Genome-Wide Investigation of Suicide Ideation and Attempt in the Context of Substance Dependence

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Research Connection

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Predisposition to Health and Disease

3.2 billion base pairs per genome

>1 billion known variants

4-5 million variants per genome

>99.9% of variants consist of single nucleotide variants (SNV) and short insertion/deletions (indels)

SNVs	Indels	Structural variants
1 bp	<50 bp	≥50 bp

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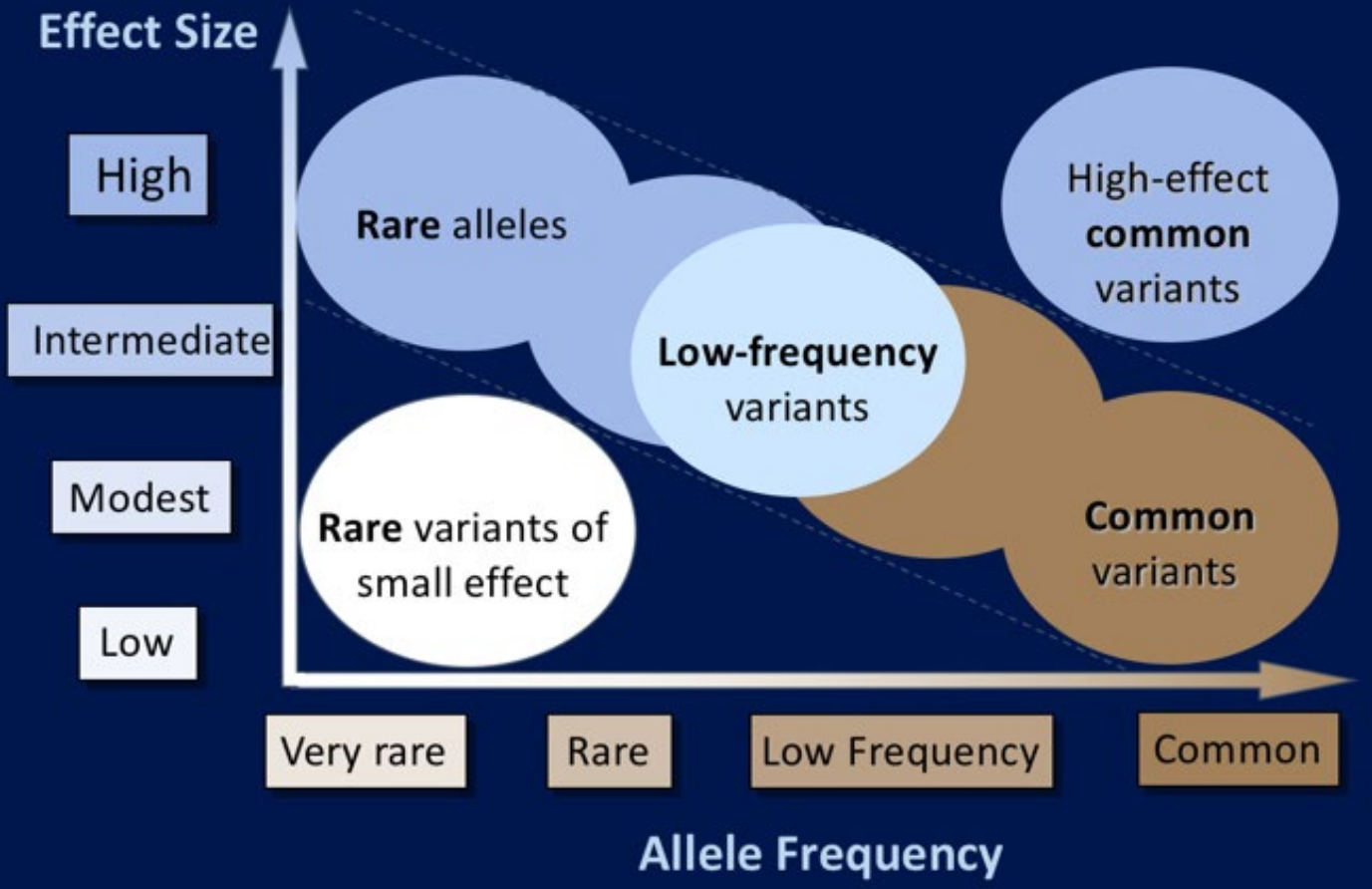
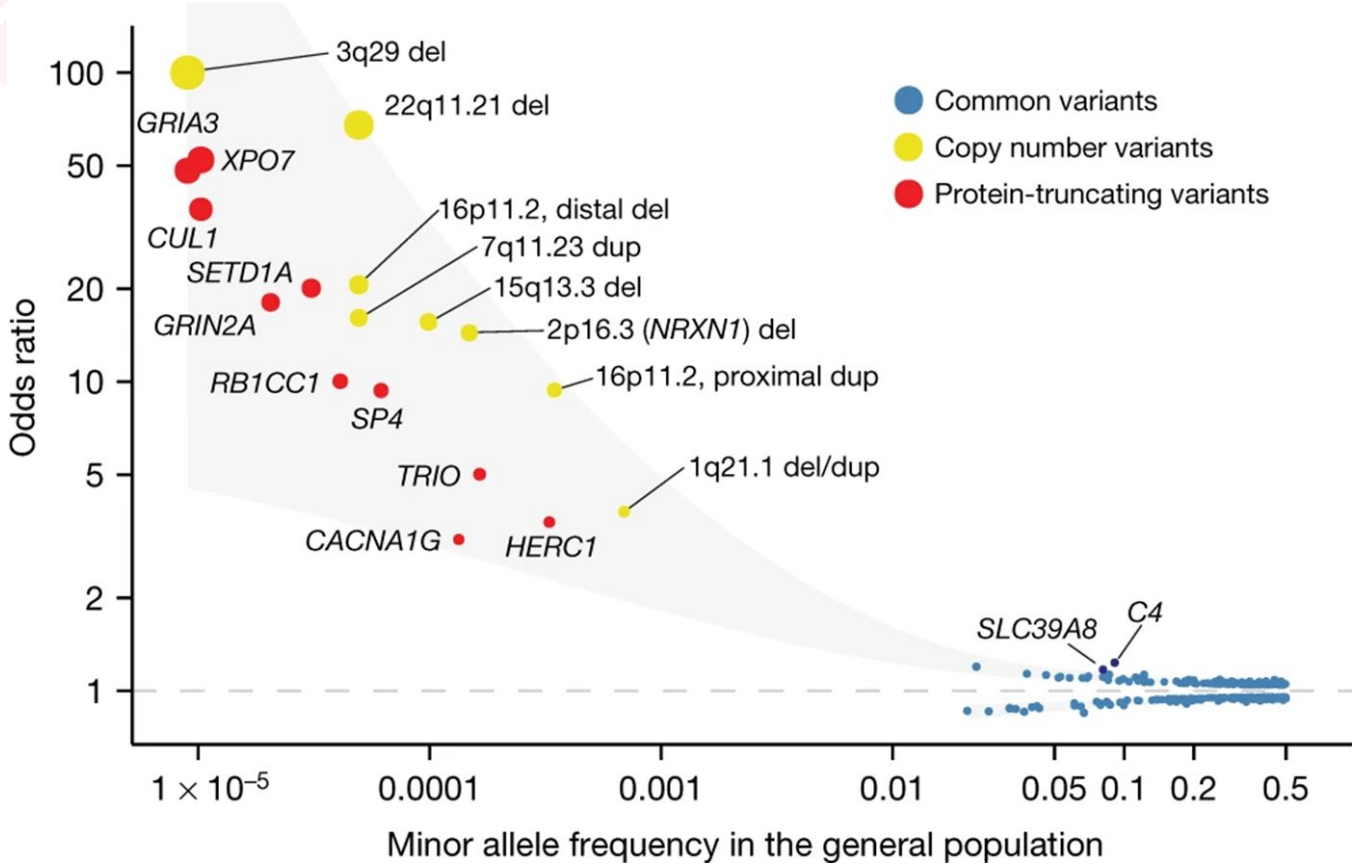
Common vs. Rare Variants



