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HessLab

Understanding Resilience to Schizophrenia through Genetics

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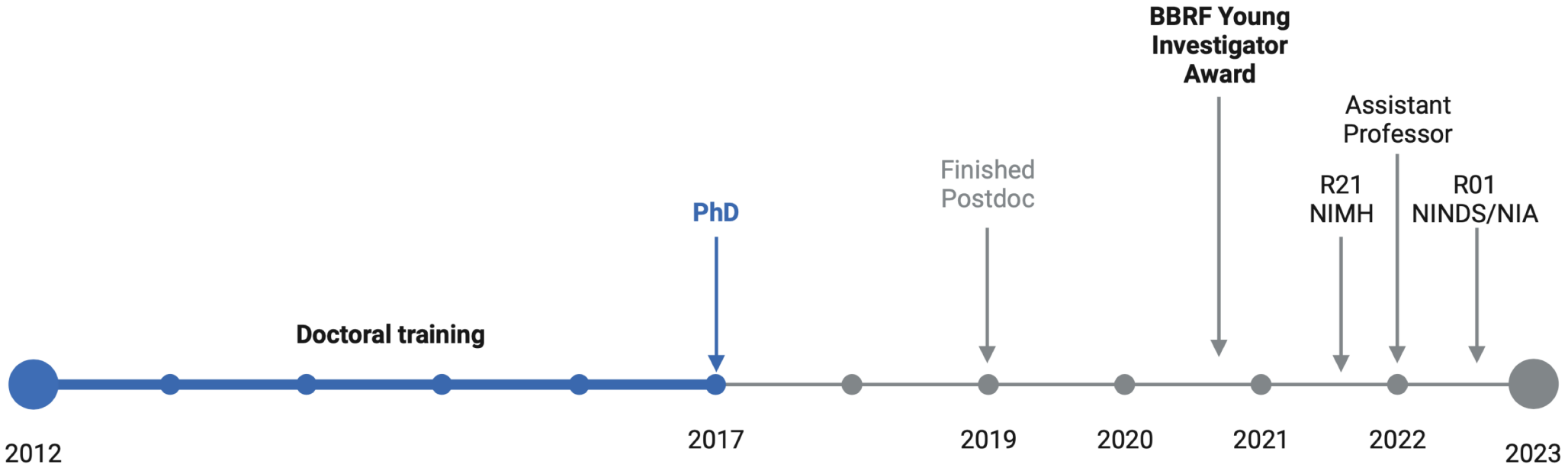
Disclosures

- I have no conflicts of interest to disclose

Personal background

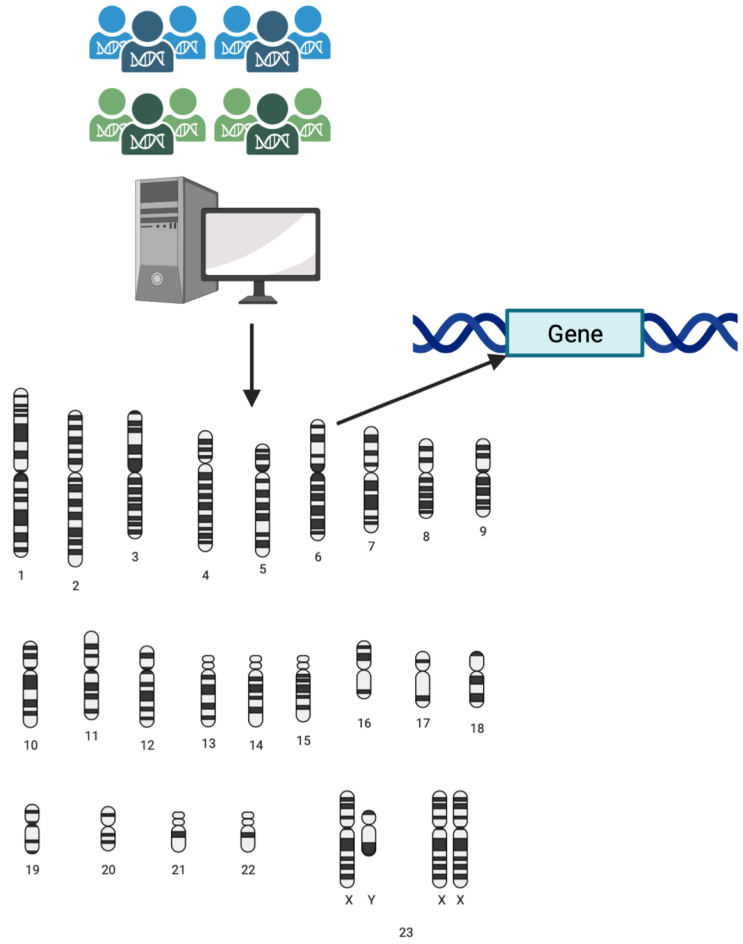
My timeline



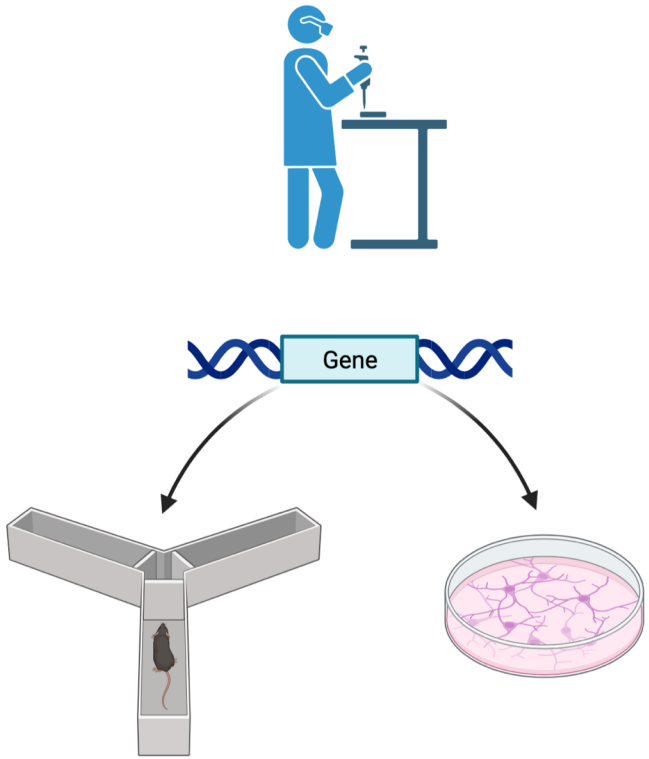
Mentor:
Stephen J. Glatt, PhD

- NARSAD: Sidney R. Baer, Jr. Prize
- Young Investigator Award

Geneticists (“Gene catalogers”)



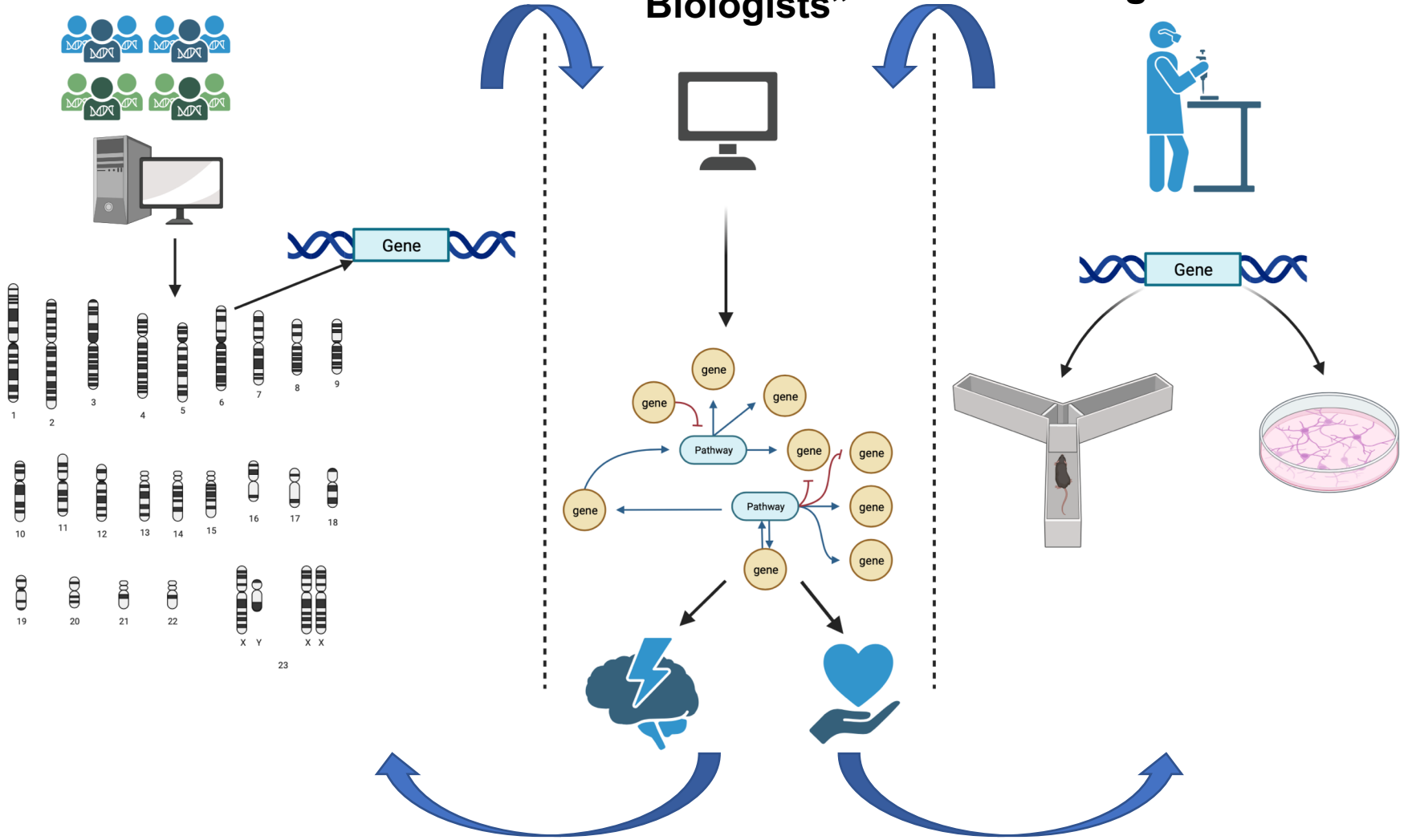
Biologists



Geneticists (“Gene catalogers”)

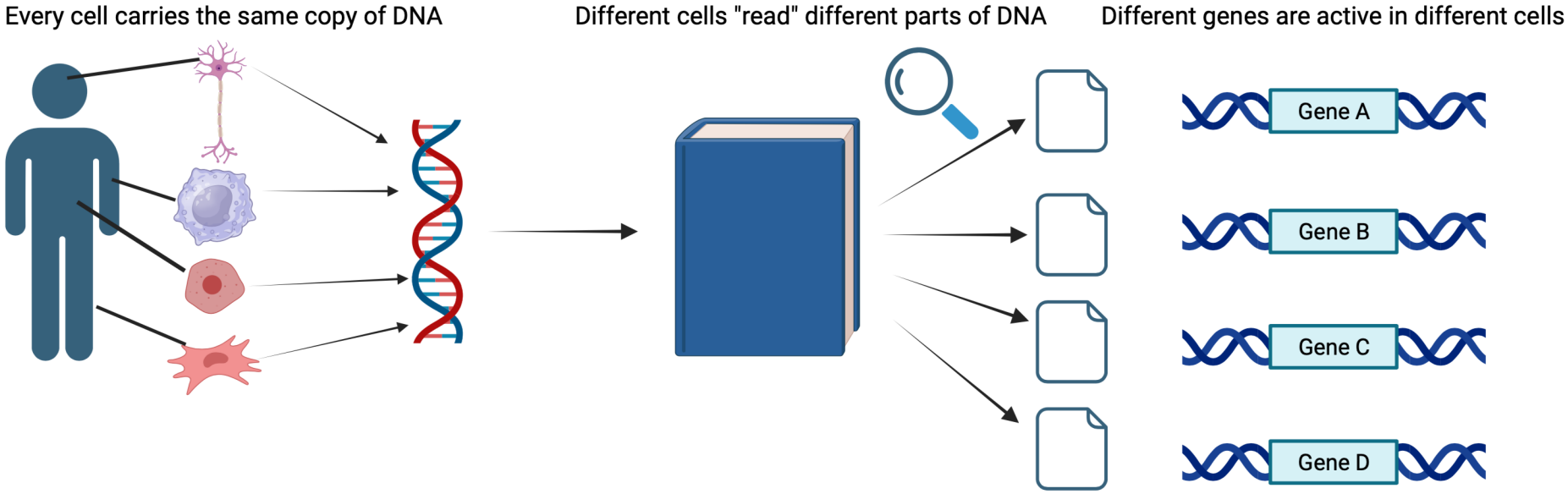
“Systems Biologists”

