STANLEY CENTER
FOR PSYCHIATRIC RESEARCH
AT BROAD INSTITUTE

Psychiatric Genomics Consortium for PTSD

The Genetics PTSD:

New findings from the Psychiatric Genomics Consortium

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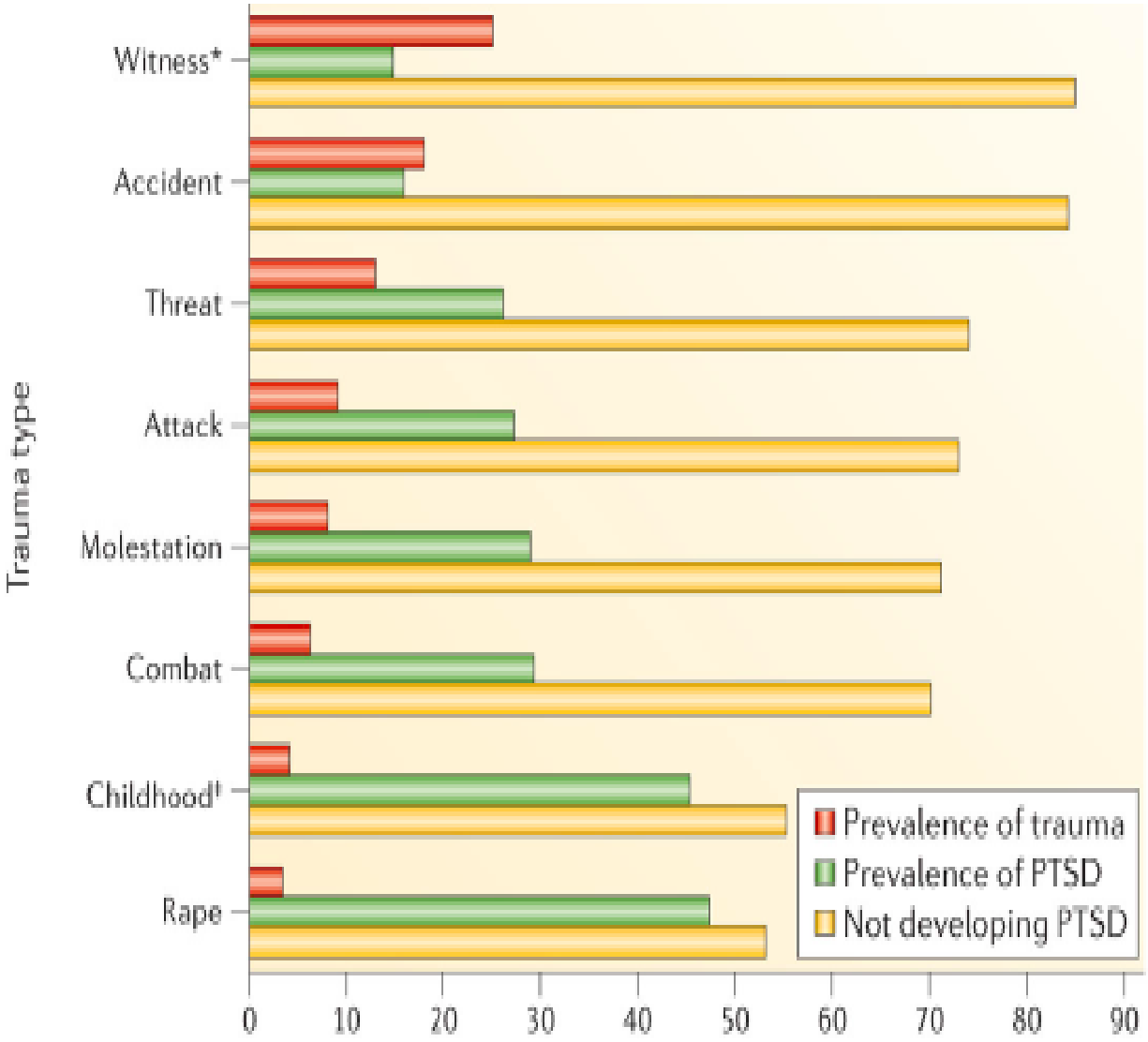
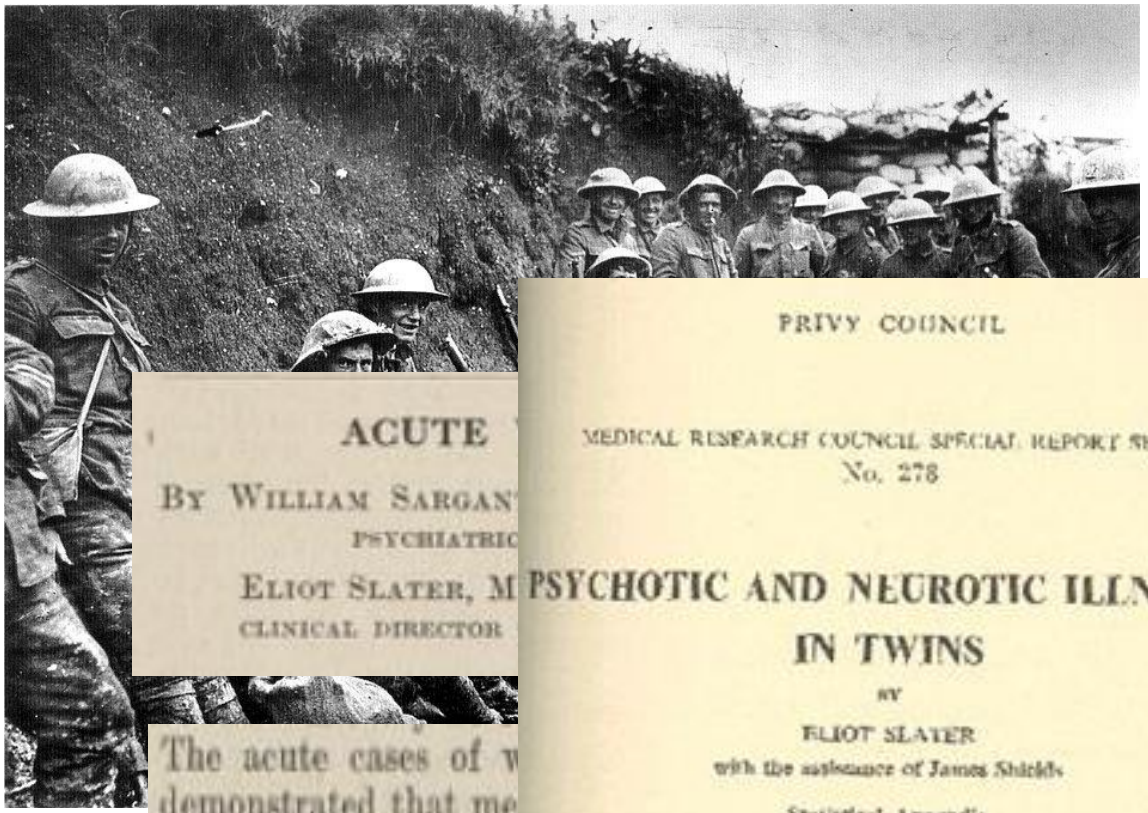
Department of Epidemiology

Why study the genetics of PTSD?



Yehuda, R. *et al*. (2015) Post-traumatic stress disorder. *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2015.57

The idea that constitutional factors – those within the individual – influence response to trauma is not new.



ACUTE

By William Sargan

Psychiatric

Eliot Slater, M

Clinical Director

The acute cases of w
demonstrated that me
may break down if th

usual symptoms of the a
terrifying bad dreams,
tendency to be startled
at the sound of an aeroplane going overhead or any sound
resembling it. The noise of a train going past outside
would make the patient jump perceptibly. In many
cases there was an amnesia, more or less extensive, for
the worst part of the past experiences. Individual cases

PRIVY COUNCIL

MEDICAL RESEARCH COUNCIL SPECIAL REPORT SERIES
No. 278

PSYCHOTIC AND NEUROTIC ILLNESSES IN TWINS

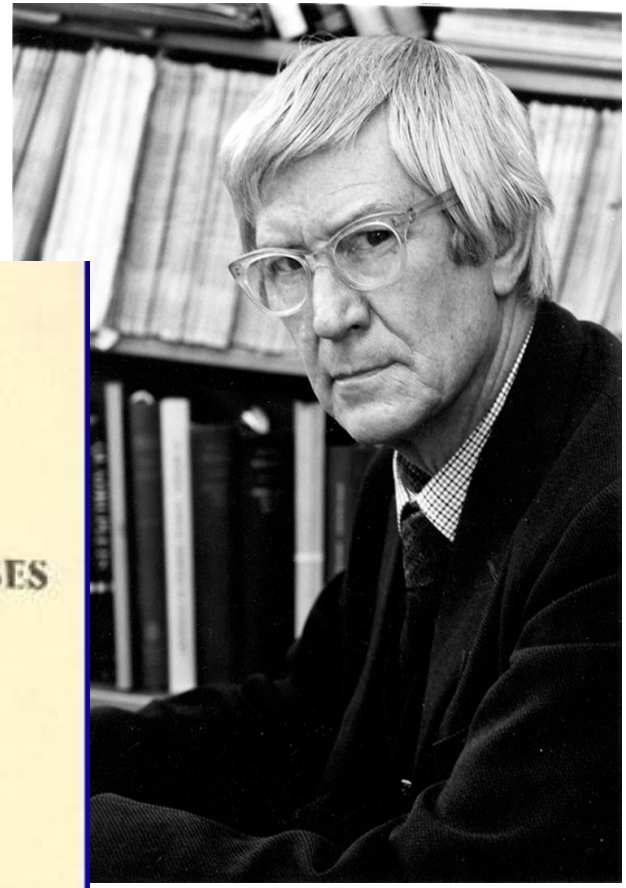
BY

ELIOT SLATER

with the assistance of James Shields

Statistical Appendix
by
Joan May

LONDON: HER MAJESTY'S STATIONERY OFFICE
1953



“There was evidence that the terrifying stresses of war tended to provoke anxiety states to a significantly preferential extent, **but they did so far from regularly**. A more important determinant of the type of response **was the constitution** of the individual, as shown by his family history, previous life, and personality.”

Eliot Slater, 1944

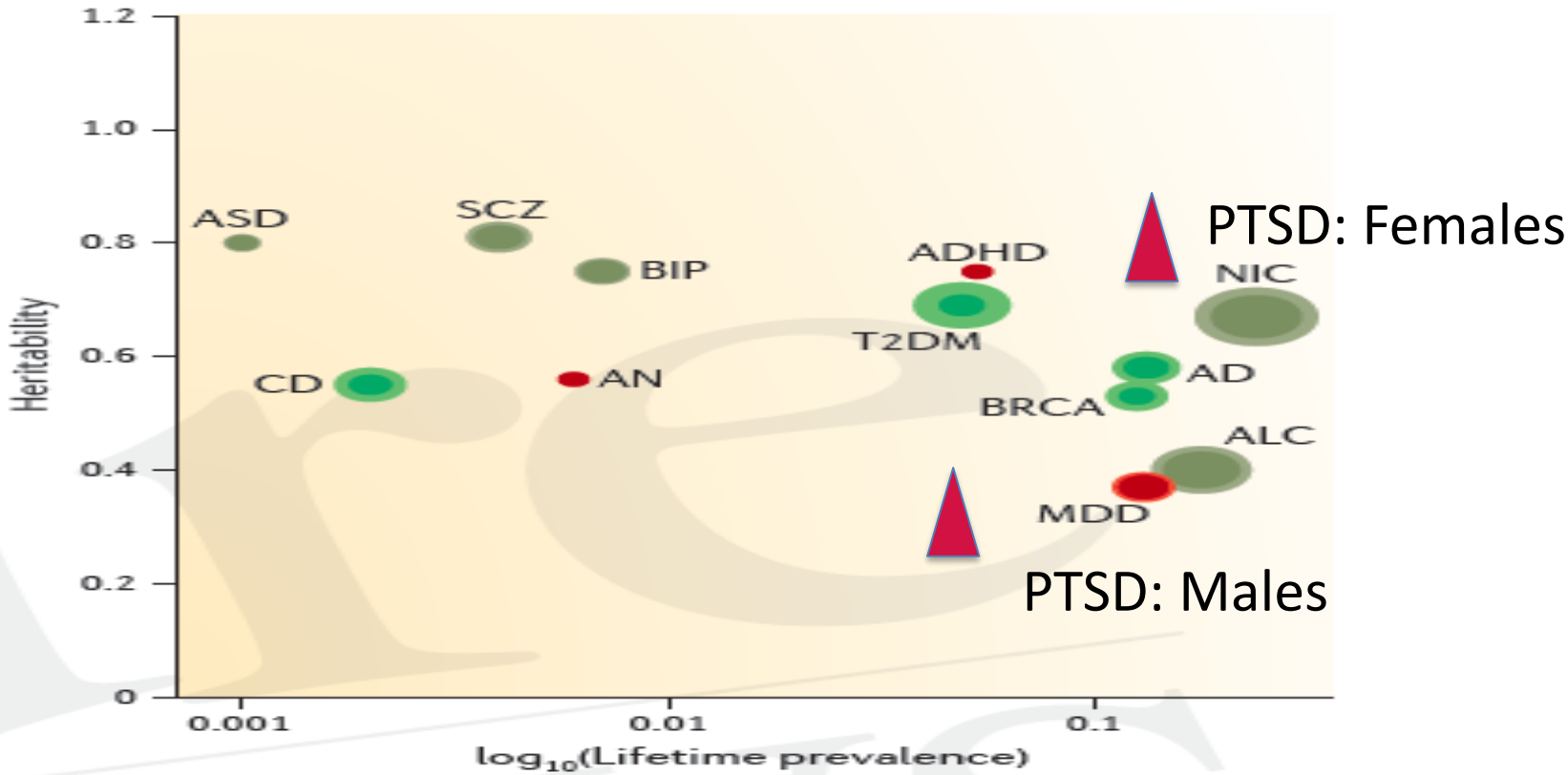
PTSD is heritable.