Single Genes vs. Polygenicity (Schizophrenia)



Nature. 2022 Apr; 604(7906):509-516

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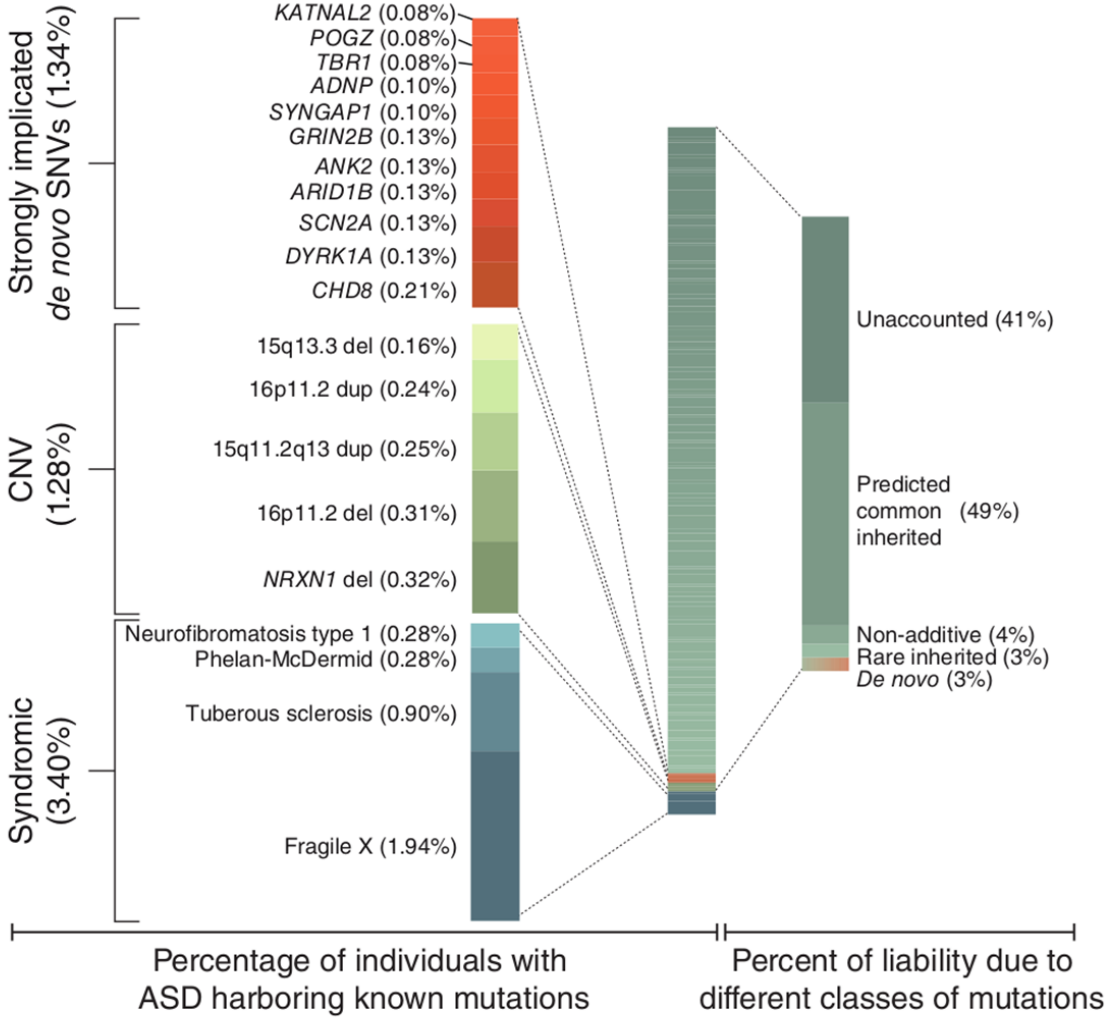

Single Genes vs. Polygenicity

(Autism Spectrum Disorder)

Nat Med. 2016 Apr;
22(4):345-61

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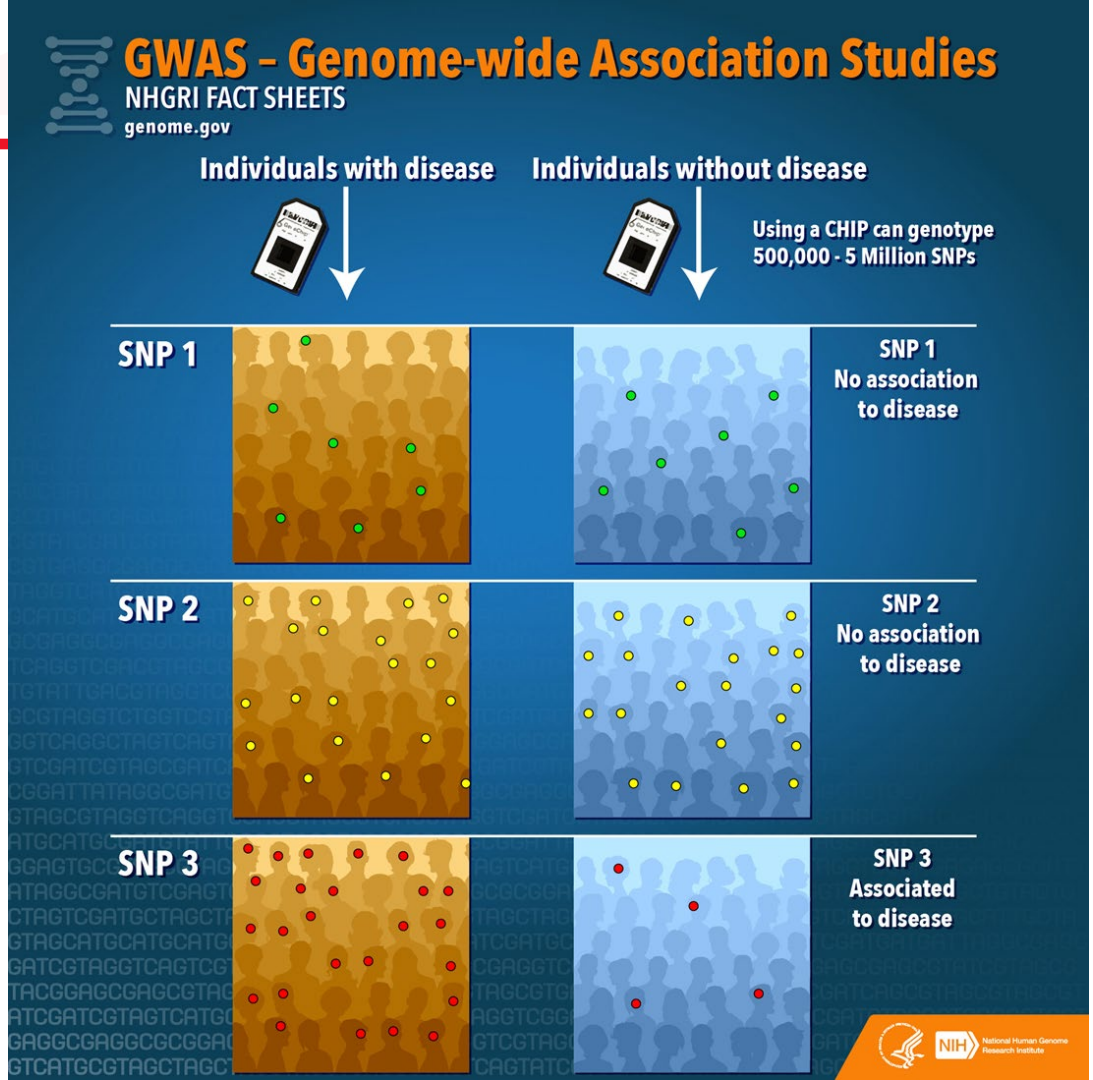

