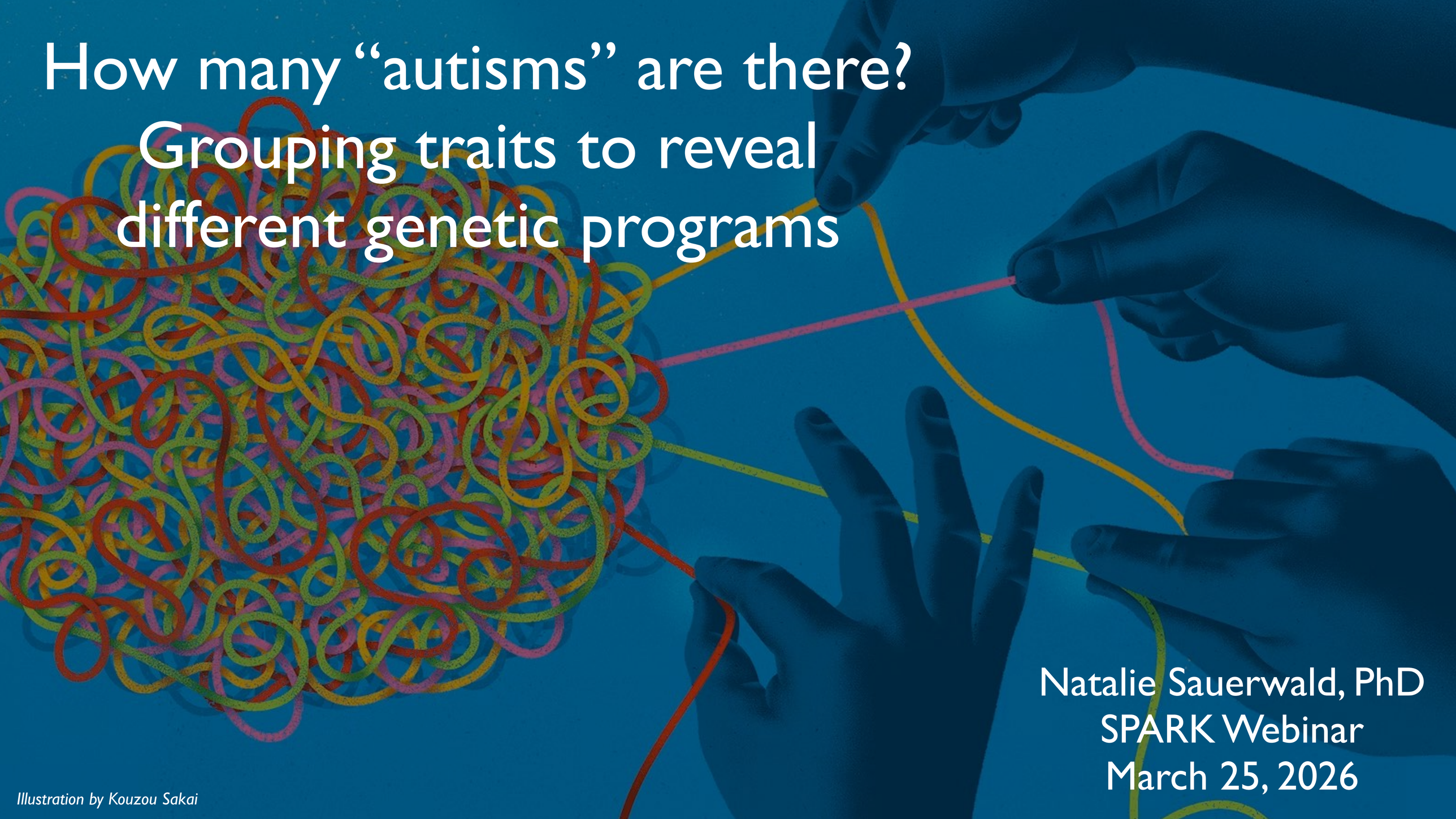
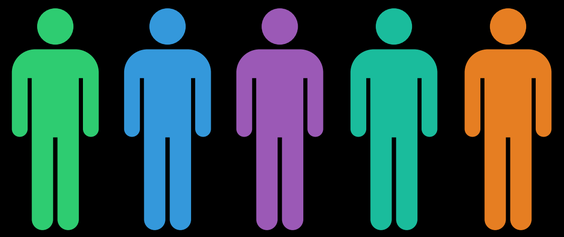
How many "autisms" are there?
Grouping traits to reveal different genetic programs



Natalie Sauerwald, PhD
SPARK Webinar
March 25, 2026

Illustration by Kouzou Sakai



Core diagnostic features

Social interaction

Communication

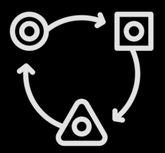
Restricted behaviors

Repetitive behaviors

Associated phenotypes

IQ

Adaptive behavior

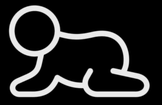


Motor coordination

Sensory sensitivities

Co-occurring conditions

Developmental disorders



Language and speech

Attention, mood, anxiety

Medical

etc…

The Heterogeneity Challenge

Autism varies widely in traits *and* in genes

We know autism is about 80% heritable (strongly genetic), but we've only found the specific cause for about 1 in 5 autistic people — even after studying thousands of genes

Do autistic individuals with similar traits also have similar genetics?

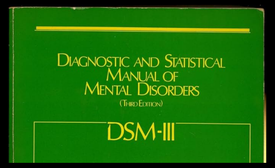
Brief history of autism diagnosis and subtypes

1943: first description of "infantile autism"

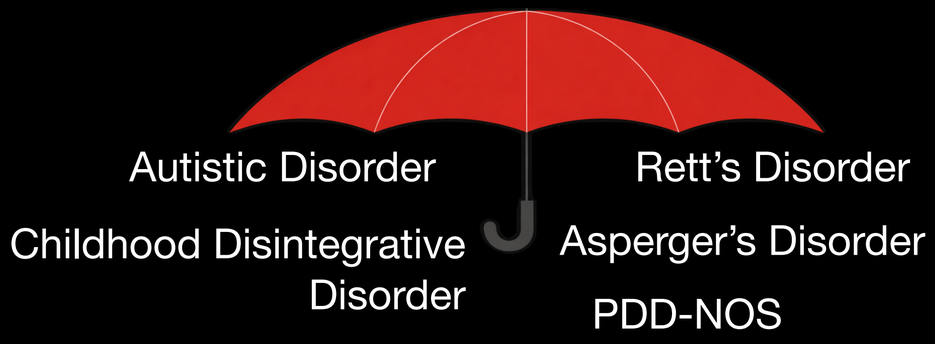
AUTISTIC DISTURBANCES OF AFFECTIVE CONTACT

By LEO KANNER

1980: DSM III includes autism as an official diagnosis



1994: DSM IV introduces an umbrella of "pervasive developmental disorders"



2013: DSM V includes single diagnosis of autism spectrum disorder (ASD) based on multiple dimensions

Study authors

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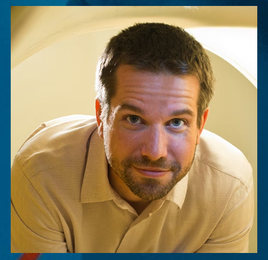
Simons Foundation

Chandra Theesfeld
Princeton University

Natalie Sauerwald
Flatiron Institute

Christopher Y. Park
Flatiron Institute



Ilan Dinstein
Ben Gurion University

LeeAnne Snyder
Simons Foundation

Yun Hao
Flatiron Institute

Olga Troyanskaya
Princeton University
Flatiron Institute

Outline

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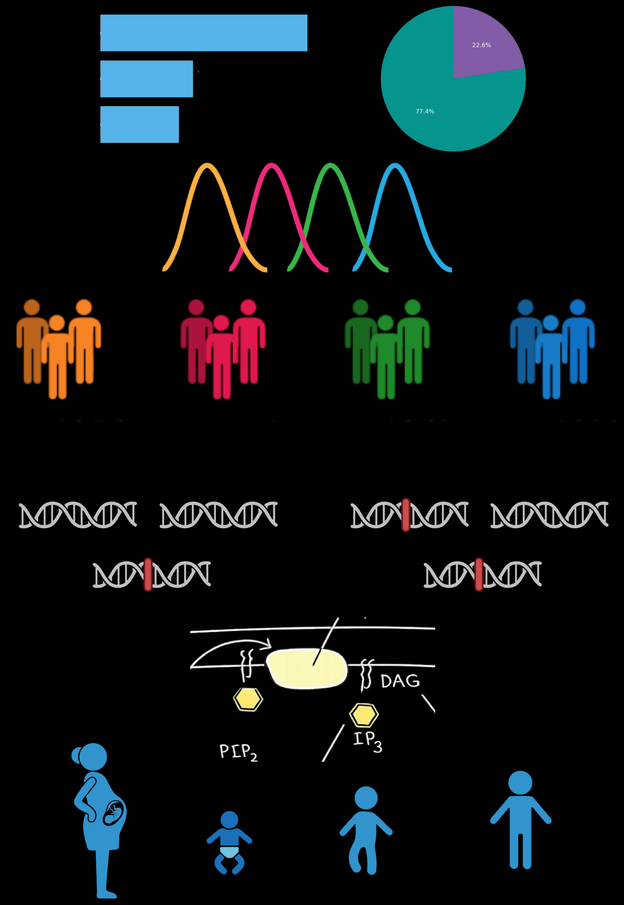
2. Our approach to the heterogeneity challenge
3. Description of the groups we identified
4. Genetics!
   - Common & rare genetic variation
   - Genetic pathways
   - Developmental timing of genetic effects
5. Conclusions



SPARK

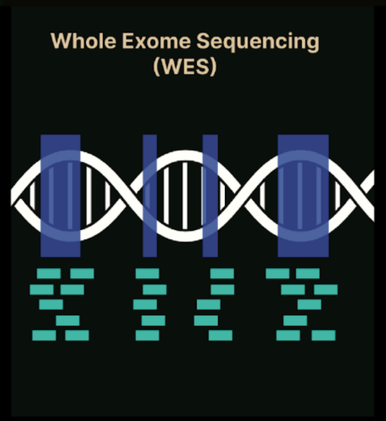
Simons Powering Autism Research

300,000 individuals and growing

Genomic Data

11,549 WGS samples
(3,193 ASD)

61,382 WES samples
(31,641 ASD)



Phenotypic Data

310,649 individuals (123,280 autistic individuals)

92,147 male probands

31,297 female probands

Medical screening

Child Behavior Checklist
Vineland Adaptive Behavior
Repetitive Behavior Scale
Language level

Area Deprivation Index

IQ, ID, predicted cognitive impairment

Social Communication Questionnaire

Autism Diagnostic Observation Schedule (ADOS)

Cohort description

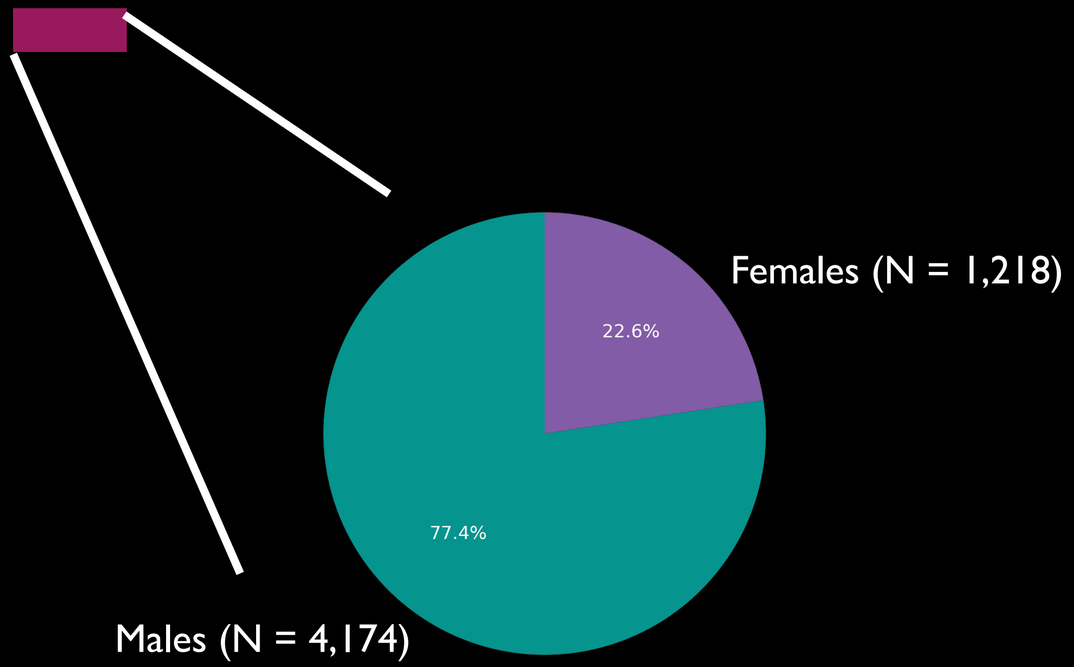
All probands < 18yo (N = 105,082)

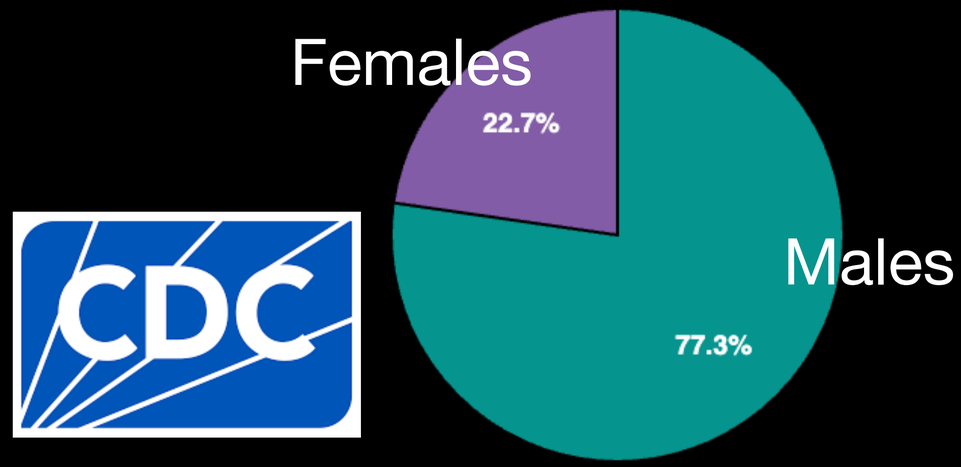
+ SCQ (N = 55,277)

+ background history (N = 37,721)

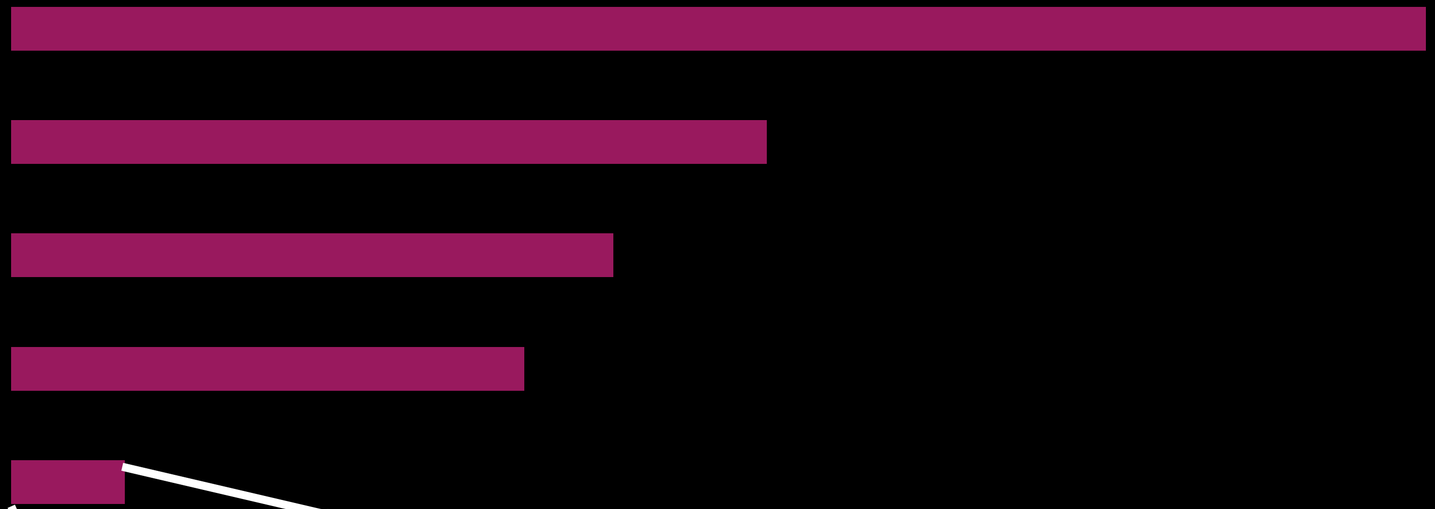
+ RBS-R (N = 33,790)

+ CBCL (N = 5,392)