Biologists



Genetics Primer

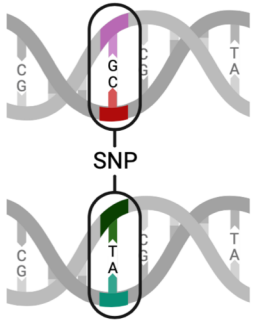
Genetics Primer

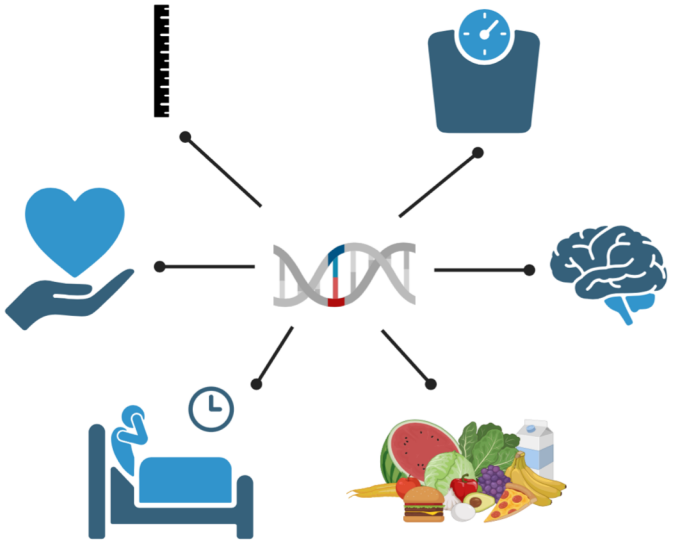


Genetics Primer

Our genetic makeup is 99.9% identical to one another

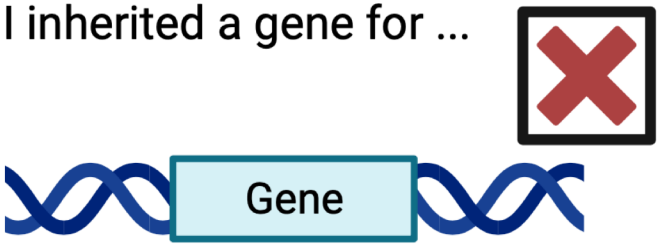
<0.01% of differences (things that make us unique) are what we are studying



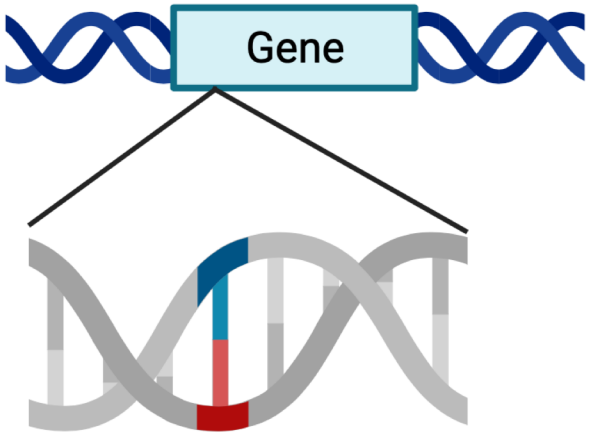


Genetics Primer

I inherited a gene for ...



I inherited a *change* in the *sequence* of a gene for ...



What is Schizophrenia?

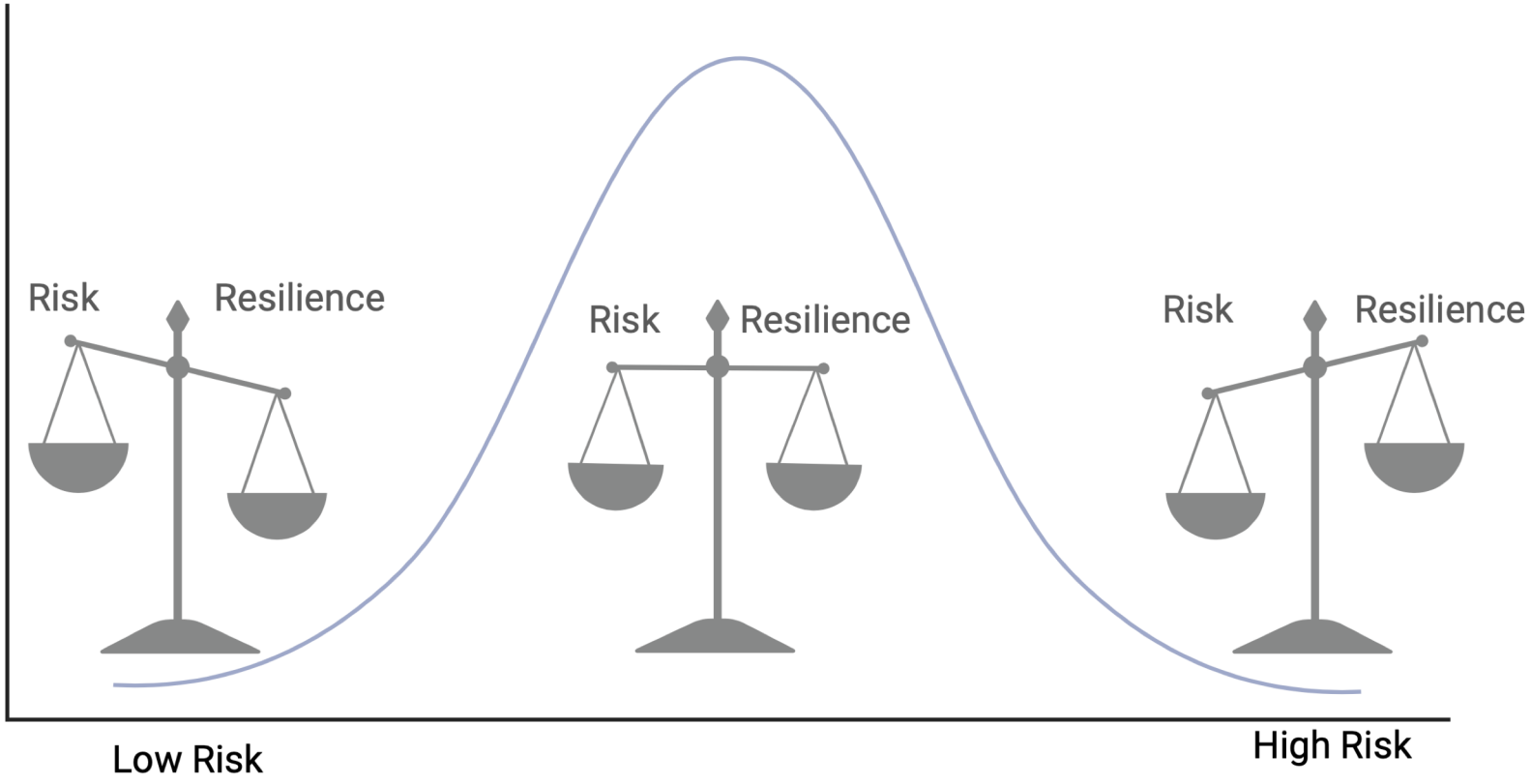
- It is a collection of symptoms related to abnormal thoughts and behavior
  - Visual or auditory hallucinations
  - Delusions or paranoid thoughts
  - Anhedonia, blunted affected
- Symptoms must persist for a length of time
- Rule out other explanations: drug/alcohol use, bipolar disorder, depression
- Diagnostic criteria outlined in DSM (national) and ICD (international)
- Typically onsets in late adolescence to early adulthood

Genetics Primer: Schizophrenia

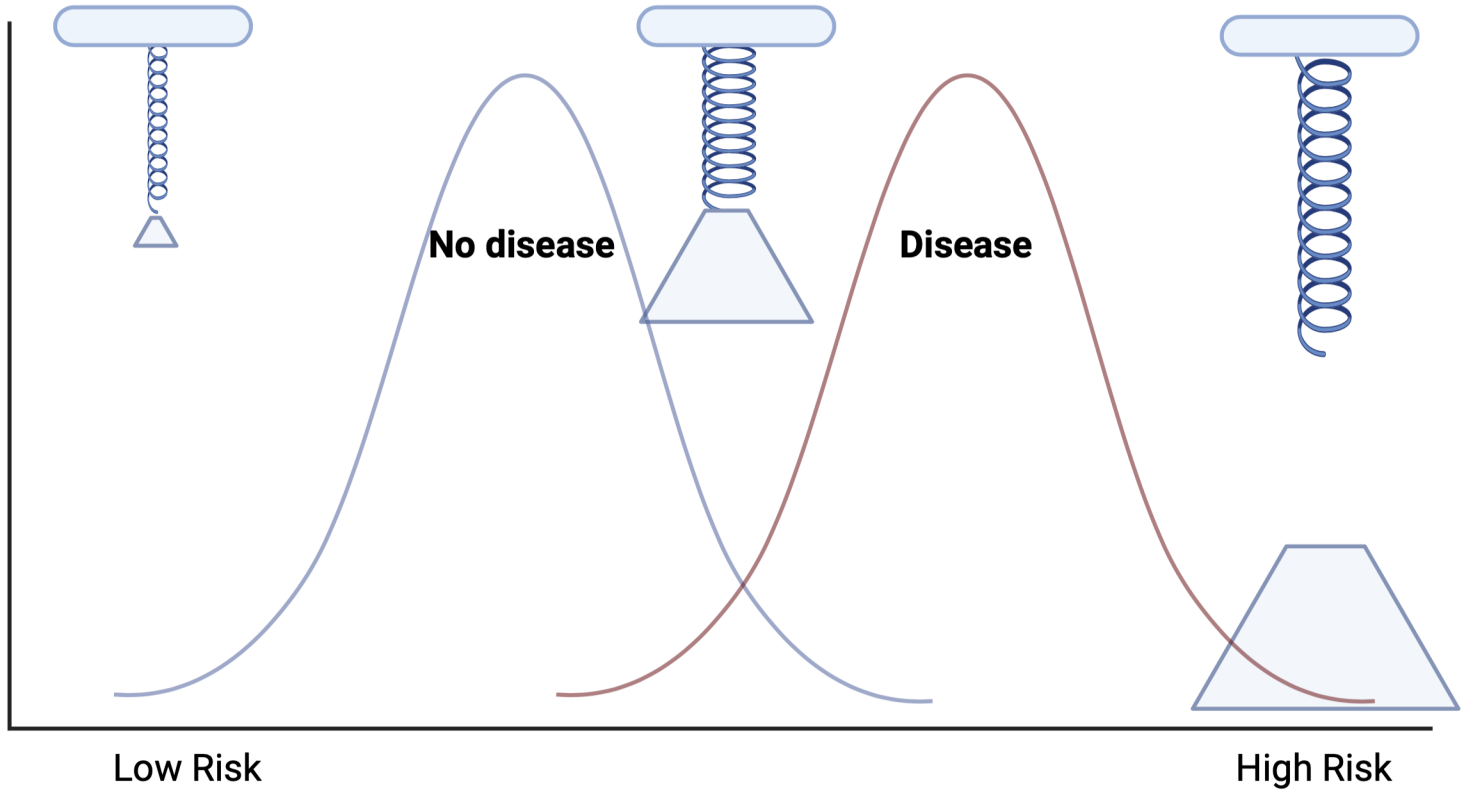
- Schizophrenia is **multi-factorial**: genes & environment shape one's overall risk
- While it is familial (*i.e.*, runs in families), having an affected relative does not guarantee that another member will develop schizophrenia
  - *E.g.,* Identical twins, who share 100% of their DNA, have 50% chance of being affected if other twin is affected
- There is NO single gene that ***causes*** schizophrenia.
  - Genes *are not* deterministic
- Several ***hundred*** genes are linked with ***risk for*** schizophrenia
  - Each gene found contributes a small % increase in risk


Endurance
Evade
Hardiness
Grit
Successful-aging
Reaction
Resilience
Rebounding
Support
Fortitude
Tenacity
Capacity
Bounce-back
Adaptability
Escape
Adversity
Coping

Resilience ≠ inverse (or absence) of risk



Resilience acts by *moderating* risk



Ways of defining resilience

Health/Disease

Molecular Psychiatry (2019) 24:1770–1778
https://doi.org/10.1038/s41380-019-0457-6

PERSPECTIVE

Genomics and psychological resilience: a research agenda

Karmel W. Choi[1,2,3,4] · Murray B. Stein[5,6] · Erin C. Dunn[1,3,4,7] · Karestan C. Koenen[1,2,3,4] · Jordan W. Smoller[1,2,3,4]

Received: 6 October 2018 / Revised: 14 May 2019 / Accepted: 21 May 2019 / Published online: 24 July 2019
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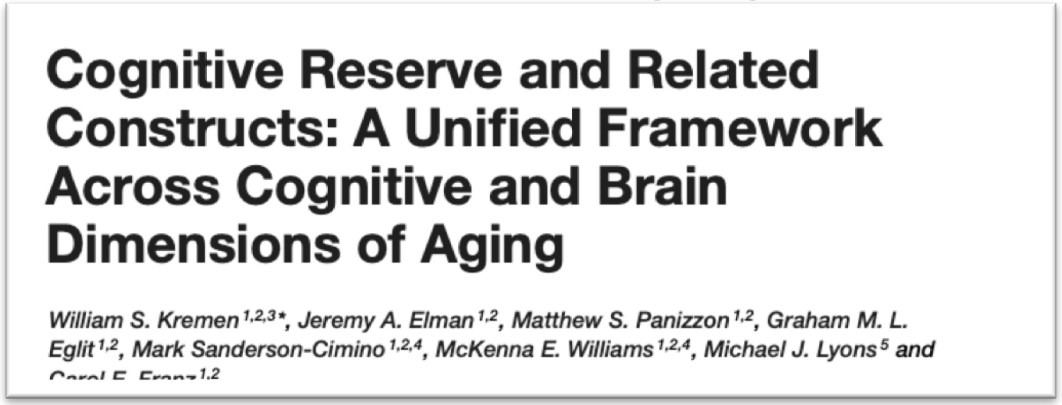
Capacity: **Precedes** adversity

Process: Unfolds **during/after** adversity

Outcome: **Follows** adversity

Brain aging



Cognitive Reserve and Related Constructs: A Unified Framework Across Cognitive and Brain Dimensions of Aging

William S. Kremen[1,2,3], Jeremy A. Elman[1,2], Matthew S. Panizzon[1,2], Graham M. L. Eglit[1,2], Mark Sanderson-Cimino[1,2,4], McKenna E. Williams[1,2,4], Michael J. Lyons[5] and*

Cognitive Reserve: Total cognitive resources

Cognitive Resilience: Maintaining cognitive performance

Brain Resilience: Relative absence of brain loss

Resistance: Avoiding cognitive decline or brain pathology despite risk factors

Why bother studying resilience?