Twin studies rely on a natural experiment to assess heritability

Monozygotic twins:
share 100% of their genes

Dizygotic twins:
share 50% of their genes

PTSD heritability from twin studies is similar to other psychiatric disorders

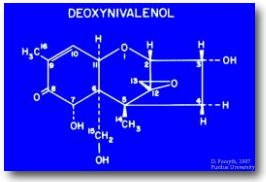


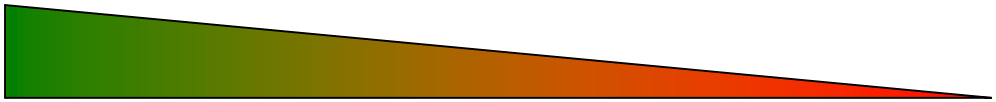
Sullivan, Daly, and O'Donovan. *Nature Reviews Genetics.* 2012

Genetics provides foundational insights into biology that may eventually impact clinical care.

PTSD psychopharmacology: Progress needed

Identify target → Chemical screening → Animal models → Clinical trials

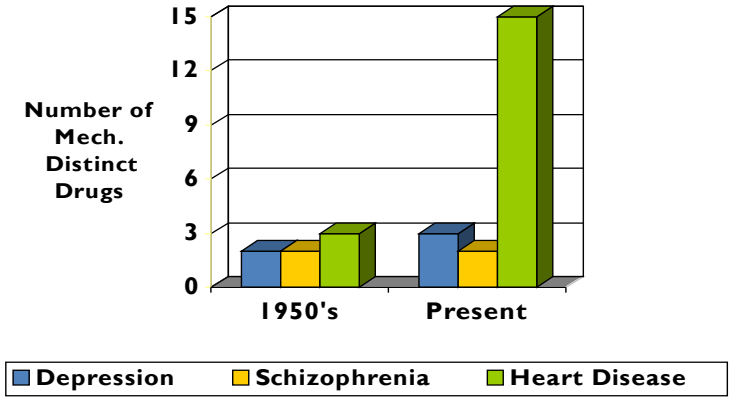




Most therapies developed through traditional approaches fail to have efficacy

- The only FDA approved drugs for PTSD are the SSRIs: sertraline (Zoloft) and paroxetine (Paxil).
- Overall response rate estimated at about 60% with only 20-30% achieving complete remission

No novel therapies for neuropsych disorders



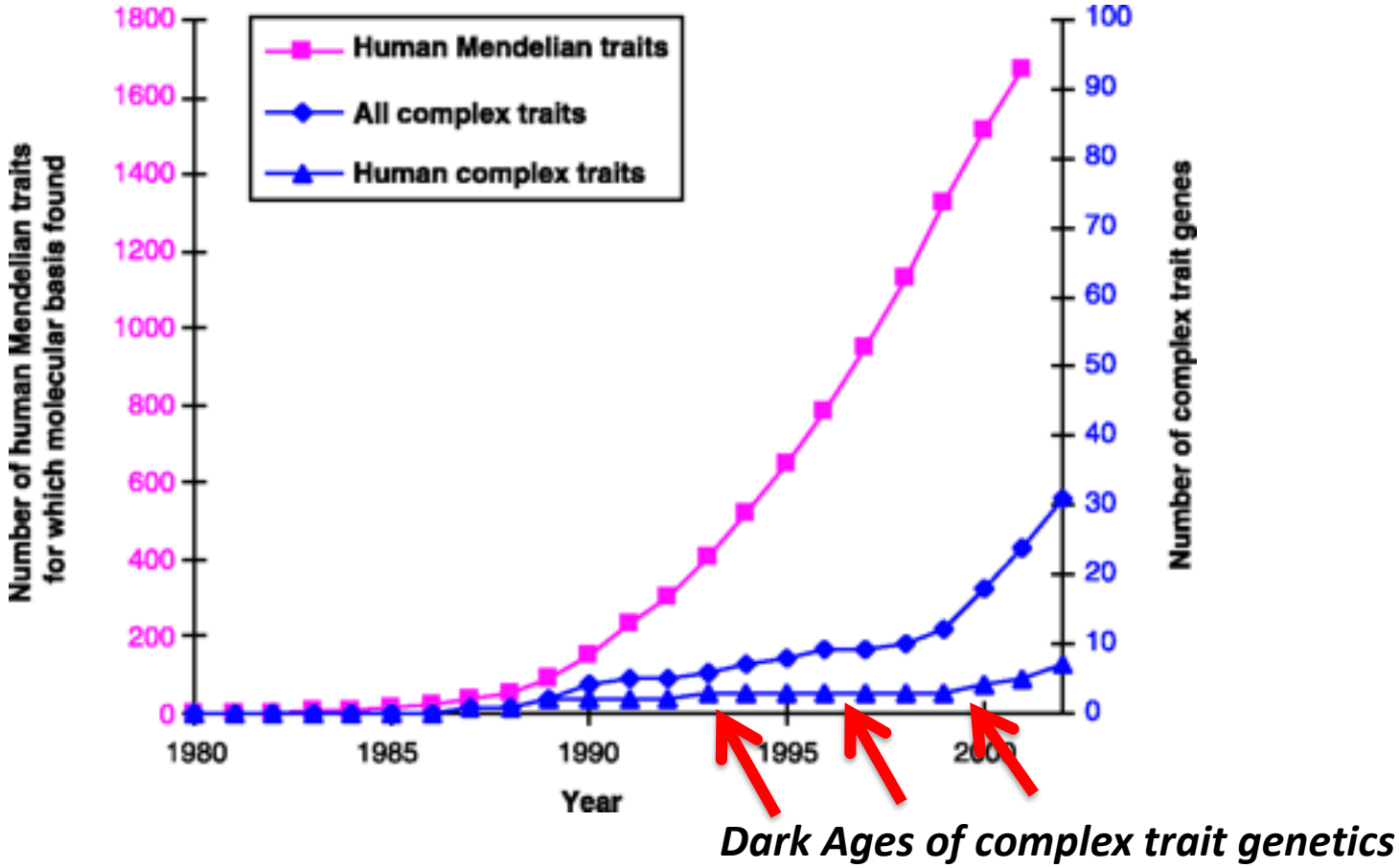
Finding the genes and mutations that cause disease is the most reliable means of gaining the insights required

So how do we find genes for PTSD?

If we knew what the genes were, they'd be easy to find…

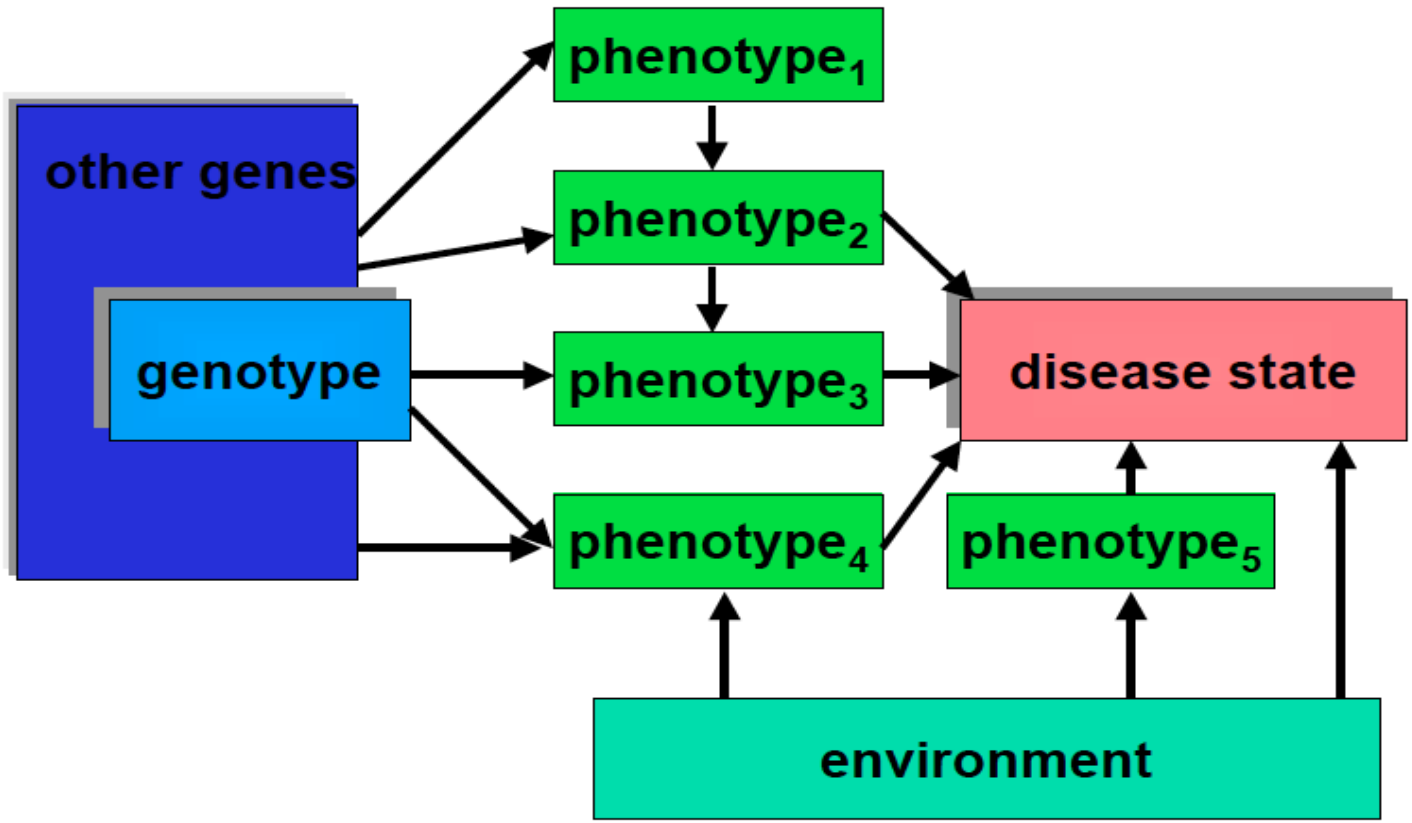
- 1991-2015 – the era of the candidate gene association study in PTSD
- Hallmarks: poor statistical practice, optimistic data interpretation, few if any reproducible results
- Outcome: little durable knowledge

Initial attempts to identify genes were not successful for complex diseases broadly . . .



Science 2002. Glazier, Nadeau & Aitman. *Finding Genes that Underlie Complex Traits*.