Cohort description



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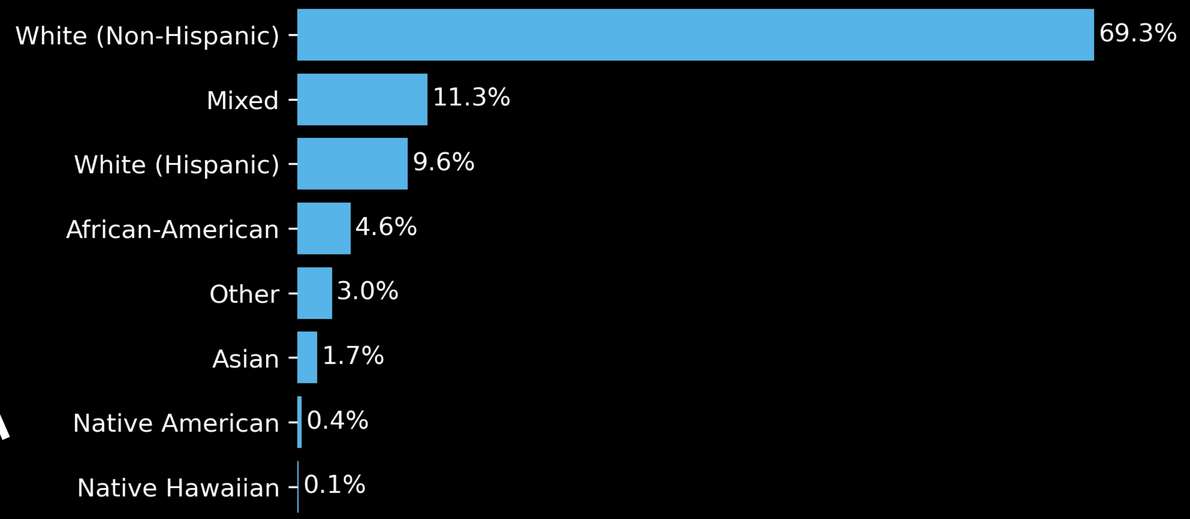
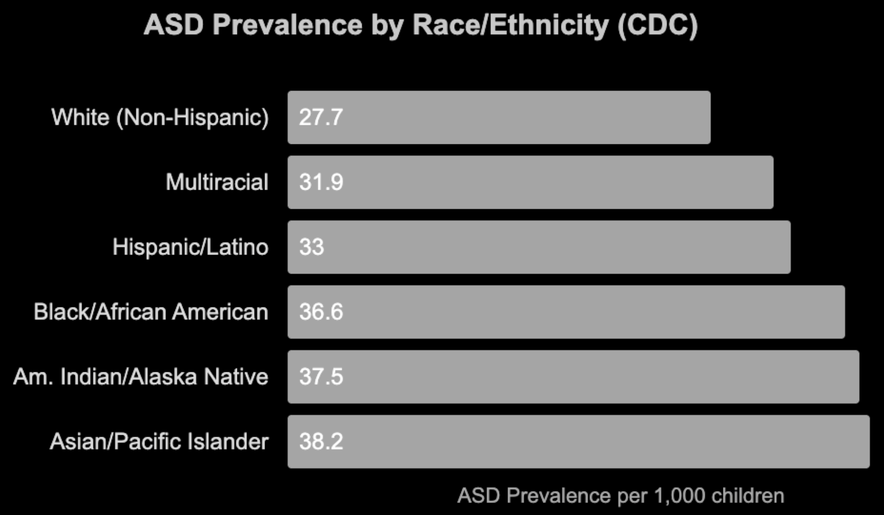
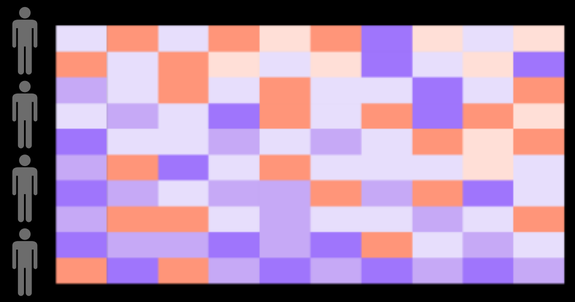


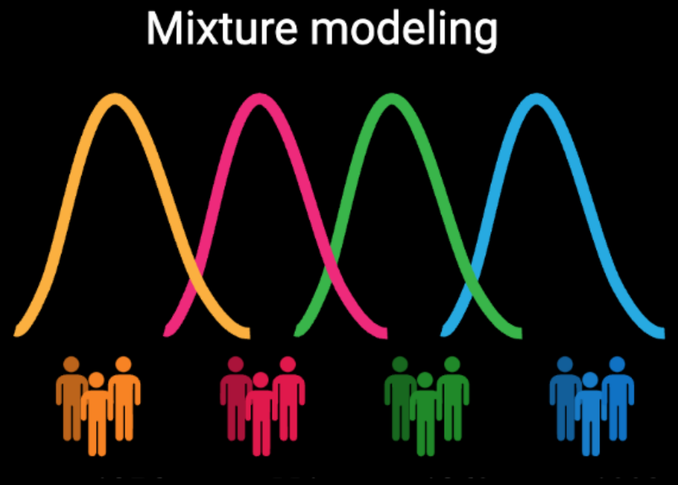


A person-centered approach: find subgroups based on traits and look at their underlying genetics

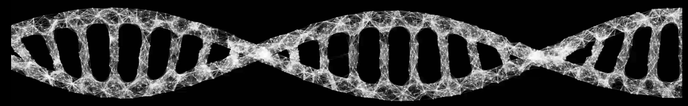


5392 autistic children x 239 traits

Social Communication Questionnaire
Repetitive Behavior Scale
Child Behavior Checklist
Background History



Replication in independent cohort
Clinical validation
Common variant signals
de novo and inherited variation
Pathways and processes
Developmental gene timing



What is a “person-centered” approach?

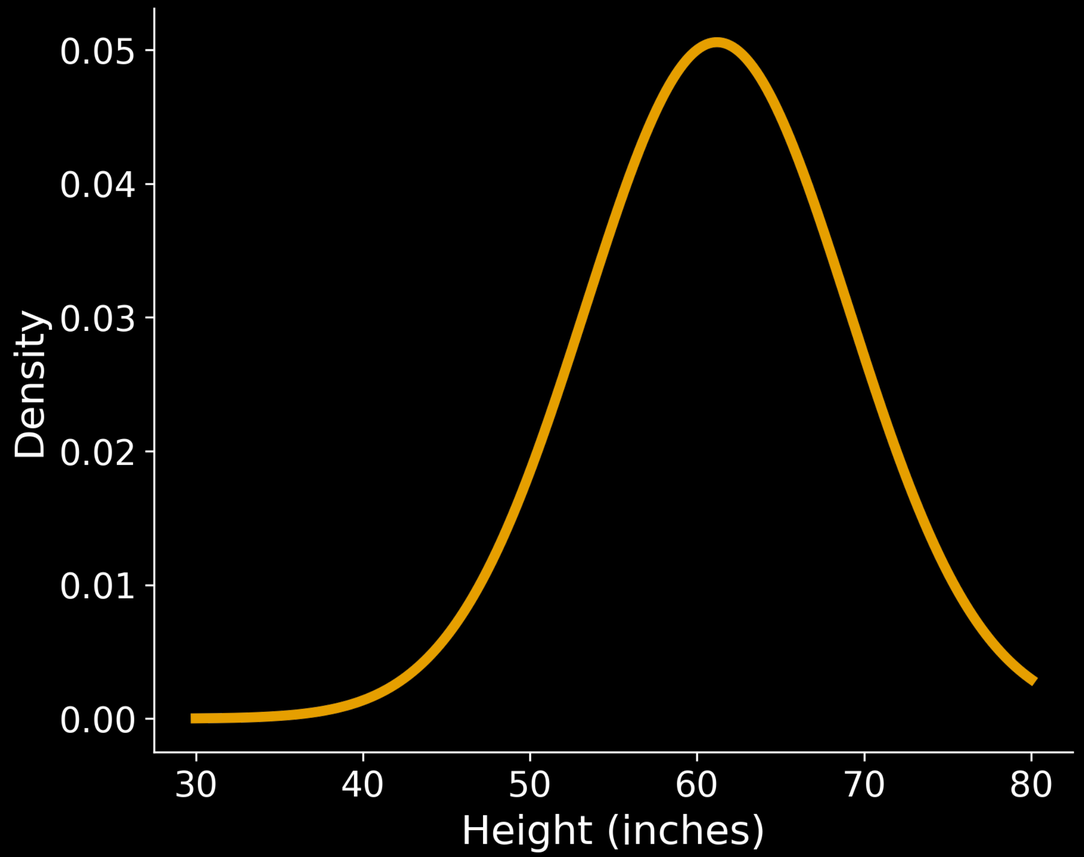
Trait-centered approach

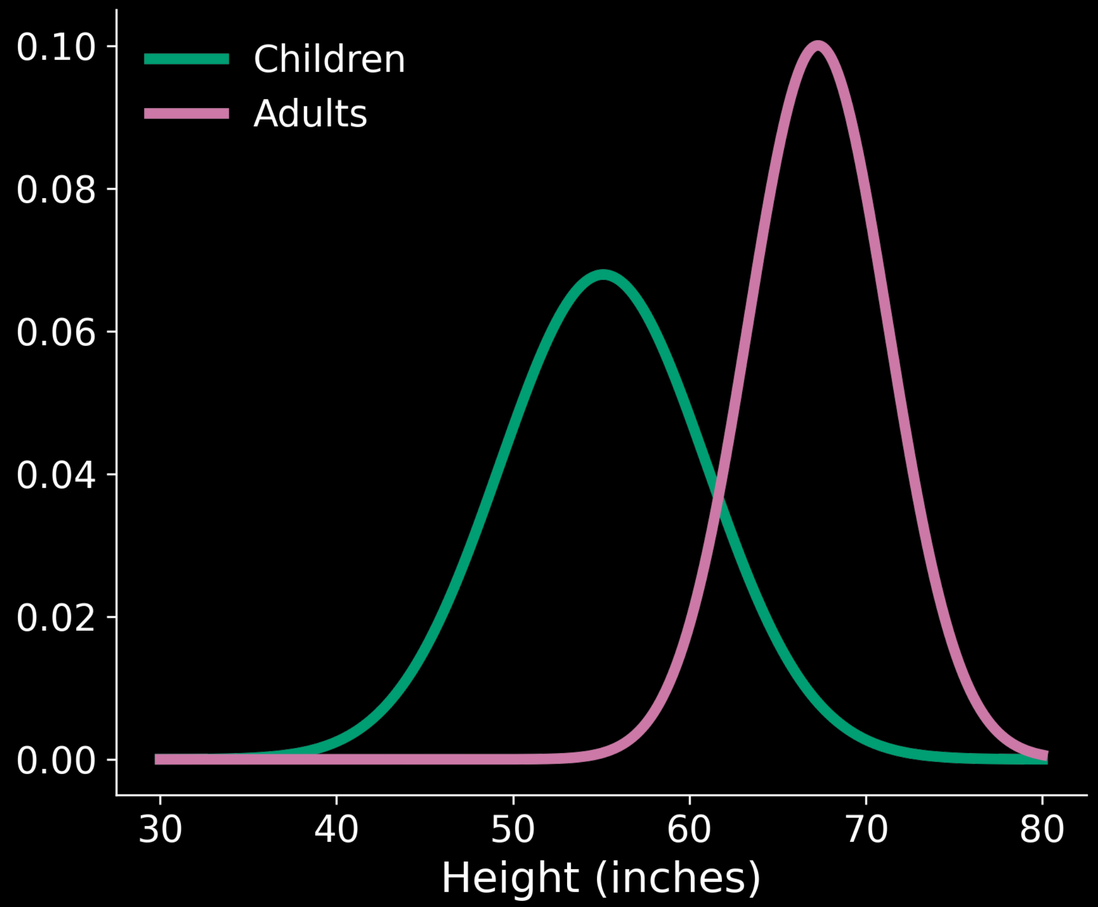
- Communication challenges
- Repetitive behaviors
- Intellectual disability
- Sensory sensitivities
- …

Person-centered approach

- Group 1
- Group 2
- Group 3

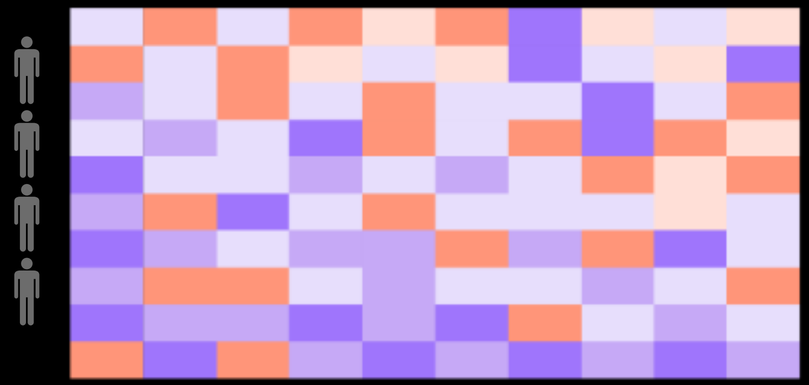
What is mixture modeling?



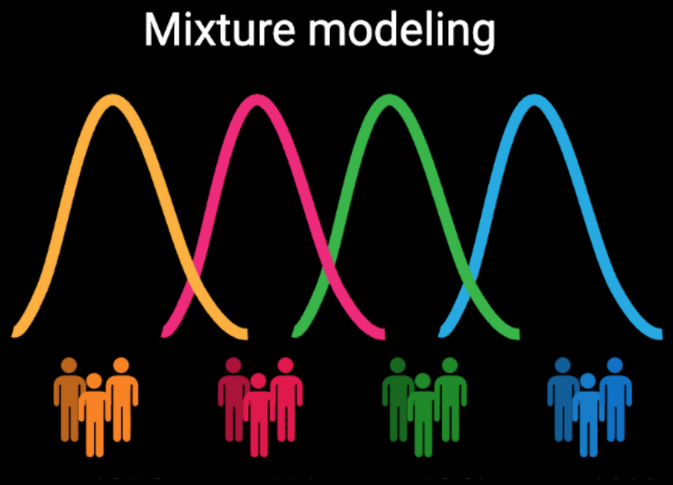


- Mathematical way to look for underlying groups that best explain the data
- Estimates how many distinct groups naturally exist in the population

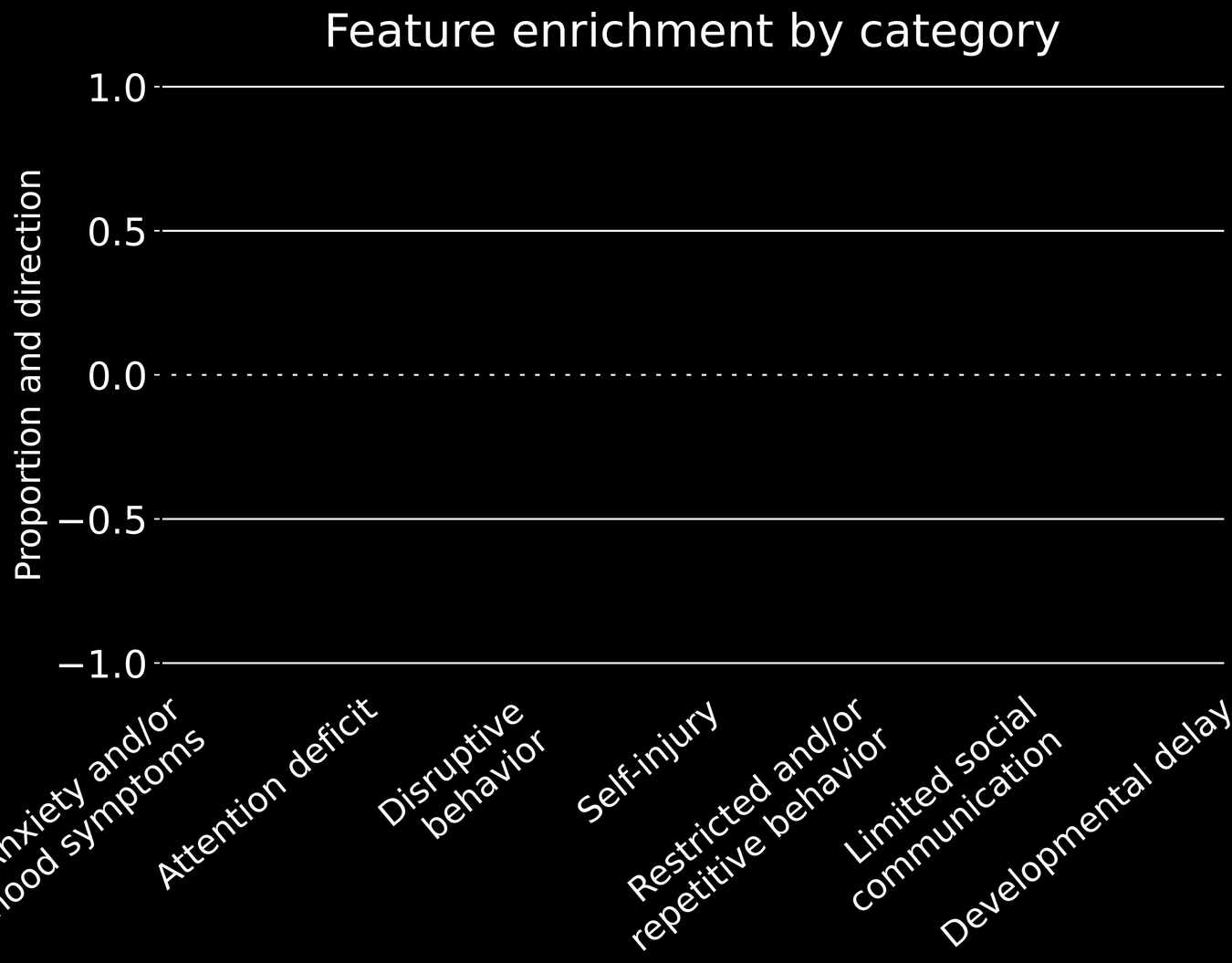
We identified 4 groups within our autism cohort