"Brute force" Experiment

No a priori hypothesis

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Gene Discovery in Psychiatry

Disorder	Total sample size (cases)	Population Groups	Loci Identified
Addiction (cross-substance)	1,118,180 (24,624)	EUR, AFR	19
Attention-Deficit Hyperactivity Disorder	225,534 (38,691)	EUR	27
Anxiety Disorders	1,266,780 (97,383)	EUR, AFR, LAT, CSA, EAS	51
Autism Spectrum Disorder	46,350 (18,381)	EUR	5
Bipolar Disorder	413,466 (41,917)	EUR	64
Cannabis Use Disorder	1,054,365 (64,314)	EUR, AFR, LAT, EAS	27
Major Depression	5,050,033 (685,808)	EUR, AFR, LAT, CSA, EAS	697
Obsessive-Compulsive Disorder	2,098,077 (53,660)	EUR	30
Opioid Use Disorder	425,944 (31,473)	EUR, AFR, LAT	14
Problematic Alcohol Use	1,079,947 (165,952)	EUR, AFR, LAT, CSA, EAS	110
Psychopathology (Cross-disorder)	727,126 (232,964)	EUR	109
Posttraumatic Stress Disorder	1,280,933 (150,760)	EUR, AFR, LAT	95
Schizophrenia	320,404 (76,755)	EUR, EAS, AFR, LAT	287
Tobacco Use Disorder	898,680 (231,763)	EUR, AFR, LAT	88

Suicidal Behaviors - Gene Discovery

Trait	Sample Size	Population Groups	Loci Identified
Suicidal Thoughts	121,211 cases, 512.567 controls	EUR, AFR, LAT, ASN	21
Suicide Attempt	43,871 cases, 915,025 controls	EUR, AFR, EAS	12
Suicide Death	3,413 cases, 14,810 controls	EUR	2
	746 cases, 14,049 controls	EAS	0
Suicidality*	122,935	EUR	3

*Ordinal scale including ‘no suicidal behaviour’, ‘contemplated self-harm’, ‘actual self-harm’, ‘suicidal ideation’ and ‘suicide attempt’

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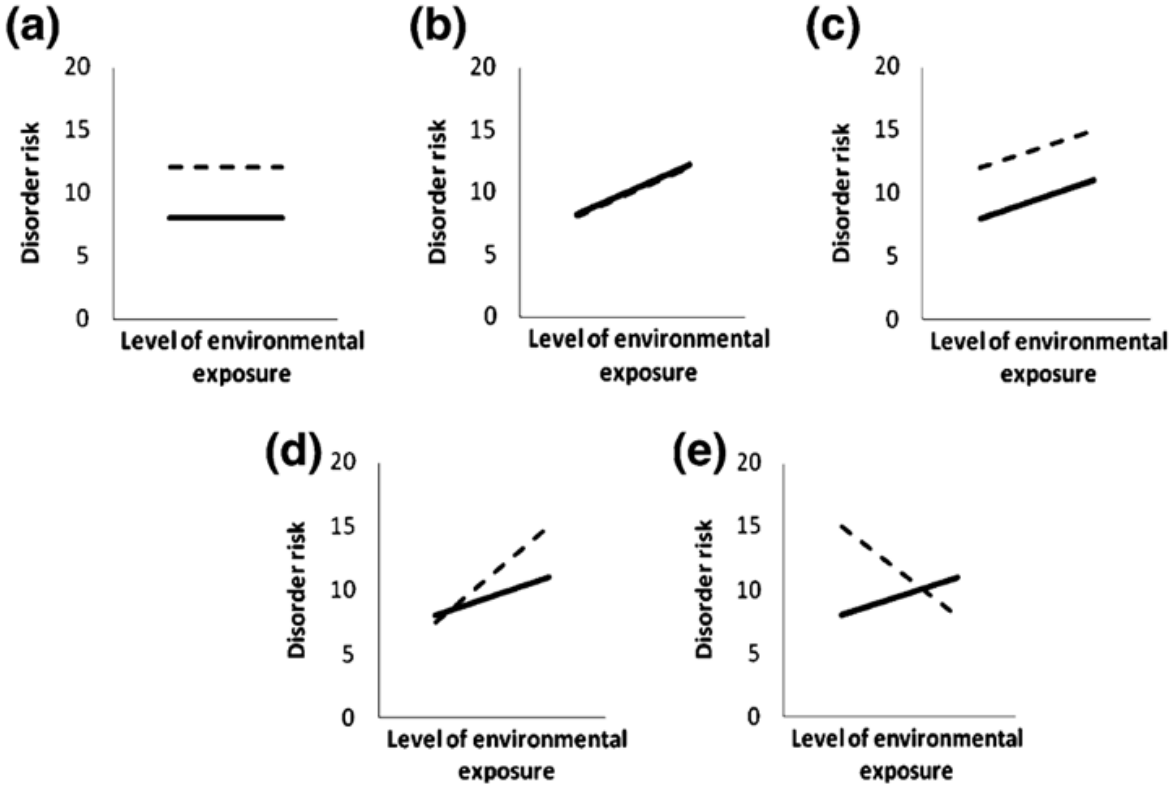
Gene-Environment Interactions



Gene-environment interactions occur when different genotypes, and their associated effects, respond to environmental variables in different ways

