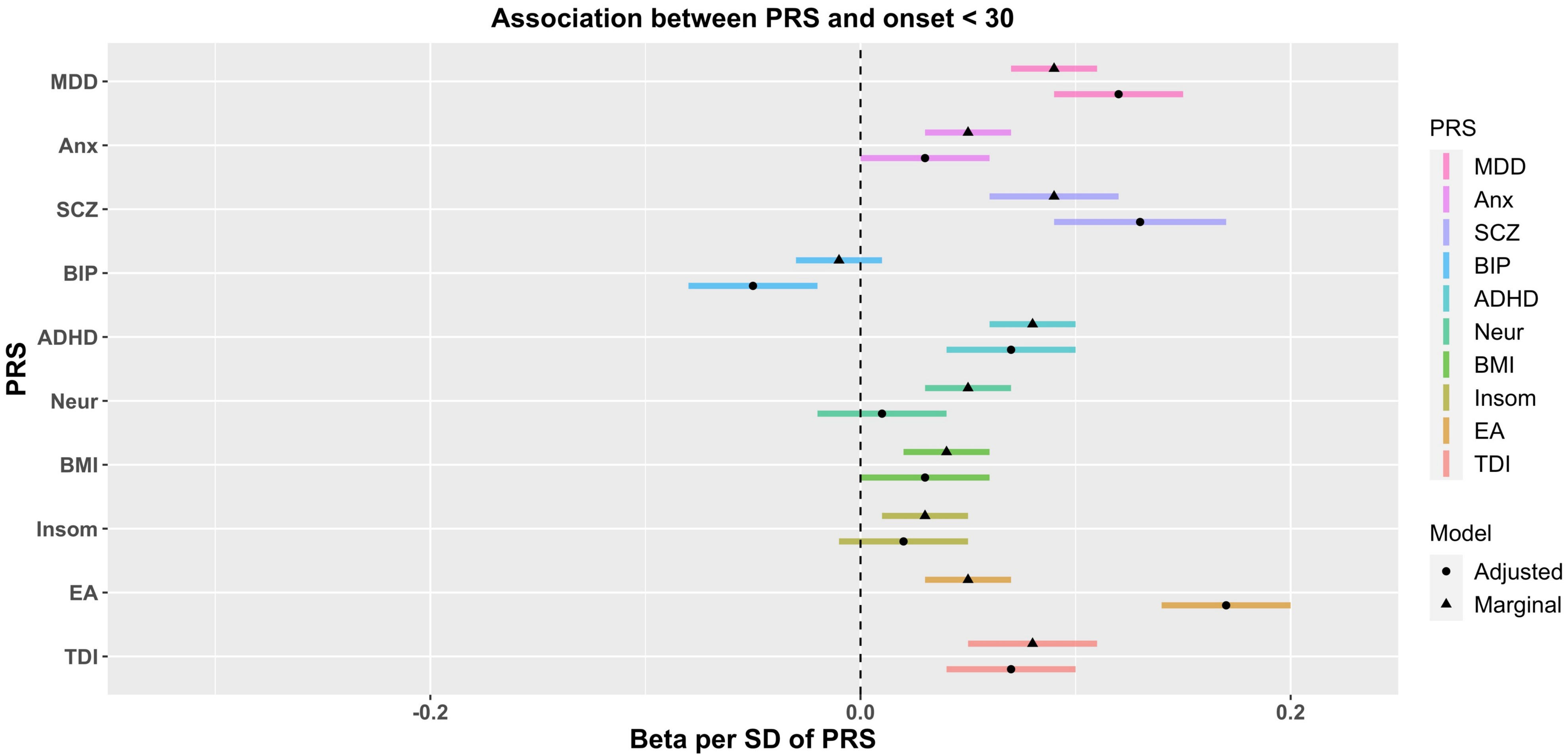
What we know about mdd

- Highly complex and heterogeneous in presentation – chronic course, age at onset, treatment response
- Heterogeneous symptom profile – DSM-5 MDD diagnosis requires at least 5 of 9 symptoms
- Debate surrounding depression reflecting one or more underlying conditions