5392 autistic children x 239 traits



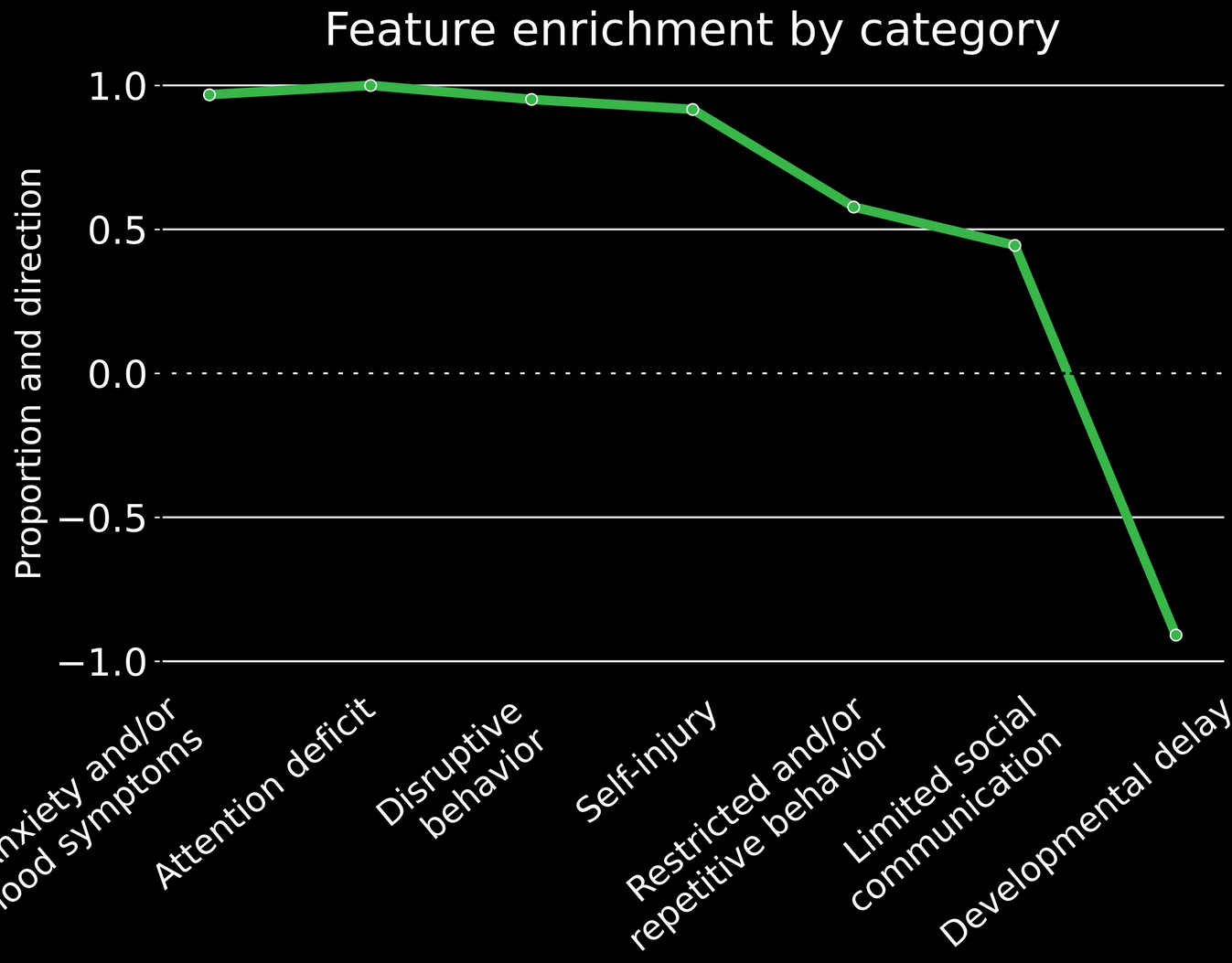
Characteristics of 4 autism classes



Jennifer Foss-Feig

LeeAnne Snyder

Characteristics of 4 autism classes

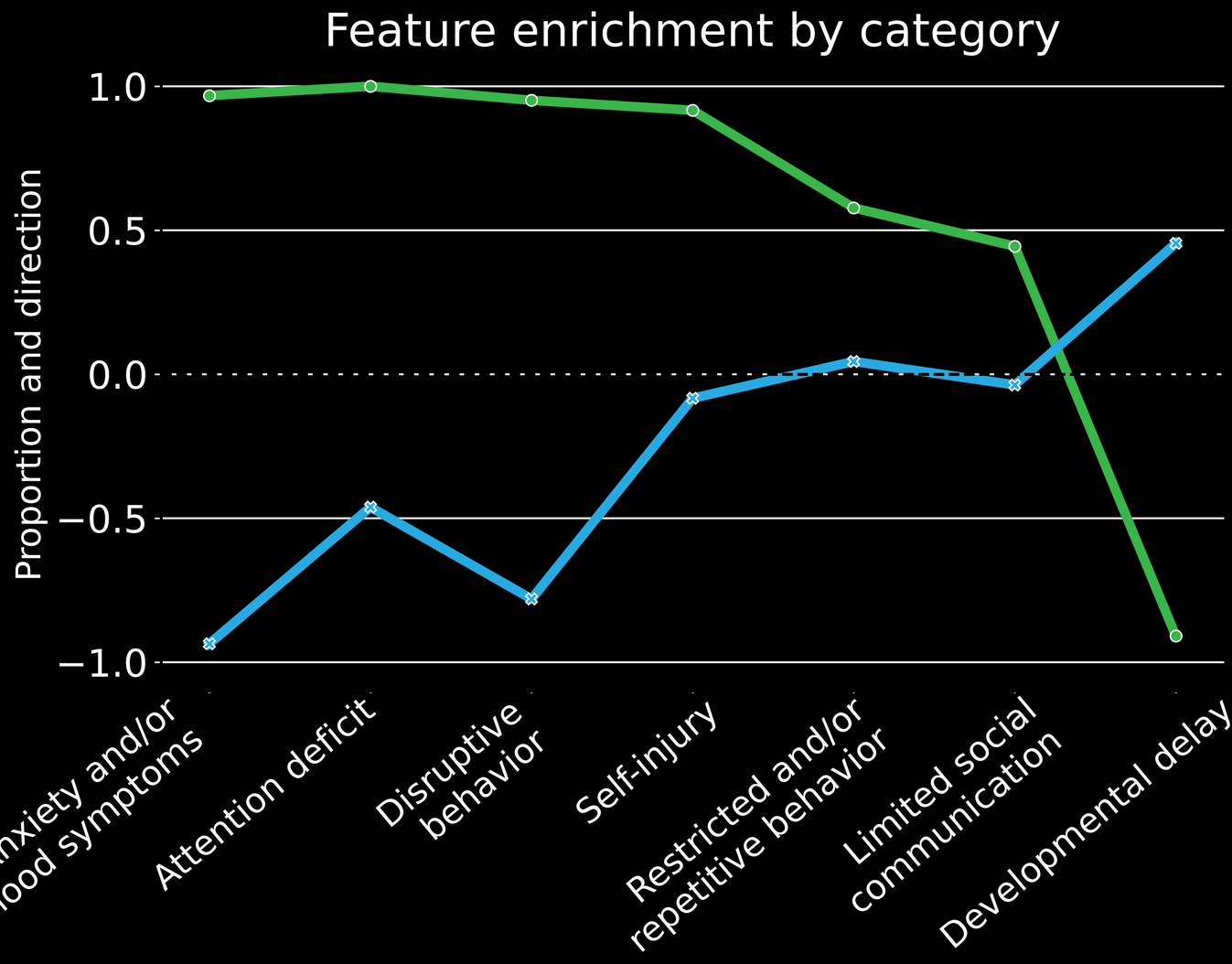


n = 1860
Social/
Behavioral

Jennifer Foss-Feig

LeeAnne Snyder

Characteristics of 4 autism classes



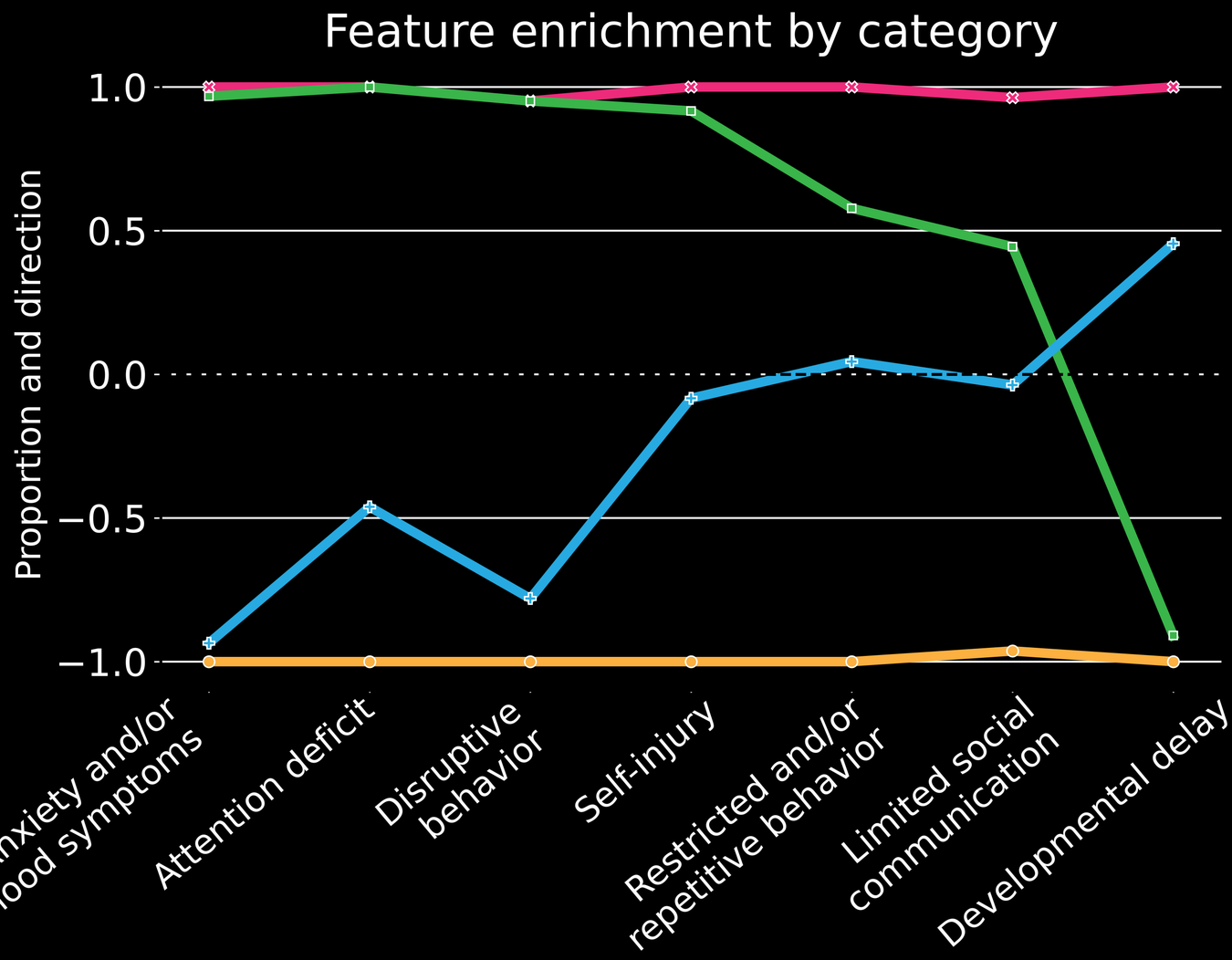
n = 1002
Mixed ASD with DD

n = 1860
Social/ Behavioral

Jennifer Foss-Feig

LeeAnne Snyder

Characteristics of 4 autism classes



n = 554 Broadly affected

n = 1002 Mixed ASD with DD

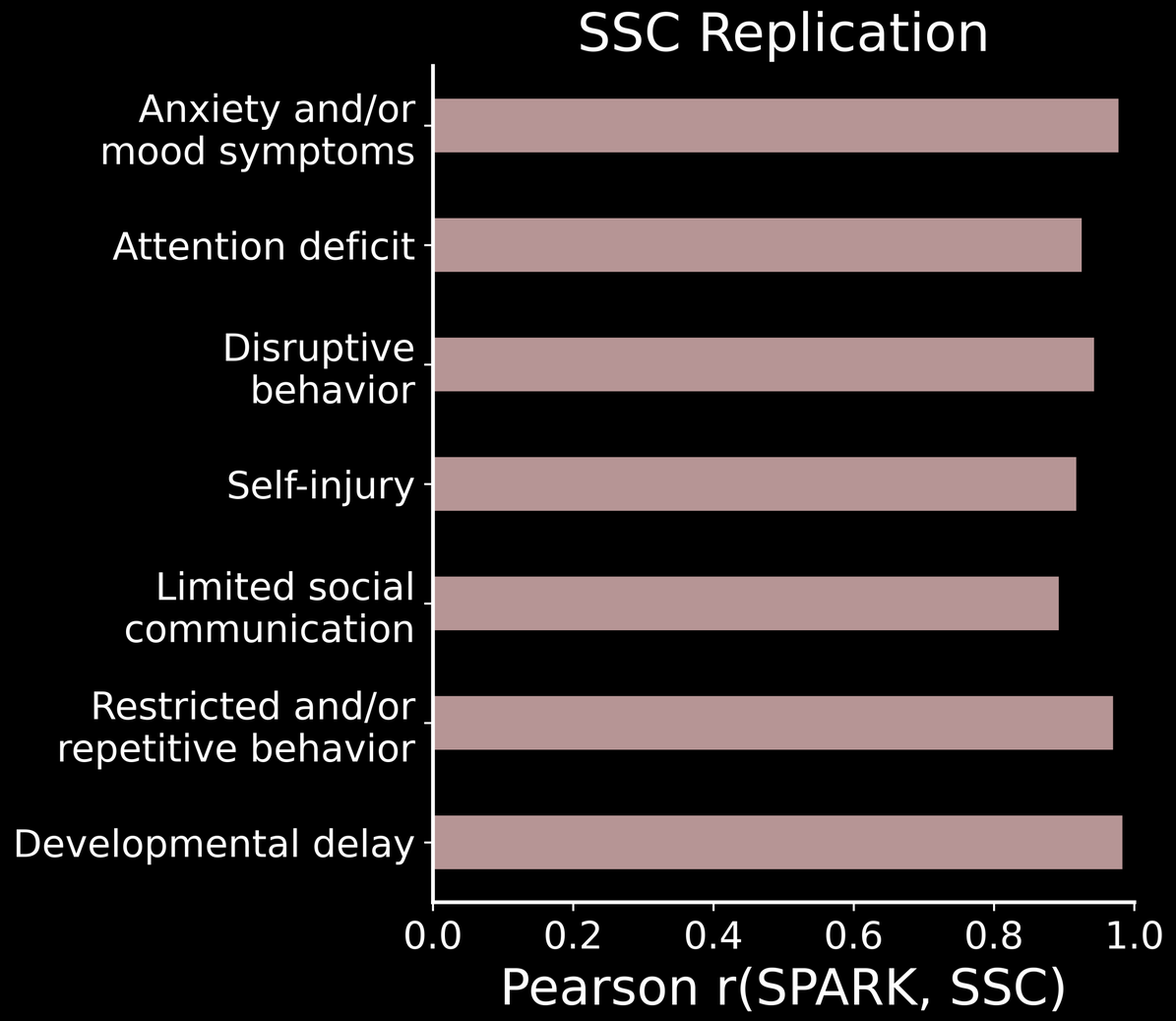
n = 1860 Social/ Behavioral

n = 1976 Moderate Challenges

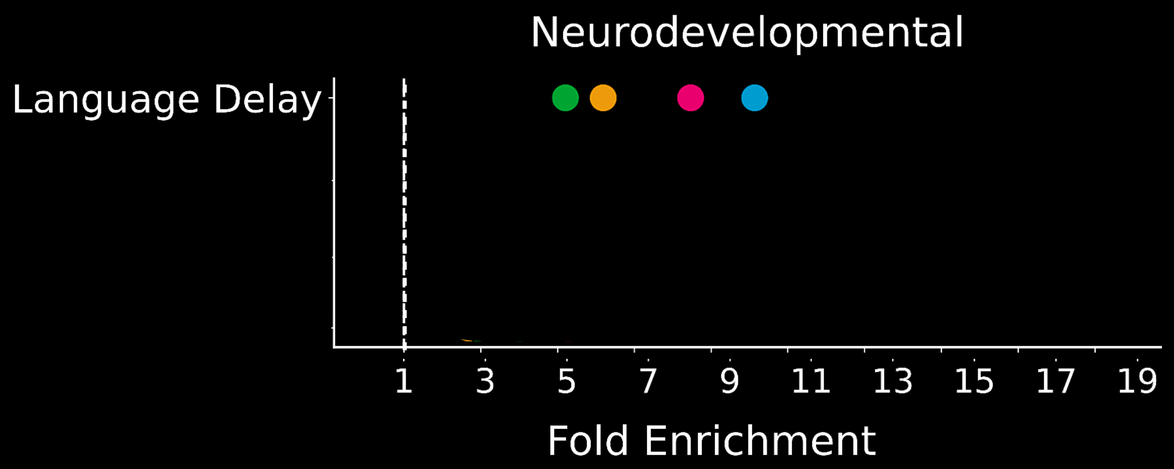
Jennifer Foss-Feig

LeeAnne Snyder

When we tried this with another group of autistic children (Simons Simplex Collection), we saw very similar groups



Clinical validations and characterization



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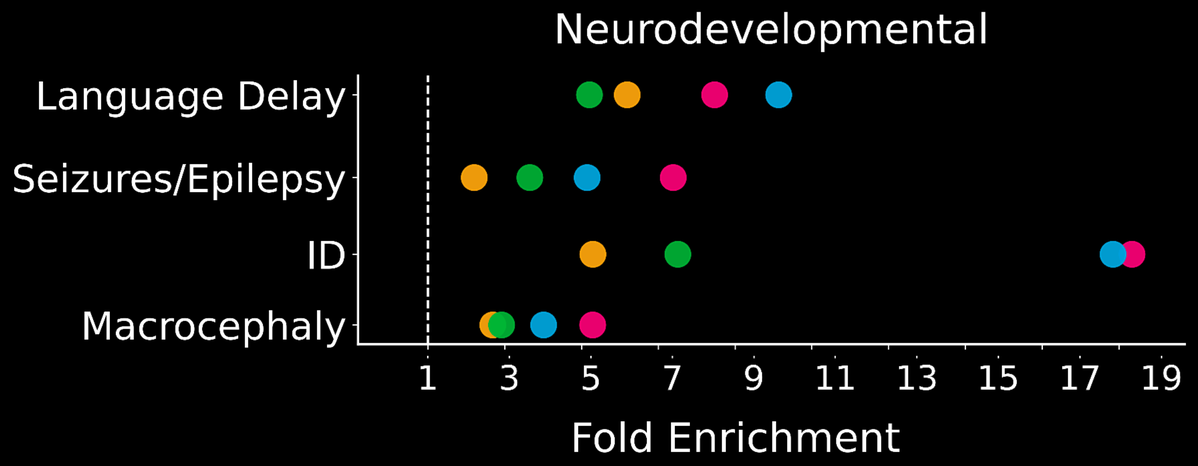