- Much of our knowledge of schizophrenia (and related disorders) is based on *risk* factors
  - While useful, provides an overly simplified view of disease

- Identifying the factors that allow someone to *evade* illness can potentially inform us of:
  - Genes, pathways, or modifiable factors that may *promote* resilience
  - Improving detection
  - New targets for intervention or prevention

Prior studies of genetic resilience

Genetic "Unexpected Heroes" Project

- 13 individuals that evaded highly penetrant Mendelian mutations
- No "resilience" genes identified

Analysis of 589,306 genomes identifies individuals resilient to severe Mendelian childhood diseases

Rong Chen[1,2,12], Lisong Shi[1,2,12], Jörg Hakenberg[1,2], Brian Naughton[3,11], Pamela Sklar[1,2,4], Jianguo Zhang[5], Hanlin Zhou[5], Lifeng Tian[6], Om Prakash[7], Mathieu Lemire[8], Patrick Sleiman[6], Wei-yi Cheng[1,2], Wanting Chen[5], Hardik Shah[1,2], Yulan Shen[5], Menachem Fromer[1,2,4], Larsson Omberg[9], Matthew A Deardorff[6], Elaine Zackai[6], Jason R Bobe[1,2], Elissa Levin[1,2], Thomas J Hudson[8], Leif Groop[7], Jun Wang[10], Hakon Hakonarson[6], Anne Wojcicki[3], George A Diaz[1,2], Lisa Edelmann[1,2], Eric E Schadt[1,2] & Stephen H Friend[1,2,9]

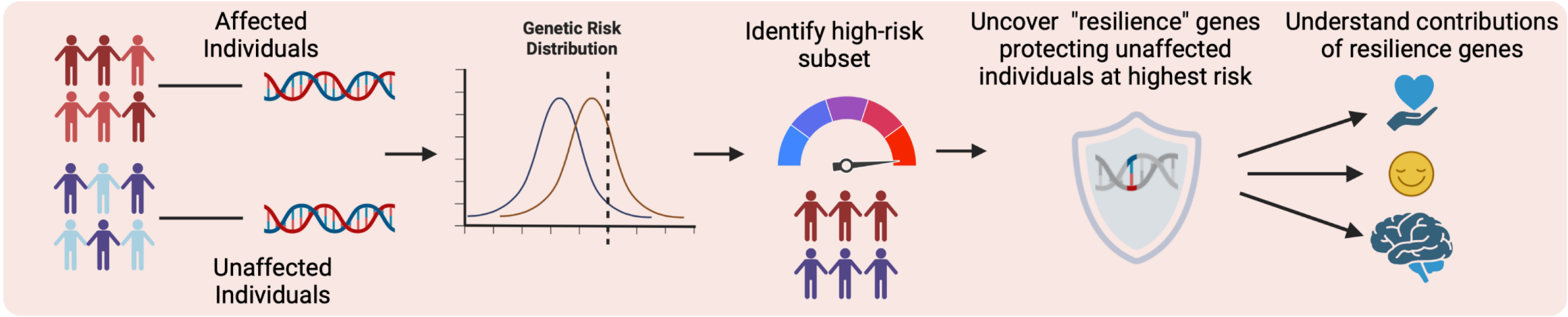
Christchurch mutation, a case study

- *PSEN1* autosomal dominant carrier
- Mild cognitive impairment, onset in **40s**
- Woman cognitively spared until 70s
- Genetic modifier: *APOE3ch* mutation

Resistance to autosomal dominant Alzheimer's disease in an *APOE3* Christchurch homozygote: a case report

Joseph F. Arboleda-Velasquez[1,23*], Francisco Lopera[2,23], Michael O'Hare[1,23], Santiago Delgado-Tirado[1], Claudia Marino[1], Natalia Chmielewska[1,3], Kahira L. Saez-Torres[1], Dhanesh Amarnani[1], Aaron P. Schultz[4], Reisa A. Sperling[4,5], David Leyton-Cifuentes[1,6], Kewei Chen[7,8,9], Ana Baena[2], David Aguillon[2], Silvia Rios-Romenets[2], Margarita Giraldo[2], Edmarie Guzmán-Vélez[10], Daniel J. Norton[10,11], Enmanuelle Pardilla-Delgado[10], Arabiye Artola[10], Justin S. Sanchez[4], Juliana Acosta-Uribe[2,12], Matthew Lalli[12], Kenneth S. Kosik[12], Matthew J. Huentelman[13], Henrik Zetterberg[14,15,16,17], Kaj Blennow[14,15], Rebecca A. Reiman[13], Ji Luo[7], Yinghua Chen[7], Pradeep Thiyyagura[7], Yi Su[7], Gyungah R. Jun[18], Marcus Naymik[13], Xiaowu Gai[19,20], Moiz Bootwalla[19], Jianling Ji[19,20], Lishuang Shen[19], John B. Miller[21], Leo A. Kim[1], Pierre N. Tariot[7,8], Keith A. Johnson[4,5,22], Eric M. Reiman[7,8,9,13*] and Yakeel T. Quiroz[2,4,10*]

Genetic Moderators of Schizophrenia Risk



First Study (2015 – 2019)

Second study (2020 – 2023)

Current work

Relevant papers

Schizophrenia (**Hess et al., *Molecular Psychiatry,* 2019**)

(**Hess et al., 2023, *AJMG B: Neuropsychiatric Genetics*, 2023**)

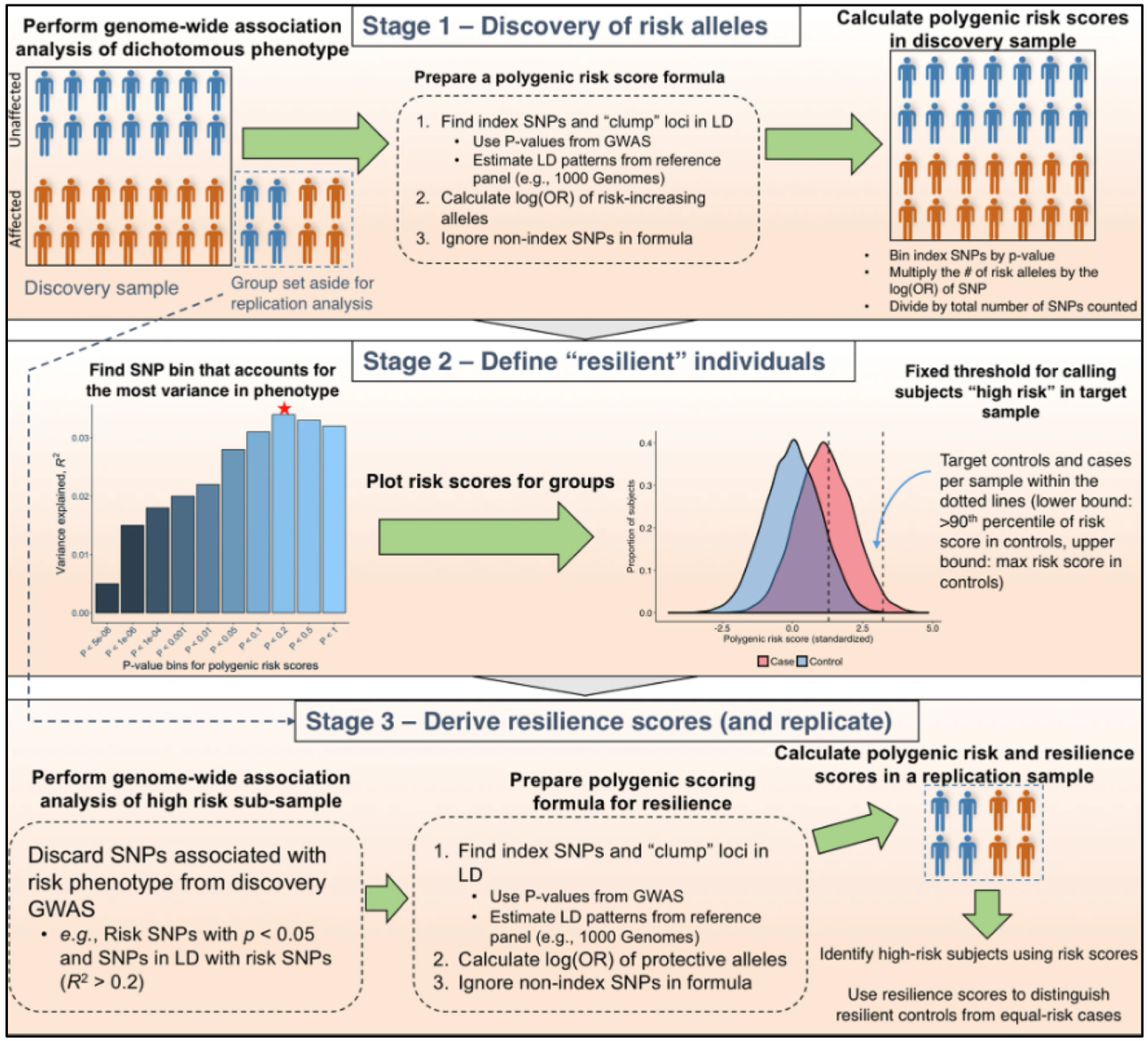
Bipolar Disorder (**Hess et al., in preparation**)

Alzheimer's Disease (**Hou *et al., Translational Psychiatry,* 2022**)

Parkinson's Disease (Liu *et al*., *Ann Neurol,* 2022)

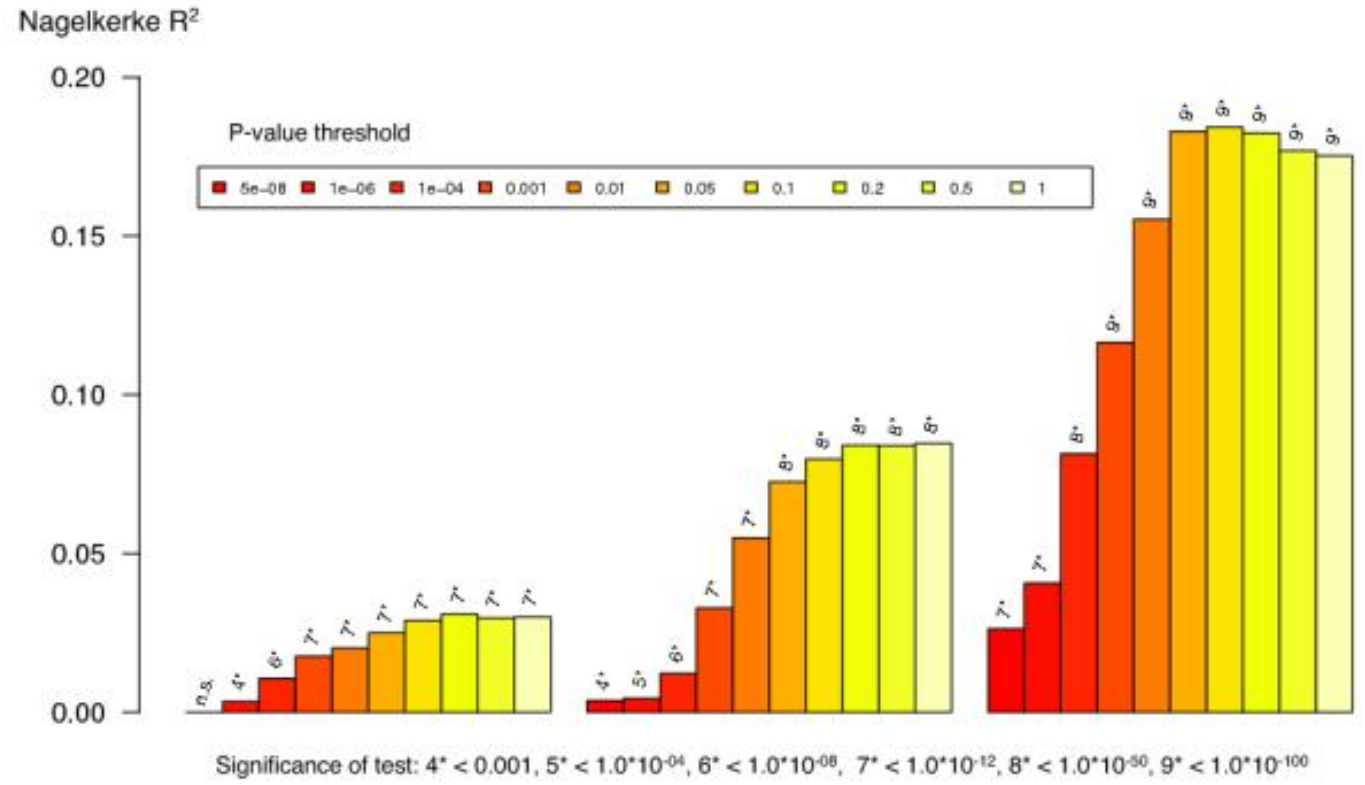
COPD (**Ghosh *et al.*, *biorXiv,* 2023**)