Progress required an intellectual shift from Mendelian to complex trait genetics



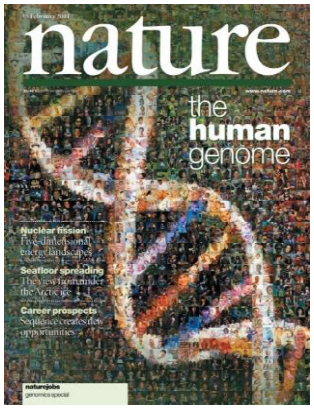
Complex trait genetics

- Instead of one gene *determining* a disease or trait, many genes each exert a small influence

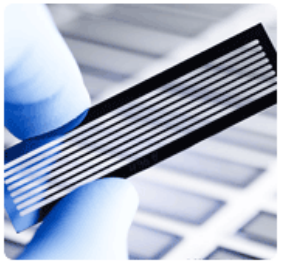
- None by themselves can “cause” or “explain” the disease or trait fully – but together with environmental influences combine to define an individual outcome

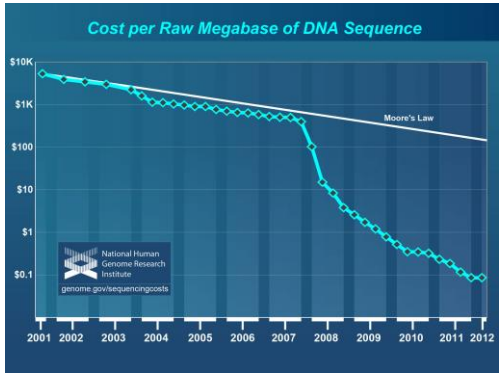
Progress also required many fundamental paradigm shifts

- Understanding the genome and the fundamental nature of human variation



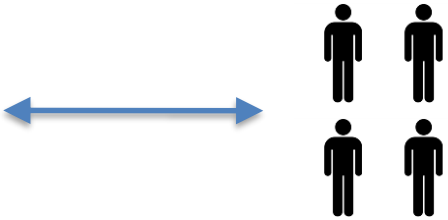
- Dramatic technological advances in our ability to access genomes





A genomic approach: Compare variation in entire genome in *many thousands* of genomes

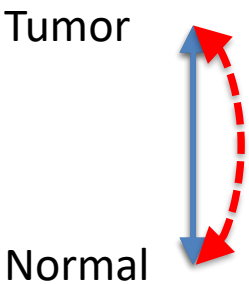
Human genome



People with and without disease

Define the genetic basis of the disease

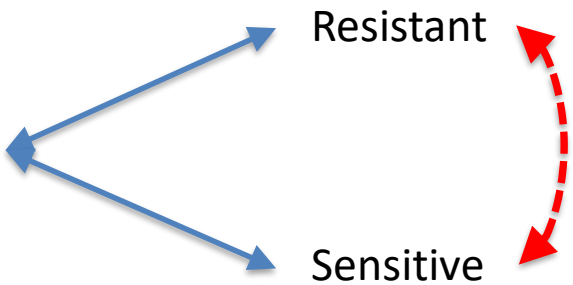
Human genome



Cells with and without cancer

Define the genetic basis of cancer

Microbial genome



Microbes that do and do not kill

Define the genetic basis of virulence

Genome-wide association study implicates a novel RNA gene, the lincRNA *AC068718.1*, as a risk factor for post-traumatic stress disorder in women

Guia Guffanti[a], Sandro Galea[b], Lulu Yan[b], Andrea L. Roberts[c], Nadia Solovieff[d,e,f], Allison E. Aiello[g], Jordan W. Smoller[d,e,f], Immaculata De Vivo[c], Hardeep Ranu[h], Monica Uddin[i,j], Derek E. Wildman[j], Shaun Purcell[d,e,f,k], Karestan C. Koenen[b,*]

ORIGINAL ARTICLE

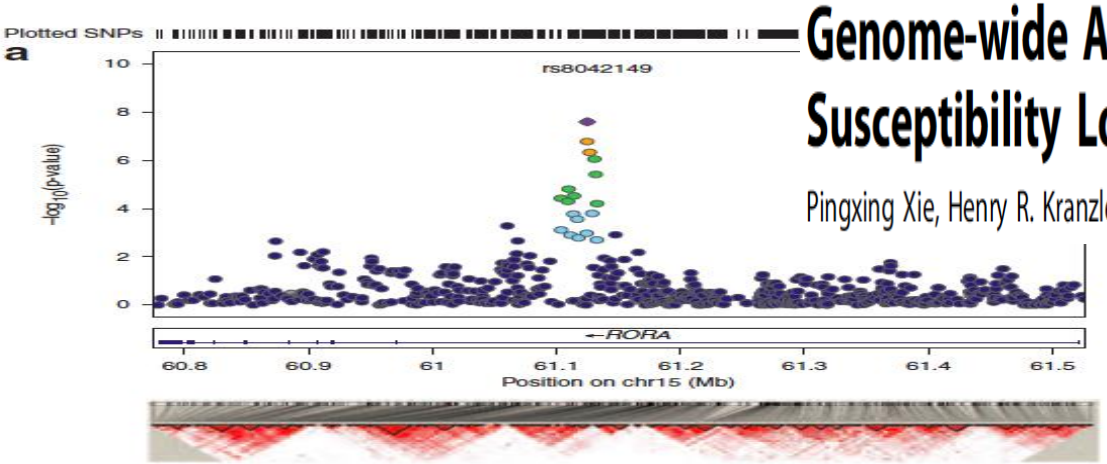
A genome-wide association study of post-traumatic stress disorder identifies the retinoid-related orphan receptor alpha (*RORA*) gene as a significant risk locus

MW Logue[1,2,11], C Baldwin[1,3,11], G Guffanti[4], E Melista[3], EJ Wolf[5,6], AF Reardon[5], M Uddin[7,8], D Wildman[7,9], S Galea[10], KC Koenen[10] and MW Miller[5,6]

ARCHIVAL REPORT

Genome-wide Association Study Identifies New Susceptibility Loci for Posttraumatic Stress Disorder

Pingxing Xie, Henry R. Kranzler, Can Yang, Hongyu Zhao, Lindsay A. Farrer, and Joel Gelernter



Consortium approach needed

PGC

Patrick Sullivan

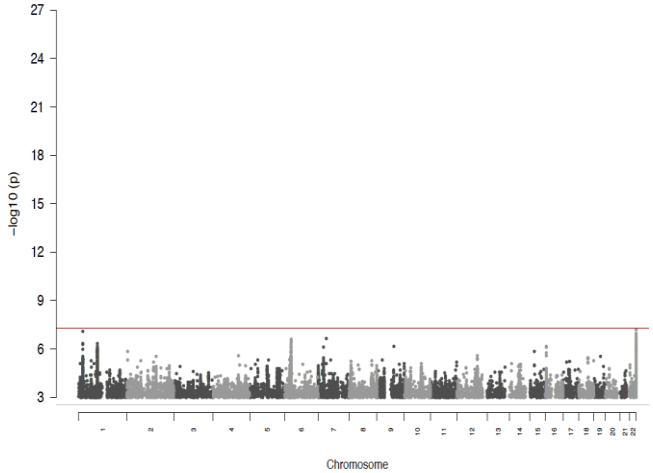
Mark Daly

Psychiatric Genomics Consortium

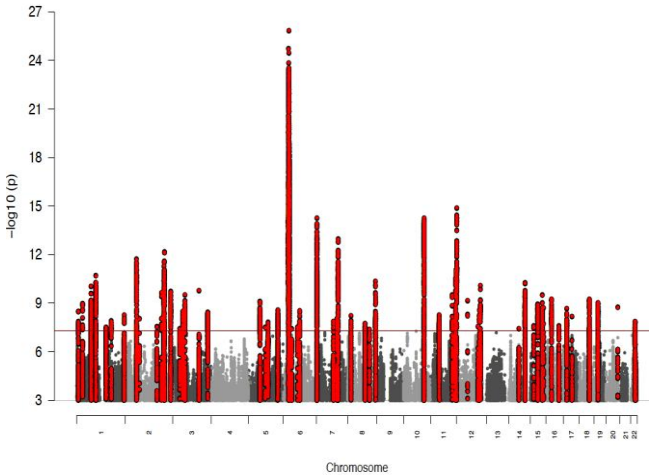
(and 800+ others)

Sample size accelerates discovery

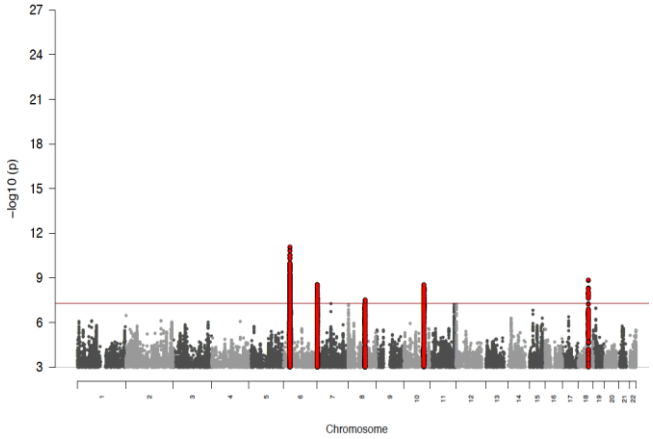
2009: 2601 cases → ***0 hits***



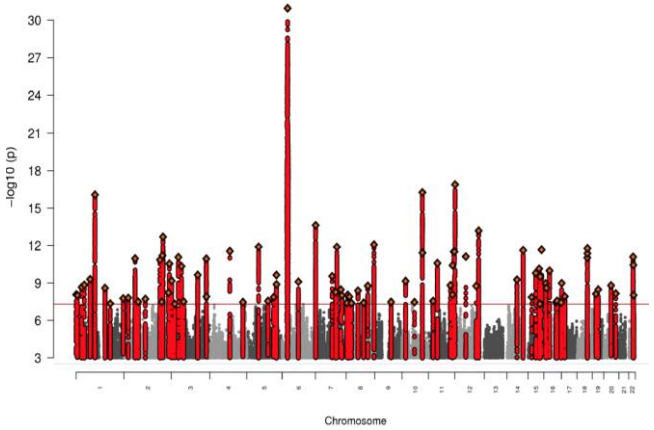
2012: 25K cases → ***62 hits***



2011: 9394 cases → ***5 hits***

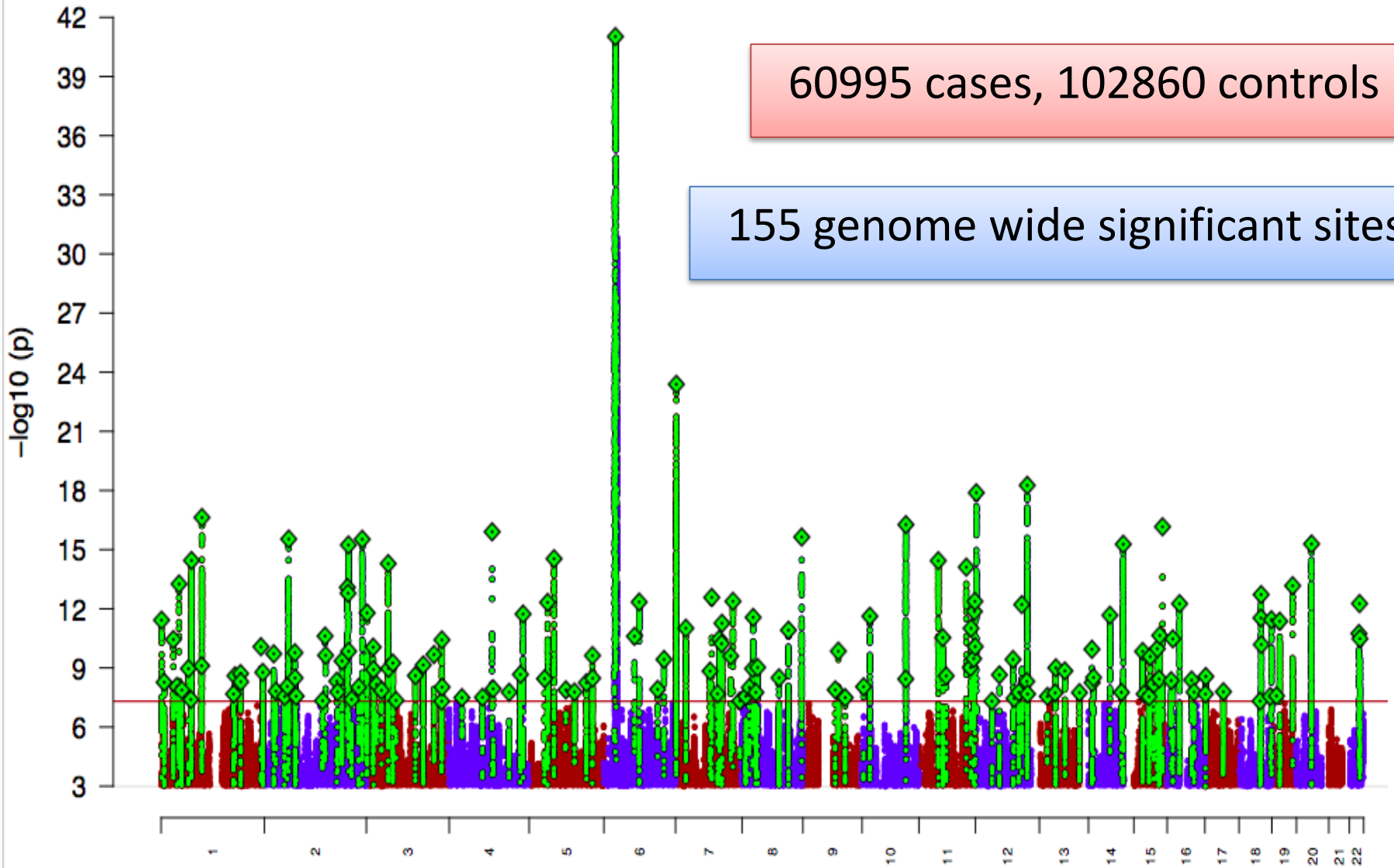


2014: 36K cases → ***108 hits***



Numbers presented represent samples of European Ancestry

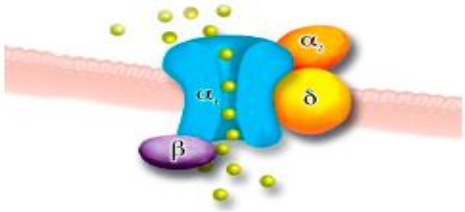
Sample size accelerates discovery (2016)