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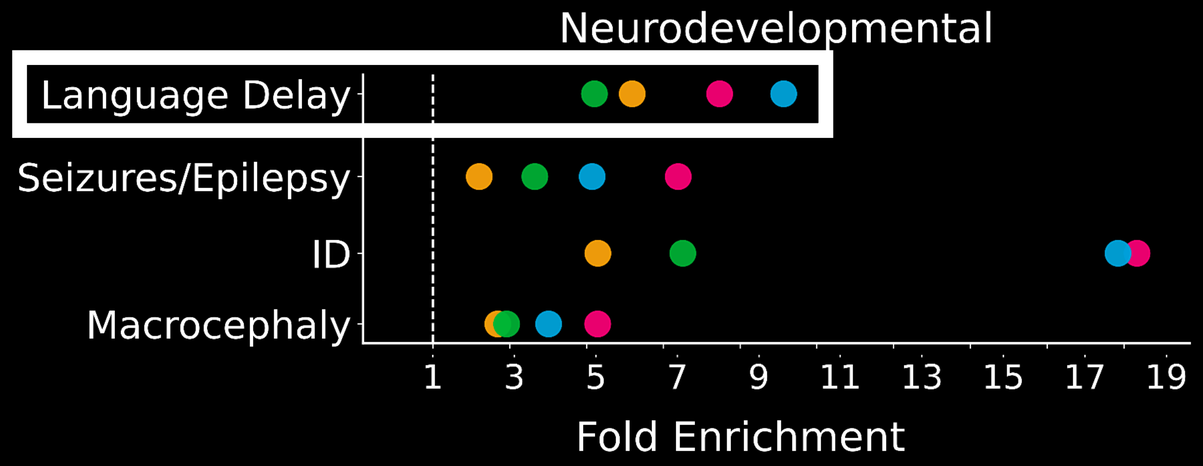
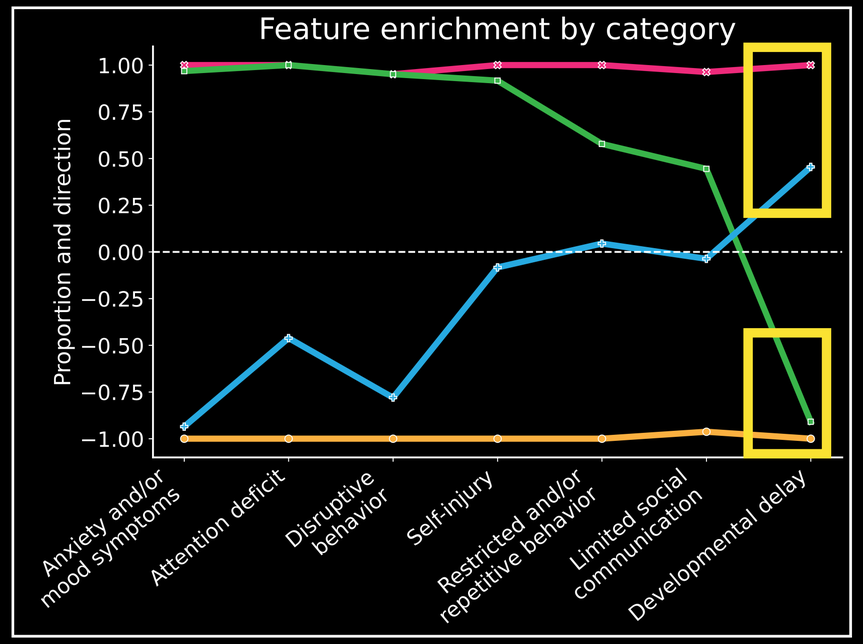
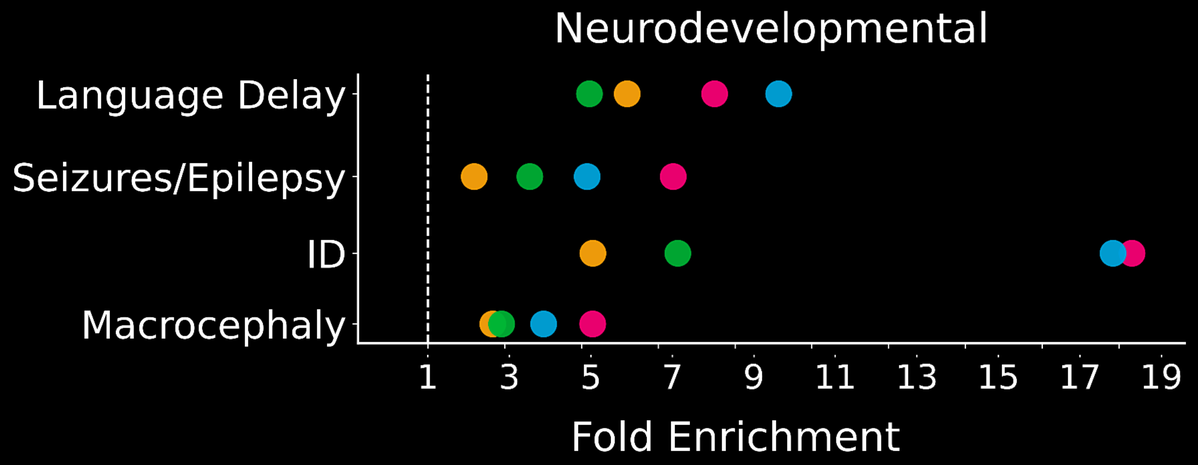


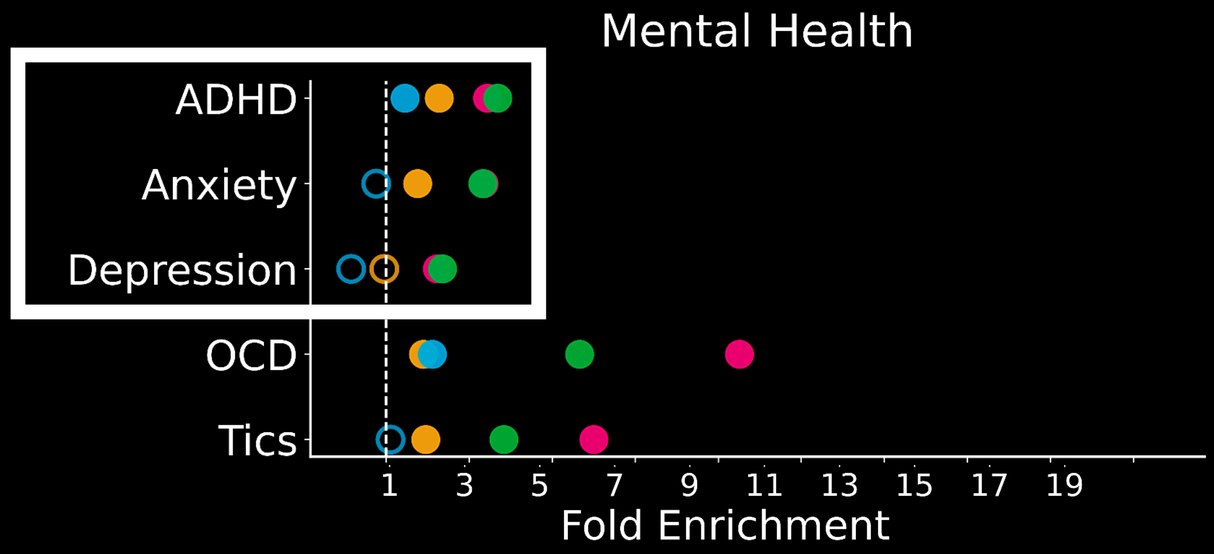


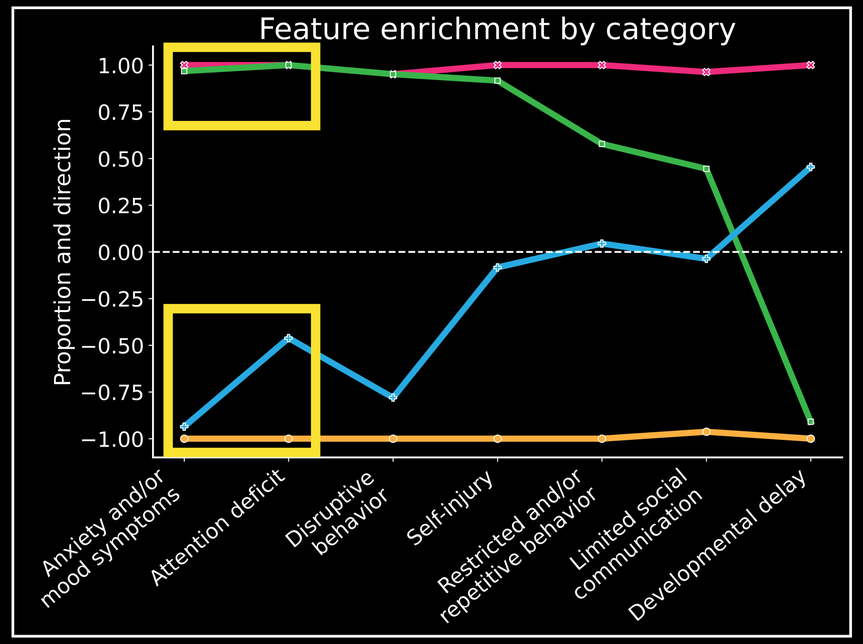
Moderate challenges
Broadly affected
Social/behavioral
Mixed ASD with DD

FDR
≤ 0.05
> 0.05

Clinical validations and characterization







Moderate challenges
Broadly affected
Social/behavioral
Mixed ASD with DD

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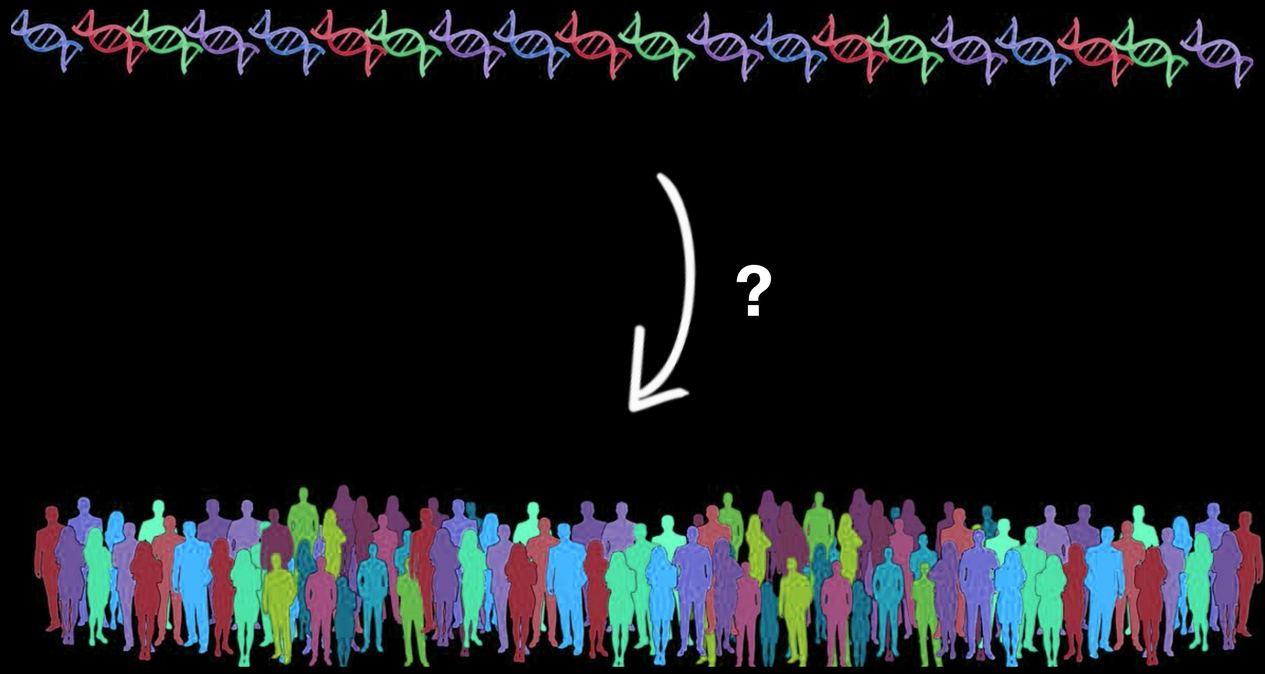
≤ 0.05
> 0.05

Are there coherent genetic patterns underlying these trait-based groups?



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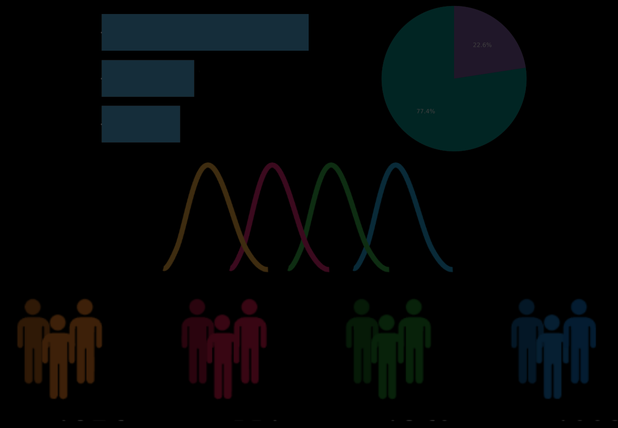
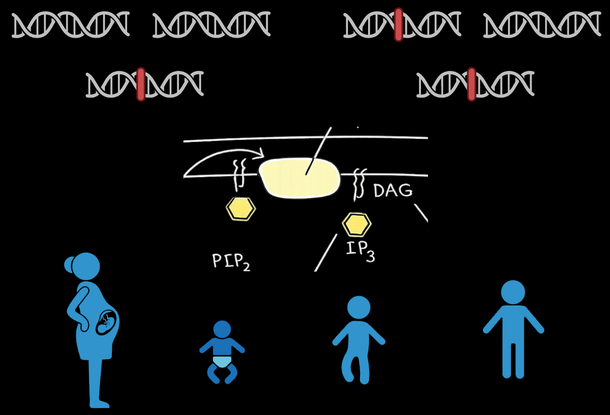
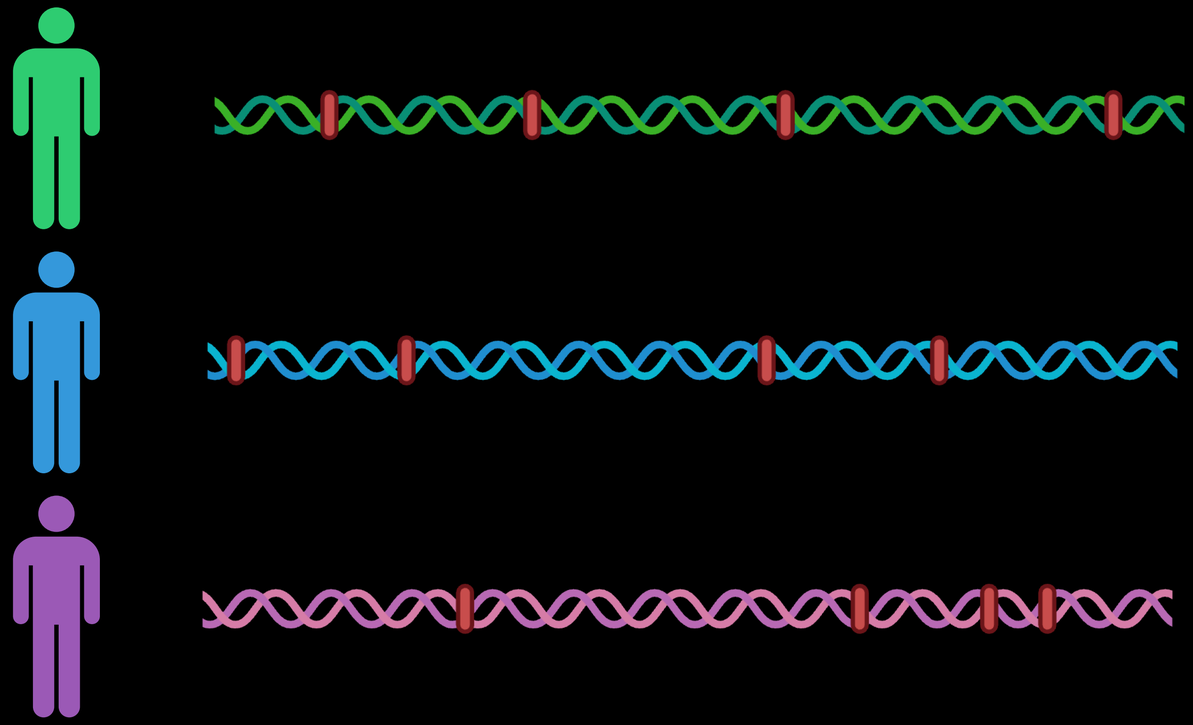




