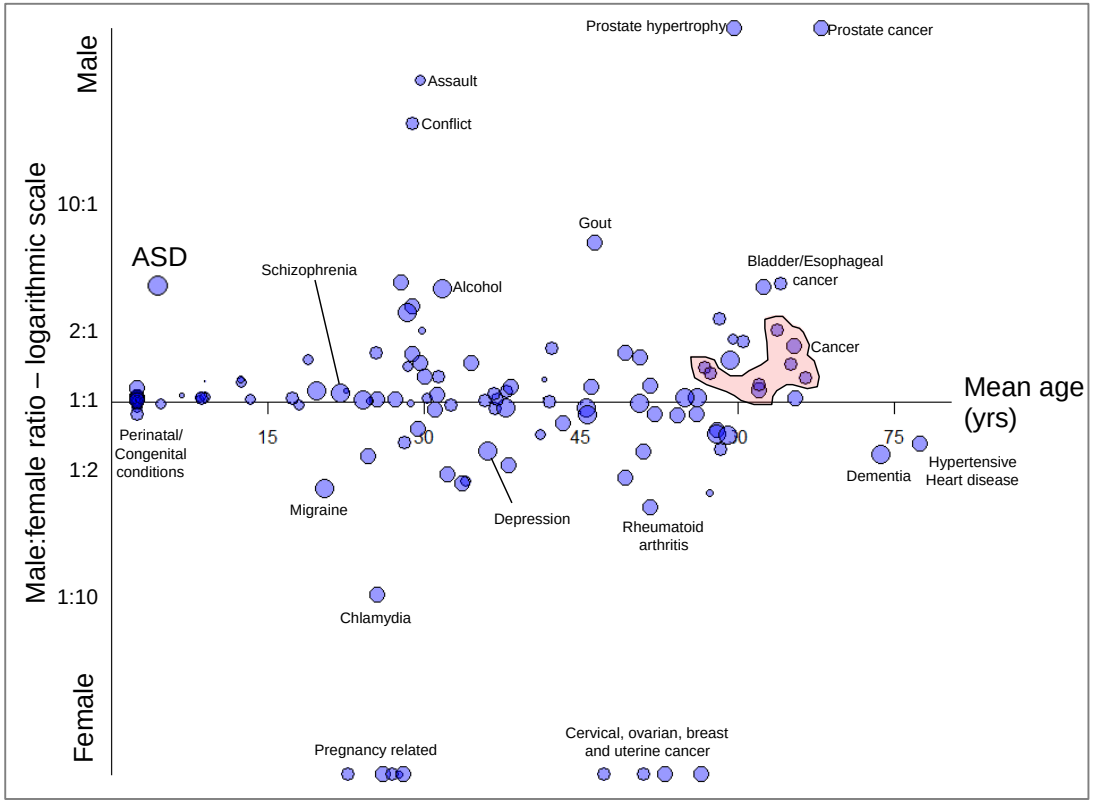
The role of genetics and sex-differential biology in risk for autism

Donna Werling, PhD
Sanders & State Labs, UCSF
October 26, 2016

Autism prevalence is sex-biased

- ~4:1 males:females have a diagnosis of autism spectrum disorder (ASD)