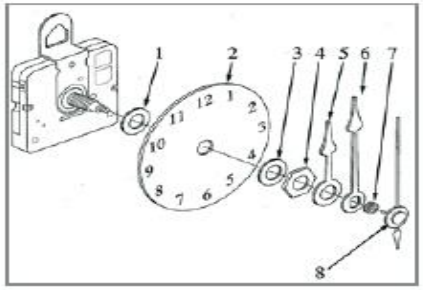


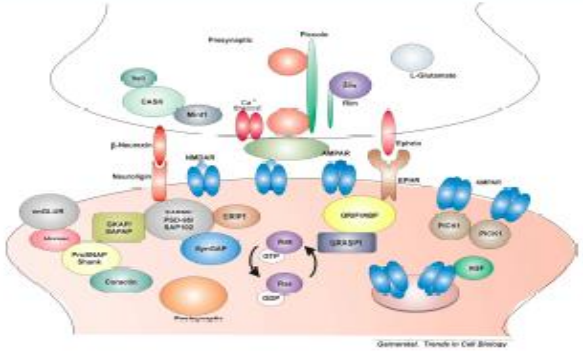
Courtesy of Stephan Ripke

Initial molecular parts list for schizophrenia

C4A
CACNA1C
CACNA1D
CANCA1I
CACNB2
GRIA1
GRIA2
GRIN2A
GRIN2B
GRM3
... 150 genes so far for schizophrenia







Can the PGC provide a road map for PTSD?

PGC PTSD Working Group founded

Karestan Koenen

Kerry Ressler

Israel Liberzon

Caroline Nievergelt

Neuropsychopharmacology (2015) 40, 2287–2297
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www.neuropsychopharmacology.org

Review Article

The Psychiatric Genomics Consortium Posttraumatic Stress Disorder Workgroup: Posttraumatic Stress Disorder Enters the Age of Large-Scale Genomic Collaboration

Mark W Logue*[,1,2,3], Ananda B Amstadter[4], Dewleen G Baker[5,6], Laramie Duncan[7,8,9], Karestan C Koenen[10], Israel Liberzon[11,12], Mark W Miller[13,14], Rajendra A Morey[15,16,17], Caroline M Nievergelt[5,6], Kerry J Ressler[18,19,20], Alicia K Smith[18], Jordan W Smoller[21,22,23], Murray B Stein[5], Jennifer A Sumner[10] and Monica Uddin[24,25]

PGC PTSD: Data freeze I

PGC PTSD: Data freeze I

Lead Analyst
Laramie Duncan,
PhD

ORIGINAL ARTICLE

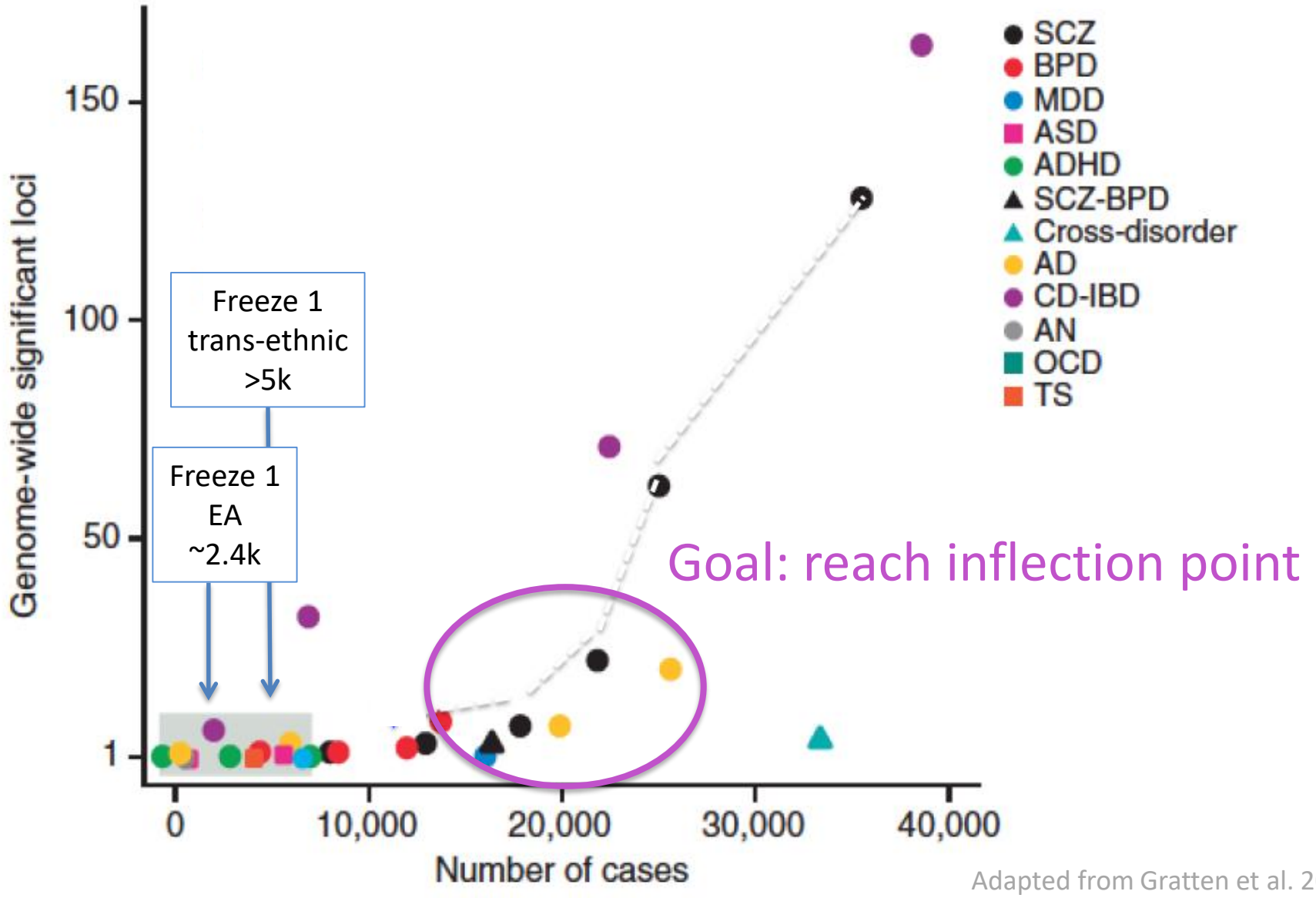
Largest GWAS of PTSD ($N = 20070$) yields genetic overlap with schizophrenia and sex differences in heritability

LE Duncan[1,2,3], A Ratanatharathorn[4], AE Aiello[5], LM Almli[6], AB Amstadter[7], AE Ashley-Koch[8], DG Baker[9,10], JC Beckham[11,12], LJ Bierut[13], J Bisson[14], B Bradley[15,16], C-Y Chen[3,17,18], S Dalvie[19], LA Farrer[20], S Galea[21], ME Garrett[8], JE Gelernter[22], G Guffanti[18,23], MA Hauser[8], EO Johnson[24], RC Kessler[25], NA Kimbrel[11,12], A King[26], N Koen[27,28], HR Kranzler[29], MW Logue[30,31], AX Maihofer[32], AR Martin[2,3], MW Miller[30,33], RA Morey[12,34], NR Nugent[35,36], JP Rice[37], S Ripke[2,3,38], AL Roberts[39], NL Saccone[40], JW Smoller[2,17], DJ Stein[27,28], MB Stein[32,41,42], JA Sumner[43], M Uddin[44], RJ Ursano[45], DE Wildman[46], R Yehuda[47,48], H Zhao[49], MJ Daly[2,3], I Liberzon[26,50], KJ Ressler[18,23], CM Nievergelt[9,10] and KC Koenen[2,17,51]

The Psychiatric Genomics Consortium-Posttraumatic Stress Disorder group (PGC-PTSD) combined genome-wide case–control molecular genetic data across 11 multiethnic studies to quantify PTSD heritability, to examine potential shared genetic risk with schizophrenia, bipolar disorder, and major depressive disorder and to identify risk loci for PTSD. Examining 20 730 individuals, we report a molecular genetics-based heritability estimate (h^2_{SNP}) for European-American females of 29% that is similar to h^2_{SNP} for schizophrenia and is substantially higher than h^2_{SNP} in European-American males (estimate not distinguishable from zero). We found strong evidence of overlapping genetic risk between PTSD and schizophrenia along with more modest evidence of overlap with bipolar and major depressive disorder. No single-nucleotide polymorphisms (SNPs) exceeded genome-wide significance in the transethnic (overall) meta-analysis and we do not replicate previously reported associations. Still, SNP-level summary statistics made available here afford the best-available molecular genetic index of PTSD—for both European- and African-American individuals—and can be used in polygenic risk prediction and genetic correlation studies of diverse phenotypes. Publication of summary statistics for ~10 000 African Americans contributes to the broader goal of increased ancestral diversity in genomic data resources. In sum, the results demonstrate genetic influences on the development of PTSD, identify shared genetic risk between PTSD and other psychiatric disorders and highlight the importance of multiethnic/racial samples. As has been the case with schizophrenia and other complex genetic disorders, larger sample sizes are needed to identify specific risk loci.

Molecular Psychiatry advance online publication, 25 April 2017; doi:10.1038/mp.2017.77

Trajectories of GWAS discoveries



Adapted from Gratten et al. 2014

PGC PTSD: Data freeze 2

GWAS analysis strategy needs to account for diverse ancestries

51 European Ancestry (EUA)

MRSC	FEEN
ONGA	DCSR
NHS2	TEIC
GSDC	NIUT
FSCD	NCMH
COGA	EACR
COGB	WACH
BRYA	BETR
SATU	SEEP
DEFE	COM1
NHRV	FTCB
NSS1	GRAC
NSS2	YEHU
PPDS	BAKE
STRO	VRIS
GTPC*	WANG
GMFR	VETSA
KSUD	PRIS
BOBA	INTR
KMCT	DAMI
PORT	DAIP
GUTS	QIMR
NHSY	MIRE
RING	NCPT
BRY2	TRAC
	UKBB

30 African Ancestry (AFA)

MRSC	FEEN
SAFR	DCSR
DNHS	TEIC
GSDC	NIU
FSCD	WACH
COGB	EGHS
NSS1	ADNH
NSS2	COM1
PPDS	GRAC
STRO	YEHU
GTPC*	BAKE
KSUD	VRIS
BOBA	WANG
KMCT	MIRE
PORT	NCPT

6 Latino (AMA)

MRSC
NSS1
NSS2
PPDS
STRO
PROM

Dataset Type

- Freeze 1
- CVB RFA
- GWAS summary data
- Studies analyzed together

AMA
N = 5,703
1,981 cases (34.7%)

AFA meta-analysis
N = 15,339
4,363 cases (28.4%)

EUA meta-analysis
N = 174,659
23,212 cases (13.3%)

Meta-analysis across ancestry groups
N = 195,701
29,556 cases (15.1%)

Three major findings:

1. PTSD is heritable.

PTSD is heritable

Heritability (h^2) Proportion of phenotypic variation accounted for by genetic variation.

SNP-chip heritability (h^2_{SNP}) Proportion of phenotypic variation accounted for by *measured* genetic variation.