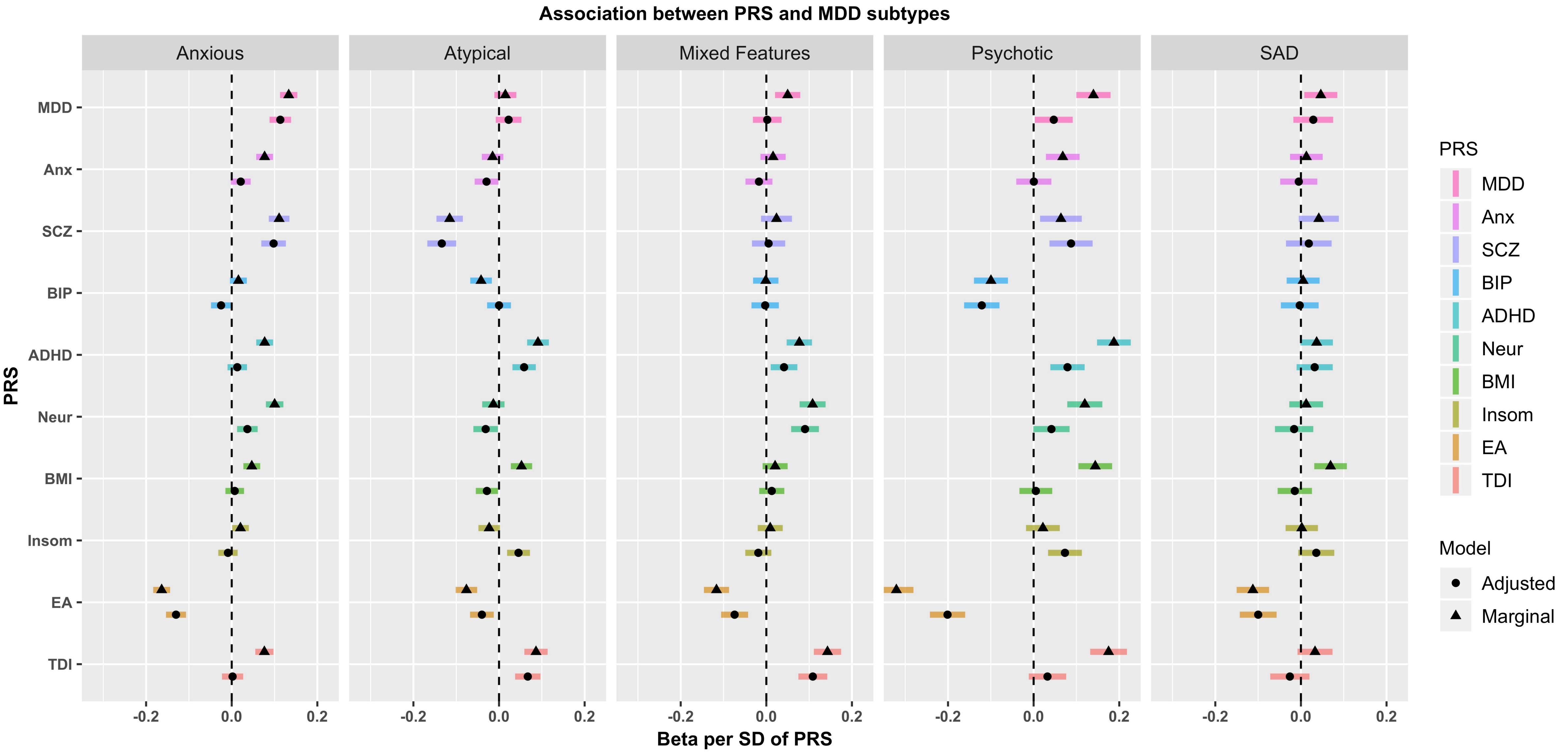


Australian Genetics of Depression Study

Associations with age of onset



Are there differences in PRS between subtypes of depression?



Going forward…

- Differences in genetic risk factors underlying features and subtypes?
- Do these influence treatment response and/or side-effects?
- Incorporating anxiety and other highly co-morbid disorders - Can we find any genetic distinctions?