Human genetic variation



4-5 million genetic variants

~300,000 rare

~4 million common

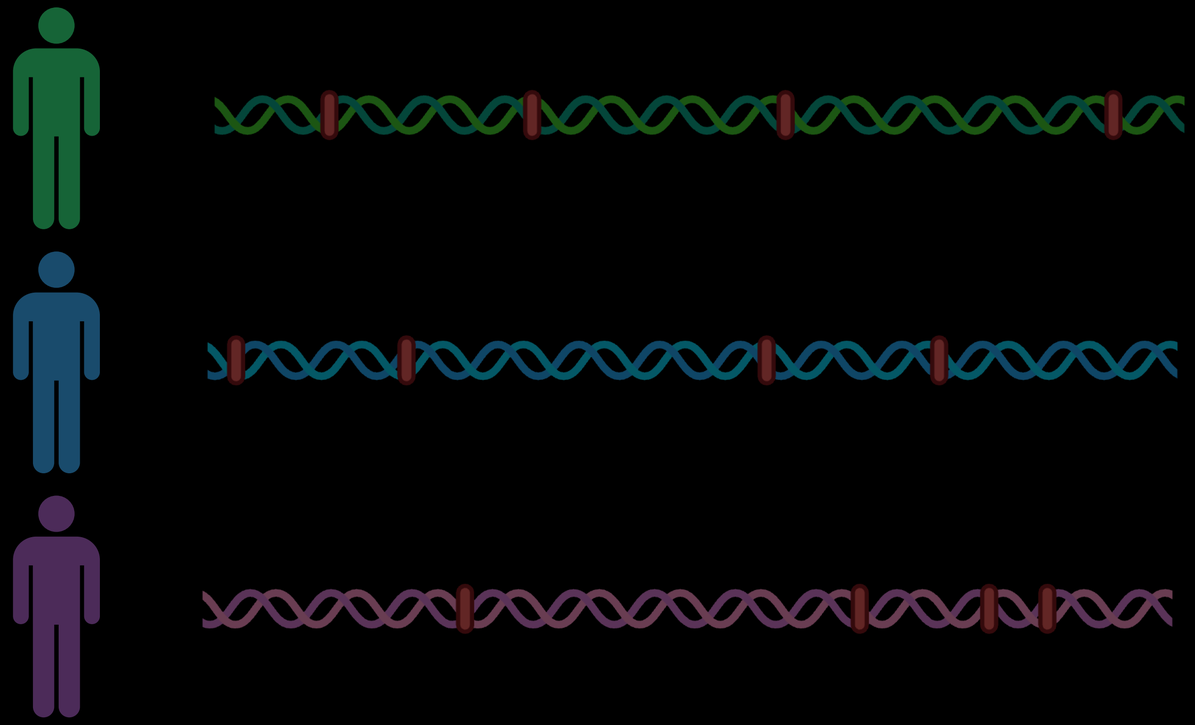
~70 *de novo*

4-5 million inherited

Benign or no effect

Pathological

Human genetic variation



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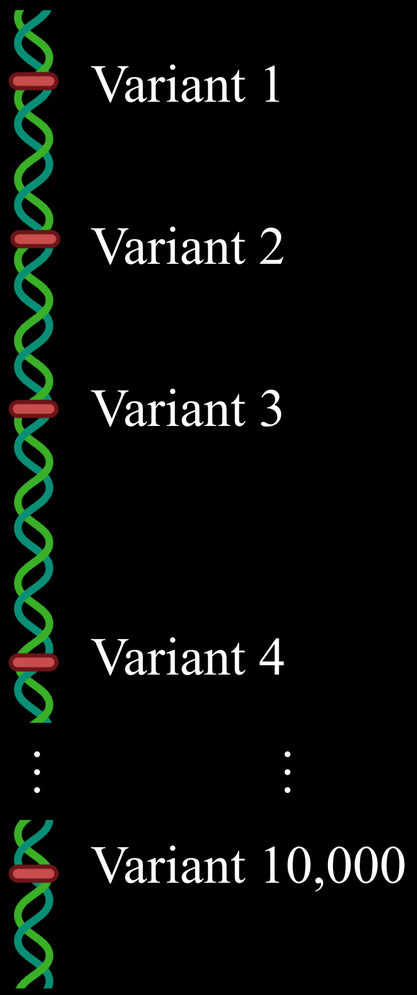
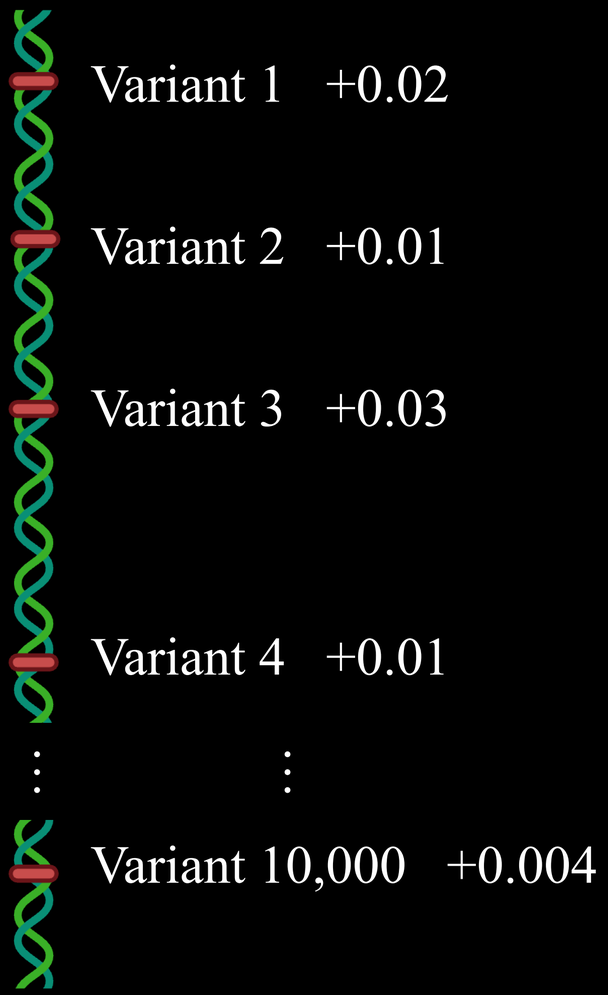
Polygenic risk scores add up common variant contributions to traits or diseases



Polygenic risk scores add up thousands of tiny genetic effects from common variants

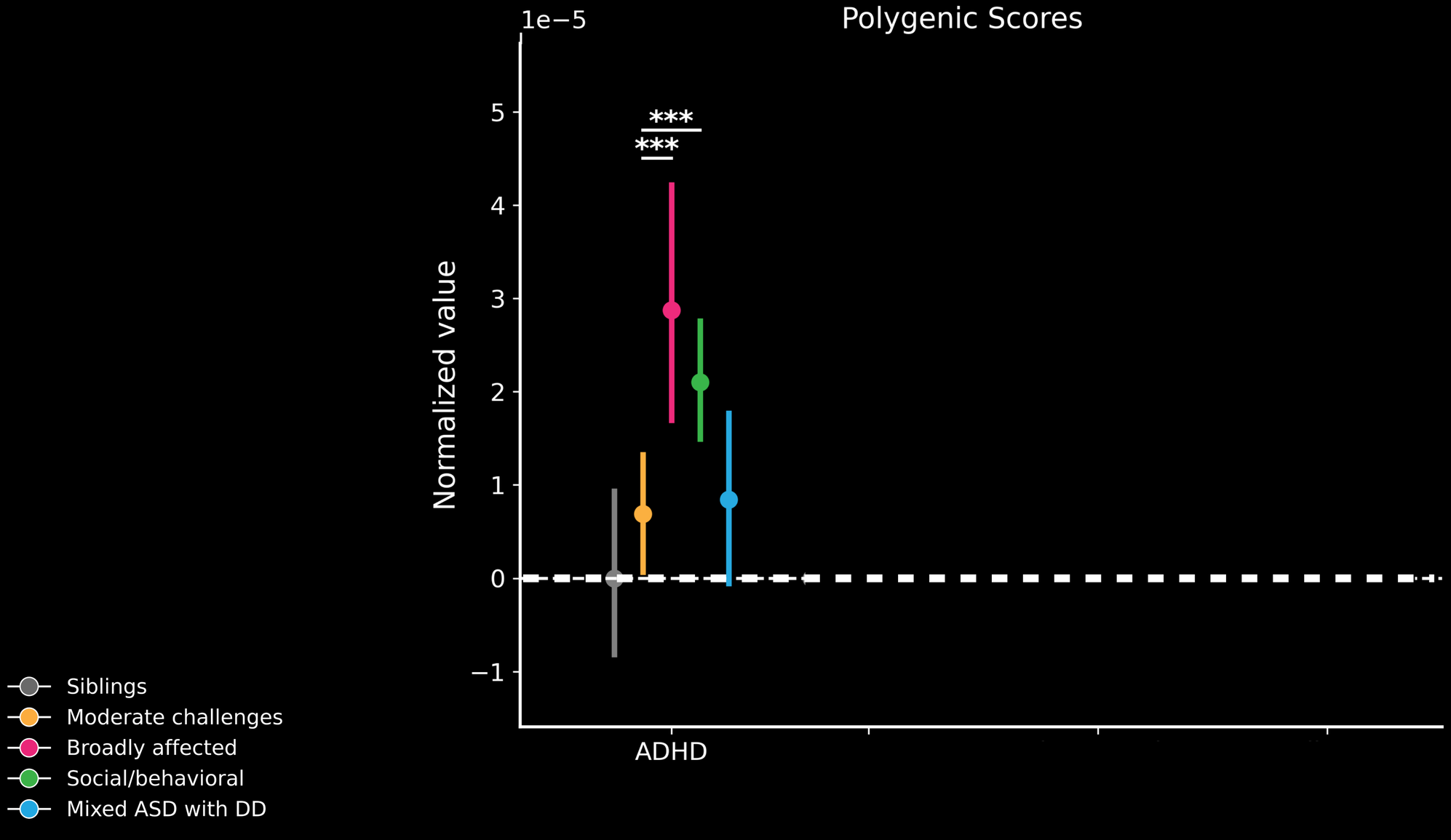
Polygenic risk scores add up common variant contributions to traits or diseases



Polygenic score = 0.87

Polygenic risk scores add up thousands of tiny genetic effects from common variants

These groups have very different polygenic scores for common traits and comorbidities



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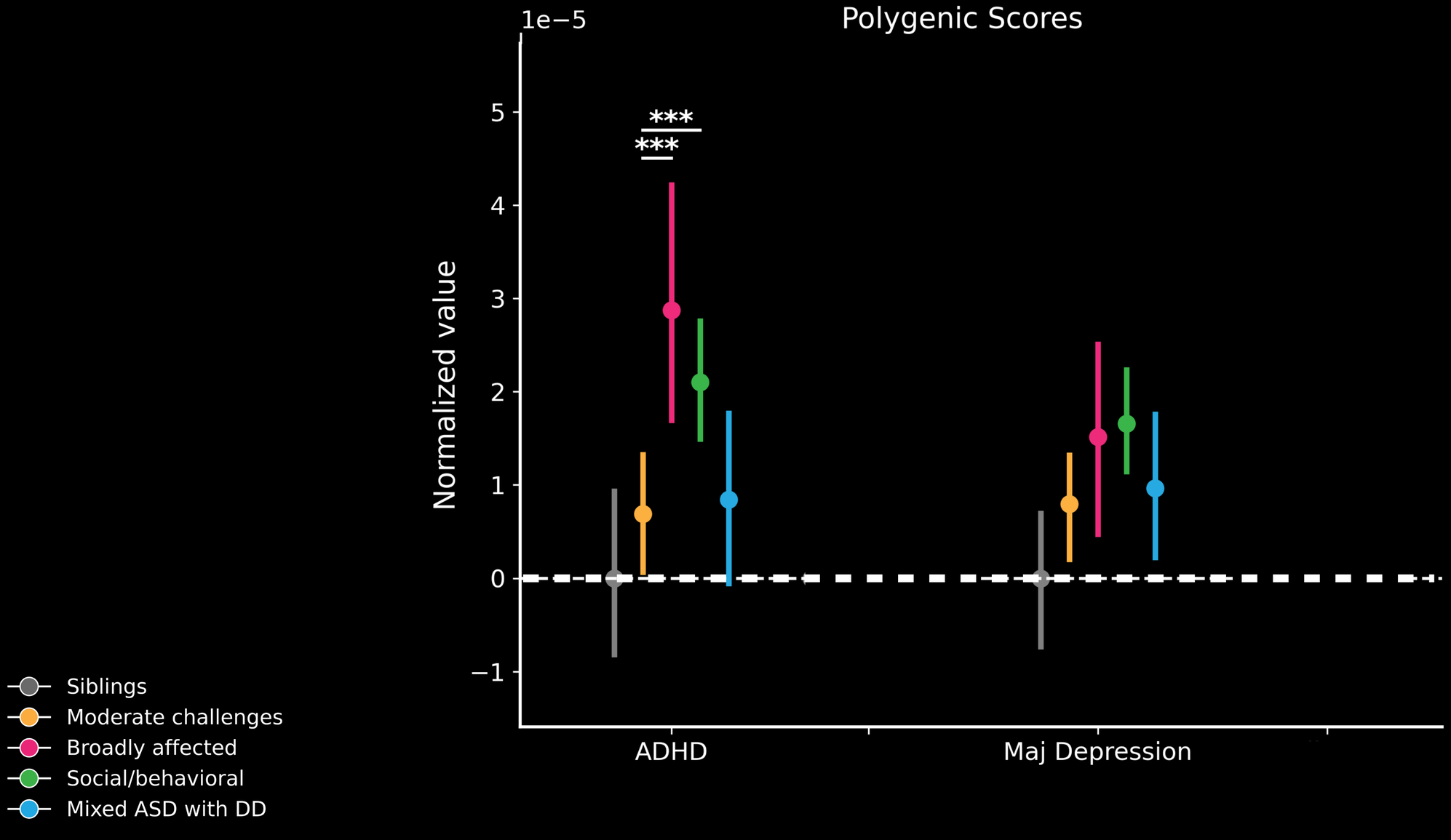
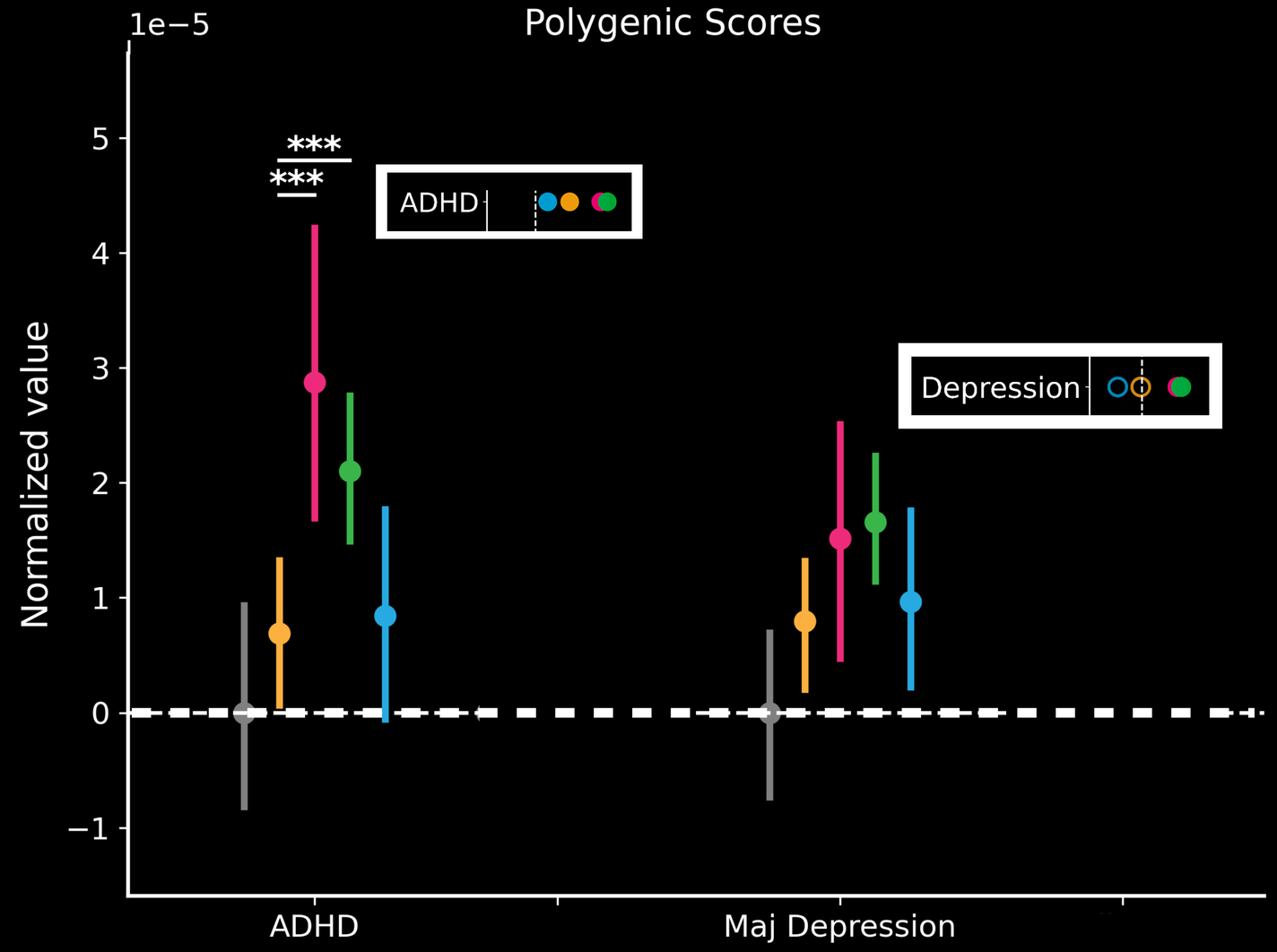