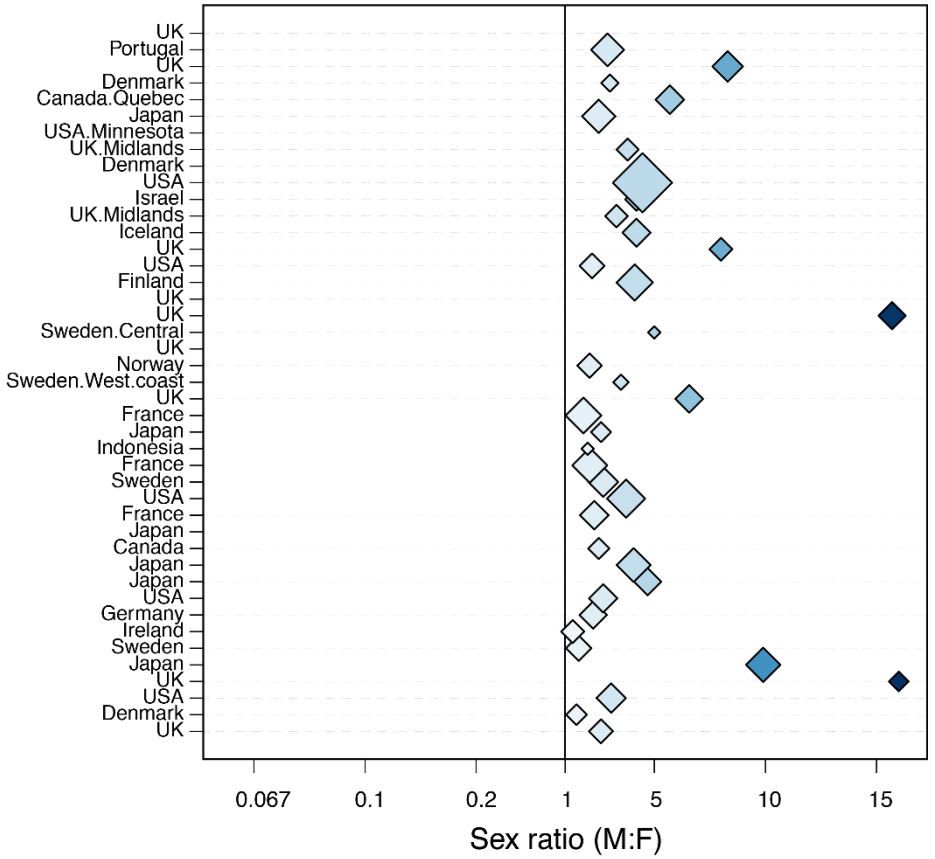
World Health Organization, The global burden of disease: 2004 update (2004).

Autism prevalence is sex-biased

- ~4:1 males:females have a diagnosis of autism spectrum disorder (ASD)[1]

- 8 males and 3 females in the 11 cases originally reported by Leo Kanner, 1943[2]

- Male bias consistent over time and across countries[1]



[1]Fombonne, 2009, *Pediatr Res.* [2]Kanner, 1943, *Nervous Child.*

Why study sex bias in ASD from a biological perspective?

Sex appears to be a potent modulator of ASD risk

Males: 1 in 42 diagnosed

Females: 1 in 189 diagnosed

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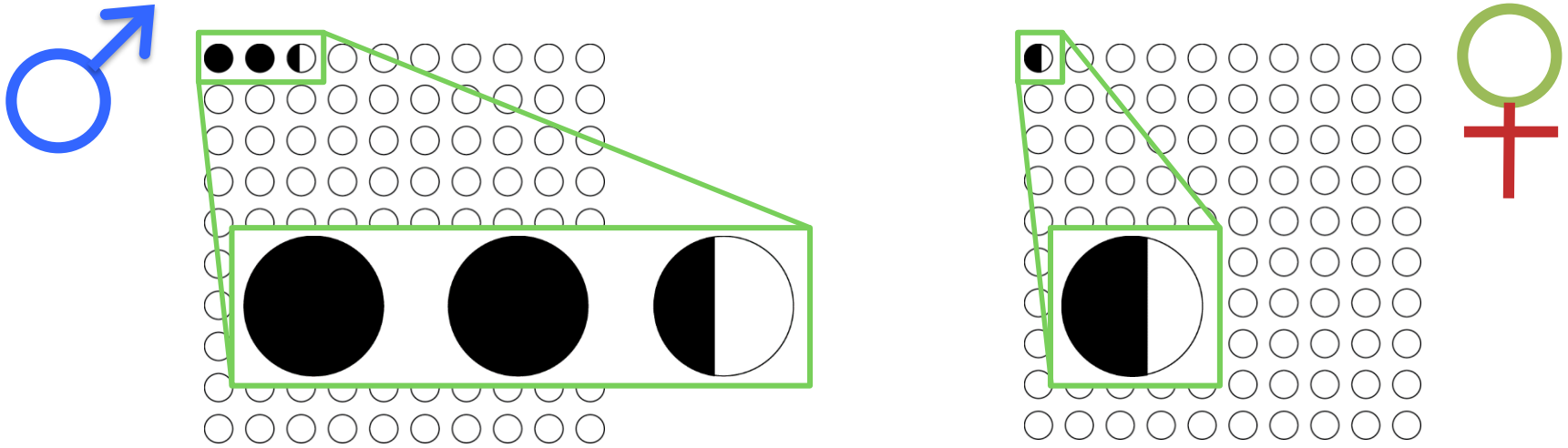