Australian Genetics of Depression Study

GENETIC LINKS TO GLAD ANXIETY & DEPRESSION

BIONIC

VU

PGC Psychiatric Genomics Consortium

Michael Neale

Product of Variables (PoV) Modeling

Michael C Neale & Steven M Boker
Virginia Institute for Psychiatric and Behavioral Genetics
Virginia Commonwealth University

Boulder Colorado NIMH Workshop July 2023

Multiple Regression with Interaction

- Standard Approach: $y = a + \beta_1 X1 + \beta_2 X2 + \beta_3 X$
- Uses OBSERVED X1, X2 and OBSERVED product X1X2
- How Do you Multiply Latent Variables, e.g., GxE Interaction?
- Individuals' Scores are Unknown

A New Kind of Variable

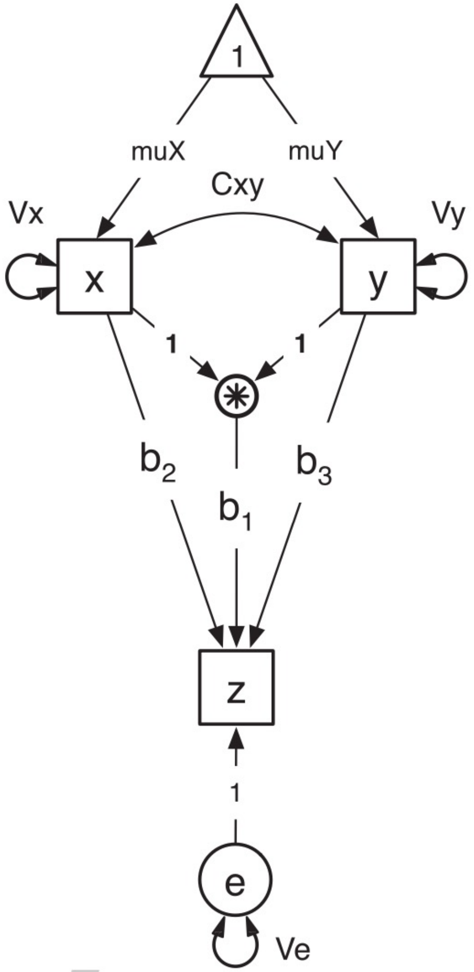
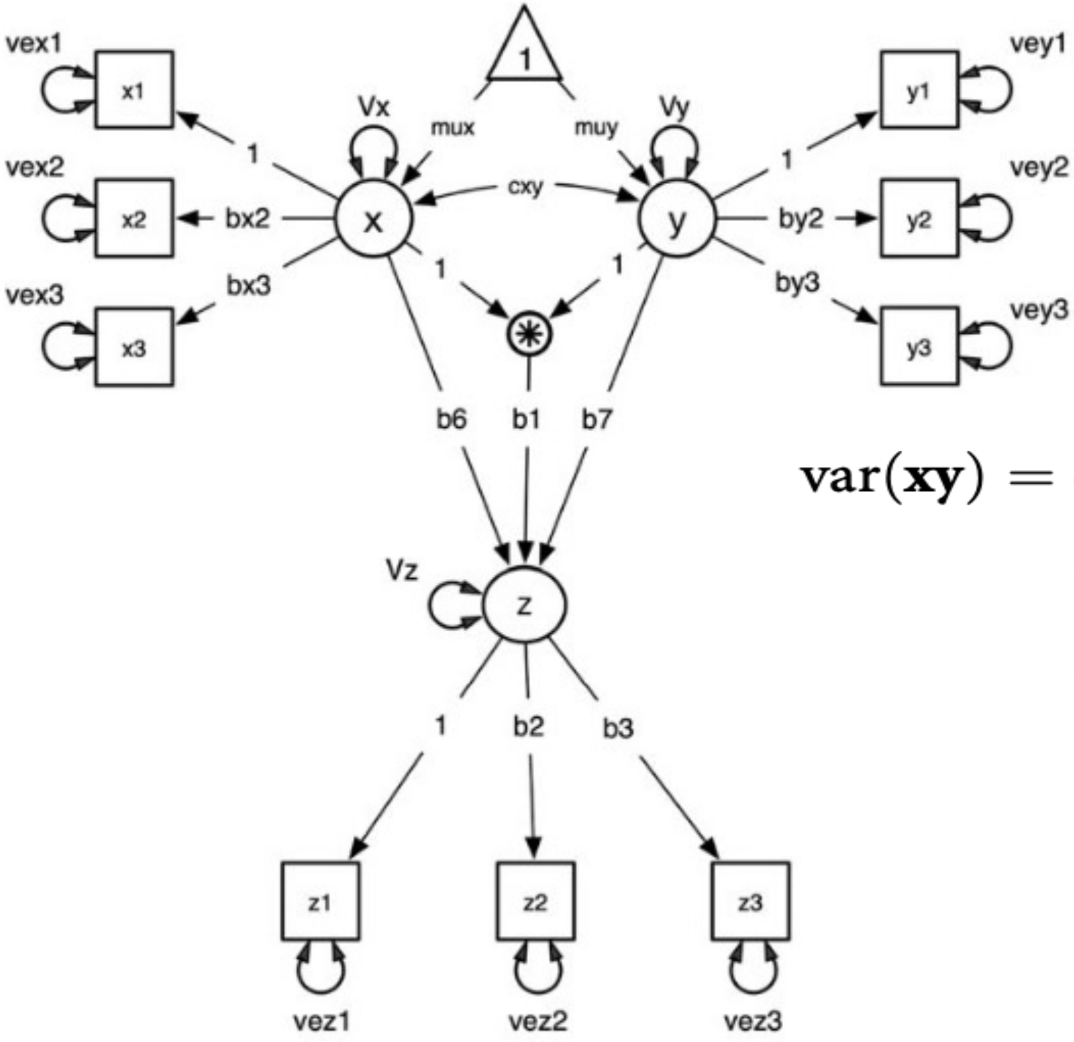