Designing of Our First Study of Genetic Resilience



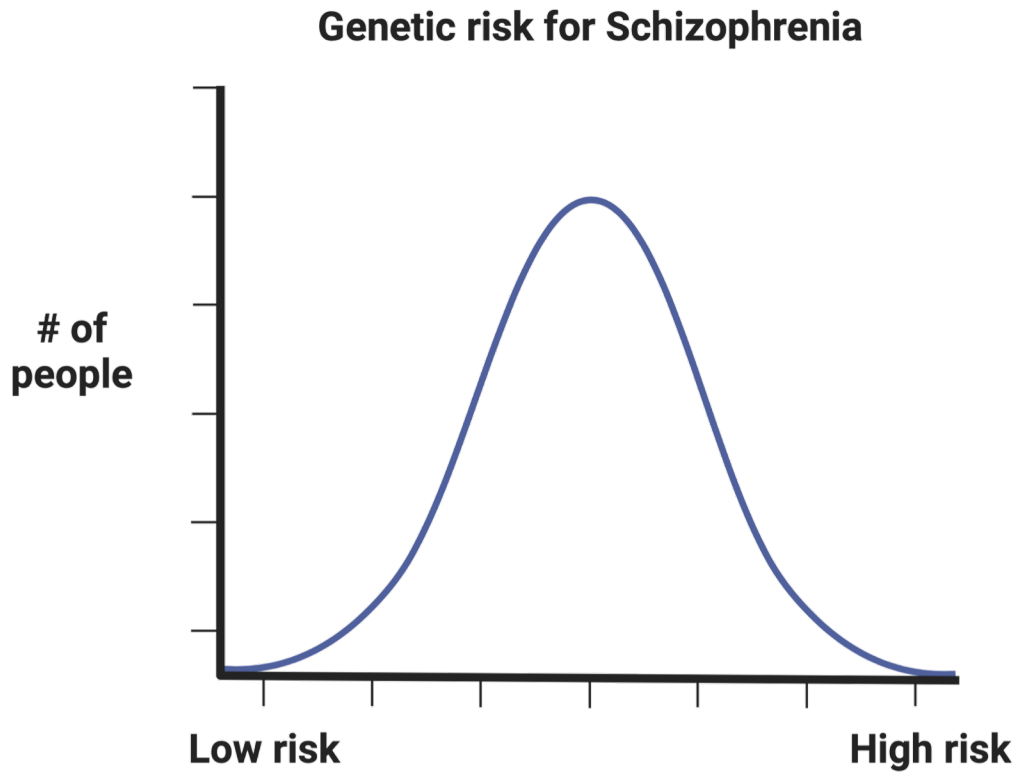
Genetic risk for schizophrenia

- Not one, but ***many*** genes used to calculate risk



Ripke et al., 2014

How genetic risk varies in the population



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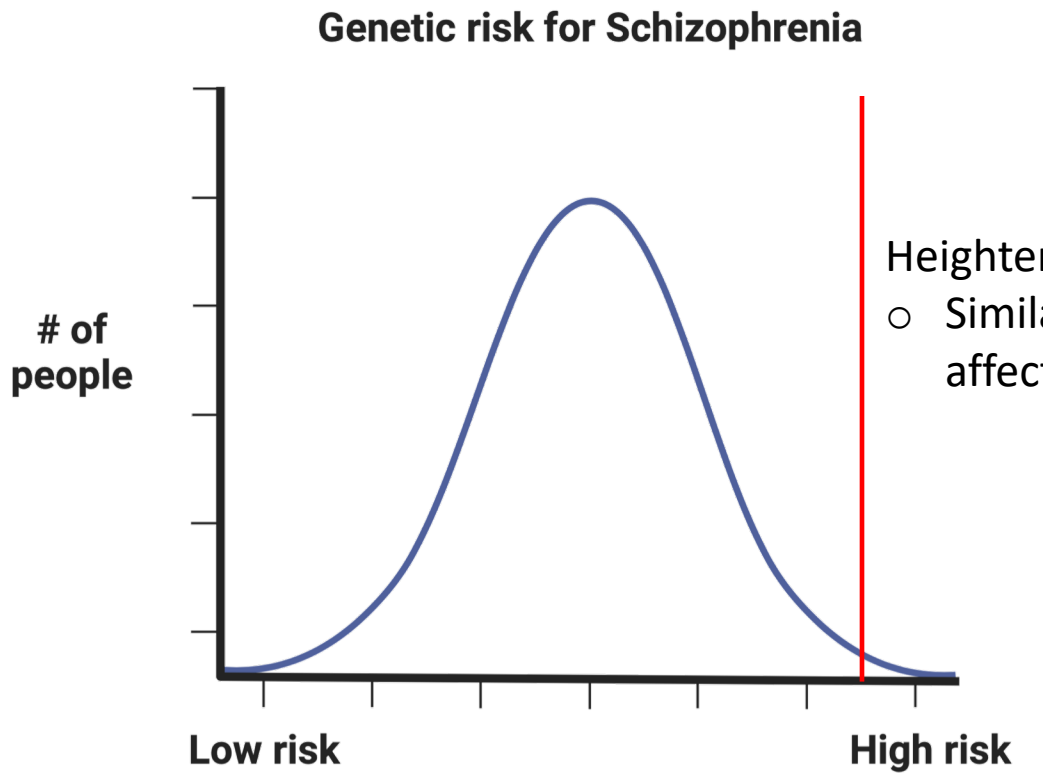