The polygenic scores match up with real diagnoses



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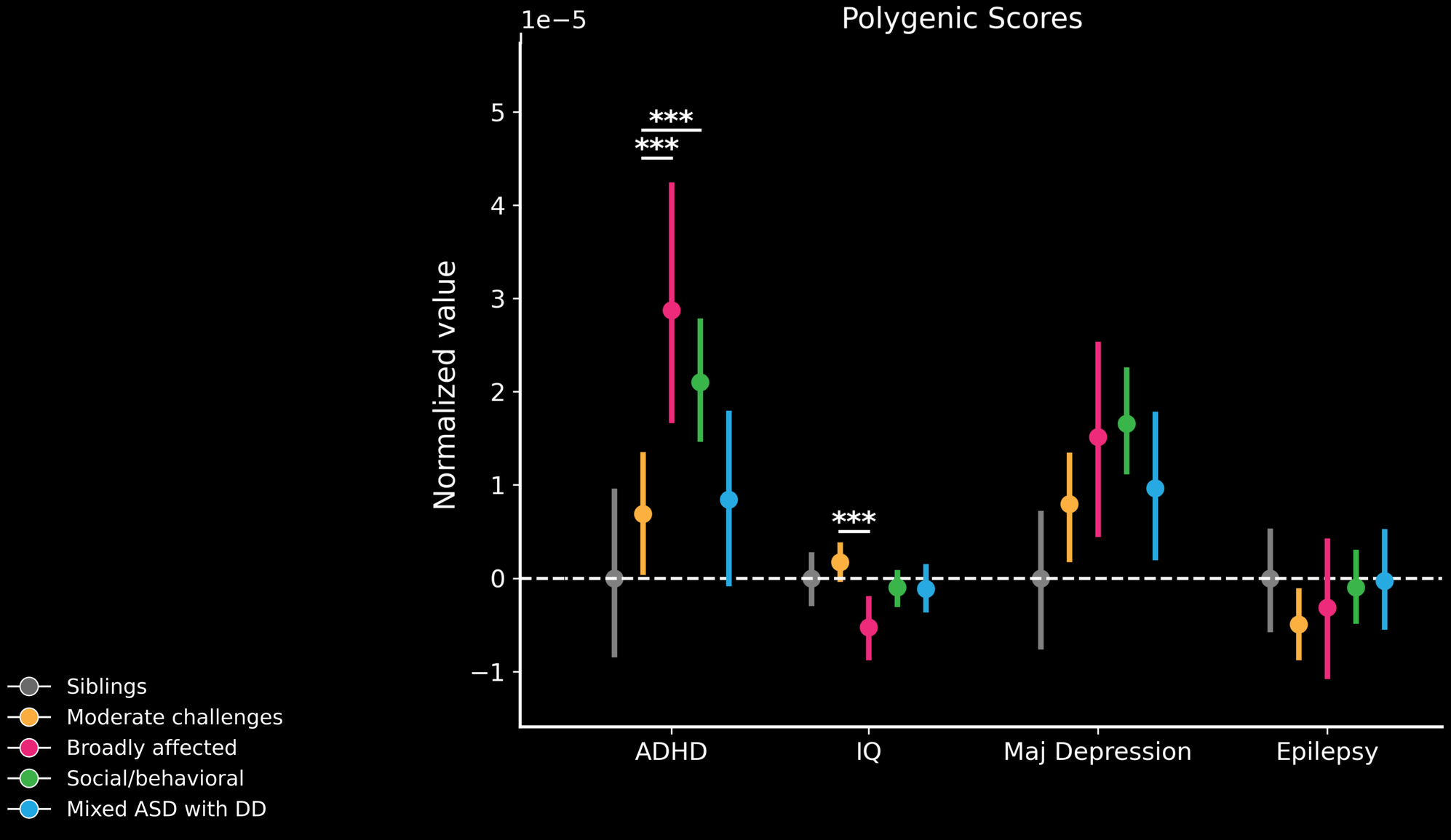
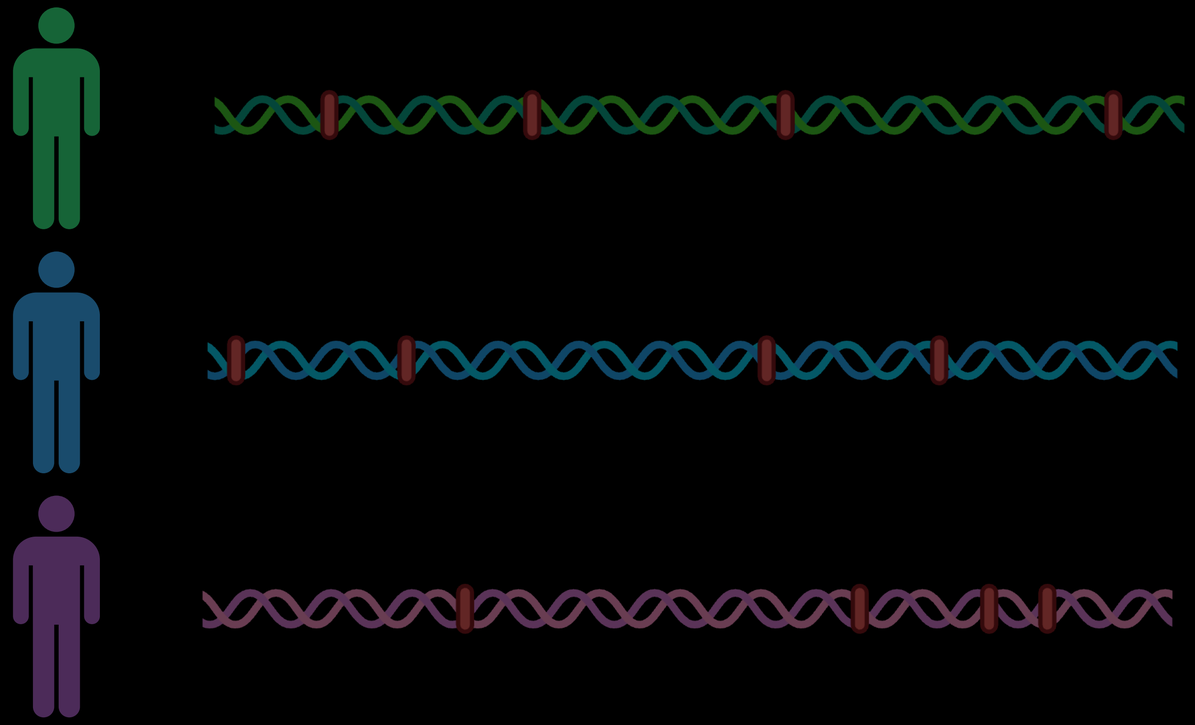


Human genetic variation



4-5 million genetic variants

~300,000 rare

~4 million common

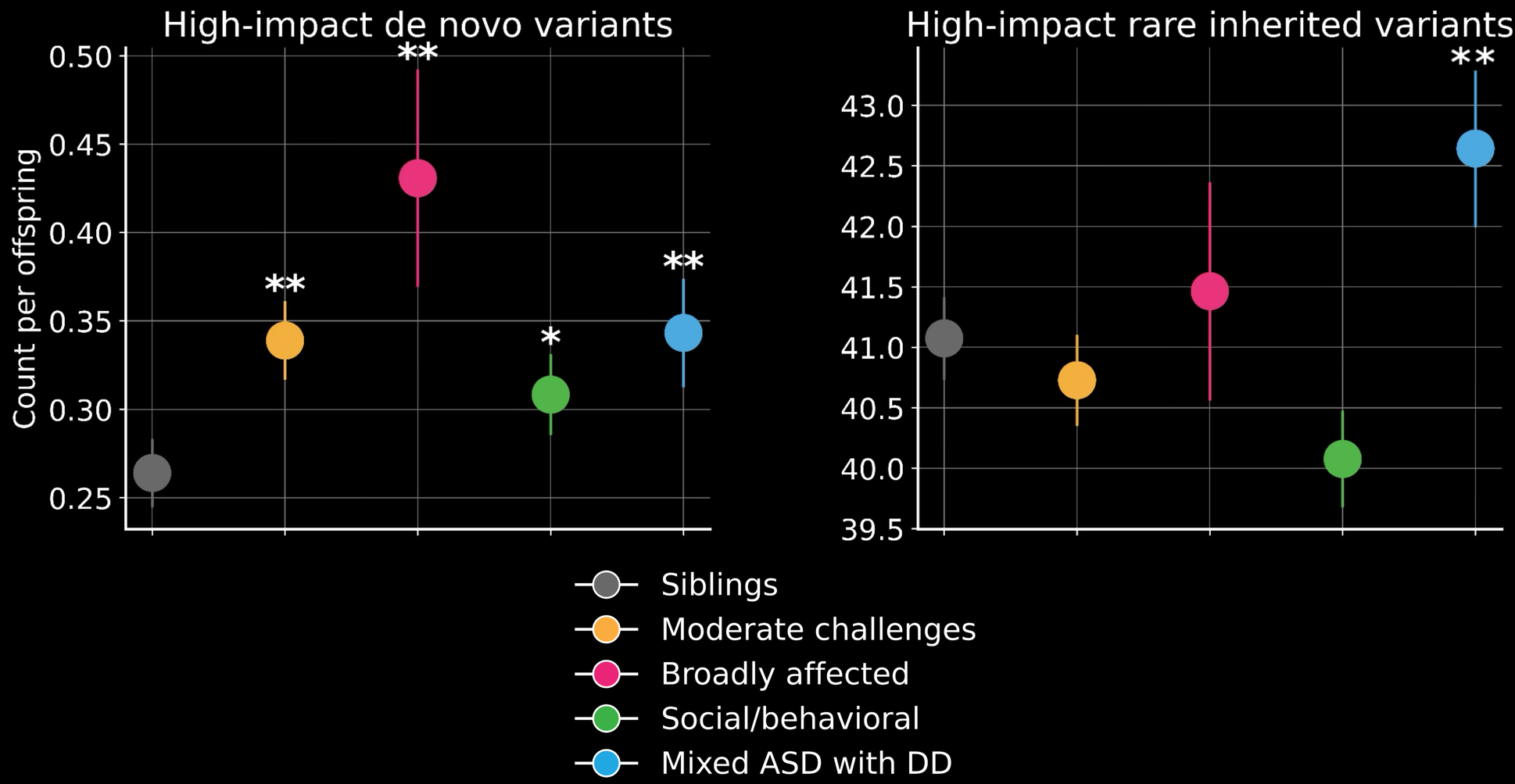
~70 *de novo*

4-5 million inherited

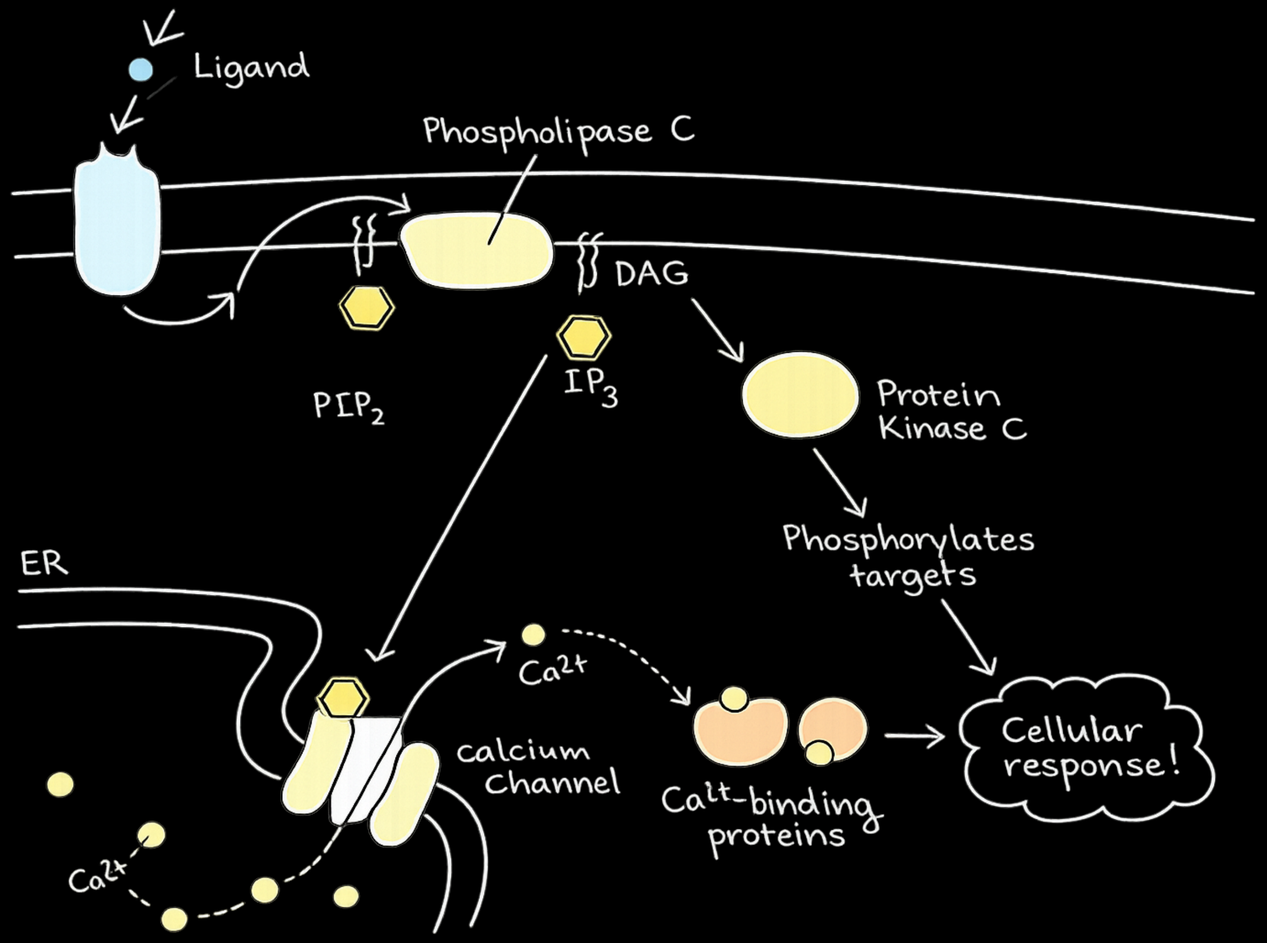
Benign or no effect

Pathological

The groups also show different patterns in rare de novo and rare inherited variants



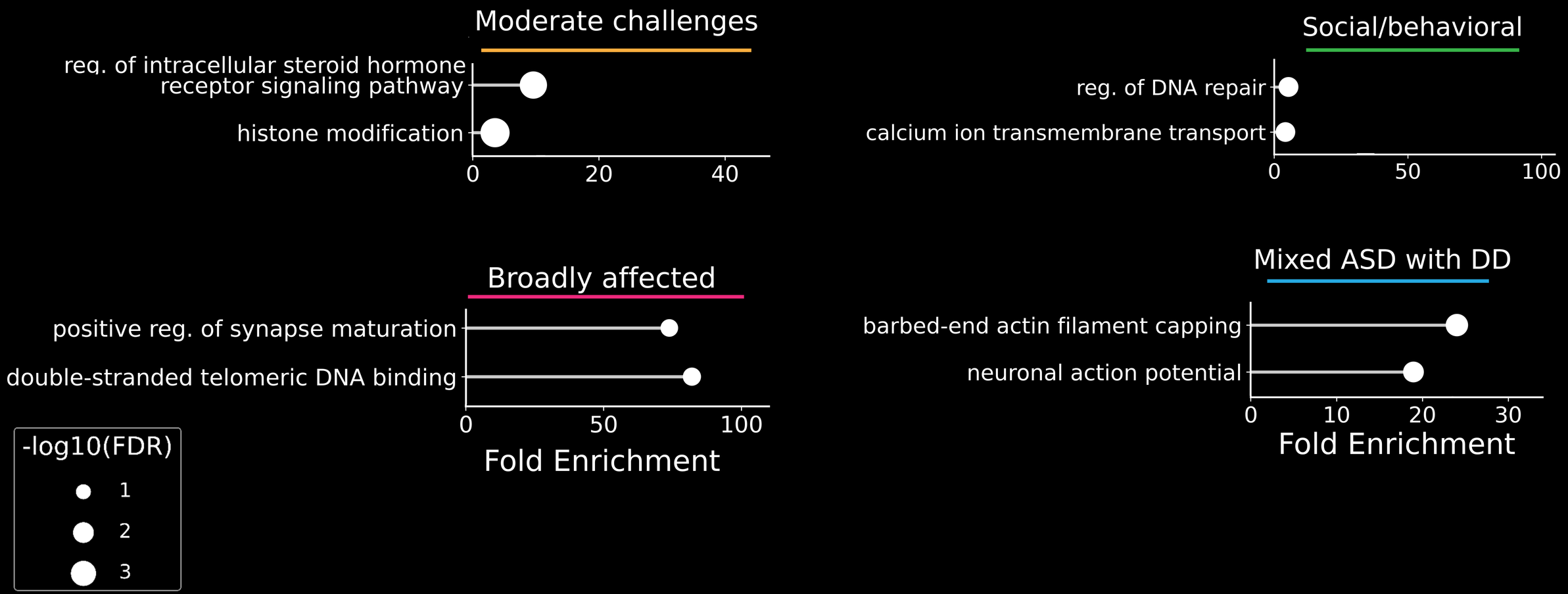
Genes work together in biological pathways



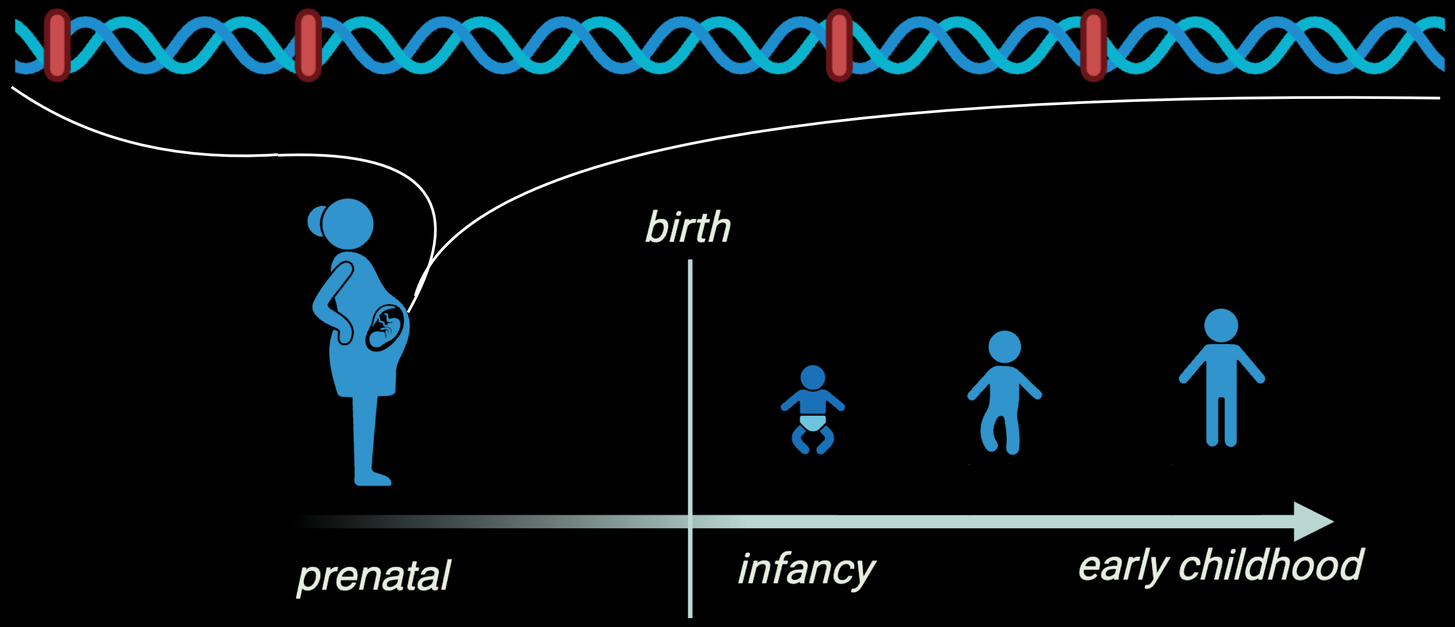
- Genes can be grouped into pathways by the shared jobs they perform in a cell
- Disruptions in multiple genes in the same pathway can lead to the same outcome
- Looking at pathways lets us understand broader biological explanations than single genes