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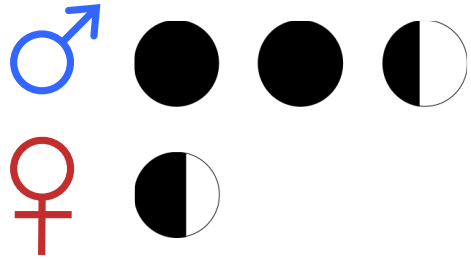
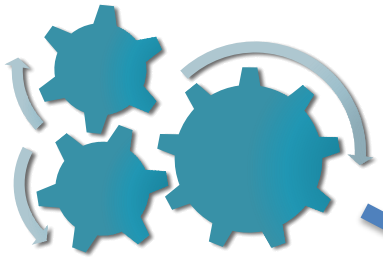
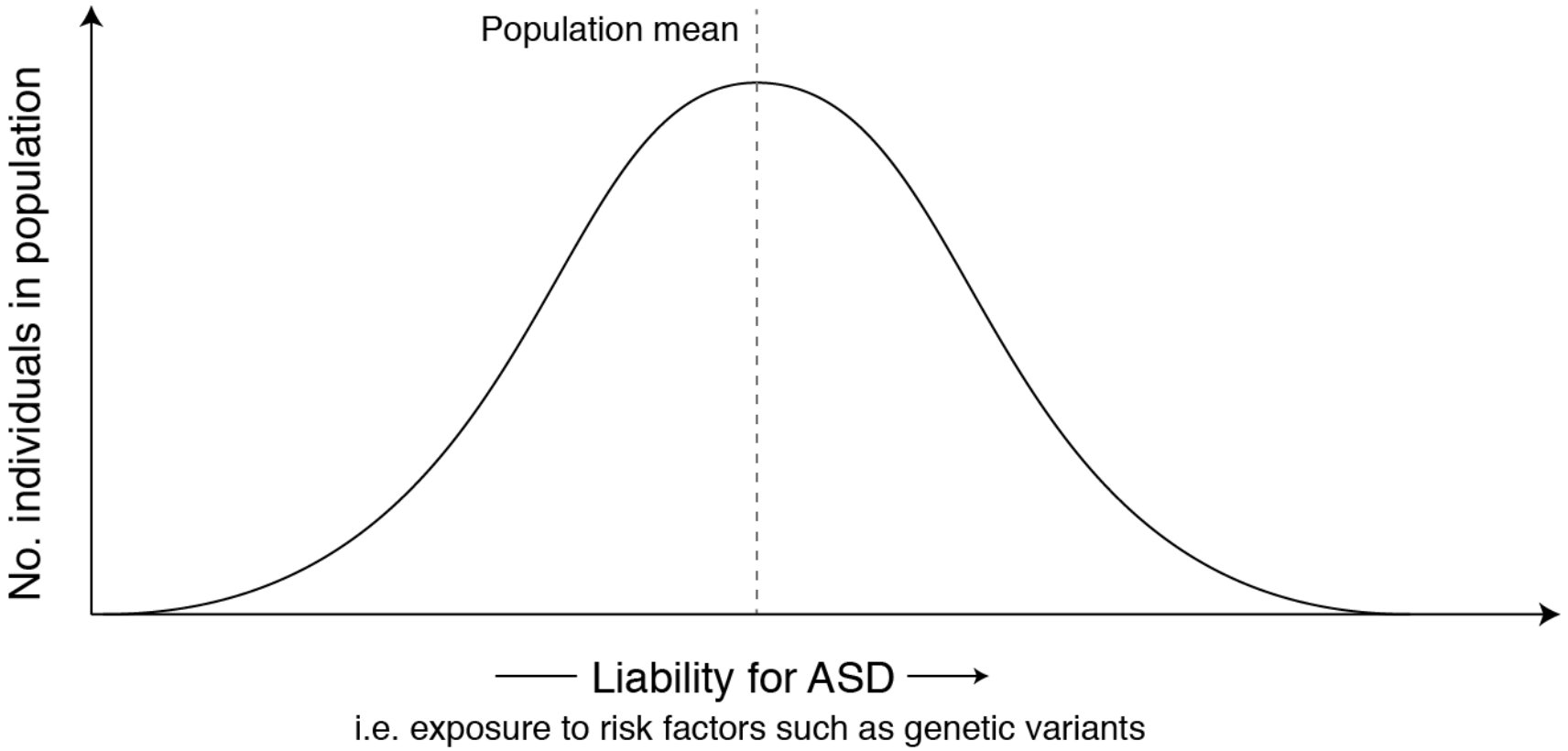