Heightened risk for schizophrenia

- Similar risk as having first-degree affected relative

Samples that Contributed to Our Genetic Study of Resilience to Schizophrenia

Psychiatric Genomics Consortium

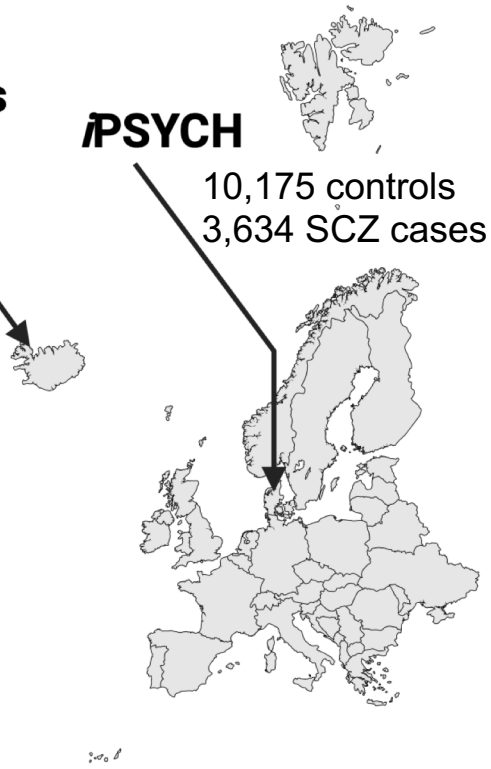
3,786 controls
18,619 SCZ cases

deCODE Genetics

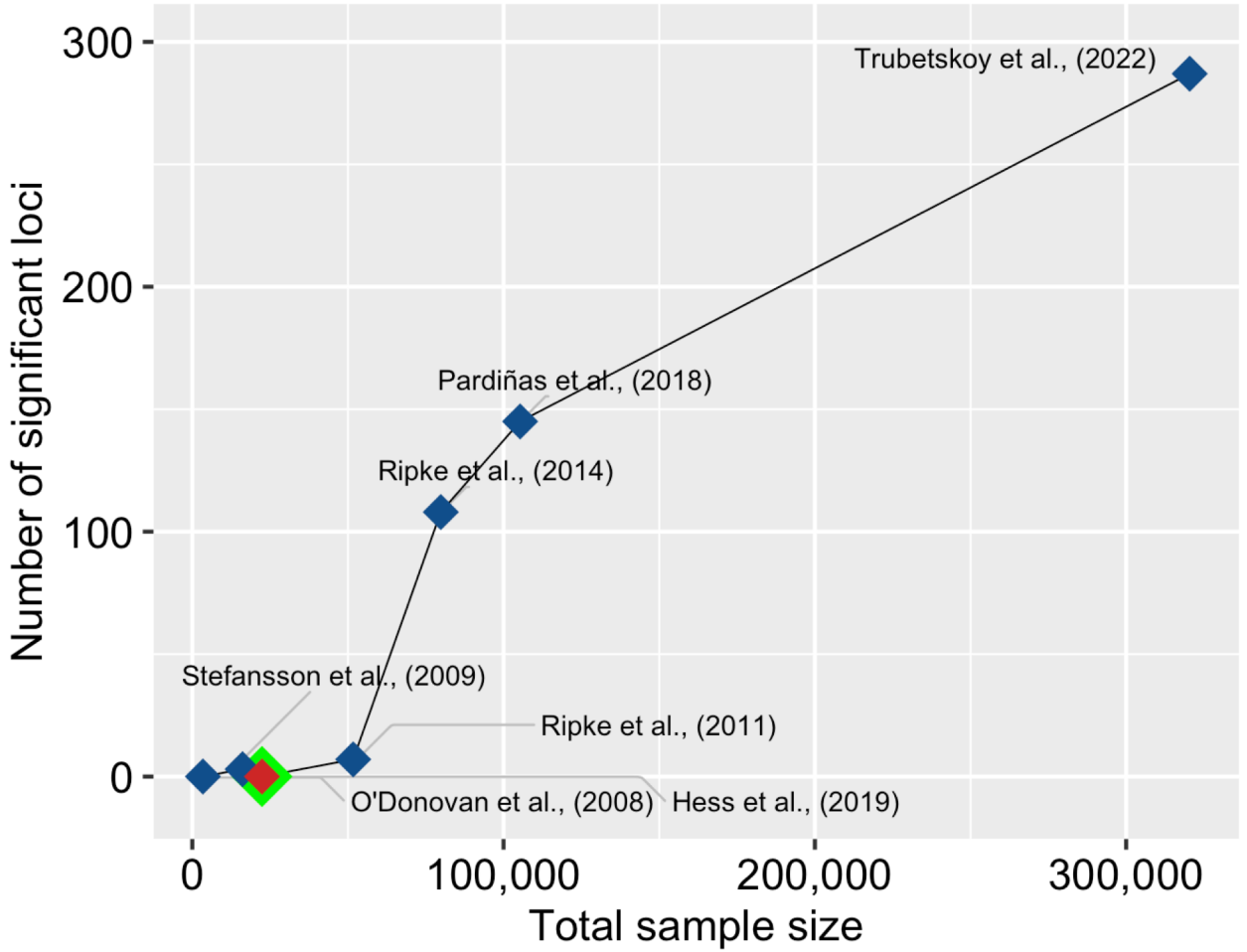
138,761 controls
873 SCZ cases

iPSYCH

10,175 controls
3,634 SCZ cases

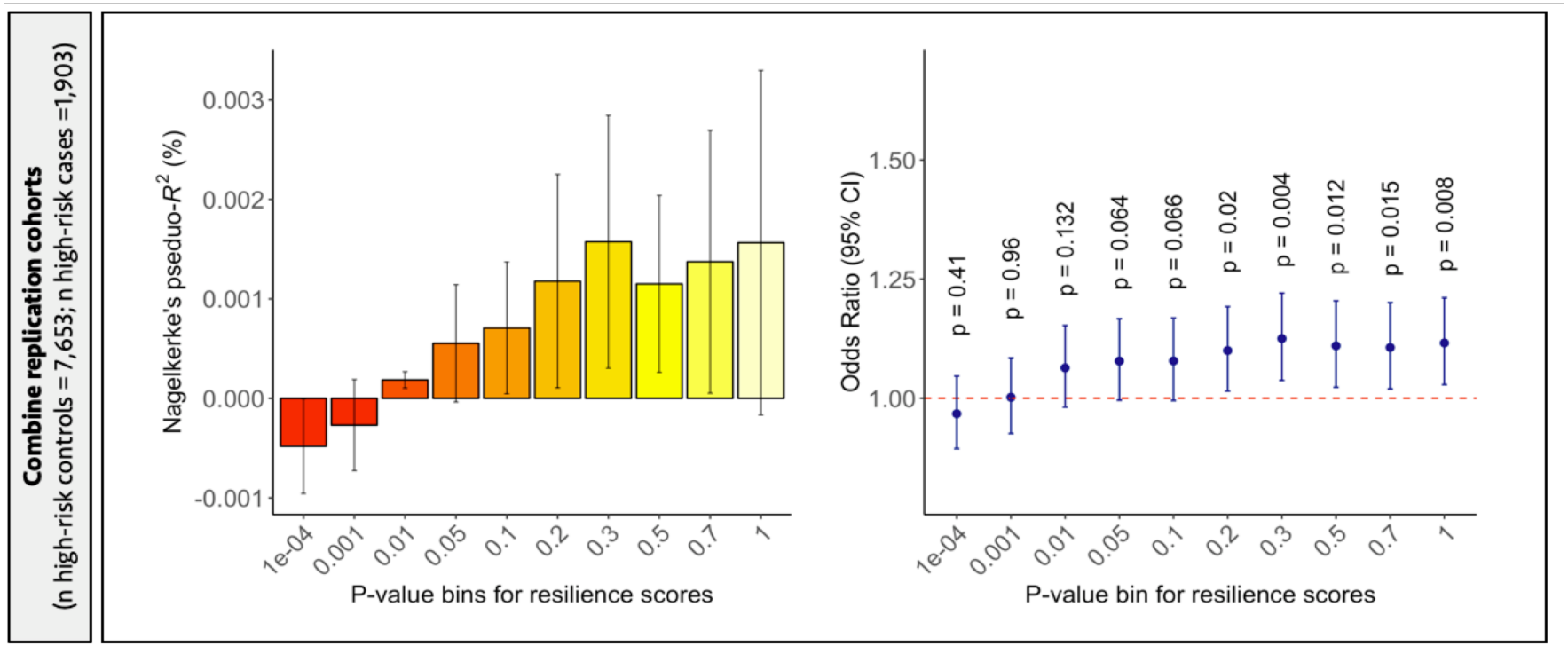


Under-powered to find individual resilience *genes*

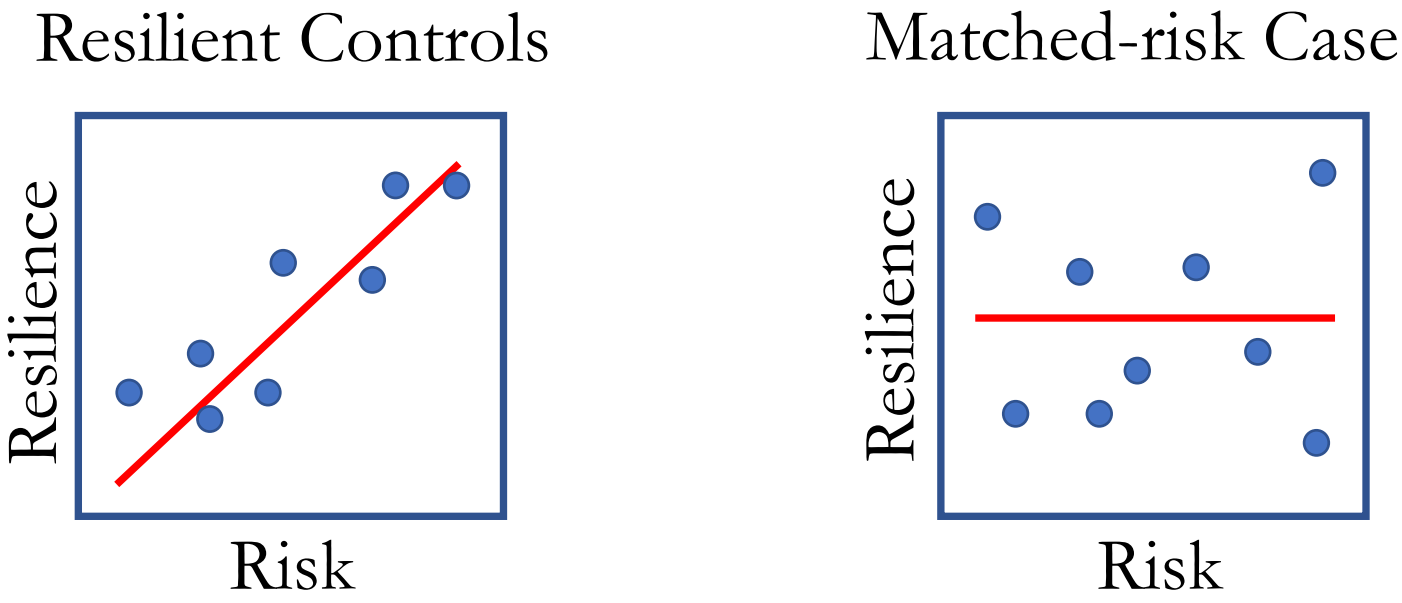


Successfully identified the **first-ever** *genetic resilience profile* for schizophrenia

- Indeed, first-ever resilience score for a *complex* disorder



Resilience increases commensurate with risk



Second Study: BBRF Young Investigator Project

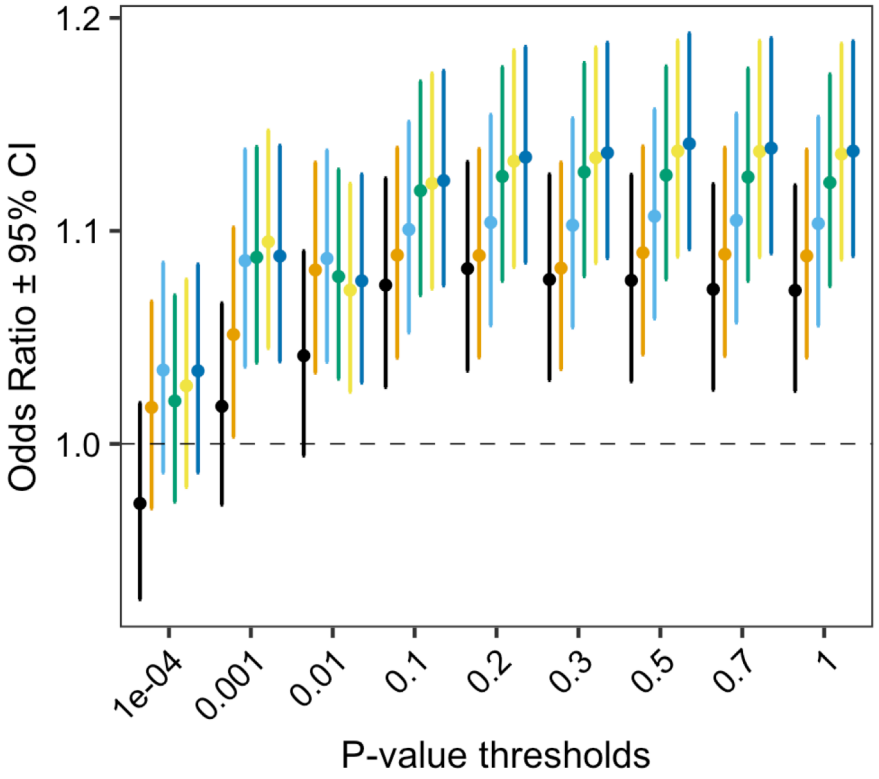
- Replicate and refine the resilience scoring model in new samples

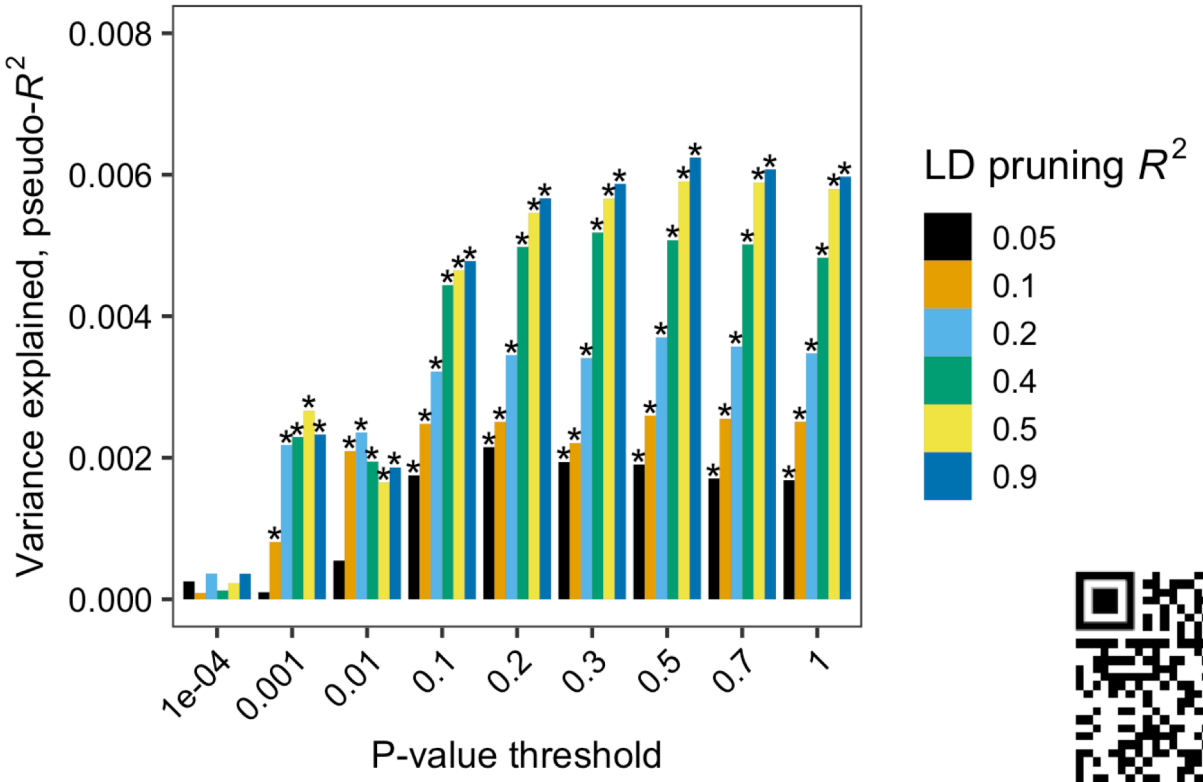
Psychiatric Genomics Consortium

#1: 3,786 controls; 18,619 SCZ cases
#2: 2,821 controls; 5,150 SCZ cases

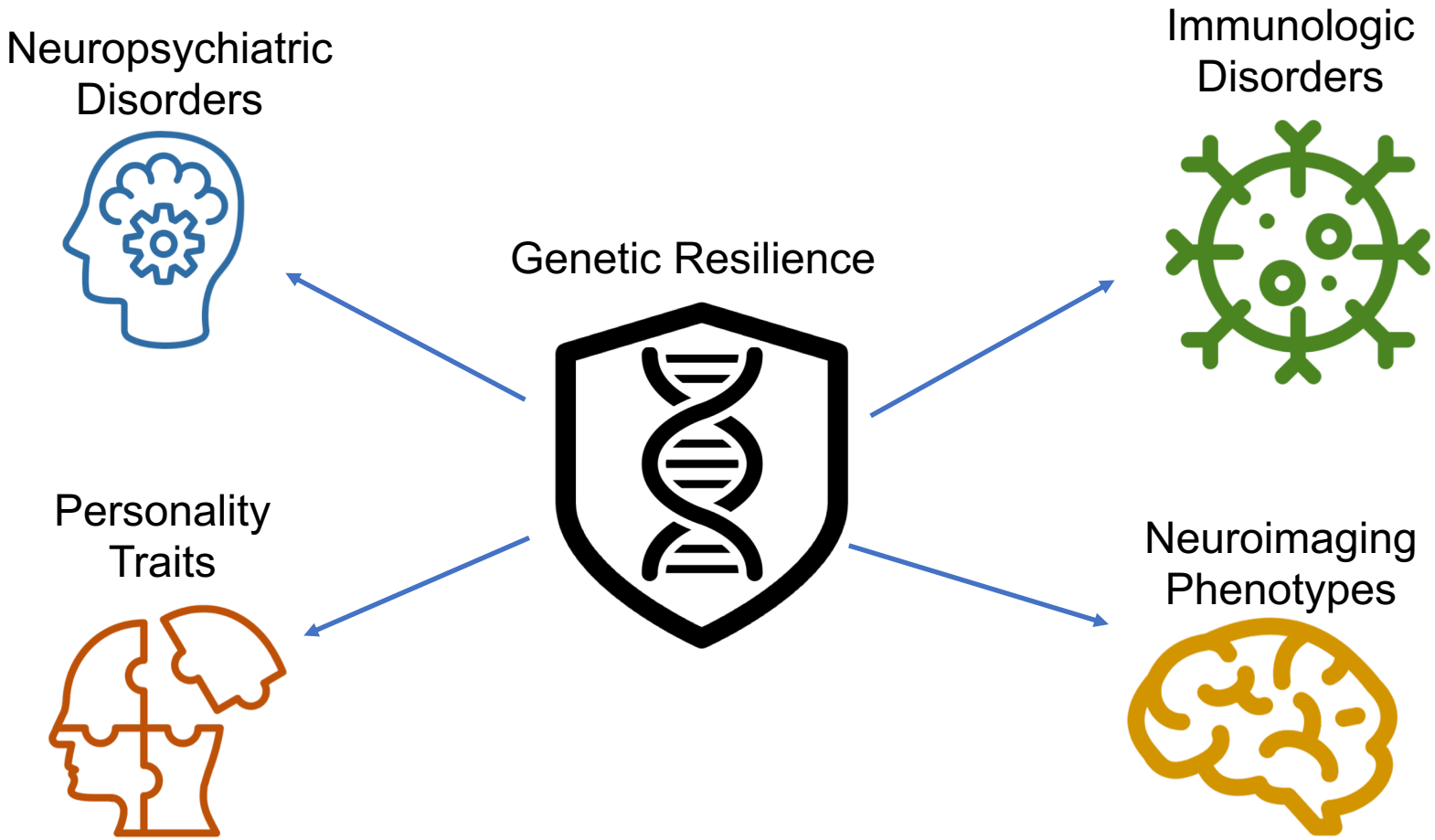
Successfully replicated our resilience scores