SNP heritability is lower than twin heritability

PGC Group	Cases	Hits	Twin h^2	SNP h^2
Schizophrenia	60,995	155	81%	45%
Major depressive disorder	130,664	44	30%–40%	8.9%
Bipolar disorder	20,352	19	80%	21%
Attention deficit hyperactivity disorder	20,183	12	70%–80%	22%
Autism spectrum disorder	18,381	3	75%	12%
Anorexia nervosa	3,495	1	56%	~20%
Substance use disorders	12,798	1	50%	~8%
Tourette syndrome	4,232	1	60%–80%	58%
Obsessive-compulsive disorder	2,688	0	45%–65%	37%
Posttraumatic stress disorder	5,131	0	30%–40%	5%–35%

[a] Hits: independent associations reaching genome-wide significance. Twin h^2: heritability estimated from twin studies. SNP h^2: heritability estimated from results of genome-wide association studies (GWAS).

Sullivan et al. 2017

PTSD is heritable, in the range found for major depression

Group	Sample	N Cases	N Controls	h^2_{snp}	95% CI	z	p-value
All	PGC2	23,212	151,447	**0.05**	0.03–0.07	5.53	3.18E-08
	PGC1.5	12,823	35,648	**0.05**	0.01–0.08	2.54	0.011
	UKBB	10,389	15,799	**0.17**	0.14–0.21	8.75	2.06E-18
Men	PGC2	9,908	75,605	**0.01**	-0.03–0.05	0.49	0.63
	PGC1.5	6,364	23,905	**0.01**	-0.05–0.07	0.39	0.69
	UKBB	3,544	1,700	**0.15**	0.05–0.24	2.99	0.0014
Women	PGC2	12,973	73,627	**0.10**	0.07–0.13	6.50	8.03E-11
	PGC1.5	6,128	9,528	**0.21**	0.11–0.31	4.20	2.66E-05
	UKBB	6,845	4,099	**0.19**	0.13–0.25	6.36	2.00E-10

- Considerable range in SNP heritability
- SNP heritability women > men <u>but not</u> in UK Biobank
- Similar findings in subjects of African ancestry (using GCTA)
- SNP heritability of major depression 8.7% (Wray, 2018, Nature Genetics)

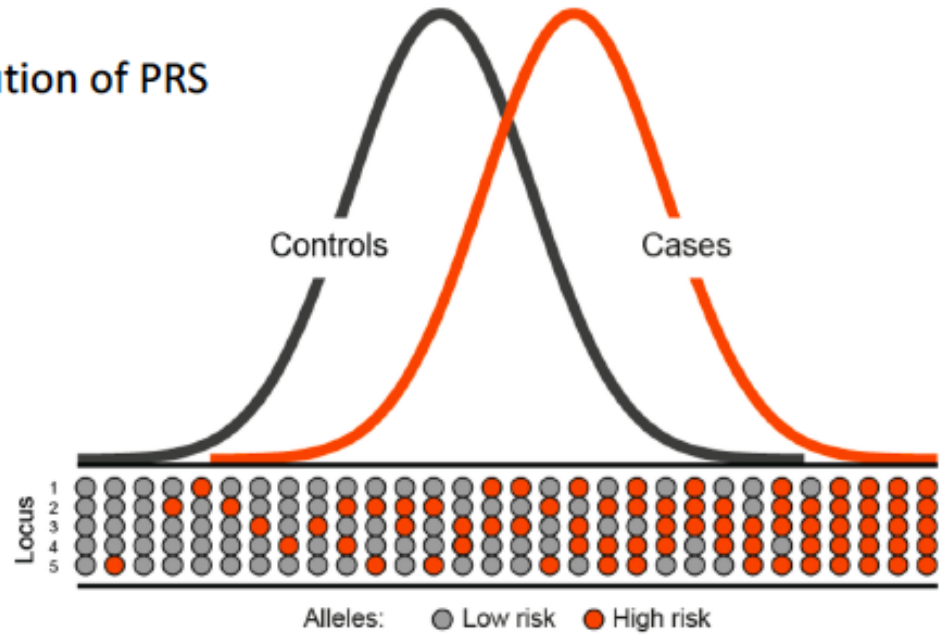
Nievergelt et al. in prep.

2. PTSD shares genetic risk with other psychiatric disorders, as well as other traits.

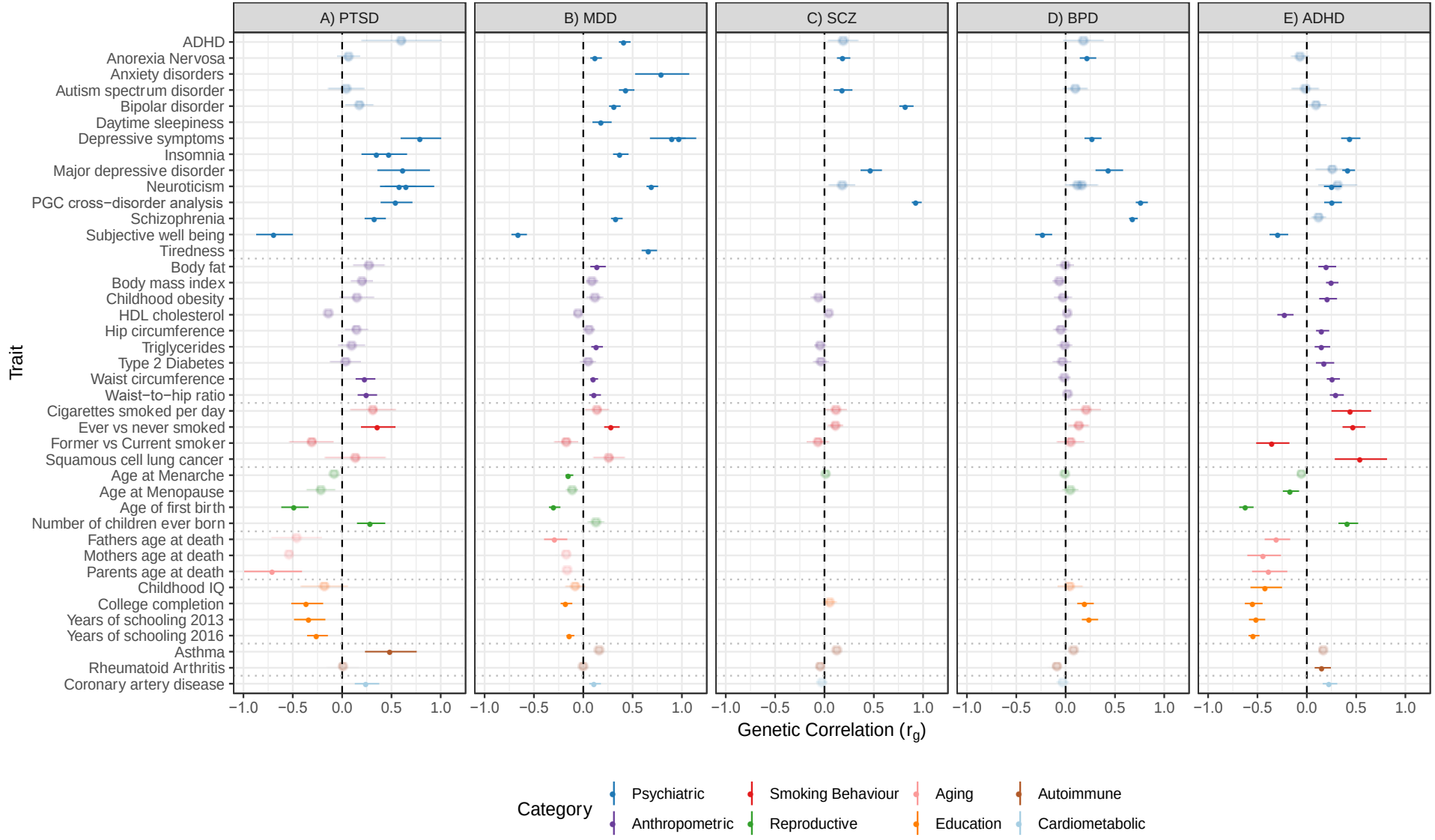
Polygenic risk score (PRS)

- A sum of trait-associated alleles across many genetic loci, weighted by effect size estimated from GWAS
- Useful for stratification by level of risk, by sub-phenotypes, for identifying overlap with other traits

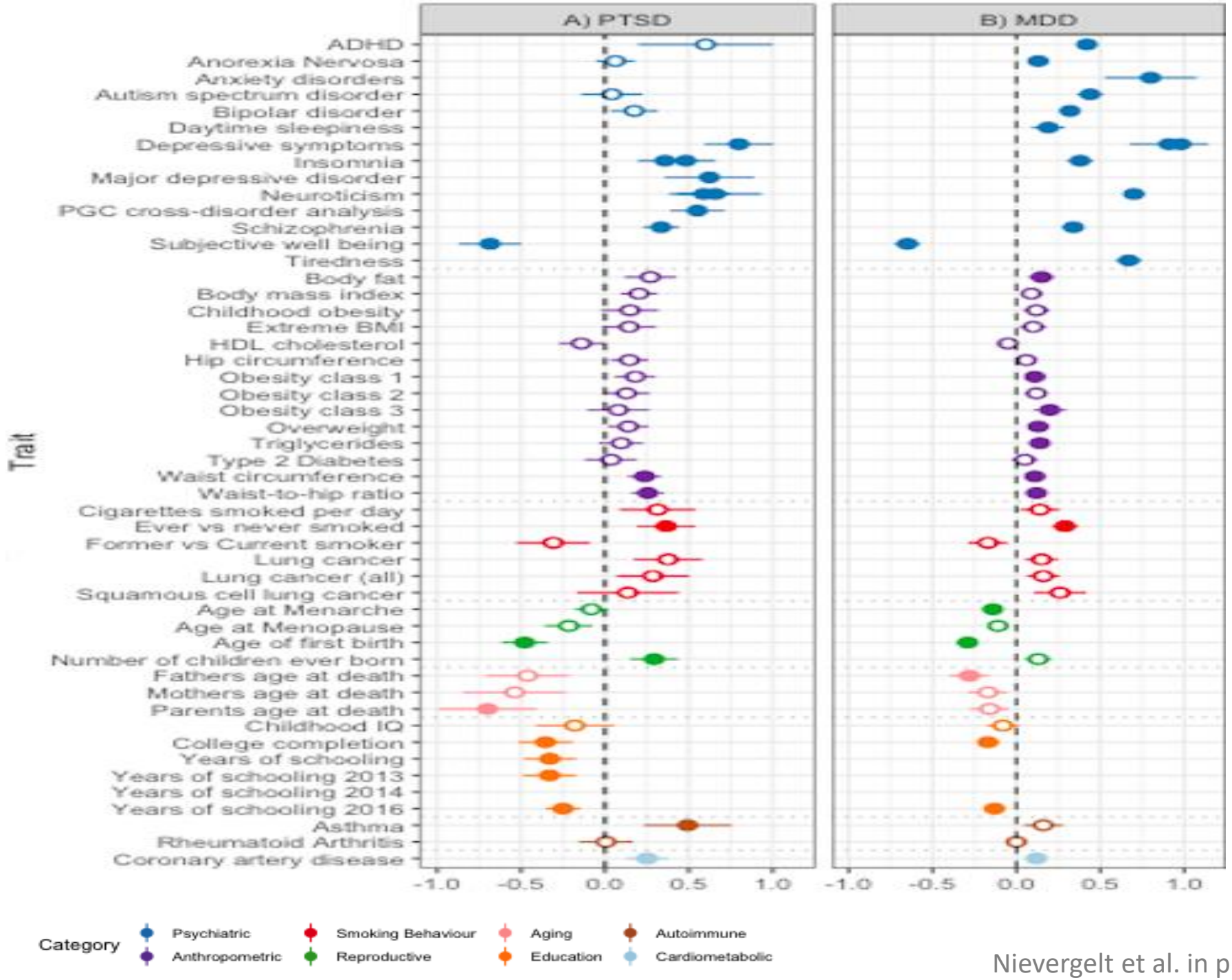
Exemplary distribution of PRS



Genetic risk for PTSD is correlated with that for other mental disorders and traits