Figure adapted from Khan Academy

Unique pathways and processes are associated with each subclass

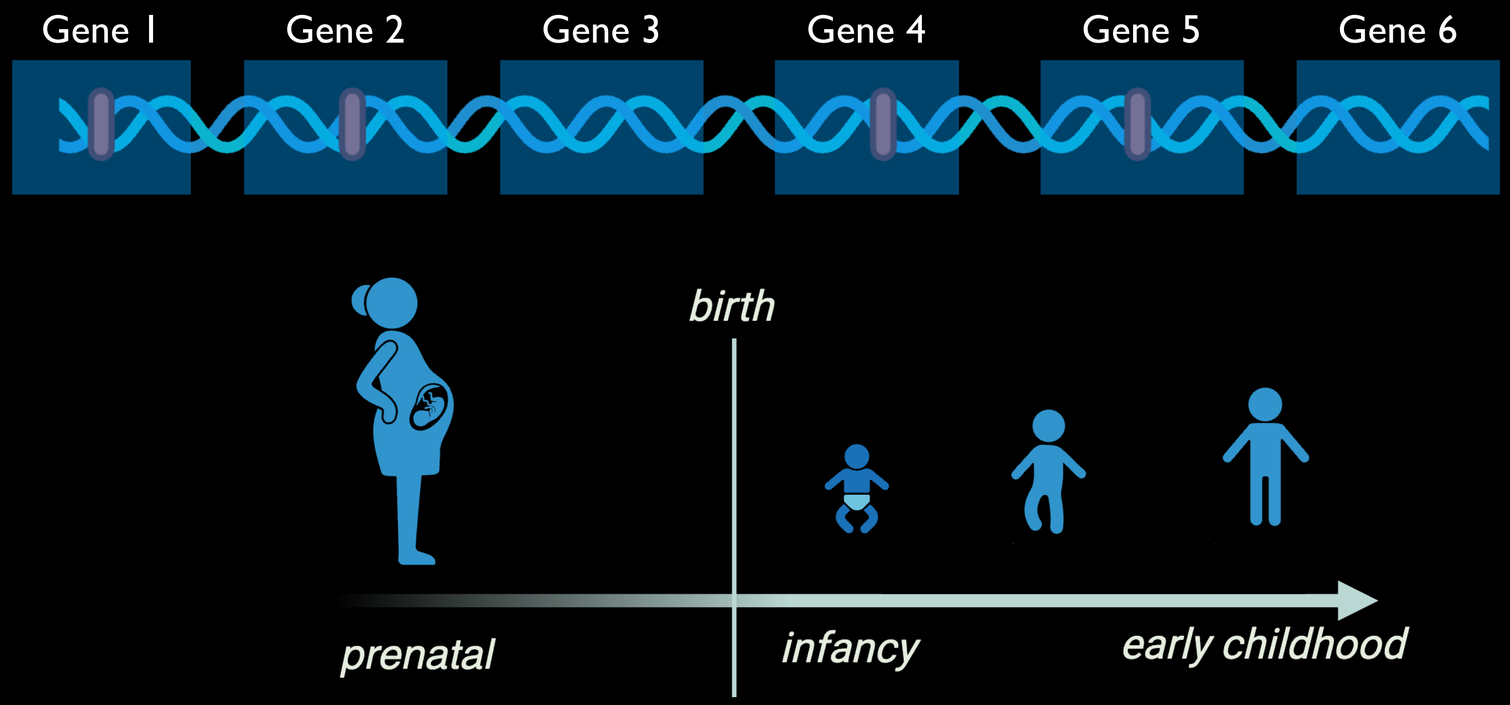


Genetic variants can display their effects at different times in development



Even though the vast majority of genetic variants are present at fertilization, they may not have any effect until later in development

Genetic variants can display their effects at different times in development



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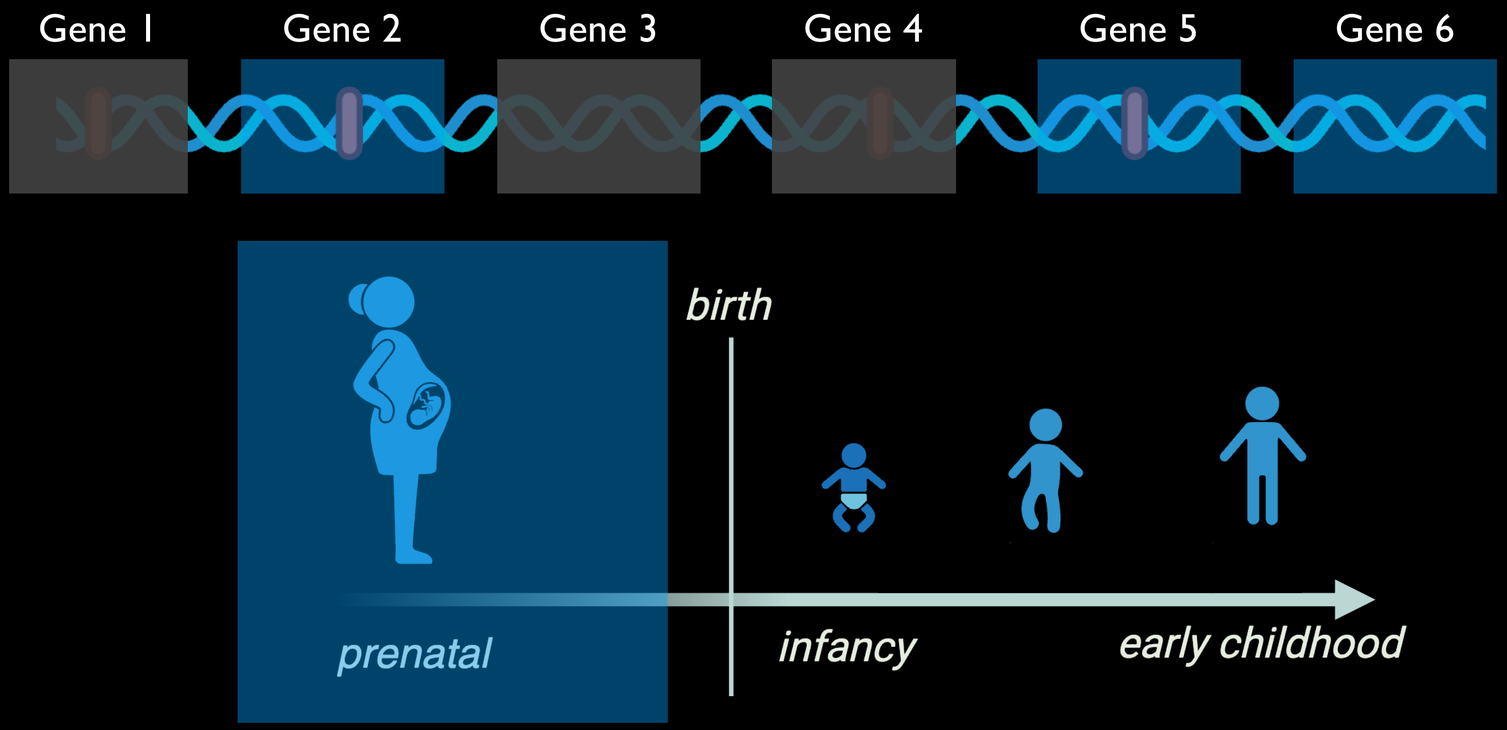

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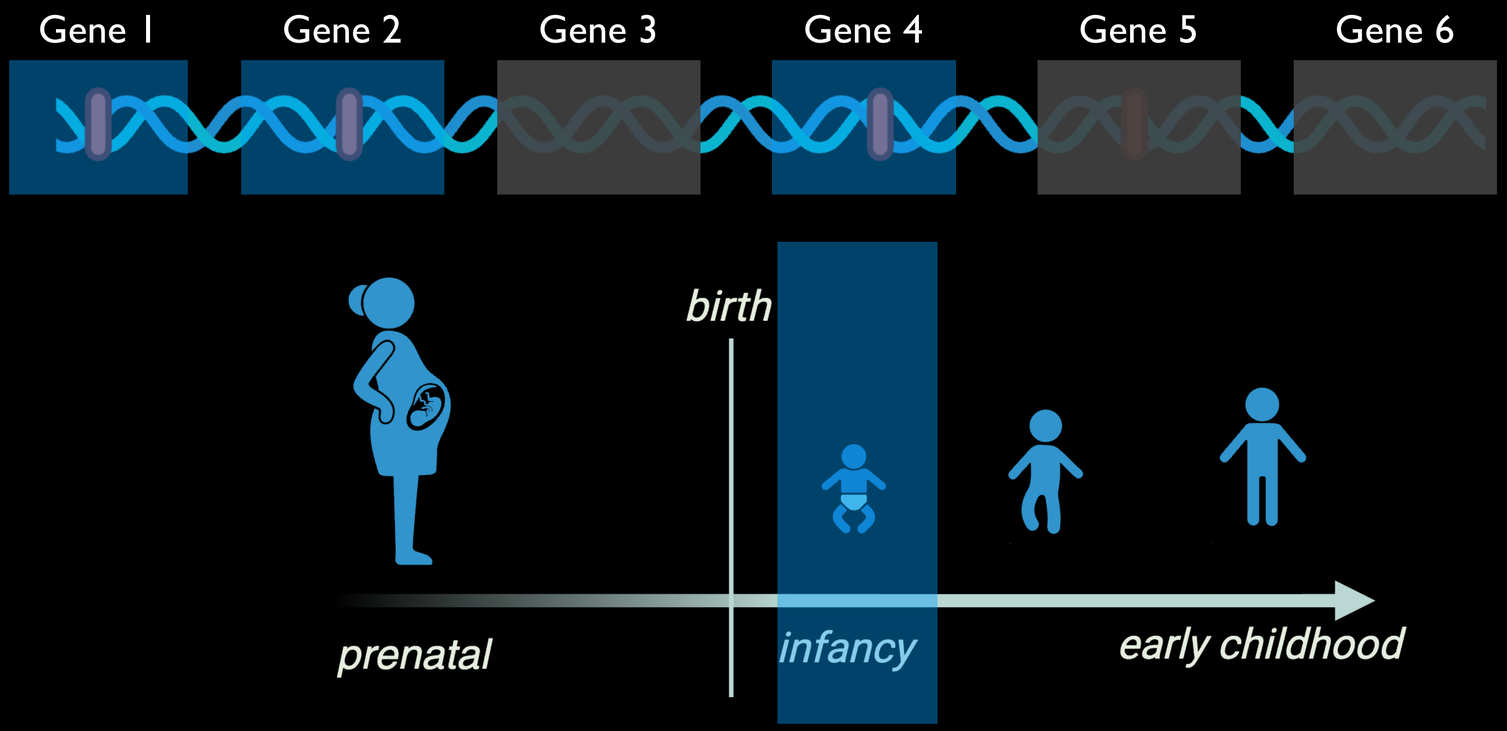

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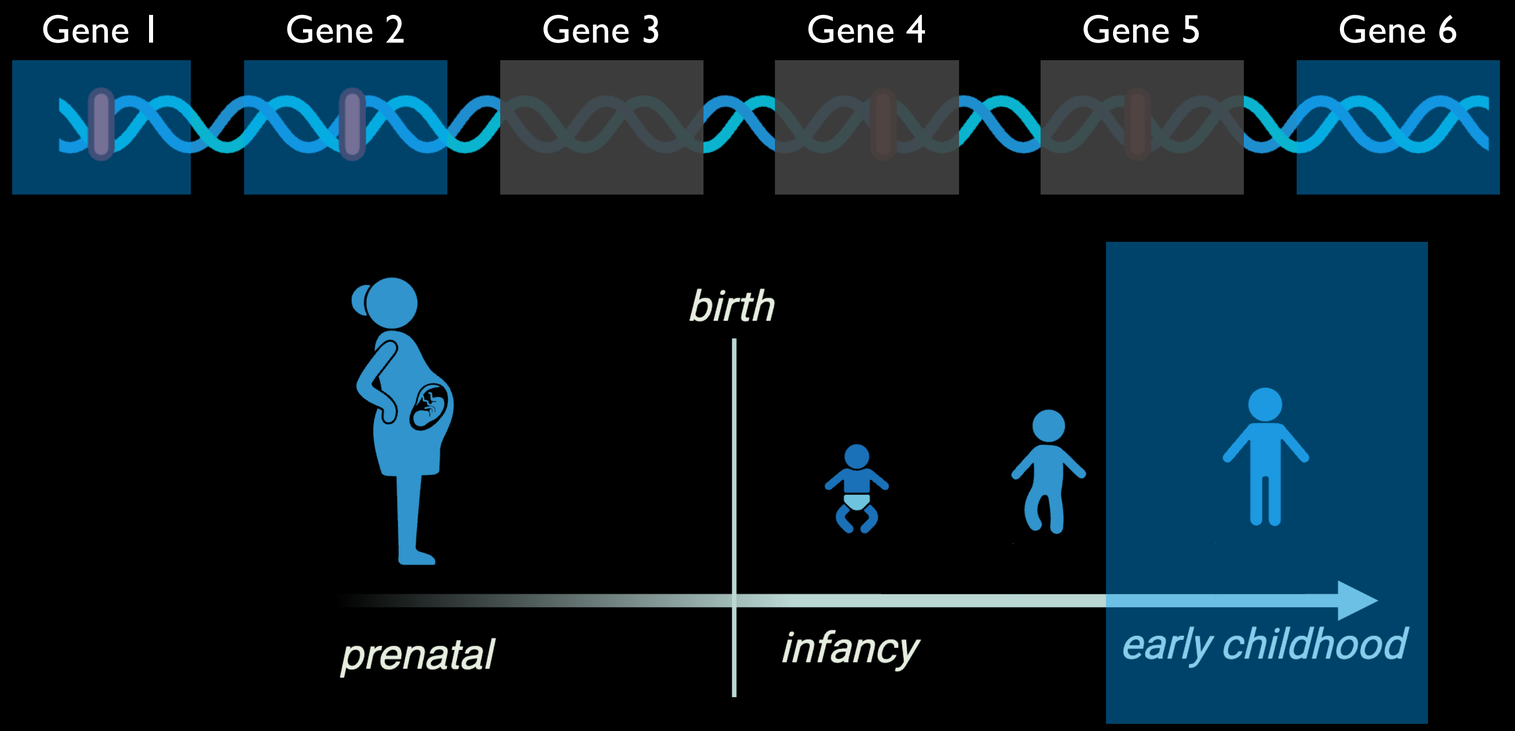

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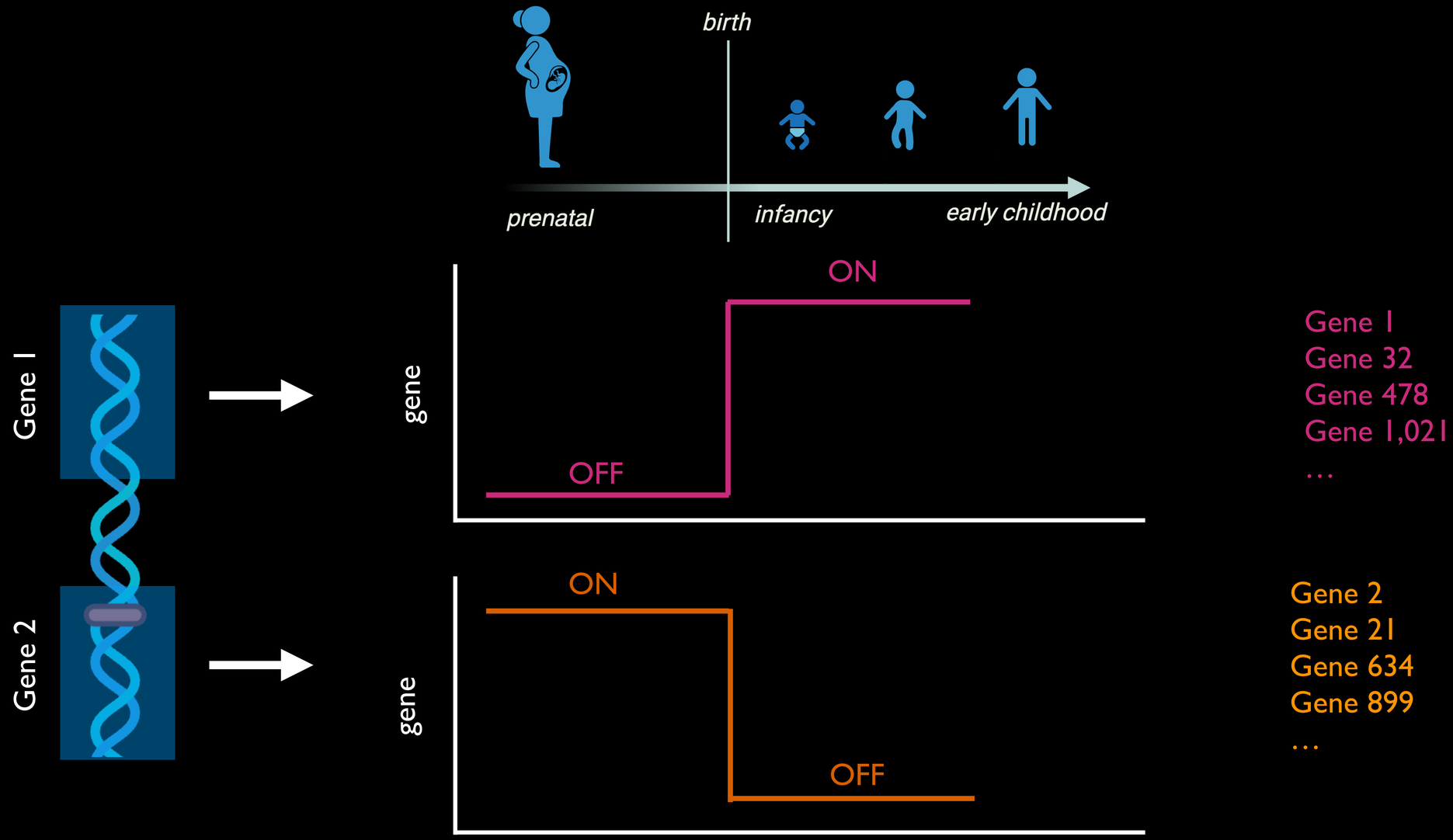
Developmental timing gene sets