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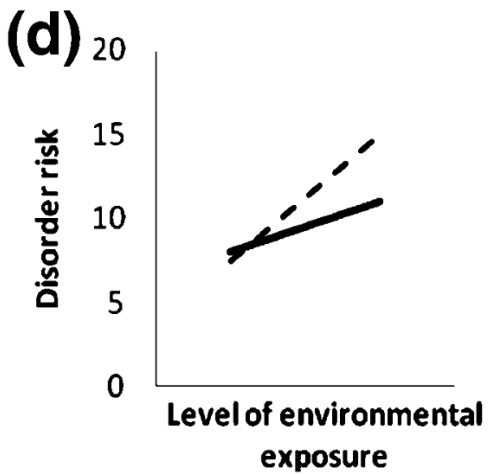
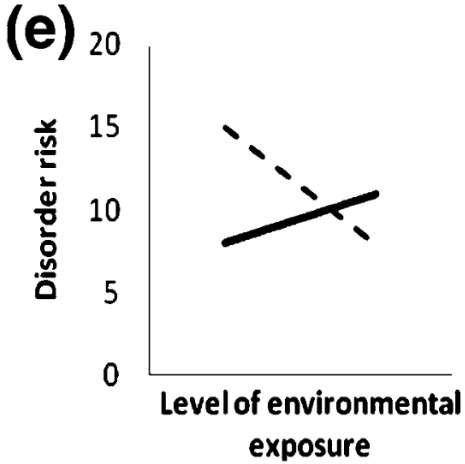
Gene-Environment Interactions

Quantitative Interaction



Qualitative Interaction



The environmental risk factor(s) can be an exposure (physical, chemical, or biological), a behavior pattern, or a life event

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No Support for Historical Candidate Gene or Candidate Gene-by-Interaction Hypotheses for Major Depression Across Multiple Large Samples

Richard Border, M.A., Emma C. Johnson, Ph.D., Luke M. Evans, Ph.D., Andrew Smolen, Ph.D., Noah Berley, Patrick F. Sullivan, M.D., Matthew C. Keller, Ph.D.

Objective: Interest in candidate gene and candidate gene-by-environment interaction hypotheses regarding major depressive disorder remains strong despite controversy surrounding the validity of previous findings. In response to this controversy, the present investigation empirically identified 18 candidate genes for depression that have been studied 10 or more times and examined evidence for their relevance to depression phenotypes.

Methods: Utilizing data from large population-based and case-control samples (Ns ranging from 62,138 to 443,264 across subsamples), the authors conducted a series of preregistered analyses examining candidate gene polymorphism main effects, polymorphism-by-environment interactions, and gene-level effects across a number of operational definitions of depression (e.g., lifetime diagnosis, current severity, episode recurrence) and environmental moderators (e.g., sexual or physical abuse during childhood, socioeconomic adversity).

Results: No clear evidence was found for any candidate gene polymorphism associations with depression phenotypes or any polymorphism-by-environment moderator effects. As a set, depression candidate genes were no more associated with depression phenotypes than noncandidate genes. The authors demonstrate that phenotypic measurement error is unlikely to account for these null findings.

Conclusions: The study results do not support previous depression candidate gene findings, in which large genetic effects are frequently reported in samples orders of magnitude smaller than those examined here. Instead, the results suggest that early hypotheses about depression candidate genes were incorrect and that the large number of associations reported in the depression candidate gene literature are likely to be false positives.

Am J Psychiatry 2019; 176:376–387; doi: 10.1176/appi.ajp.2018.18070881

Genome-Wide Investigation of Suicide Ideation and Attempt in the Context of Substance Dependence

2017 Young Investigator Grant

YIG-1-109-16

Question: What are the gene-by-environmental contributors to suicide-related behavior in people with substance dependence?

Strategy: Apply gene x environment genome-wide analysis

Impact: Uncovering of biological mechanisms of suicide-related behaviors and potential for intervention

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Study Populations

Yale-Penn Cohort – Participants recruited for studies of drug or alcohol dependence. High prevalence of misuse of legal and illegal substances

Army Study to Assess Risk and Resilience in Servicemembers (STARRS) – Participants recruited from Army personnel including new soldiers before basic combat training, active-duty soldiers, brigade combat teams about to be deployed

Yale-Penn Cohort

15,557 Participants recruited for studies of drug or alcohol dependence.

High prevalence of misuse of legal and illegal substances

Age, mean (SD)	40 (11.8)
Sex, Women (%)	7187 (46)
Self-reported Racial/Ethnic Group, *n* (%)	
Native American/American Indian	1327 (9)
Asian	101 (1)
Pacific Islander	20 (<1)
African-American/Black, not of Hispanic origin	6027 (39)
African-American/Black, of Hispanic origin	350 (2)
Caucasian/White, not of Hispanic origin	6060 (39)
Caucasian/White, of Hispanic origin	811 (5)
Other	861 (6)

DSM-IV diagnosis, *n* (%)	
Alcohol Dependence	7481 (48)
Cannabis Dependence	3897 (25)
Cocaine Dependence	8662 (56)
Nicotine Dependence	8219 (52)
Opioid Dependence	4379 (28)
Polysubstance dependence, *n* (%)	
One DSM-IV SD diagnosis	2023 (13)
Two DSM-IV SD diagnoses	2942 (22)
Three DSM-IV SD diagnoses	3345 (22)
Four DSM-IV SD diagnoses	2419 (16)
Five DSM-IV SD diagnoses	1004 (6)

Suicidality, *n* (%)	
Ideation	6112 (39)
Persistent Ideation	1450 (9)
Planning	2491 (16)
Attempt	1965 (13)

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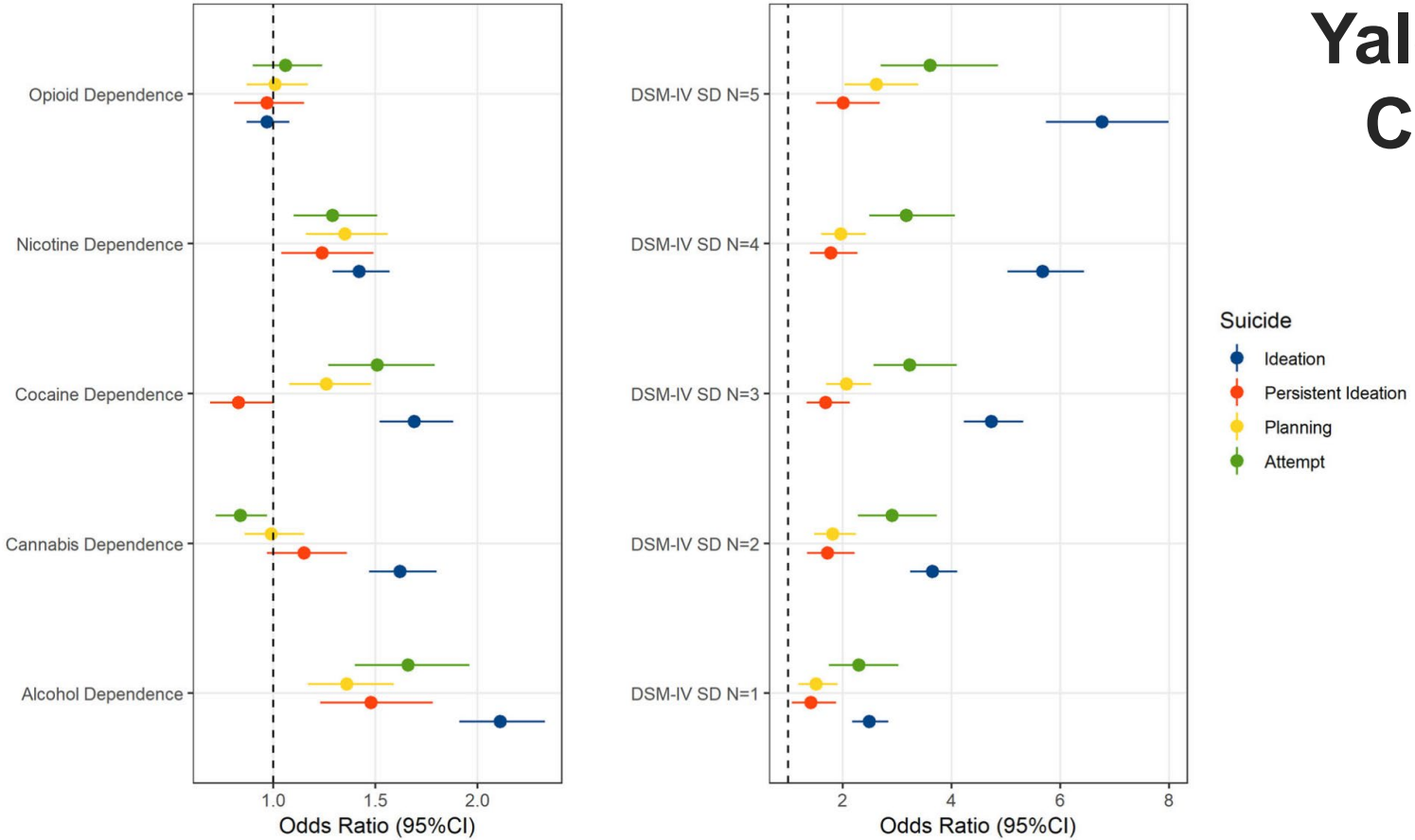
Army STARRS