- We identified ways to *improve upon* our method for measuring *genetic resilience*
  - Ensures no “leakage” of unwanted signals into the resilience scores

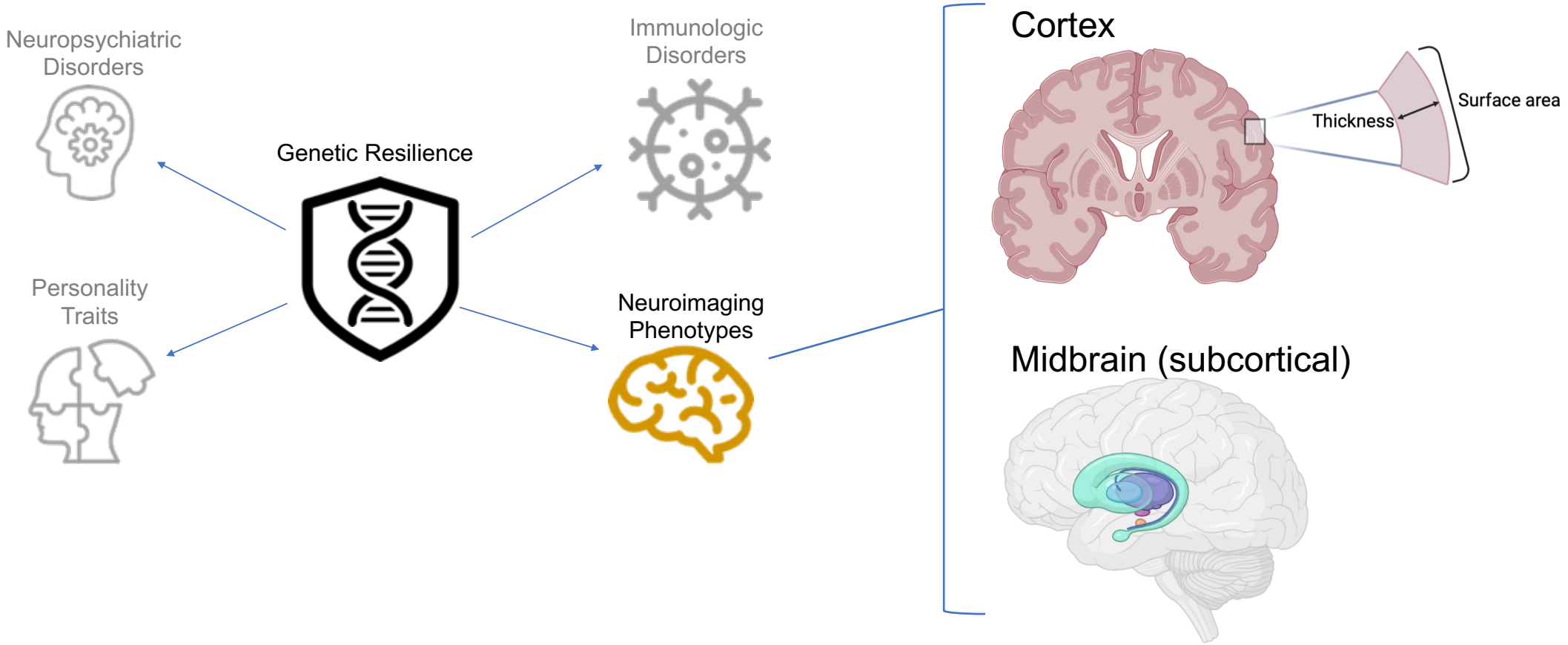




Direction of latest work



Direction of latest work



Data we are using for our latest studies

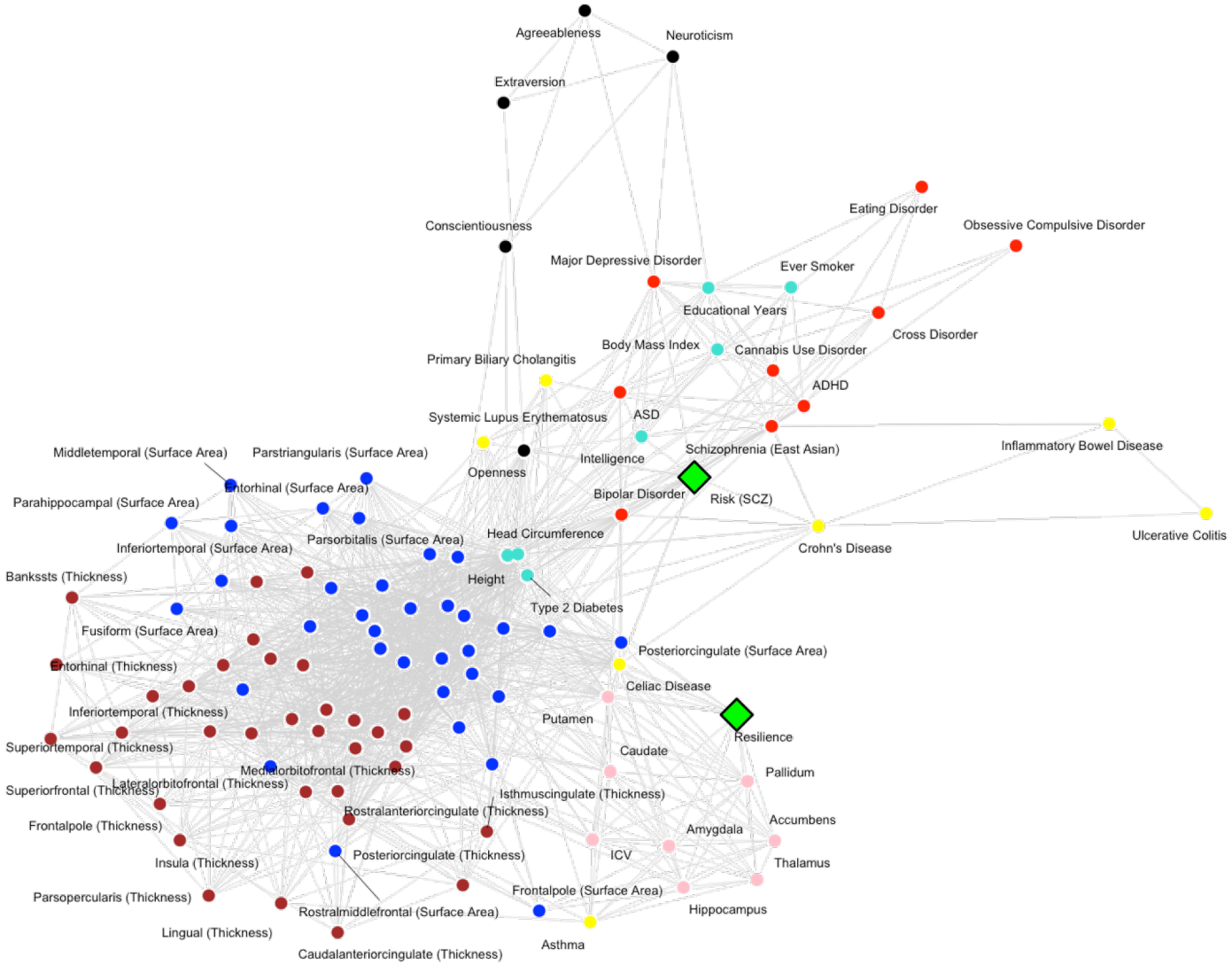
Psychiatric Genomics Consortium

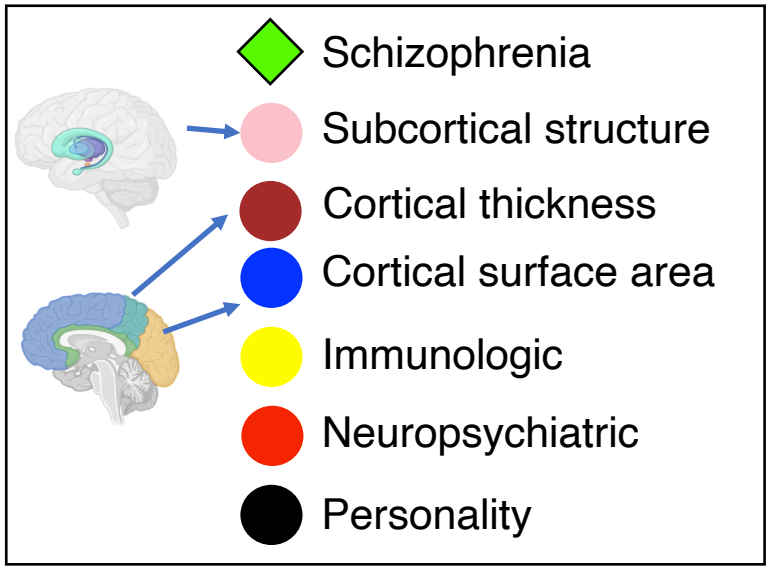
28,114 controls
17,984 SCZ cases

UK Biobank

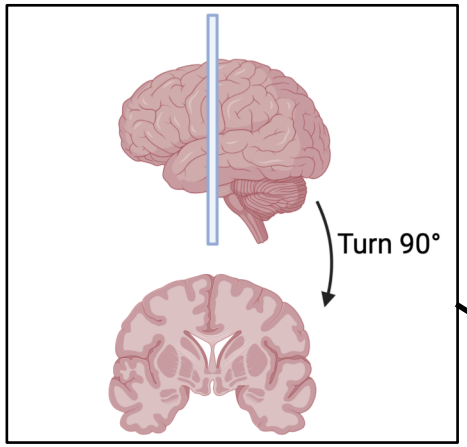
487,409 volunteers

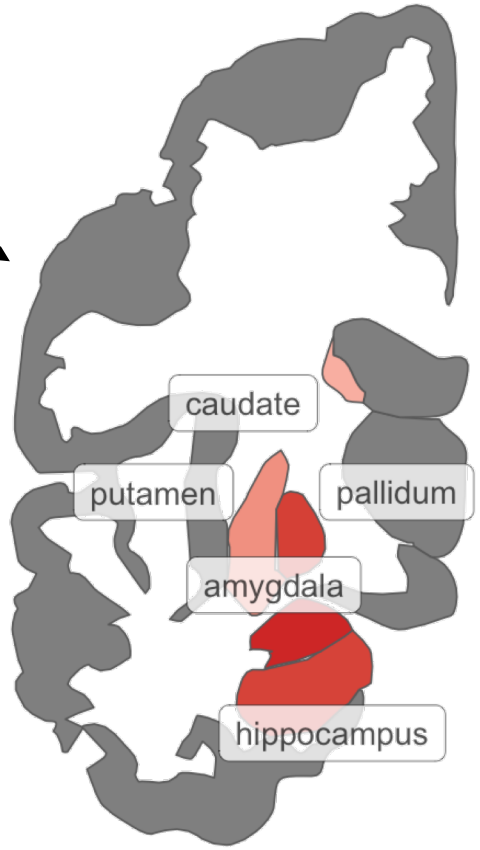
Network of Genetically Related Phenotypes



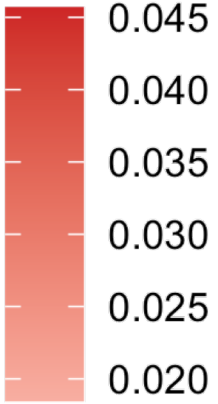


Resilience linked with larger midbrain regions



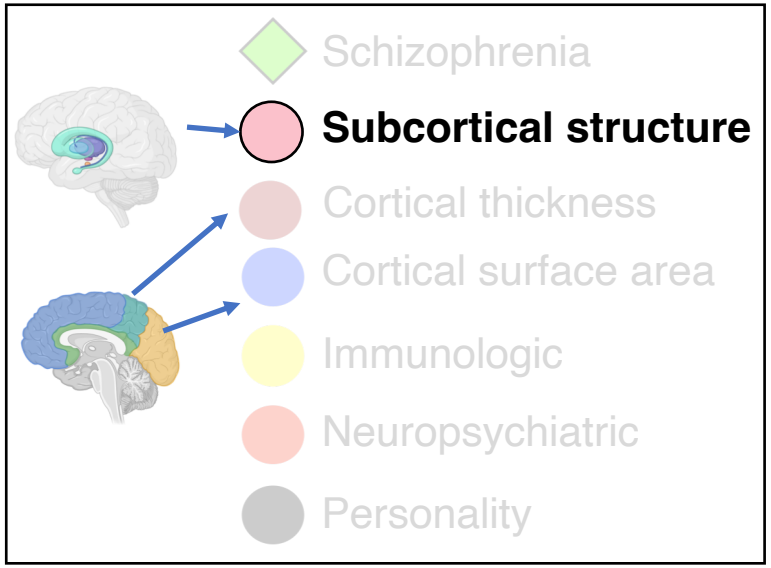


Resilience > Risk

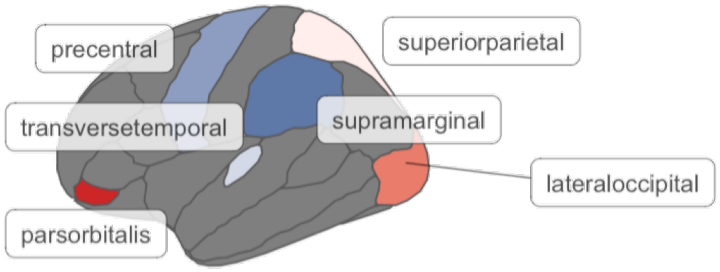


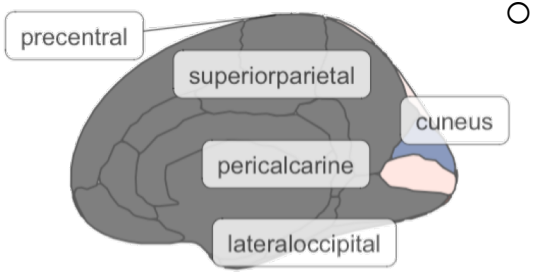
Possible Compensatory Effects?