Treatment development

Novel/key insights into **fundamental biology of ASD**

Female Protective Effect (FPE) Model for ASD = Liability model



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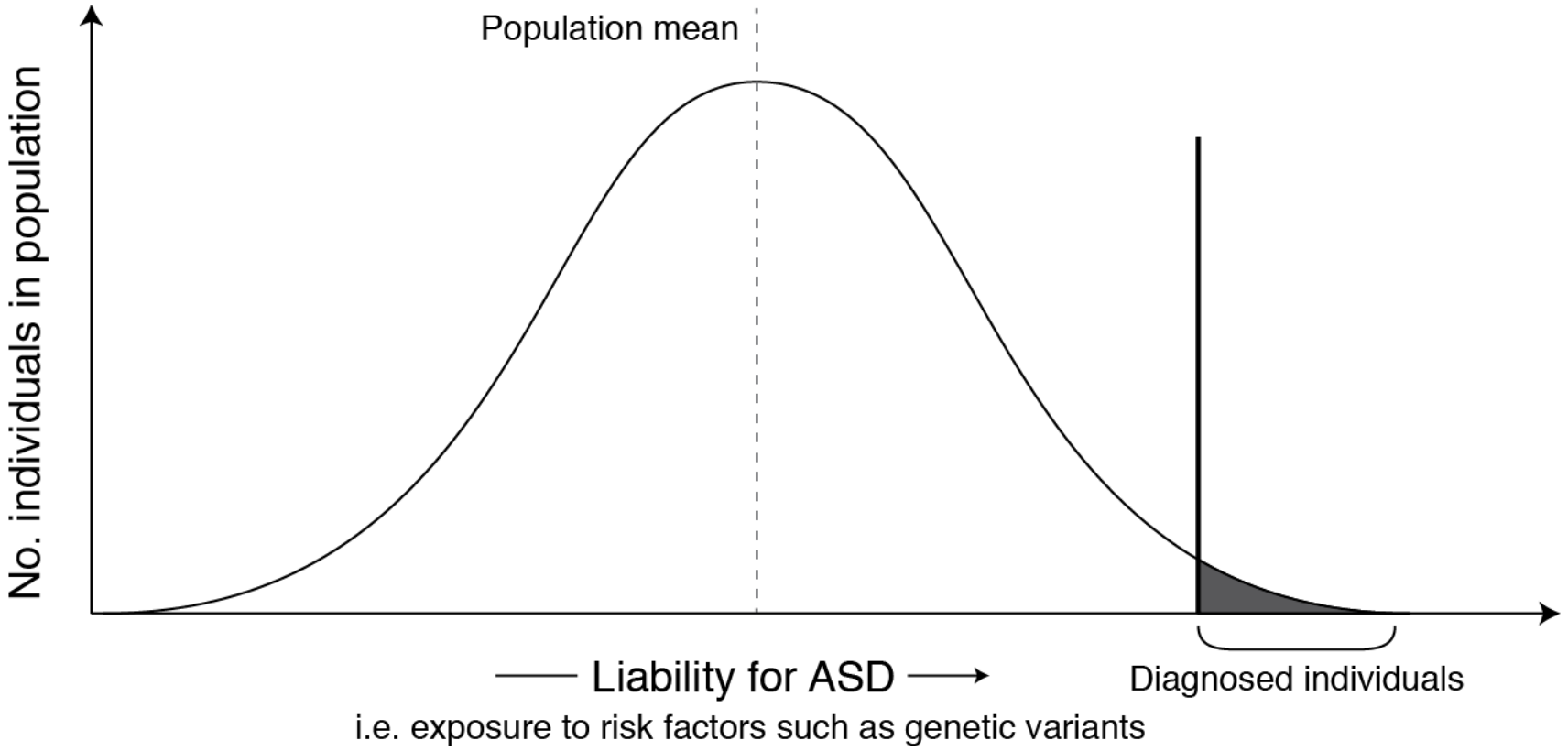