Figure 8. A manifest variable interaction model with both direct effects has more parameters than statistics and thus is unidentified.

- Latent variable with no unique variance
- Dummy variables are summation nodes
- Asterisk in a circle represents product node
- This model is under-identified has no XY observed variable
- Needs to have multiple indicators for identification

New Method



Estimated

$$
\begin{aligned}
\mathrm{var}(\mathbf{xy}) = {} & \mathrm{cov}(\boldsymbol{\Delta}\mathbf{x}^2, \boldsymbol{\Delta}\mathbf{y}^2) + \mathrm{var}(\mathbf{x})\mathrm{var}(\mathbf{y}) + \mu(\mathbf{x})^2\mathrm{var}(\mathbf{y}) \\
& + \mu(\mathbf{y})^2\mathrm{var}(\mathbf{x}) + (\mu(\mathbf{x})\mu(\mathbf{y}))^2 + 2\mu(\mathbf{x})\mu(\mathbf{y})\mathrm{cov}(\mathbf{x}, \mathbf{y}) \\
& + 2\mu(\mathbf{x})\mathrm{cov}(\boldsymbol{\Delta}\mathbf{x}, \boldsymbol{\Delta}\mathbf{y}^2) + 2\mu(\mathbf{y})\mathrm{cov}(\boldsymbol{\Delta}\mathbf{x}^2, \boldsymbol{\Delta}\mathbf{y}) \\
& - \mathrm{cov}(\mathbf{x}, \mathbf{y})^2 . \qquad (3)
\end{aligned}
$$

Works with Missing Data! (Unlike lm)