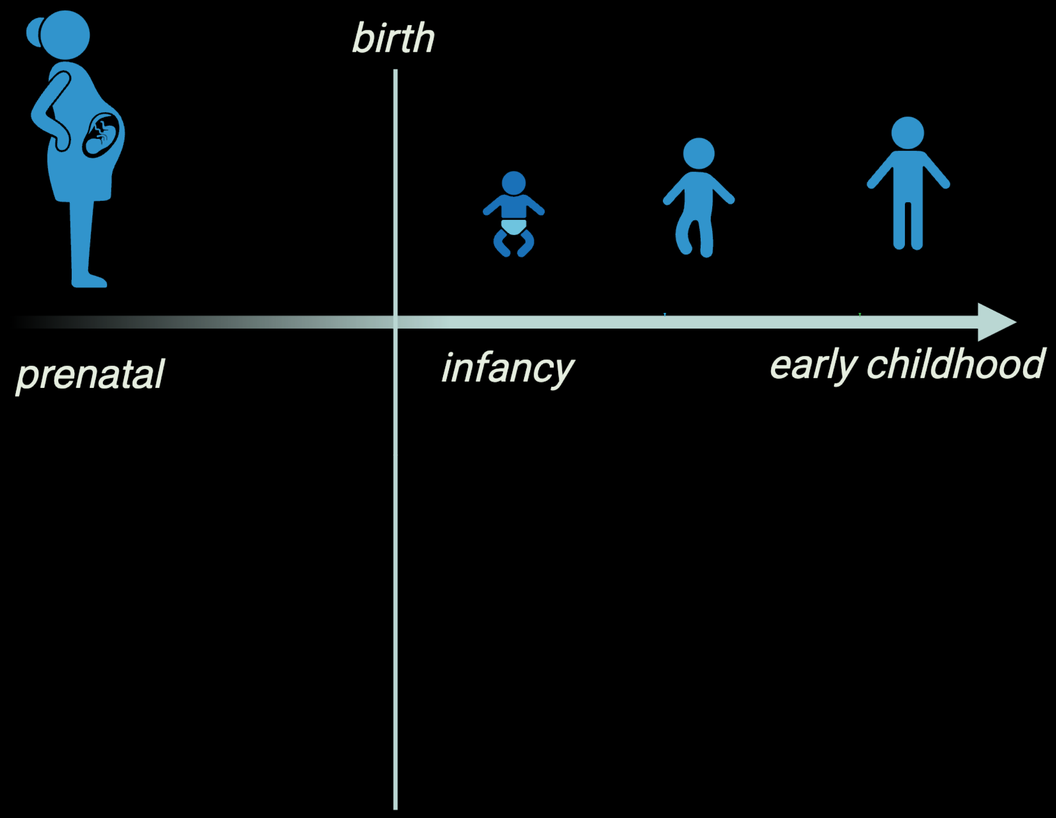


Gene 1
Gene 32
Gene 478
Gene 1,021
…

Gene 2
Gene 21
Gene 634
Gene 899
…

Data from Herring et al., "Human prefrontal cortex gene regulatory dynamics from gestation to adulthood at single-cell resolution", *Cell*, 2022

Groups show different patterns of disruption in developmental timing genes



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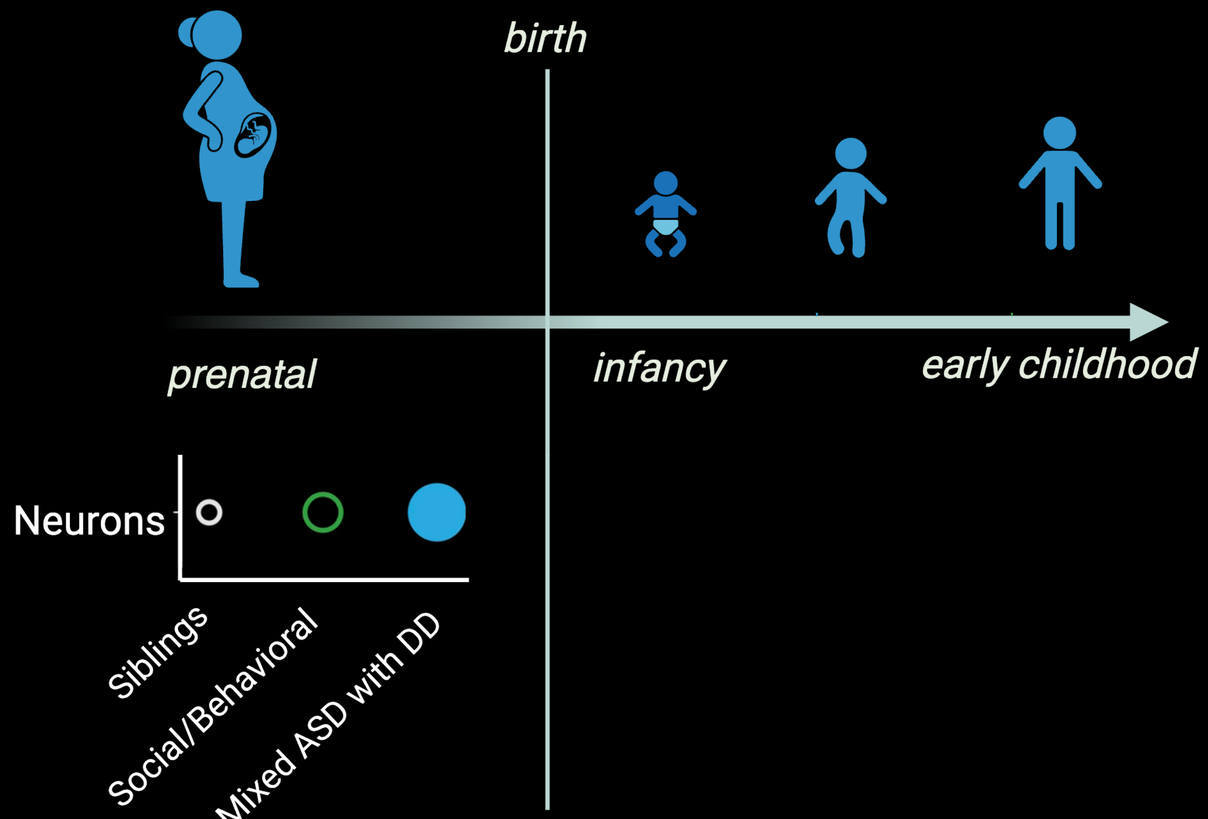
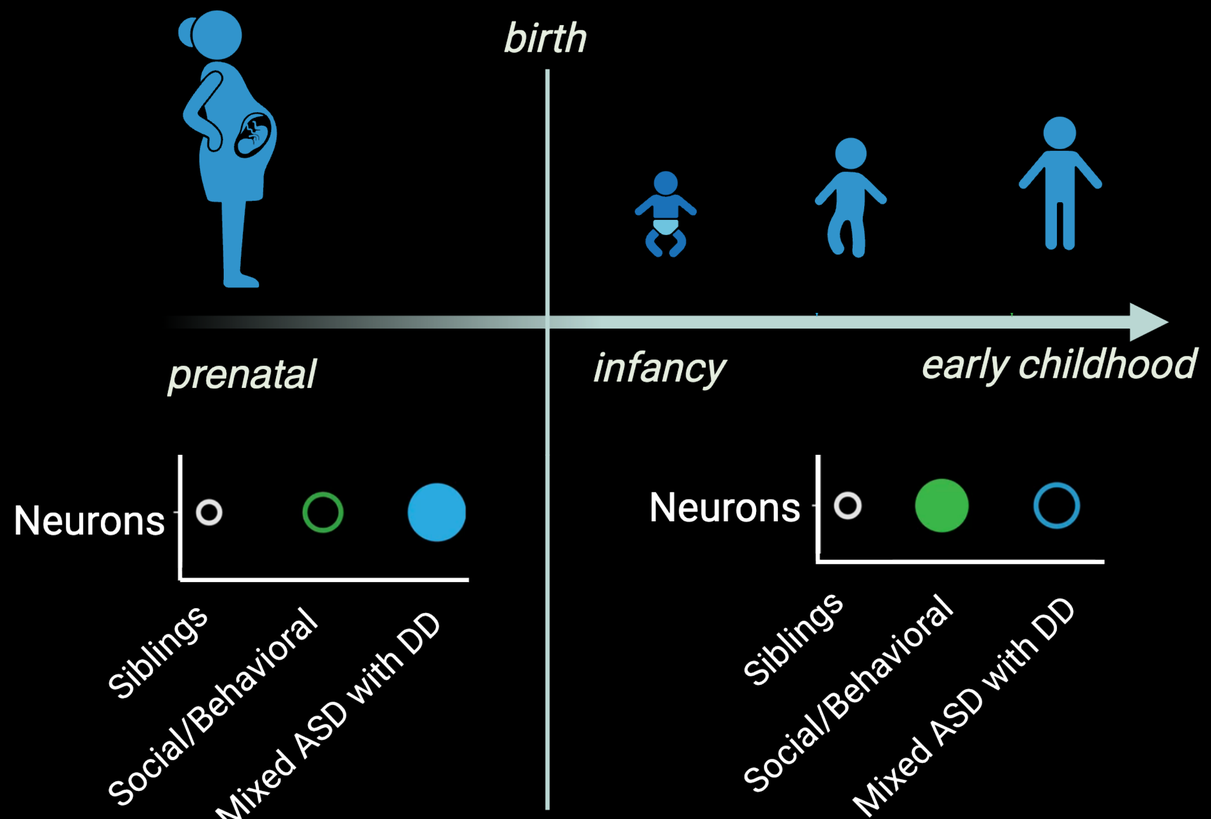


significant genetic disruption

no significant genetic disruption

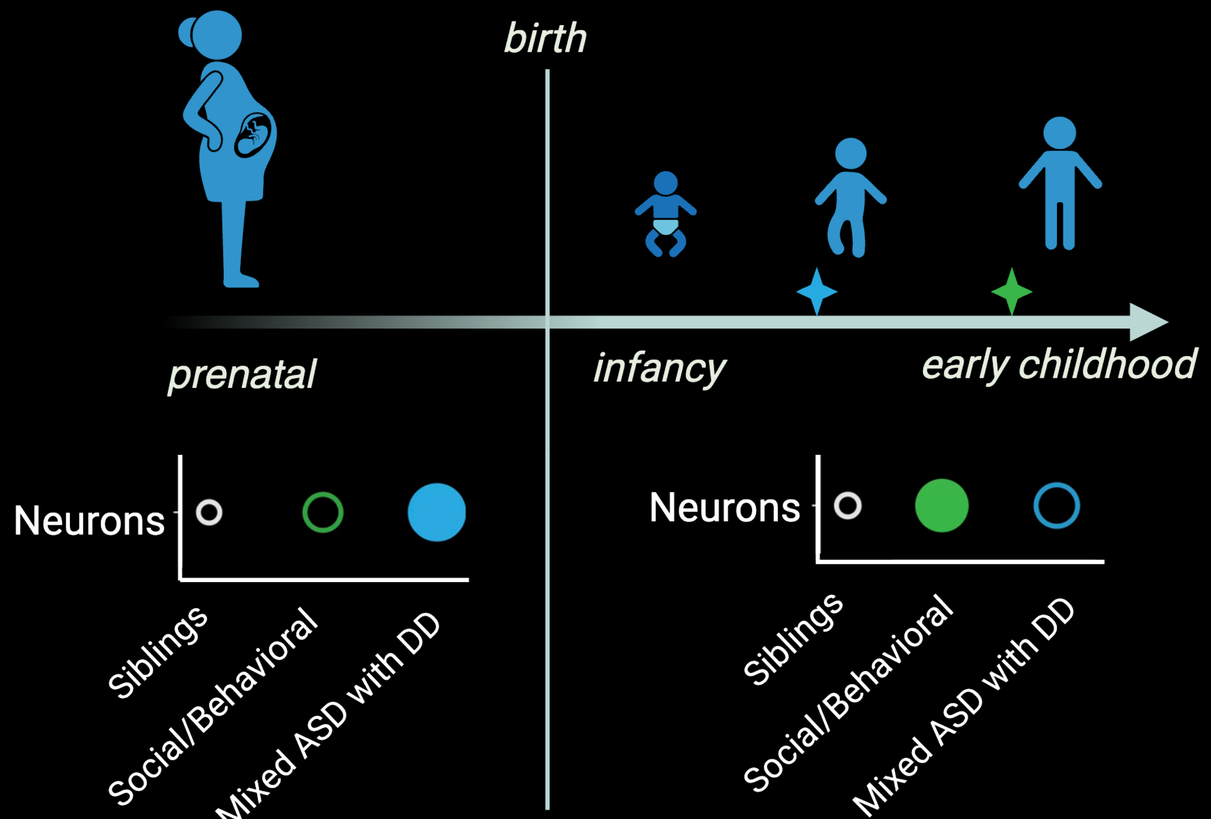
Groups show different patterns of disruption in developmental timing genes



significant genetic disruption

no significant genetic disruption

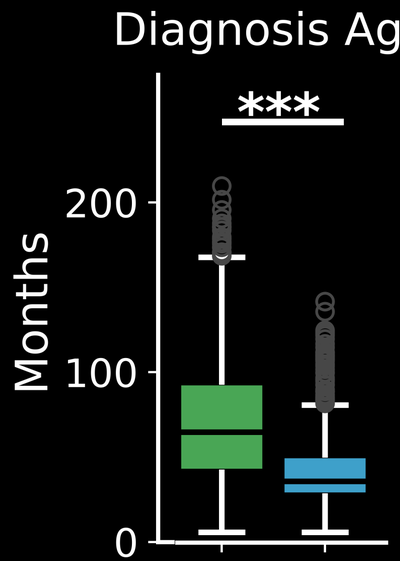
Developmental gene patterns match up with developmental milestones

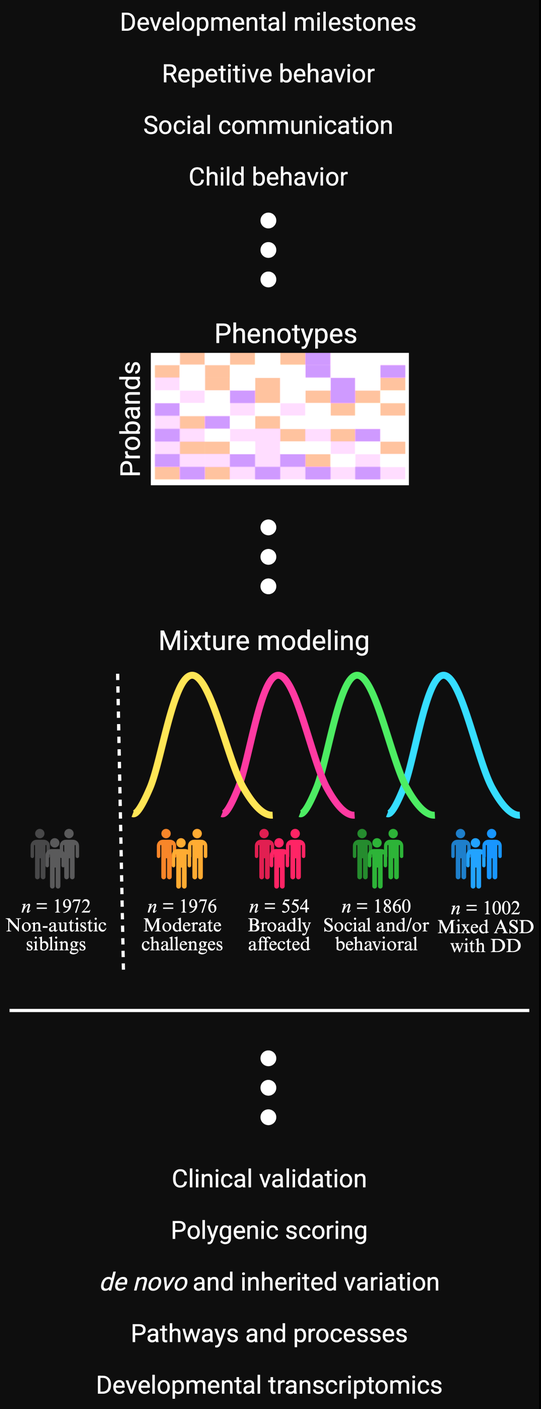


significant genetic disruption

no significant genetic disruption

average age of diagnosis





Conclusions

- A person-centered framework allows us to associate complex trait profiles with underlying genetics
- Maybe one of the reasons we have struggled to find genetic patterns across autistic individuals is that we were grouping everyone together
- There are underlying differences in how the brain develops that may affect how different individuals with the same diagnosis of autism see and experience the world
- We see genetically grounded differences that align with complex phenotypic profiles

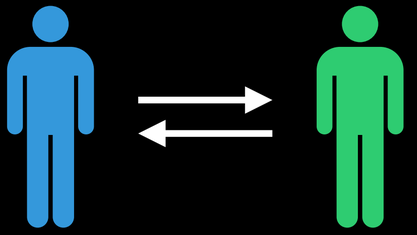
Important topics this study *doesn't* answer

- These are **not** clinically validated subtypes - your doctor cannot give you a formal diagnosis according to these groups

- How do these groups relate to adults with autism?

- Are there exactly four groups across the whole autistic population? Could there be more than four?

- Could these change over time? Could people "switch" classes?



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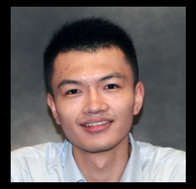
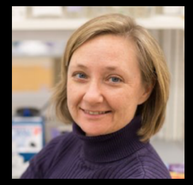

Yun Hao
Flatiron Institute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Decomposition of phenotypic heterogeneity in autism reveals underlying genetic programs

Aviya Litman, Natalie Sauerwald ✉, LeeAnne Green Snyder, Jennifer Foss-Feig, Christopher Y. Park, Yun Hao, Ilan Dinstein, Chandra L. Theesfeld & Olga G. Troyanskaya ✉

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