11,235 Participants recruited from Army personnel including new soldiers before basic combat training, active-duty soldiers, and combat teams about to be deployed

Age, mean (SD)	21 (5.2)
Sex, Women (%)	1163 (10)
$SUD_{combined}$, *n* (%)	2848 (22)

Suicidality, *n* (%)	
Ideation	2299 (20)
Planning	446 (4)
Attempt	389 (3)

Substance dependence and Suicidality



Yale-Penn Cohort

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Substance Dependence and Suicidality in ASTARRS cohort

$SUD_{combined}$

Suicide Ideation OR=2.88 (95% CI=2.6–3.19)

Suicide Planning OR=3.88 (95% CI=2.79–4.10)

Suicide Attempt OR=3.92 (95% CI=3.19–4.81)

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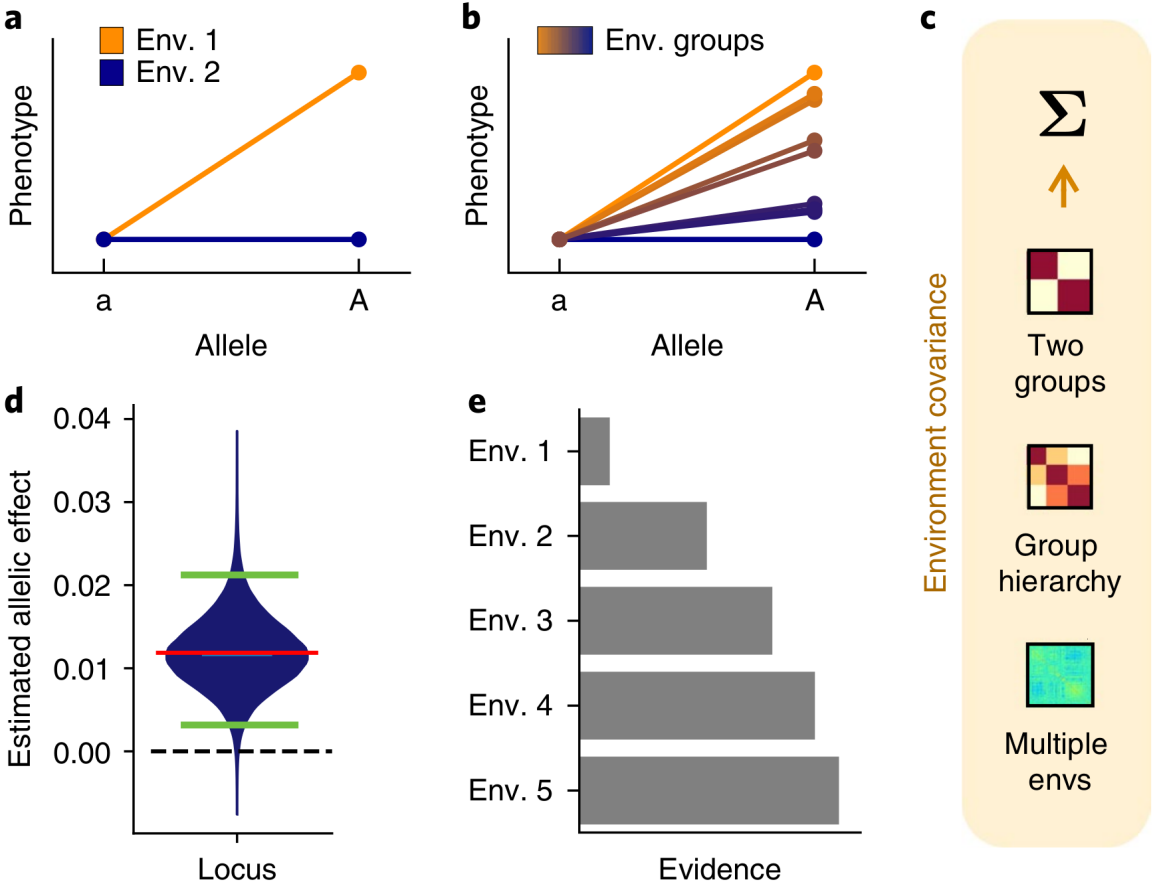
Structured Linear Mixed Model

A linear mixed-model approach to study multivariate gene-environment interactions