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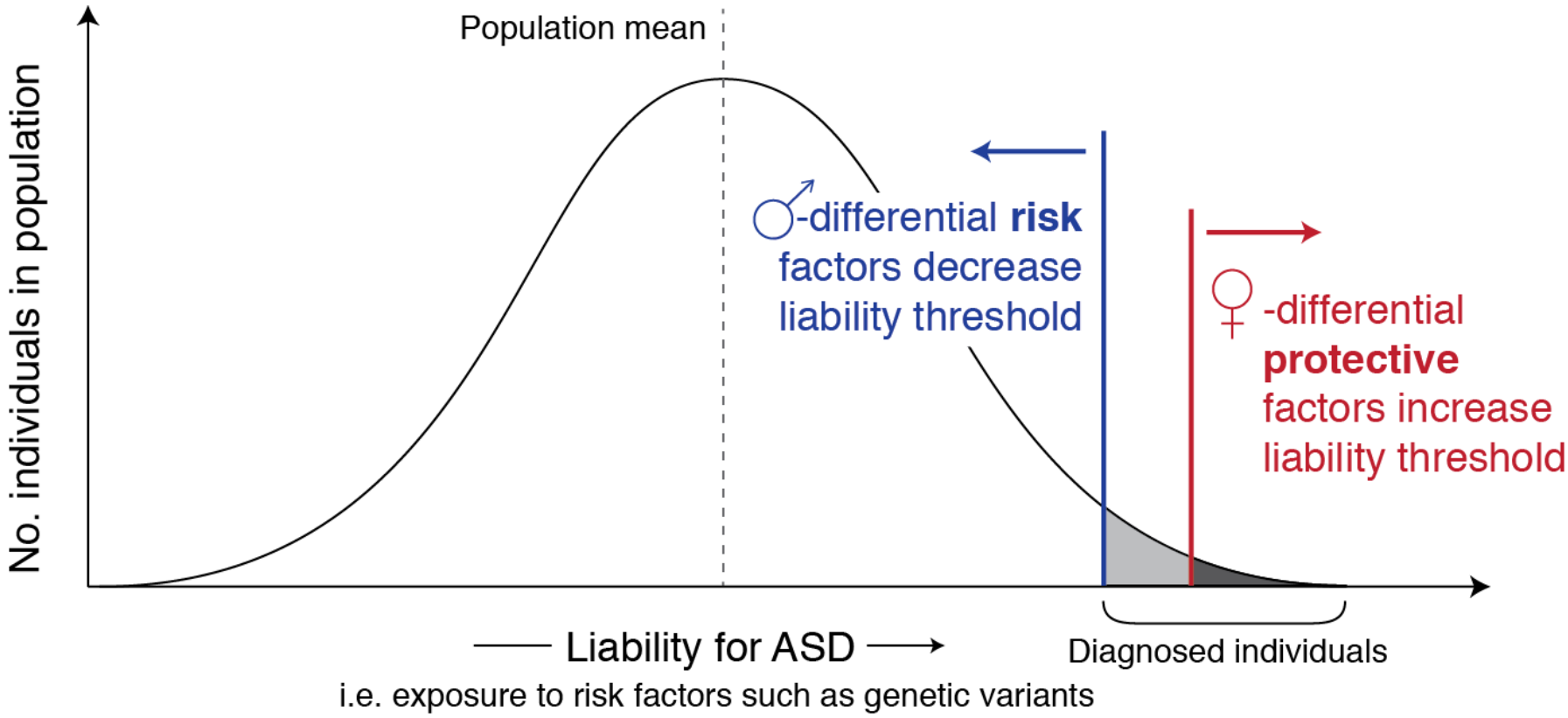