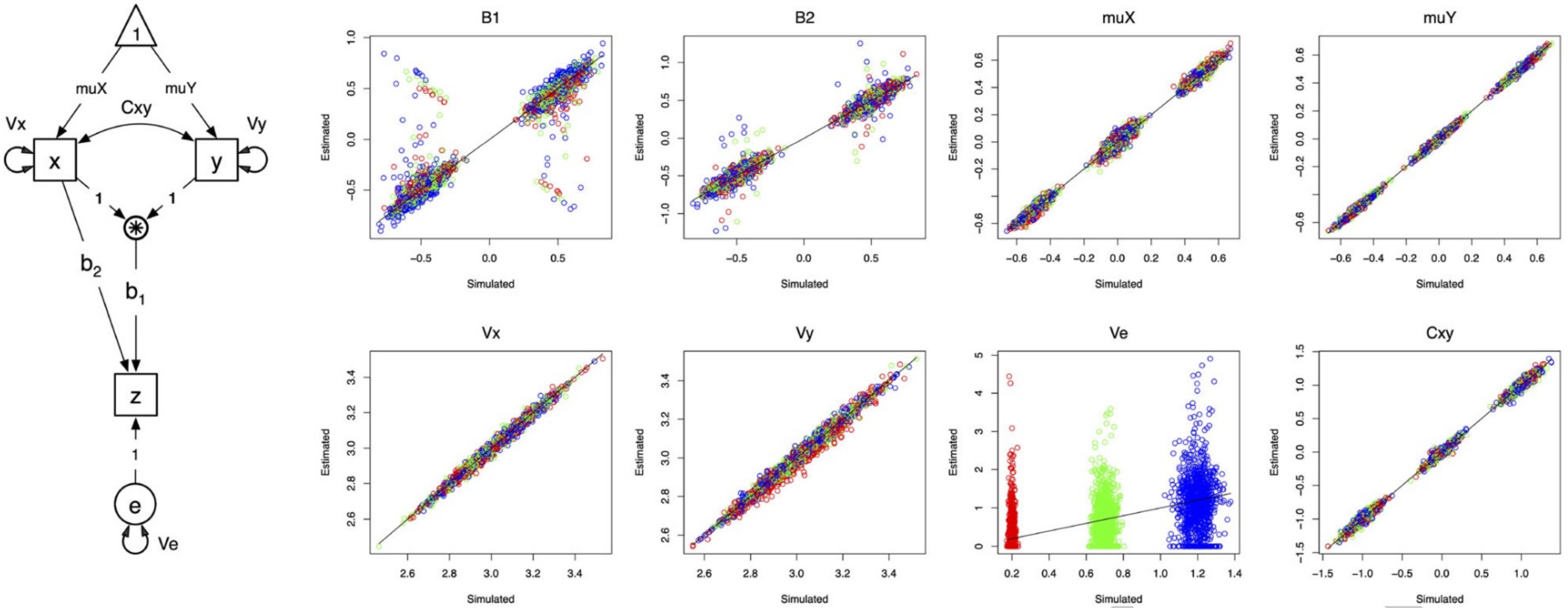


Figure 4. Path diagram and simulation outcomes for a bivariate moderation model where 20% of *y* and *z* are missing completely at random.