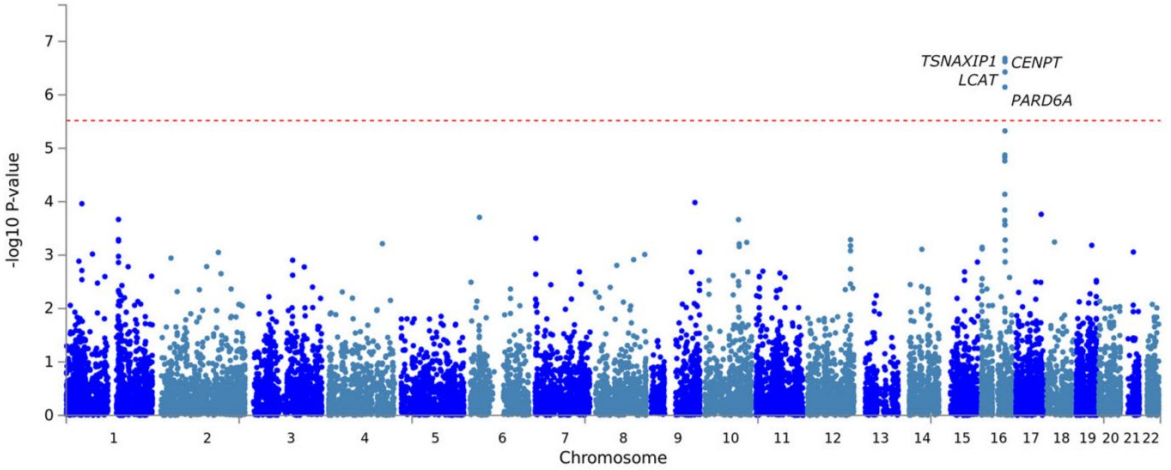
Nat Genet. 2019 Jan;51(1):180-186

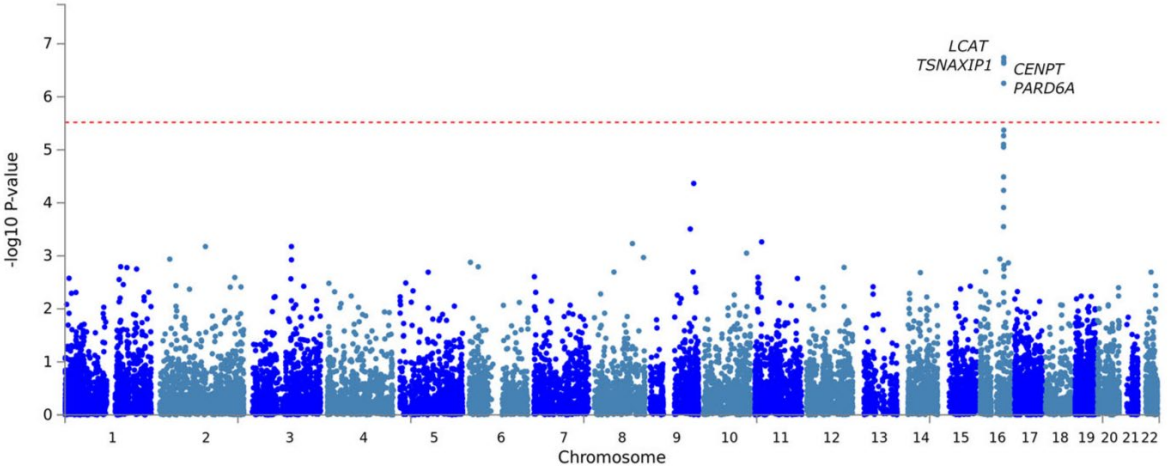


Multivariate SD–Gene Interaction Analysis of Suicide Ideation

- Multiple genes identified on chromosome 16 that showed both significant interaction and association effects

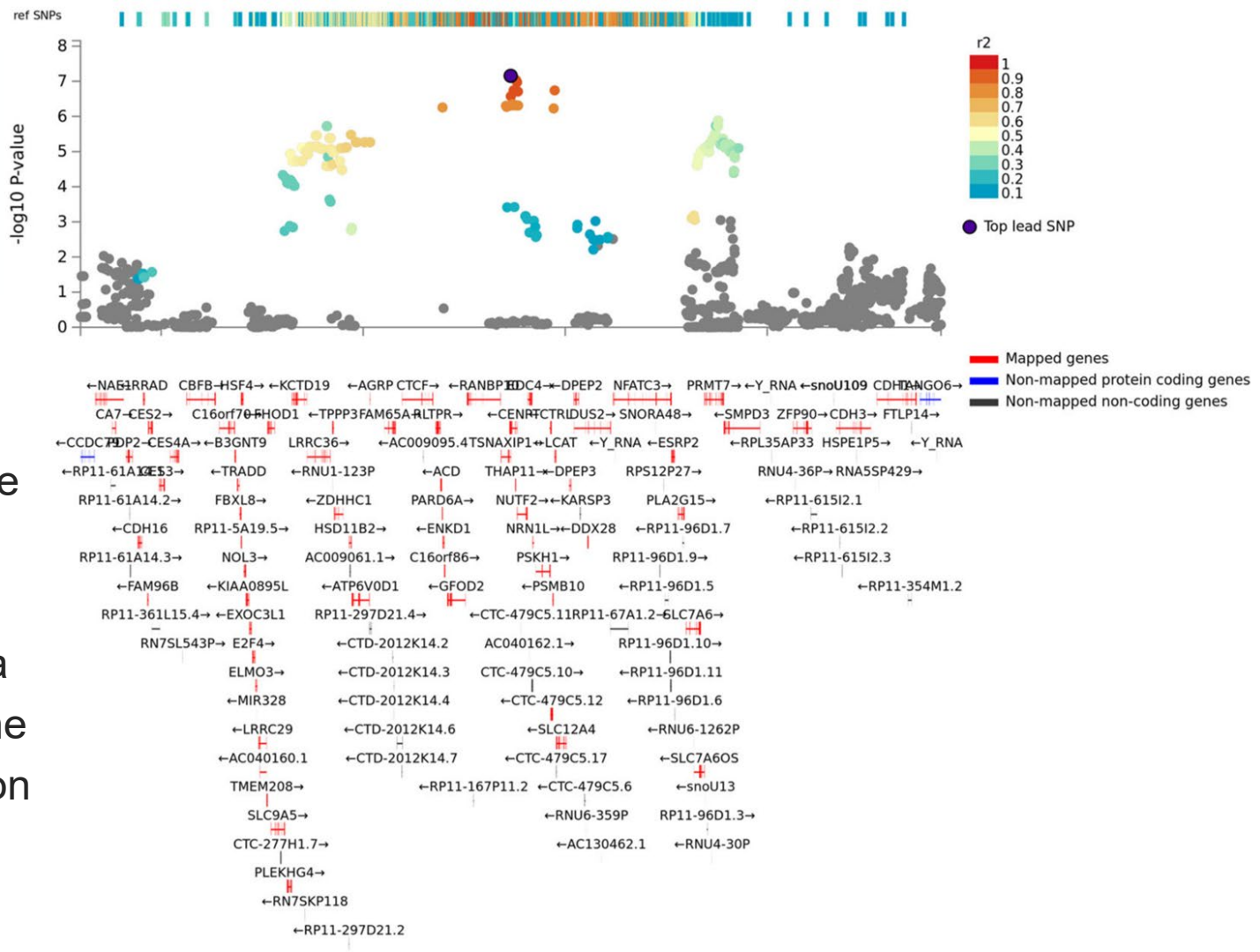
- Interactive Factors:
  - Opioid dependence severity
  - Cocaine dependence severity
  - Nicotine dependence severity
  - Polysubstance dependence