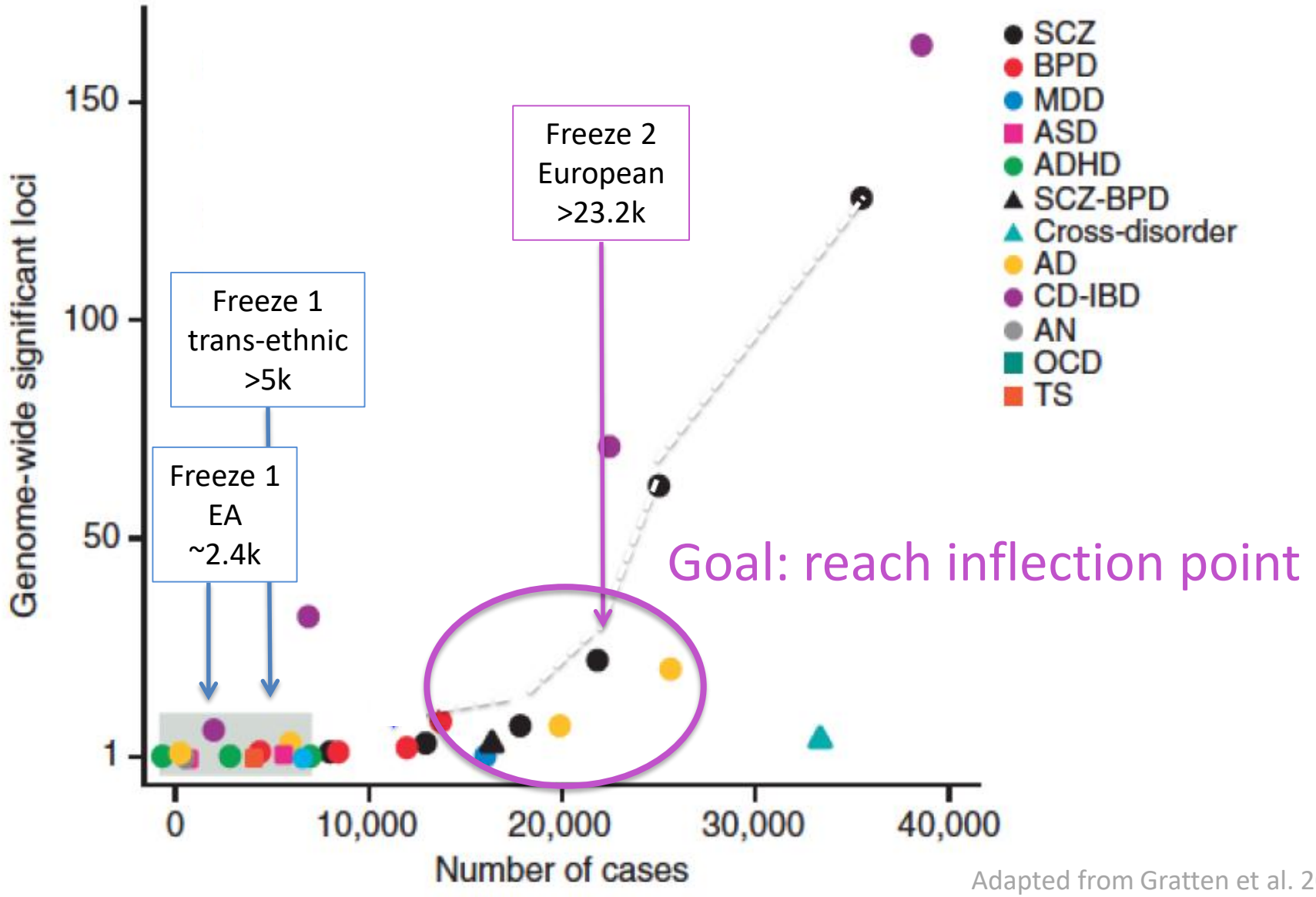
Nievergelt et al. in prep.



Nievergelt et al. in prep.

3. PTSD remains underpowered, but the first probable hits are beginning to emerge.

Trajectories of GWAS discoveries



Adapted from Gratten et al. 2014

Summary of Freeze 2 Results

Freeze 2: 32K PTSD cases, 174K trauma controls

- 10x increase from Freeze 1

- First genome-wide significant hits

GWAS in European ancestry:

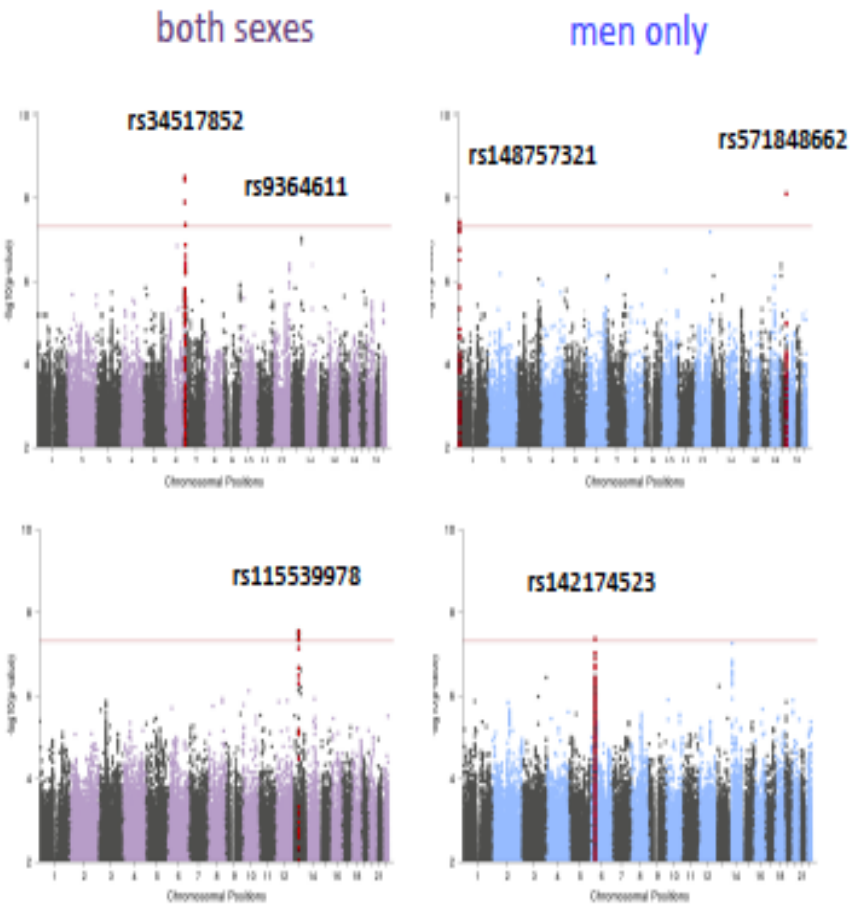
- N cases: 23,212; N controls: 151,447
- N studies: 52
- GWAS hits: 4

GWAS in African ancestry:

- N cases: 4,363; N controls: 10,976
- N studies: 30
- GWAS hits: 2

- 12 predicted genes

  - EUA: *ZDHHC14*, *PARK2*, *KAZN*, *TMRM51-AS1*, and *ZNF813*
  - AFA: *LINC02335*, *MIR5007*, *TUC338*, *LINC02571*, and *HLA-B*
  - Gene-based analyses: *SH3RF3* and *PODXL*



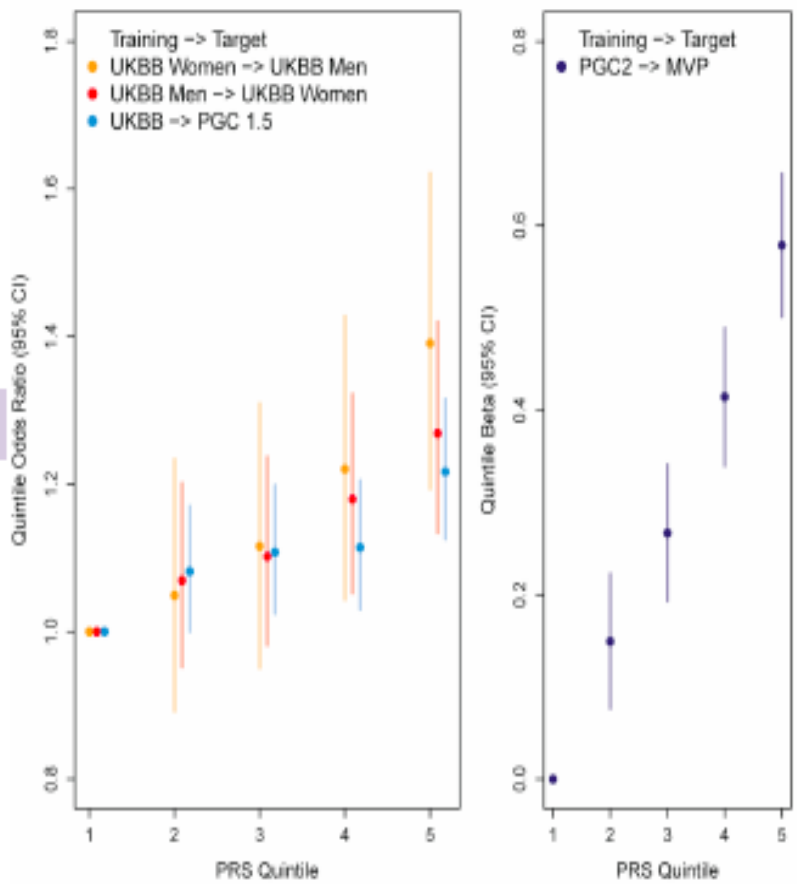
Courtesy of Caroline Nievergelt

Summary of Freeze 2 Results

Heritability (h^2_{SNP}):

- in women: ~10-20%
- in men: lower

Significant genetic risk scores (PRS):



Million Veteran Program (MVP)

N = 146,660 EA

Phenotype:

- re-experiencing symptoms

PGC2 GWAS hits:

- no replication

LDSC PGC2 vs. MVP:

- rg=0.8; p=2.85e-17

PRS prediction

- at P_T=0.88: p=2.4e-101

PGC-PTSD freeze 2 paper: on BioRxiv and in preparation for resubmission to Nature Neuroscience

Courtesy of Caroline Nievergelt

At least three challenges need to be addressed in moving forward . . .

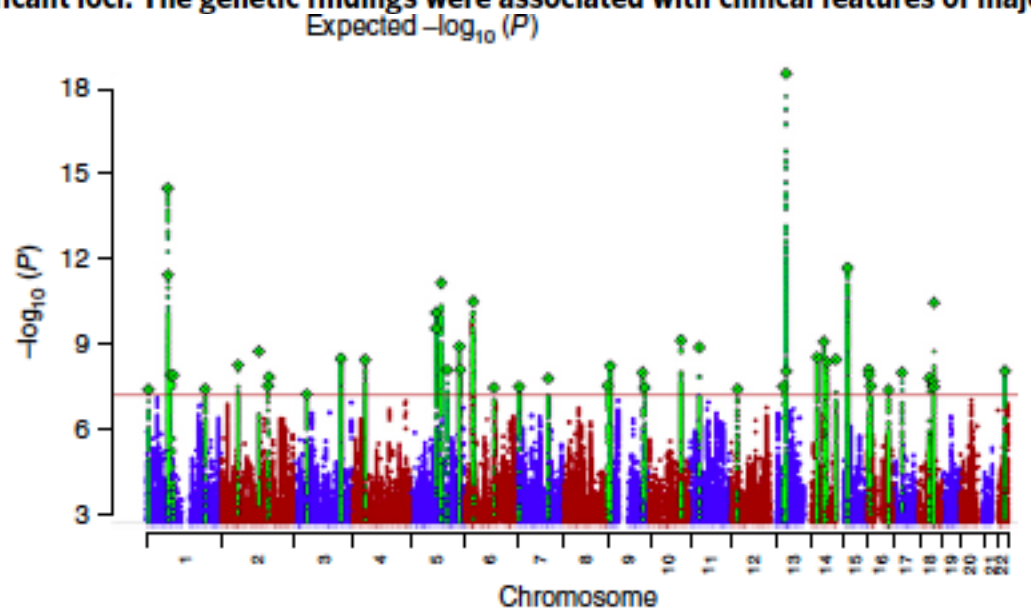
1. PTSD is still underpowered: Continue to increase sample size