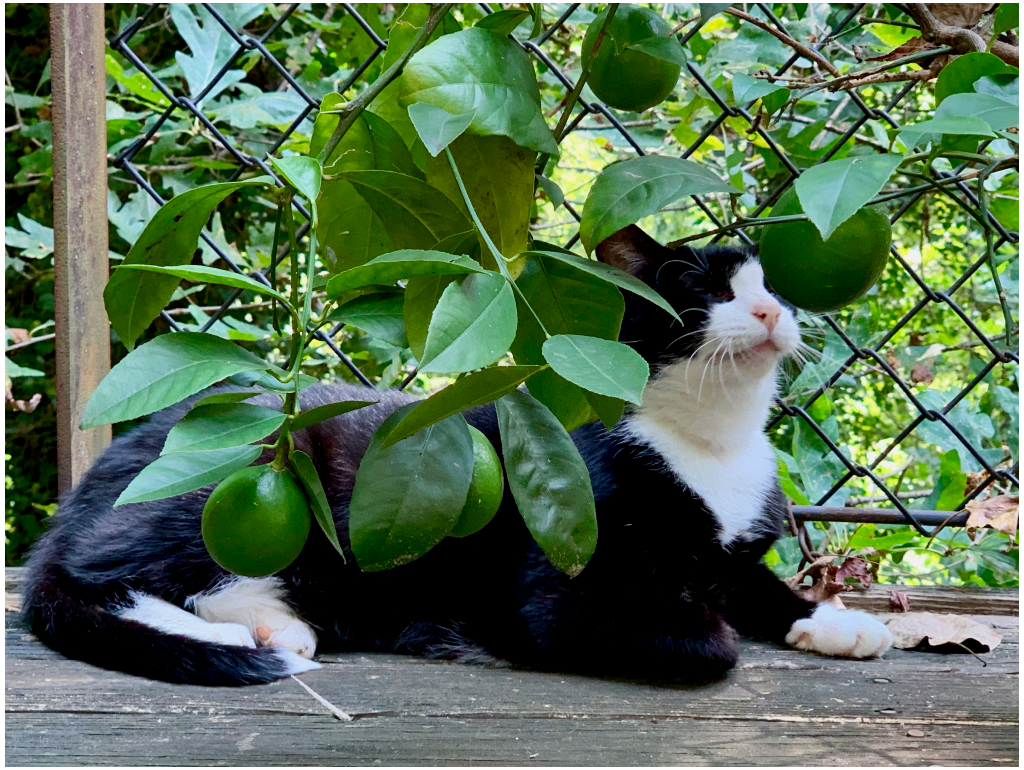
OpenMx Syntax for Product Variables

- Draw Them in Onyx
- Specify Model in mxPath Format
    - Manifest, Latent and **Product**: Legal Node Types
- New Tracing Rules for Model Evaluation: Multiply Inputs
- Experiment with it! OpenMx 2.20 or higher

Thank You!

Philip Vinh, Luis Araujo, Madhur Singh, Daniel Zhao, Joshua Pritikin, Hermine Maes

NIDA R01 DA049867, OpenMx Team



Virginia Commonwealth University

VCU

Matt Keller

Behavioral Genetics in the molecular age

Matthew Keller

CU Boulder

Recruiting postdocs in Keller Lab

- If interested in using genomic data in family-based samples to understand genetic architecture and causes of familial similarity, please contact me (matthew.c.keller@gmail.com)
- Start date from now until fall 2023…

Ability for GWAS estimates to deliver biological insights rests on them estimating **direct genetic effects**

- **Direct genetic effect:** <u>the true causal effect</u> of a genetic variant independent of genetic and environmental background
  - crucial for interpreting GWAS associations & downstream estimates in biological terms
- **Population genetic effect:** <u>the true association</u> between a genetic variant and a trait in a particular population at a given time.
  - includes direct effect PLUS the effects of all genetic and environmental factors correlated with the genetic variant

Increasing evidence calls into question the expectation that GWAS associations always reflect direct genetic effects

- **Population-based samples provide estimates of the population genetic effect, not the direct genetic effect**
- 3 major confounders of direct genetic effect estimates in population-based samples:
  - Population stratification
  - Indirect genetic effects
  - Assortative mating

Within-family GWAS studies present a simple and elegant solution to the most concerning confounders of population-based GWAS

- Genetic variation within families is due to random segregations of chromosomes during production of sperm and eggs (meiosis) in the parents.
- These random segregations are independent of confounding factors in the environment and non-random mating in the parents.

Family-based samples have incredible value to GWAS and beyond

- Despite lower power, within-family estimates of direct effects can be more accurate than pop-based estimates at reasonable n (e.g., 250k – 500k)
- Estimate indirect genetic effects and the full variance accounted for by vertical transmission (Balbona et al., 2022)
- Estimate the strength, change over time, and causes of assortative mating (Kim et al, in prep)
- Estimate individual-level de novo mutation rates, recombination rates, parent-of-origin effects, and uniparental disomy
- Improve phenotypic and genetic data quality
- Investigate many family-centric issues of interest to sociology, economics, psychology, etc. – divorce, kinship networks, social inequality, etc.

Summary

- We are entering an exciting time where BG methods and family data are going to be increasingly central to molecular genetics methods
- These are exactly the types of approaches we have emphasized at the workshop

2024 ISG Workshop

Biometrical Genetics
Classical Twin Design
Genomewide Association [GWAS]
Causes of Variation
Measurement
Extended Pedigree Models
Heterogeneity
plink
GwSEM
Sex Limitation
Mendelian Randomization [MR]
Matrix Algebra
OpenMx
LD score regression
Simulation
GxE interaction
Power
Structural Equation Modeling [SEM]
Genetic Nurture
Genetic Factor Models
Binary & Ordinal Data
Developmental Models
Within-family Designs
Path Analysis
Genetic correlation
Genetic Relationship Matrix [GRM]
Polygenic Scores
Model Assumptions
MR-DOC
Likelihood
Genomic SEM
ACE model
Multivariate Models
AC covariance
Cross-lagged Models
Direction of Causation [DOC]
M-GCTA
Ascertainment
GREML
Genetic Complex Trait Analysis [GCTA]

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