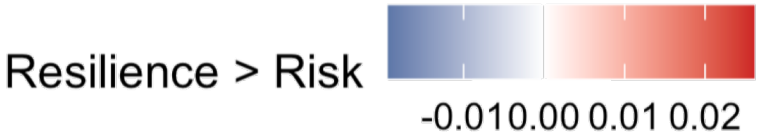
- Midbrain regions show decreased volumes in schizophrenia



Resilience linked with genes related to ***thicker*** object recognition and language centers

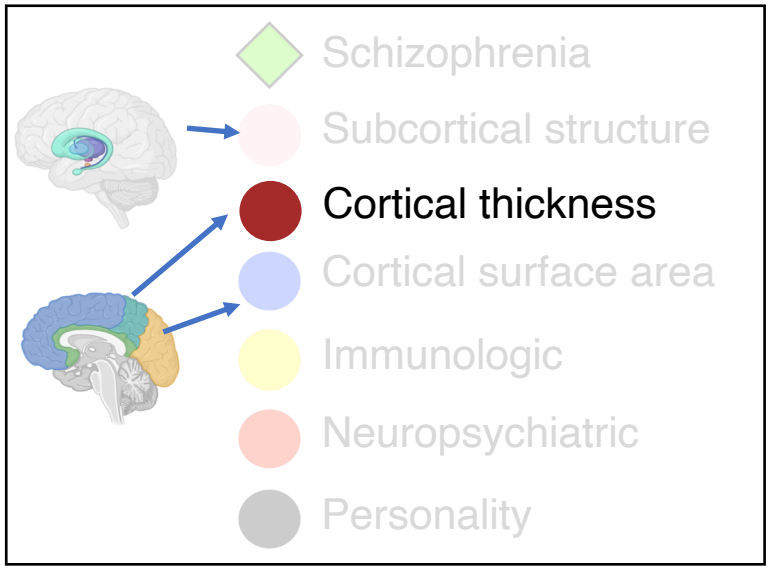




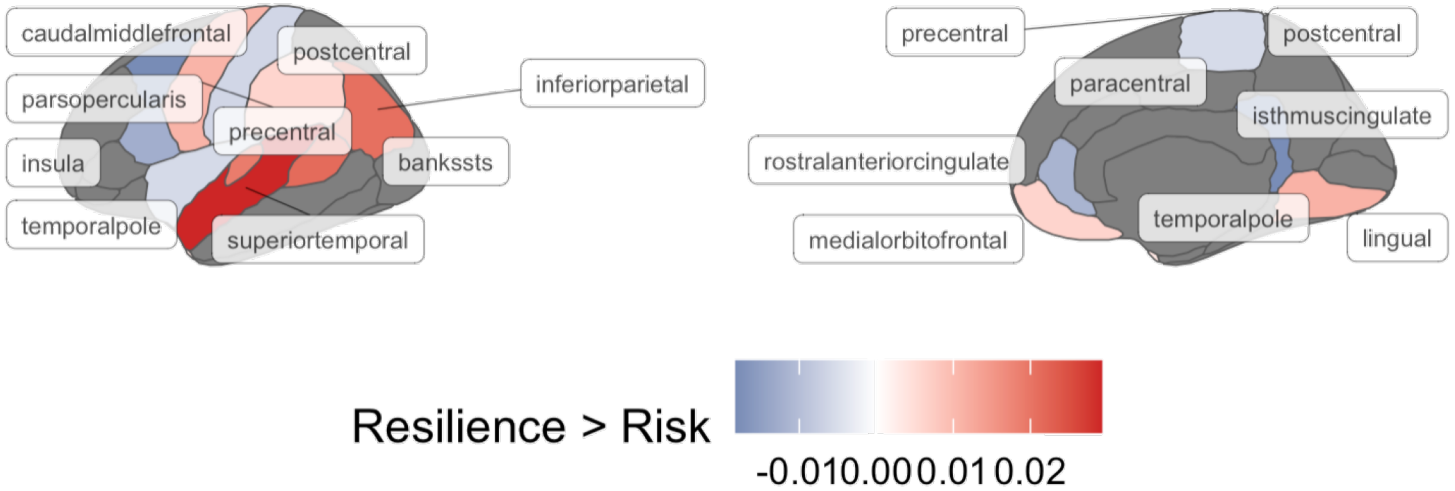


Possible Compensatory Effects?

- Impairments in object recognition and language in schizophrenia
- Hyperactivity in default mode (resting state) network in schizophrenia

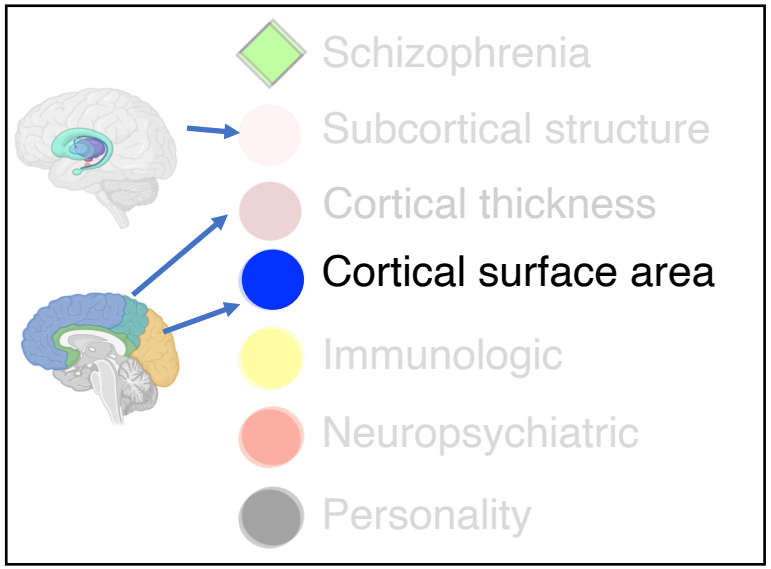


Resilience linked with genes related to ***larger area*** default mode network

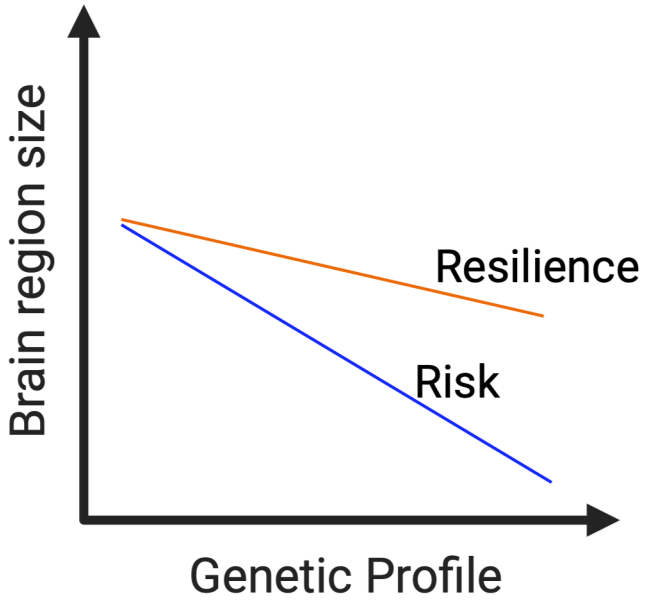


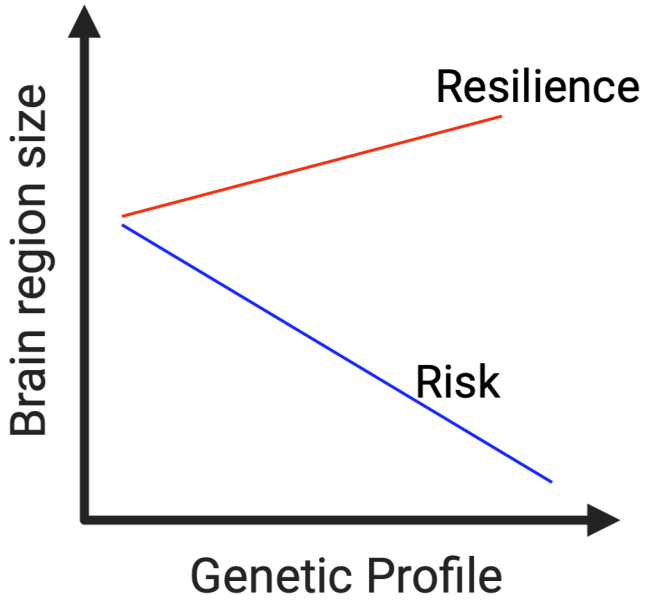
Possible Compensatory Effects?

- Hyperactivity in default mode (resting state) network in schizophrenia



Summary of brain structural findings

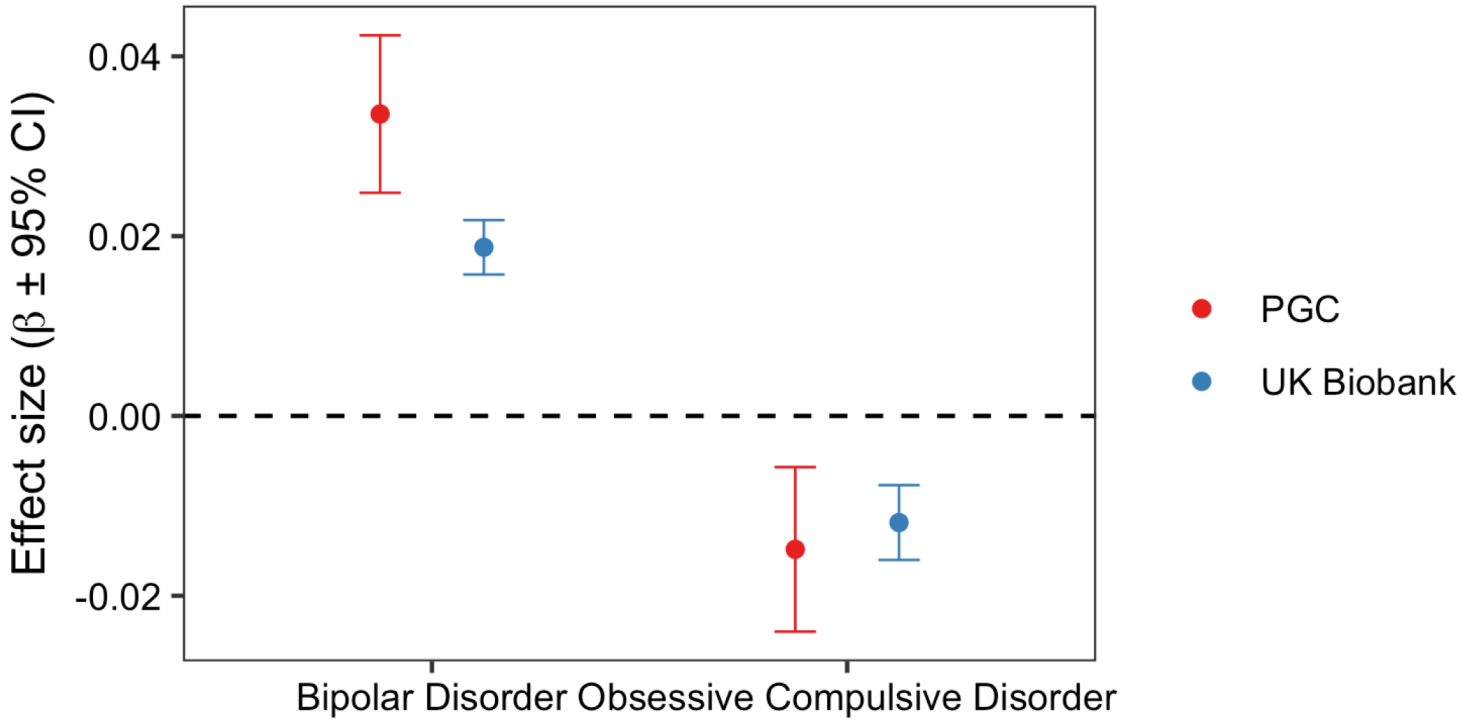




Schizophrenia resilience in context of other psychiatric disorders

- Resilience ***cross protects*** against risk for bipolar disorder
  - Schizophrenia and Bipolar Disorder have *many overlapping* risk genes