ARTICLES
https://doi.org/10.1038/s41588-018-0090-3

nature genetics

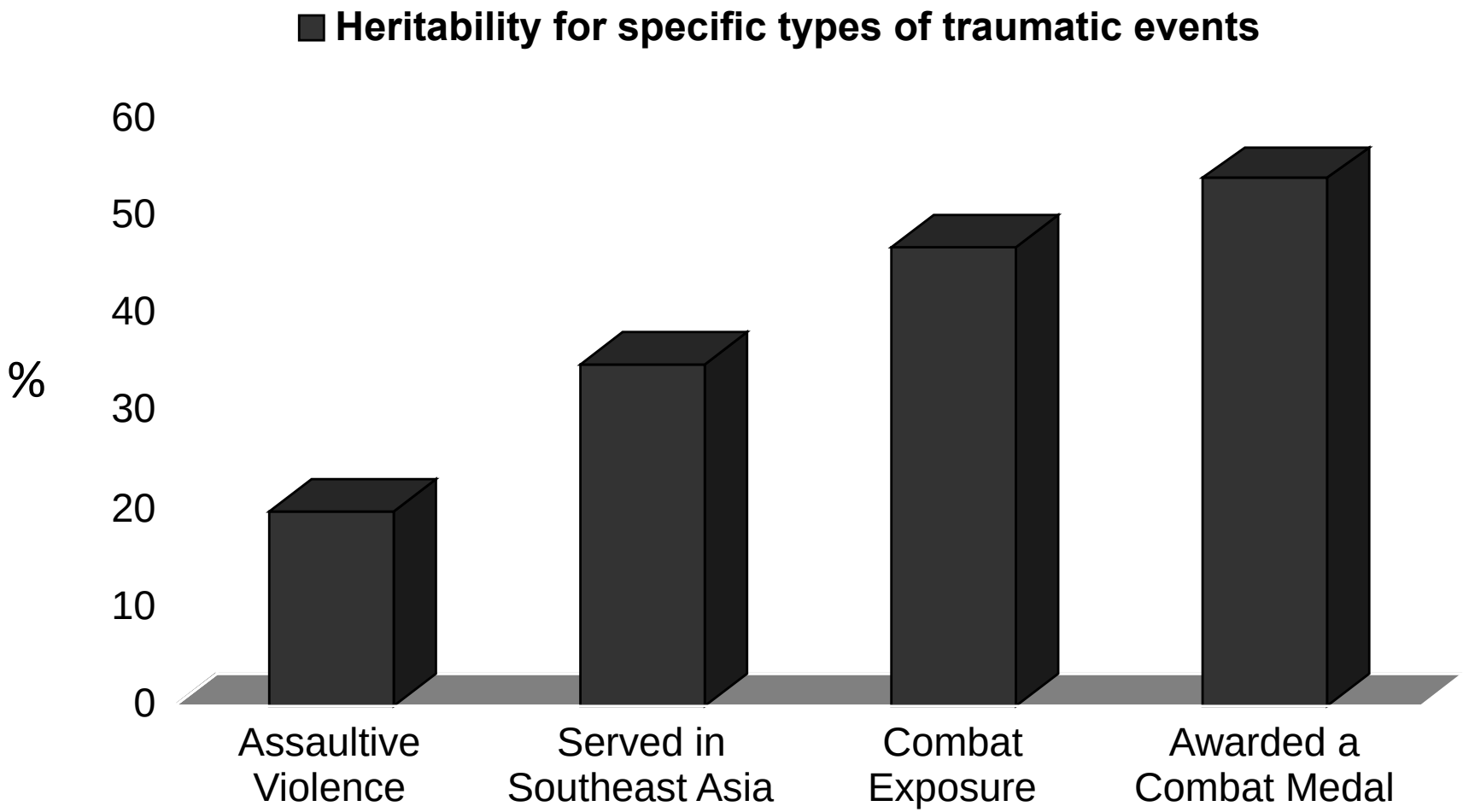
Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression

Major depressive disorder (MDD) is a common illness accompanied by considerable morbidity, mortality, costs, and heightened risk of suicide. We conducted a genome-wide association meta-analysis based in 135,458 cases and 344,901 controls and identified 44 independent and significant loci. The genetic findings were associated with clinical features of major depression and implicated brain regions genes involved in gene splicing were enr r major depression with educational at ody mass were putatively causal, where ll humans carry lesser or greater number ajor depression and imply that a continu



2. PTSD is conditional on trauma and heterogeneous: Refine trauma and PTSD phenotypes

Trauma exposure is heritable



Stein et al. (2002) American Journal of Psychiatry
Lyons et al. (1995) American Journal of Medical Genetics

Heritability of childhood trauma

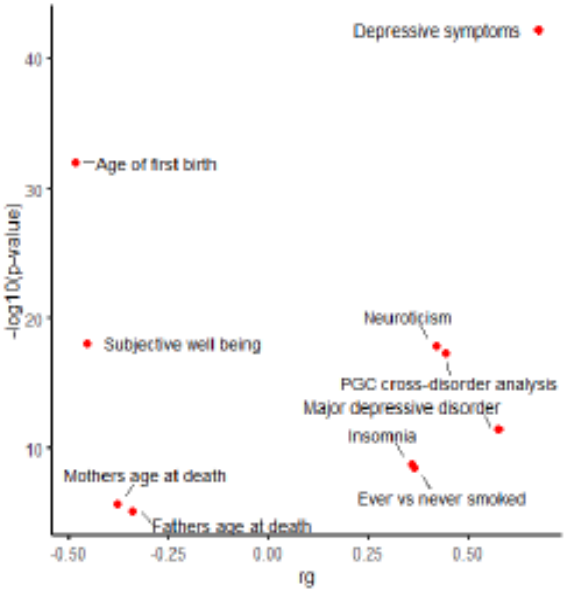
Shareefa Dalvie

Sample	N	h^2_{snp}	SE	z	P-value
UKBB	124,711	0.057	0.005	11.4	1.60E-32
PGC1.5	26,290	0.07	0.02	3.5	5.00E-04
PGC2	151,001	0.051	0.004	12.75	1.46E-43

Cross-Cohort Genetic Correlation:

UKBB and PGC 1.5

- rg= 0.62
- P-value= 1.35e-06



Courtesy of Shareefa Dalvie

PTSD is heterogeneous

Criterion*	Description	Specific examples	Requirements
Criterion A	Exposure to stressor	• Direct exposure • Witnessing trauma • Learning of a trauma • Repeat or extreme indirect exposure to aversive details	DSM-5 recognizes that exposure to trauma can occur either by direct or indirect confrontation with extreme trauma
Criterion B	Intrusion symptoms	• Recurrent memories • Traumatic nightmares • Di	At l examples
Criterion C			examples
Criterion D		...self or others for ...using trauma • Negative trauma-related emotions: fear, horror, guilt, shame and anger • Diminished interest in activities • Detachment or estrangement from others • Inability to experience positive emotions	...amples are required
Criterion E	Alterations in arousal and reactivity	• Irritable and aggressive behaviour • Self-destructive and reckless behaviour • Hypervigilance • Exaggerated startle • Problems concentrating • Sleep disturbance	At least two of these six examples are required

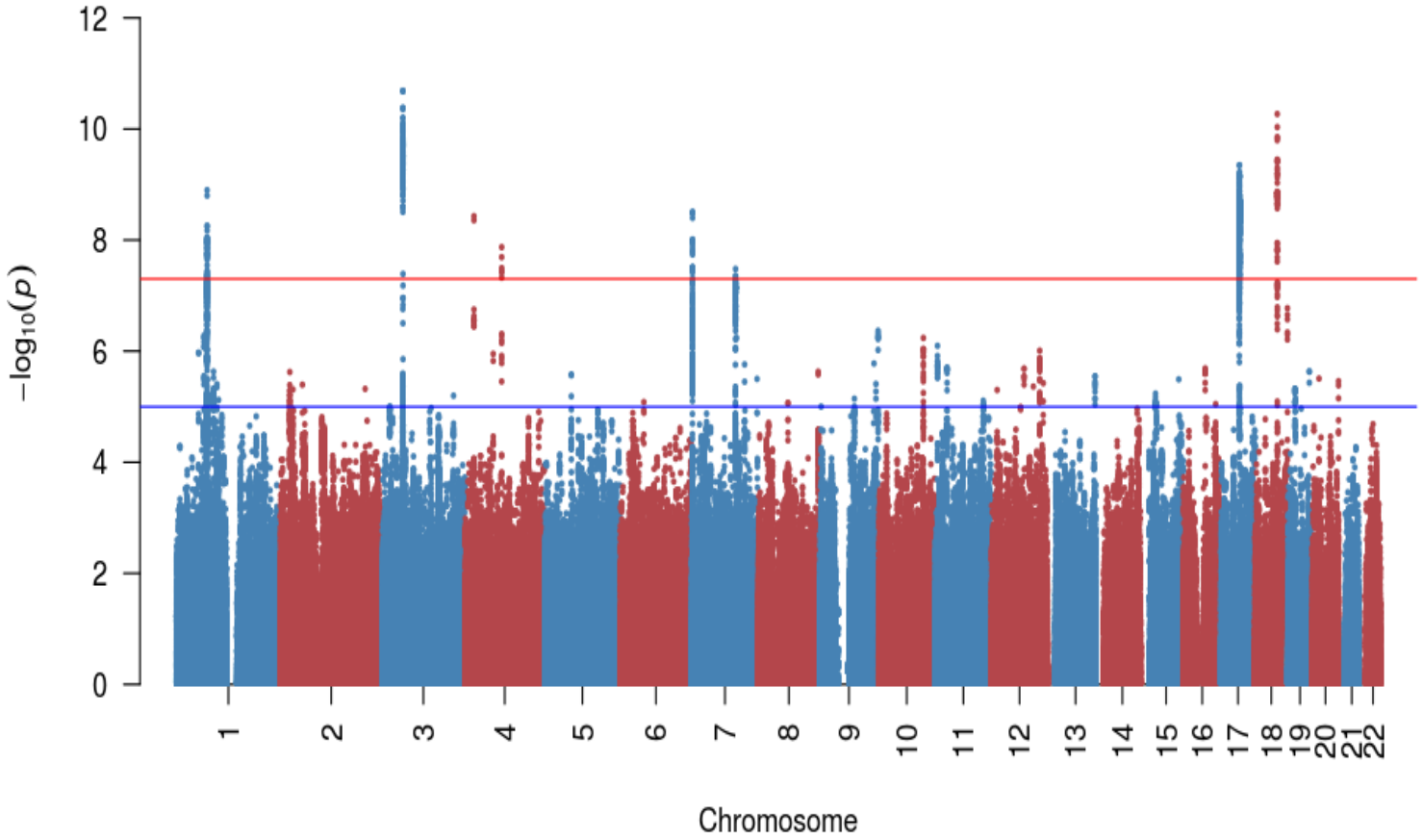
high level of symptom profile heterogeneity

"636,120 Ways to Have Posttraumatic Stress Disorder"

Galatzer-Levy and Bryant 2013

PTSD diagnosis: Crit. A plus 1B, 1C, 1C, 2D, 2E symptoms

Results from the Million Veterans Program CSP575b: GWAS of Reexperiencing in European Americans



Courtesy of Joel Gelernter, In Press, Nature Neuroscience

N=146,660 European-American

Cohen Veterans Bioscience

BRAIN Commons

3. GWAS hits are not an end in themselves: Translation needed to improve patients' lives

Genetic findings

↓

Biology

↓

Pathways / “read outs”

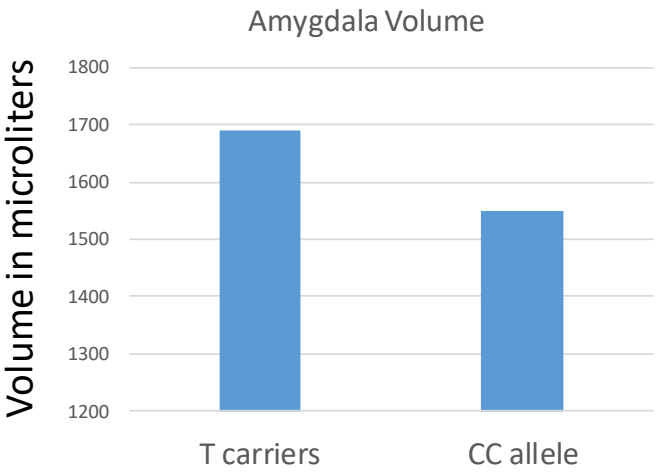
↓

<u>Rational</u> drug discovery

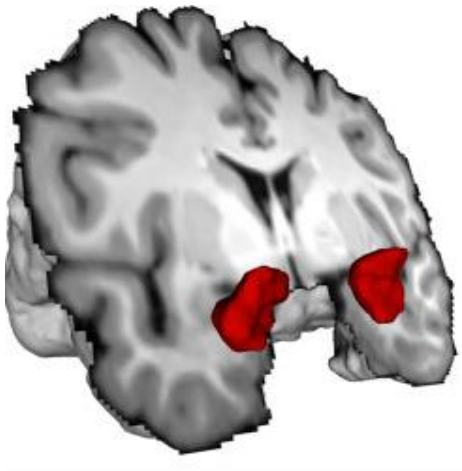
Genetic findings inform follow-up studies.