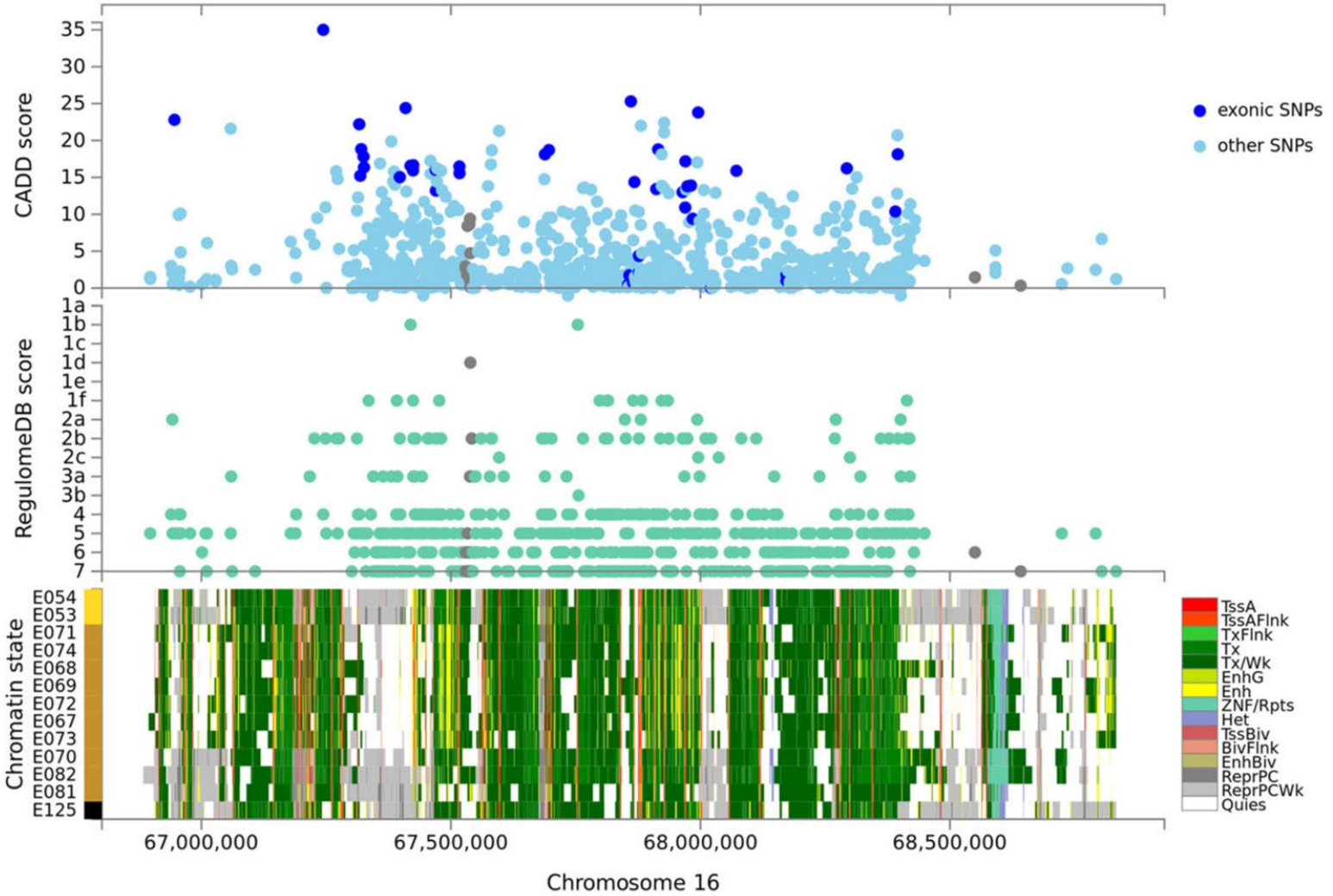
Multivariate SD–Gene Interaction Analysis of Suicide Ideation

One single nucleotide polymorphism (SNP, rs8052287) in this region accounts for a large proportion of the association/interaction



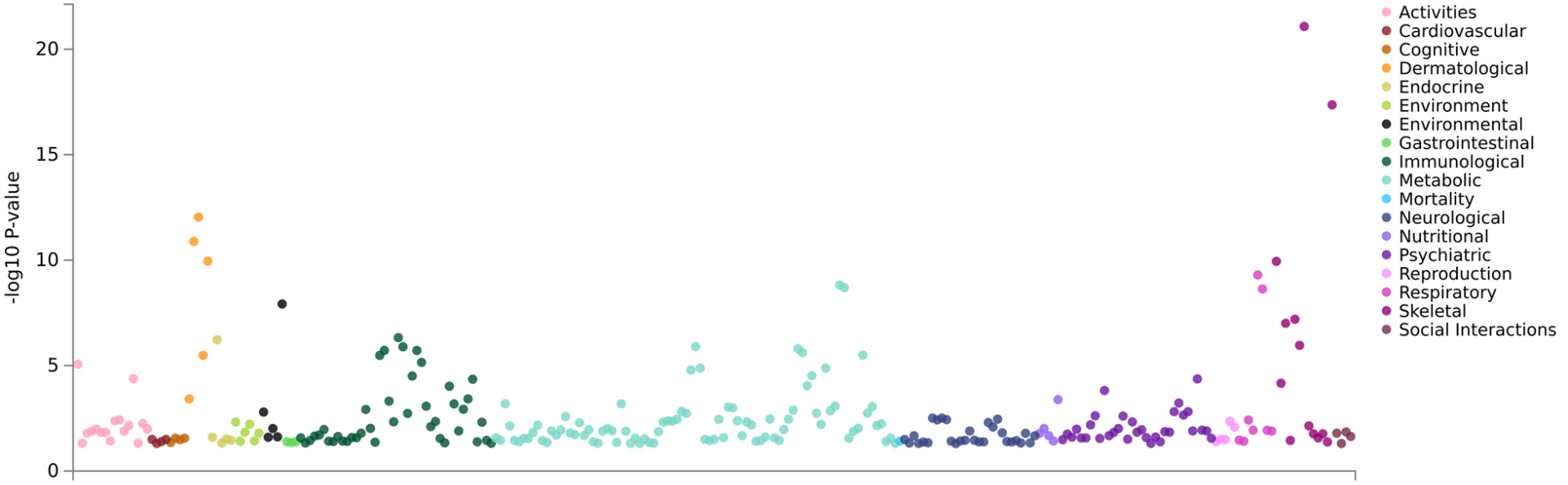
Multivariate SD–Gene Interaction Analysis of Suicide Ideation