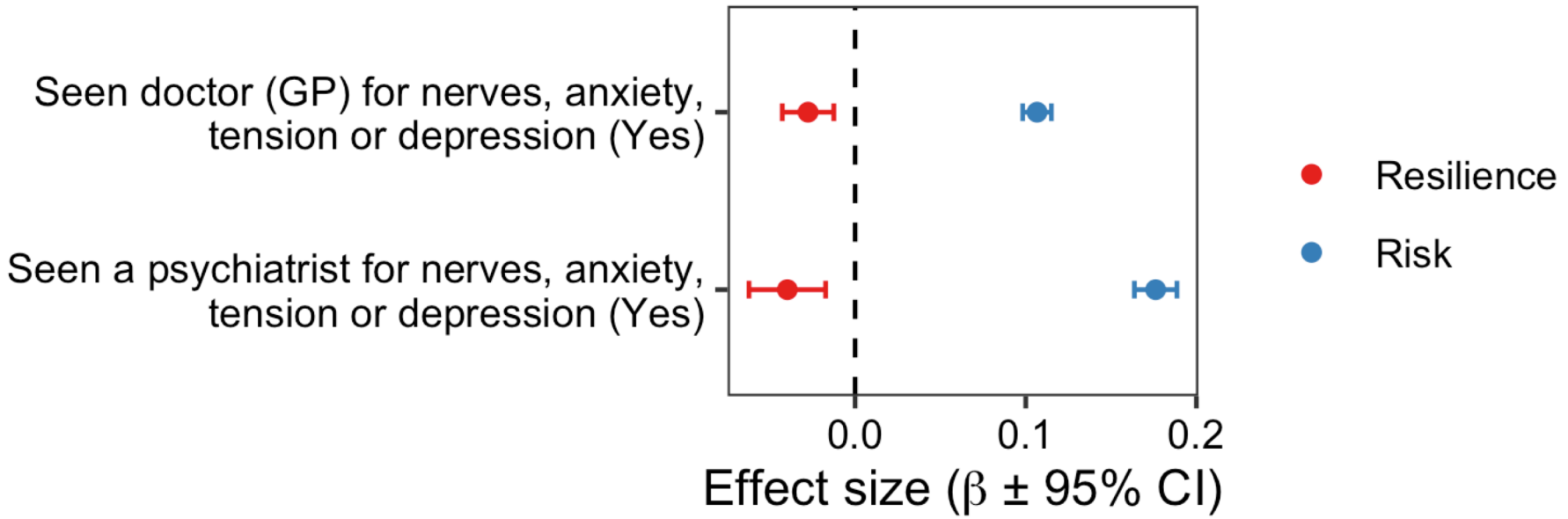
- Individuals with **higher** OCD risk show **decreased** *resilience* to schizophrenia
  - Continuing to explore this finding



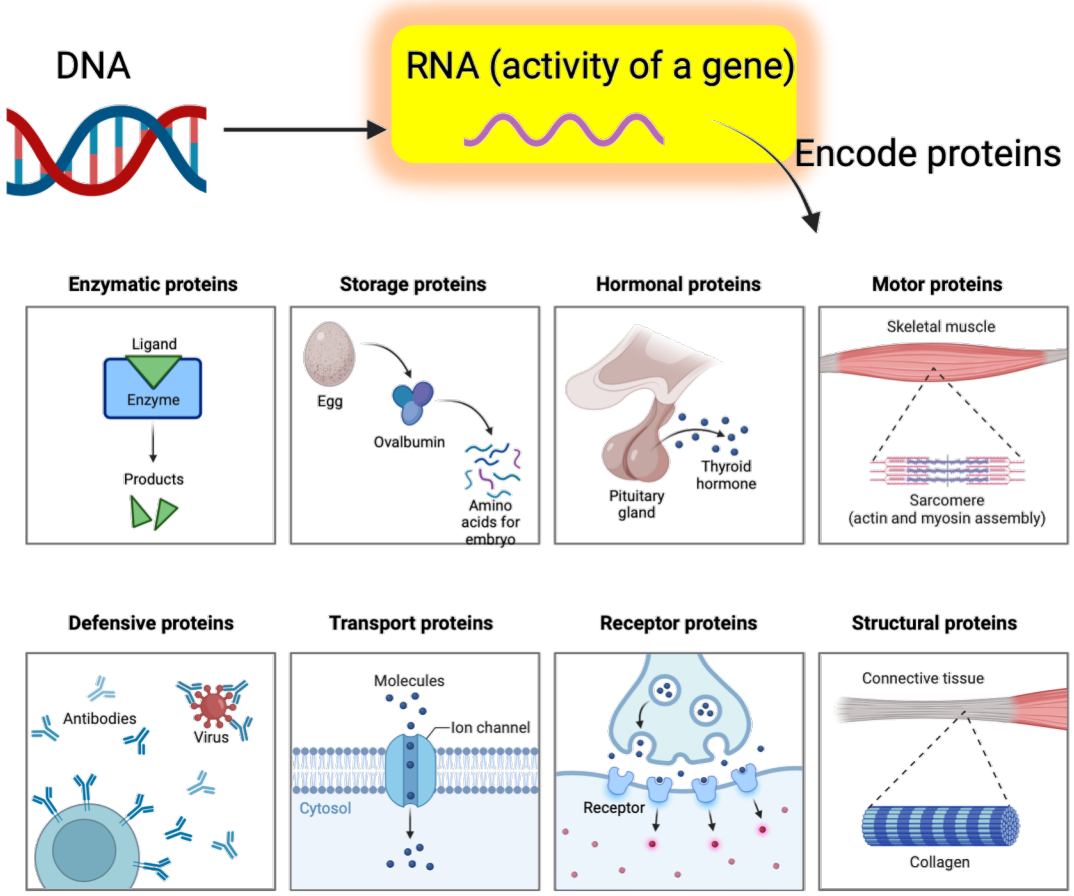
Schizophrenia resilience in context of mental health questionnaire

UK Biobank

- Volunteers with higher *resilience* are *less likely* to self-report anxiety/depression



New direction: Resilience factors of *gene activity*



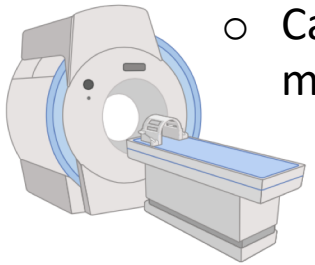
New direction: Resilience factors of *gene activity*

- Challenges with **proxy models** for gene activity in the human brain

Animal models

- ↓ Homology

Imaging

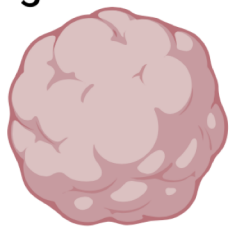


- Cannot profile molecules

Cell cultures

- Incomplete; simplified

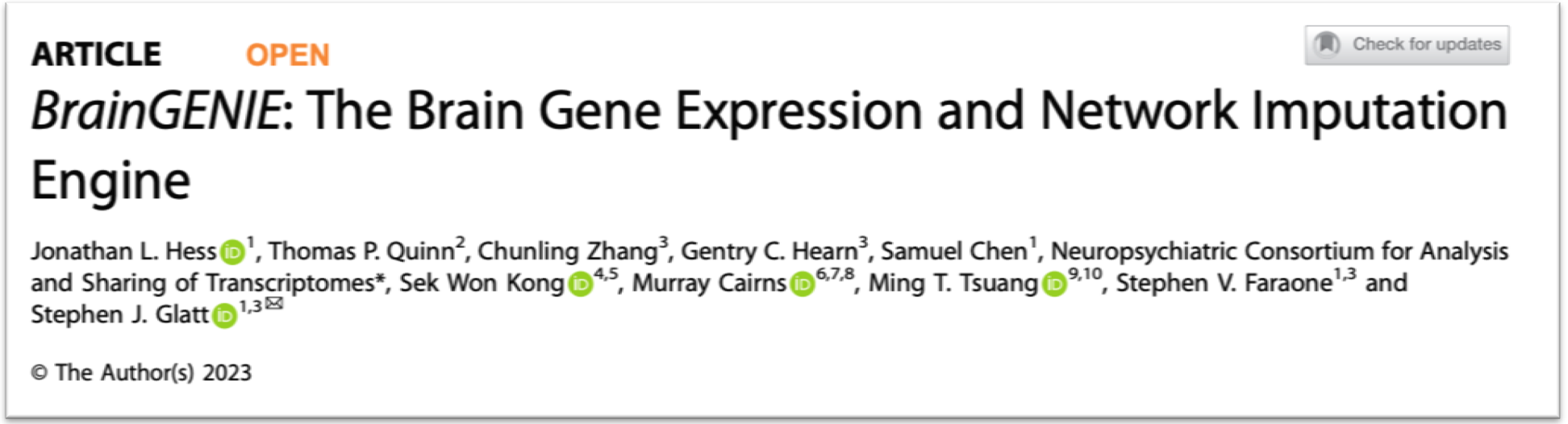
Organoids



- $$$, low yield, lack intricacies of human brain

New direction: Resilience factors of *gene activity*

- Proposed **solution** to address issues with proxy models of gene activity in human brain



ARTICLE OPEN

Check for updates

BrainGENIE: The Brain Gene Expression and Network Imputation Engine

Jonathan L. Hess[1], Thomas P. Quinn[2], Chunling Zhang[3], Gentry C. Hearn[3], Samuel Chen[1], Neuropsychiatric Consortium for Analysis and Sharing of Transcriptomes*, Sek Won Kong[4,5], Murray Cairns[6,7,8], Ming T. Tsuang[9,10], Stephen V. Faraone[1,3] and Stephen J. Glatt[1,3]✉

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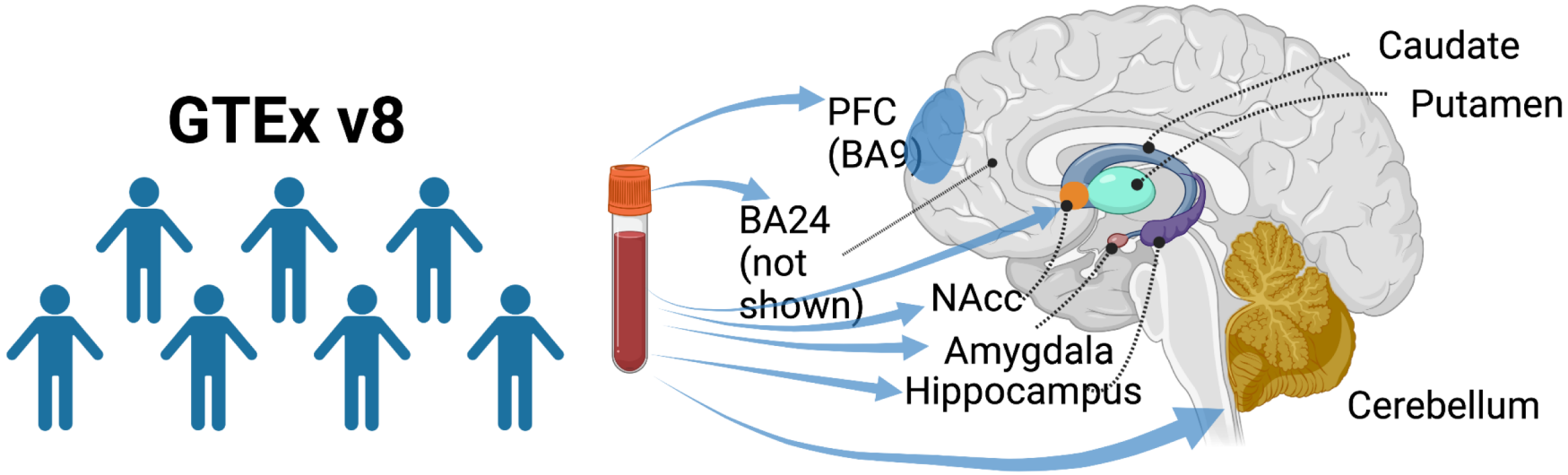
New direction: Resilience factors of *gene activity*

- **BrainGENIE** allows us to *noninvasively* infer **gene activity** in the living human brain
- This could help us to uncover new **genes** and **pathways** related to resilience



Hess et al., 2023. *Transl Psychiatry*

Summary

- Identified first-ever genetic resilience profile for schizophrenia
- Collaborations with consortia and other large groups (iPSYCH, deCODE, UK Biobank) have been essential for our projects to be successful
- In spirit of transparency and accessibility, we made our pipeline freely available
  - Regularly advising researchers who are adapting our work to other disorders
- Significant progress being made to understand links between *resilience genetic profiles* and schizophrenia + many other related conditions and phenotypes
- Funding from BBRF was VITAL to this work, so BIG THANK YOU to Foundation and its generous donors!!

Acknowledgements

PsychGENe Lab

Stephen Glatt, PhD

Jiahui Hou

Faraone Lab

Stephen Faraone, PhD

Yanli Zhang-James, MD/PhD

Eric Barnett, PhD

Collaborators:
Manuel Mattheisen
Tiffany Greenwood
Peter Holmans
Ming Tsuang
Howard Edenberg

Support Staff:
Juanita Gamble
Pat Forken
Meg Mariano

Data Access:
PGC Psychiatric Genomics Consortium
Schizophrenia Working Group

Funding:
BBRF Young Investigator (PI)
R21MH126494 (MPI)
R01NS128535 (PI)
R01AG064955 (Co-I)

BRAIN & BEHAVIOR RESEARCH FOUNDATION
Awarding **NARSAD** Grants

National Institute of Neurological Disorders and Stroke
NIMH National Institute of Mental Health
NIH National Institute on Aging