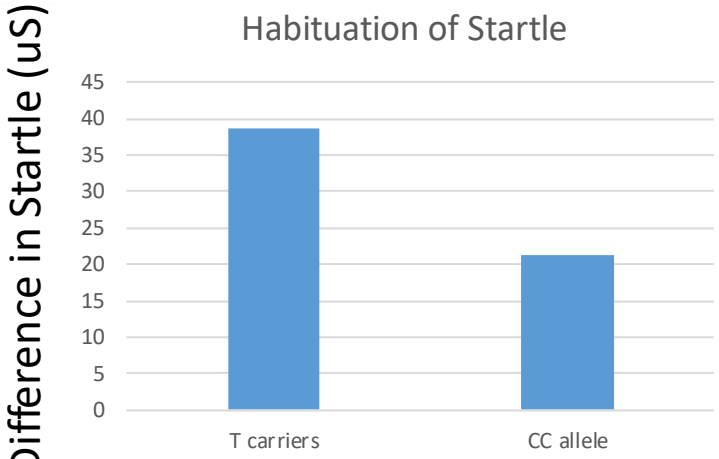
Functional imaging and psychophysiology in the Grady Trauma Project

Torsten Klengel



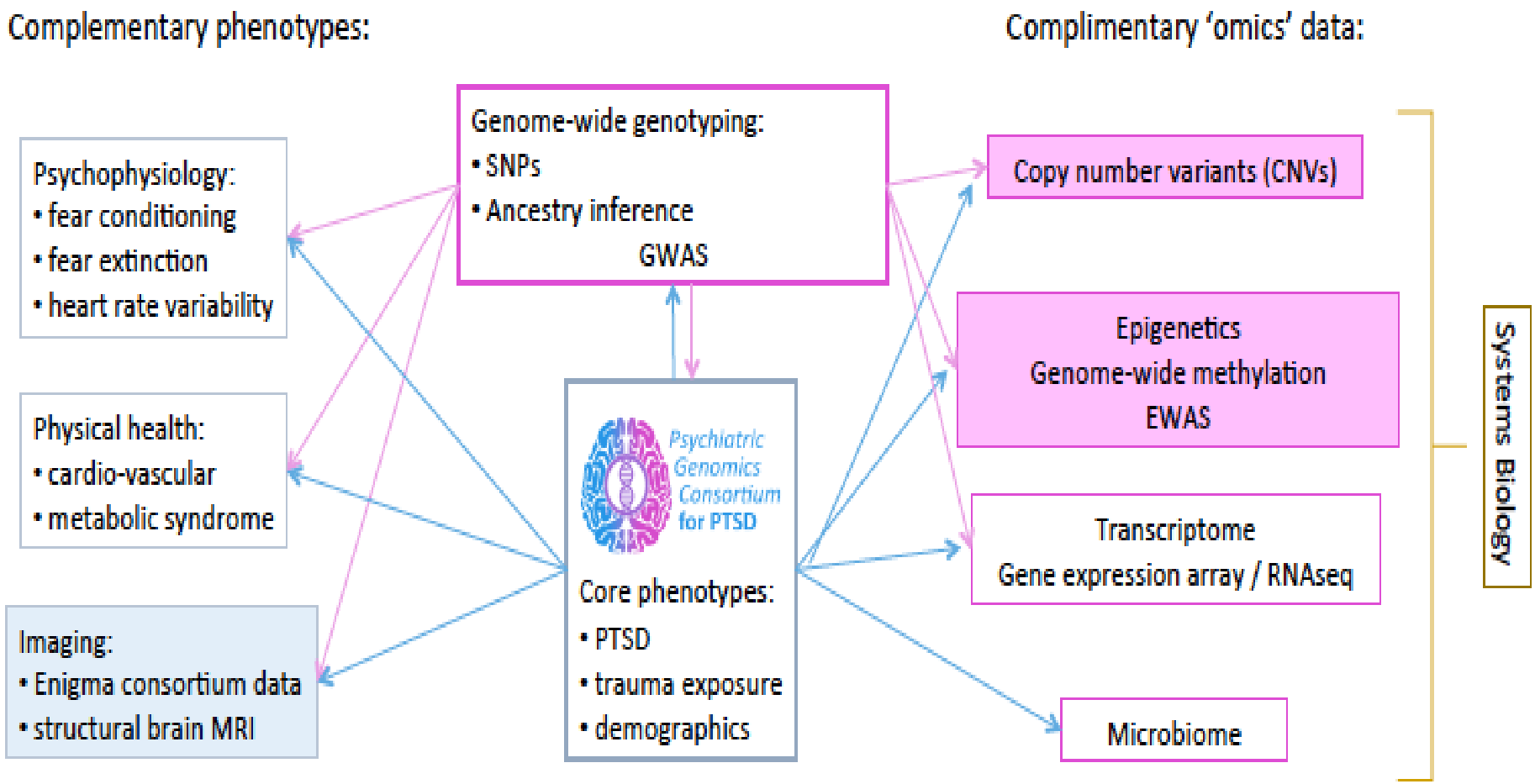
rs115539978 SNP





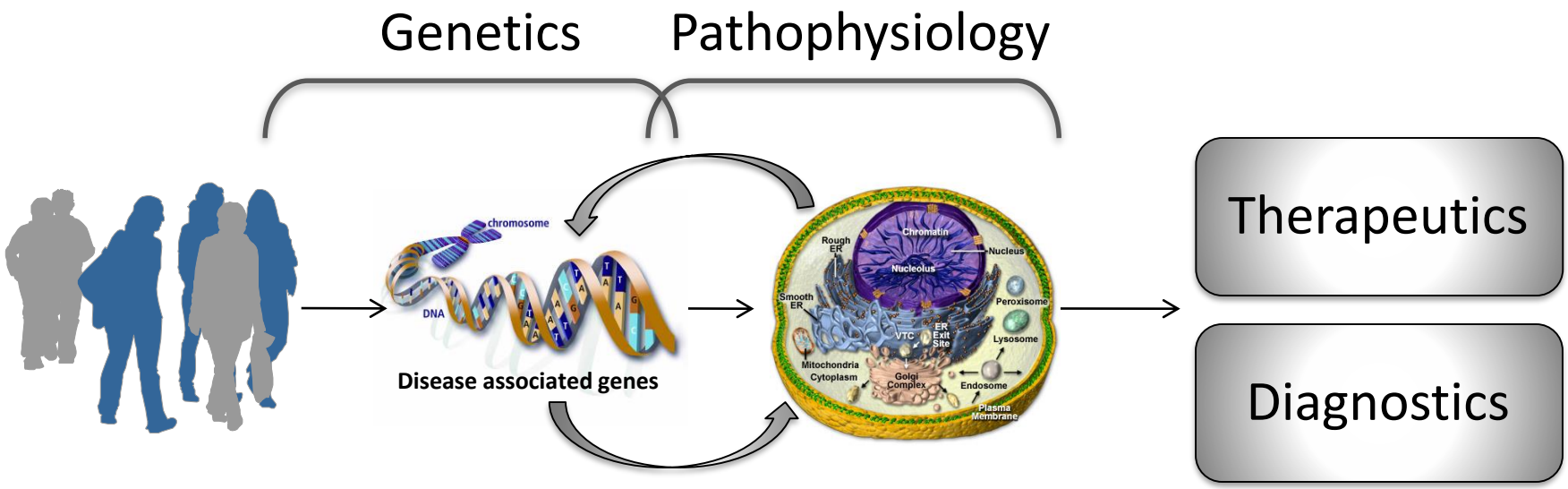
rs115539978 SNP

PCG PTSD Working Group



Nievergelt et al. Biol. Psychiatry 2018

From the population to clinical medicine



Goal: to provide durable insights into disease biology that ultimately impact clinical care

PGC PTSD Working Group Funding

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(Stanley Center)

Acknowledgments: MVP Results

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Acknowledgements: PGC PTSD Freeze 2

Marine Resiliency Study (MRS)
Ohio National Guard (ONG)
Drakenstein Child Health Study - South African sample (DCHS, South Africa)
Detroit Neighborhood Health Study (DNHS)
Nurses Health Study II (NHS2)
Yale-Penn Study (Gelernter)
Family Study of Cocaine Dependence (FSCD)
Grady Trauma Project (GTP)
Collaborative Genetic Study of Nicotine Dependence (COGEND)
Injury Vulnerability and Fire studies (Bryant IVS and fire)
Study of Aftereffects of Trauma: Understanding Response in National Guard (SATURN)
Defining Essential Features of Neural Damage (DEFEND)
National Health and Resilience in Veterans Study (NHRVS)
Army STARRS (NSS1, NSS2, PPDS)
Genetics of Posttraumatic Stress Disorder/Substance Use Disorder (Delahanty, KSUD)
Bounce Back Now (BBN)
Child Trauma and Neural Systems Underlying Emotion Regulation (McLaughlin, KMCT)
Estudo Nacional Sobre Saúde e Bem-estar Psicológico - WMH (Portugal)
Growing Up Today Study (GUTS)
Pregnancy Outcomes, Maternal and Infant Study (PrOMIS)
Vietnam Era Twin Study of Aging (VETSA)
Prospective research in stress-related military operations (PRISMO)
Mid-Atlantic Mental Illness Research Education and Clinical Center the study of Post-Deployment Mental Health Study (MIR6)
INjury and TRaumatic STress Clinical Consortium (INTRuST)
Danish military study
Danish i-PSYCH
Brisbane twin study (QIMR)
VA Boston-National Center for PTSD Study (NCPT)
Translational Research Center for TBI and Stress disorders
Readiness and Resilience in National Guard Soldiers (RINGS)
Strong Star - Genetic and Environmental Contributions to Combat-Related PTSD
Biomarkers of Anxiety Disorders and Treatment Response – SydneyNeuroimaging
CHOICE and OPT: Doubly Randomized Treatment Trials for PTSD (CHOICE and OPT)
D-cycloserine Iraq RCT (DCS Rothbaum)
Neurobiology of Traumatic Dissociation and PTSD (Teicher)
Northern Illinois University Trauma Study (NIU)
National Centre for Mental Health (NCMH Wales)
Genetic Predictors of Acute and Chronic Musculoskeletal Pain after Minor MVC (EA Crash)
Women and Children's Health Study (WaTCH)
Shared Roots (South Africa)
Biological Effects of Traumatic Experiences, Treatment and Recovery (BETER)
South East Europe (SEE) -PTSD
Cohen Veterans Center Study (CVC)
Fort Campbell study
GRACY: Genetic Research and Childbearing Year
A Cross-Sectional, Case-Control Study of the Physical Health Status of Vietnam Veterans with and without Posttraumatic Stress Disorder and Investigation of Genetics of PTSD (GMRF/QUT)
James J. Peters VA Genetic risk for PTSD (Yehuda)
VA San Diego Randomized controlled psychotherapy trial (Risbrough/Norman)
Ralph H Johnson VA Cortical Excitability: Biomarker and Endophenotype in Combat Related PTSD (WANG)
UK Biobank

NIH National Institute of Mental Health

STANLEY CENTER FOR PSYCHIATRIC RESEARCH AT BROAD INSTITUTE

Cohen Veterans Bioscience

PGC Psychiatric Genomics Consortium

plus >200 PGC PTSD GWAS collaborators

PTSD Consultation Program

FOR PROVIDERS WHO TREAT VETERANS

(866) 948-7880 or PTSDconsult@va.gov

Please enter your questions in the Q&A box and be sure to include your email address.

The lines are muted to avoid background noise.

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Return to TRAIN for evaluation.

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CEU Process (for VA employees)

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Register in TMS.

Attendance

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Certificate

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UPCOMING TOPICS

SAVE THE DATE: Third Wednesday of the Month from 2-3PM (ET)

August 21	*Focal Brain Stimulation for PTSD*	Paul Holtzheimer, MD
September 18	*Treating PTSD and Cognitive Impairment from Traumatic Brain Injury*	Amy Jak, PhD
October 16	*Unconventional Interventions for PTSD: State of the Evidence*	Paul Holtzheimer, MD
November 20	*Addressing Sleep: A Strategy for Symptom Reduction & Suicide Prevention?*	Wilfred Pigeon, PhD
December 18	*Treating Comorbid PTSD and Borderline Personality Disorder*	Melanie Harned, PhD, ABPP
January 15	*Dissociation, Somatization, and Other Challenging Presentations of PTSD*	Abigail Angkaw, PhD

For more information and to subscribe to announcements and reminders go to
www.ptsd.va.gov/consult