Rs8052287 is linkage disequilibrium with pathogenic and regulatory variants

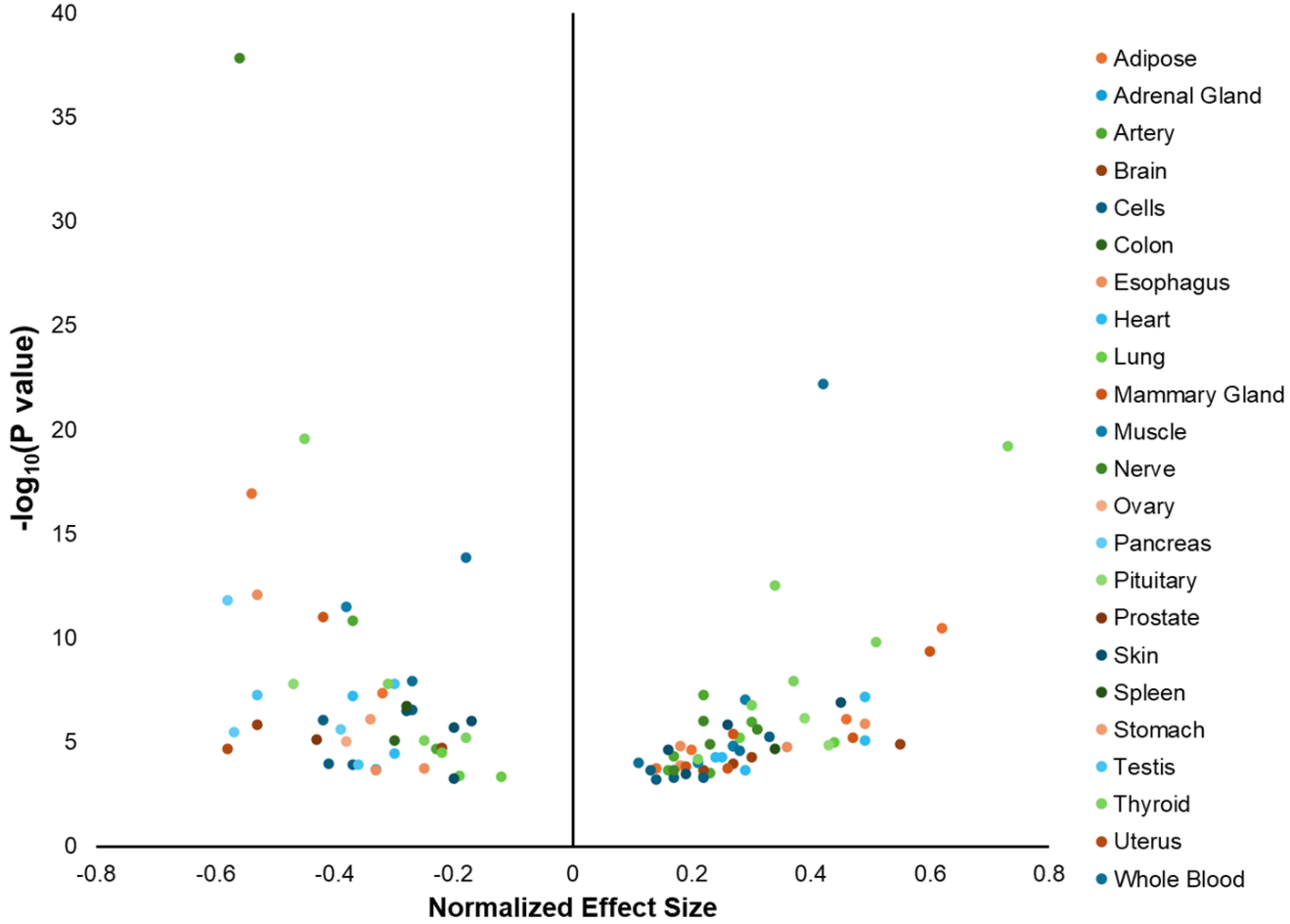


Multivariate SD–Gene Interaction Analysis of Suicide Ideation

Rs8052287 is associated with dermatological, endocrine, environmental, immunological, metabolic, respiratory, skeletal, and vision outcomes



Multivariate SD–Gene Interaction Analysis of Suicide Ideation



Rs8052287 regulates transcriptomic changes of 30 genes across 25 tissue types

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Multivariate SD–Gene Interaction Analysis of Suicide Ideation

The identification of multiple genes in the same region and rs8052287 regulatory role in multiple tissue types can support a range of hypotheses related to the interplay between suicide ideation and substance dependences

Considering convergent evidence across multiple sources, a possible mechanism may be related to thyroid hormone regulation

- **Rs8052287 is associated with hypothyroidism and use of thyroid preparations**
- **Rs8052287 regulates thyroid-specific transcriptomic changes of 10 genes**

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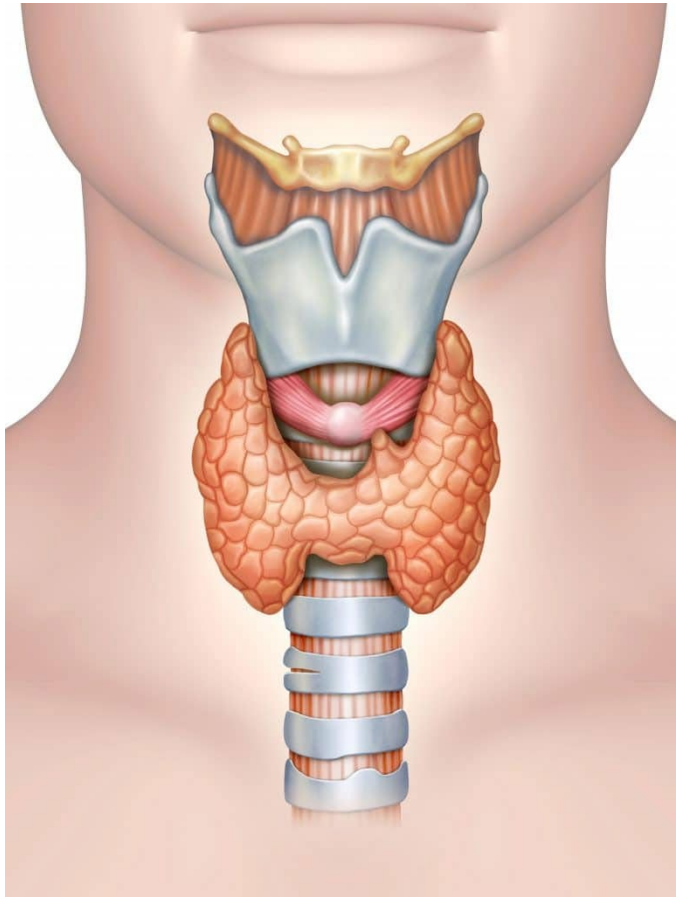
Thyroid Function, Suicidal Behaviors, and Addiction



Thyroid hormones influence the synthesis and activity of neurotransmitters

Altered thyroid function can impact mood and cognition and lead to the onset of neuropsychiatric symptoms

Substance misuse can alter thyroid hormone imbalance, and long-term misuse can directly damage the thyroid gland itself

Altered thyroid function has been associated with suicidal behaviors

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Polimanti et al. *Translational Psychiatry* (2021)11:34
https://doi.org/10.1038/s41398-020-01153-1

Translational Psychiatry

ARTICLE Open Access

Multi-environment gene interactions linked to the interplay between polysubstance dependence and suicidality

Renato Polimanti[1,2], Daniel F. Levey[1,2], Gita A. Pathak[1,2], Frank R. Wendt[1,2], Yaira Z. Nunez[1,2], Robert J. Ursano[3], Ronald C. Kessler[4], Henry R. Kranzler[5,6], Murray B. Stein[7,8] and Joel Gelernter[1,2,9]

Suicide-associated Loci Regulating Molecular Traits and Their Interaction With Environmental Factors

2022 Postdoctoral Fellowship

PDF-1-022-21

Brenda Cabrera-Mendoza, M.D., Ph.D.
Yale University School of Medicine

This study aims to characterize the function of genetic variants associated with suicidal behavior and evaluate their interaction with other factors associated with suicide

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Genomic Exploration of Brain Structure and Function and Behavioral Health in the Context of Suicidal Behaviors

2024 Postdoctoral Fellowship

PDF-0-065-23

Jun He, Ph.D.
Yale University

By applying a state-of-the-art framework to molecular, imaging, clinical, and behavioral data, this project will build high-performance machine learning models to predict the risk of suicide ideation and attempt

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Polimanti Lab @ Yale

YIG-1-109-16
PDF-1-022-21
PDF-0-065-23

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