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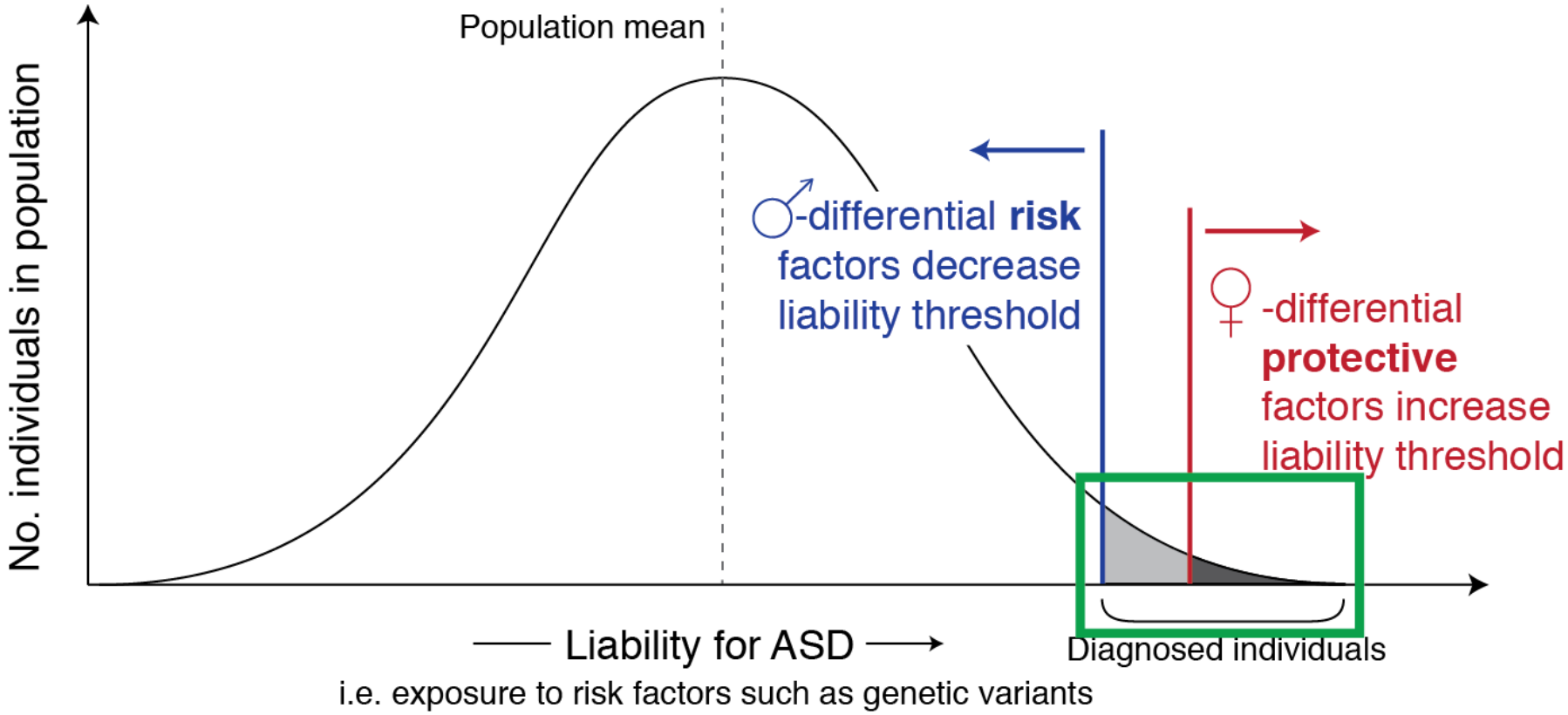
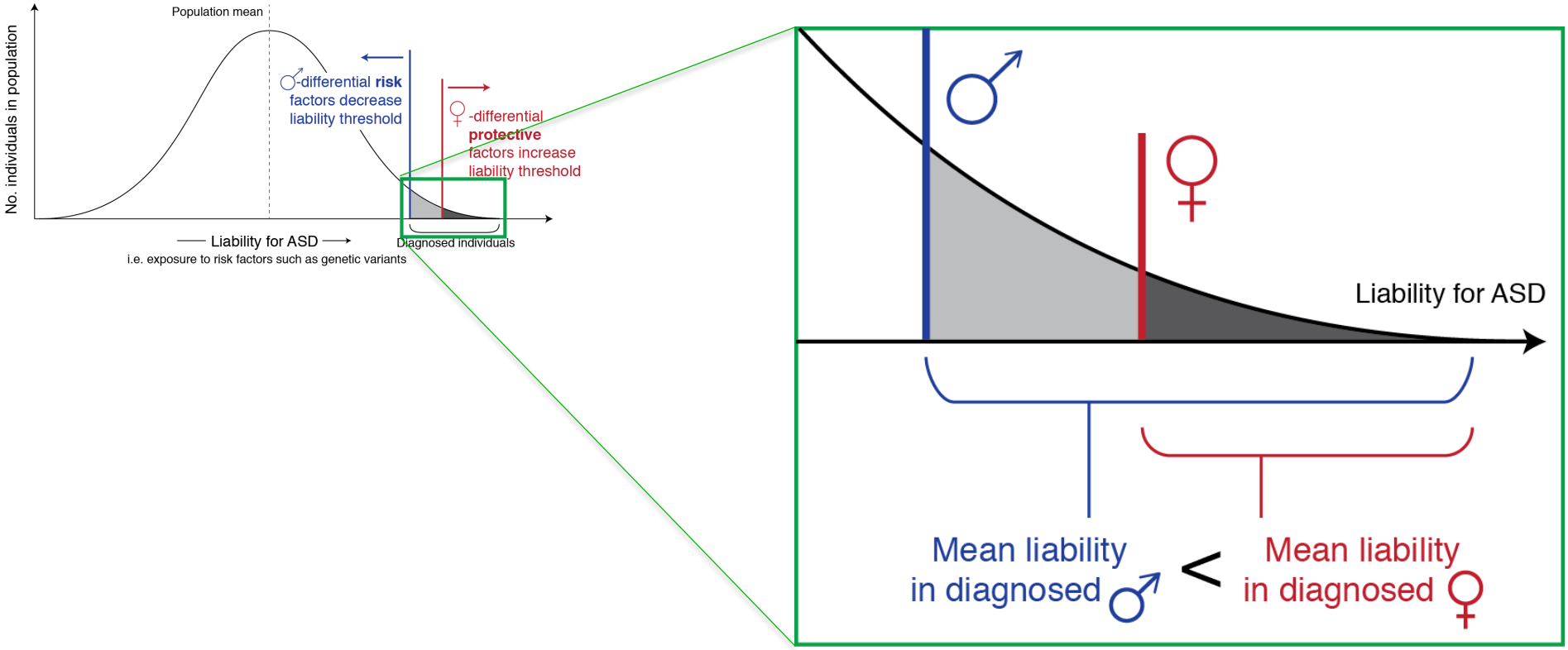


FPE model predicts that diagnosed females carry greater risk than males



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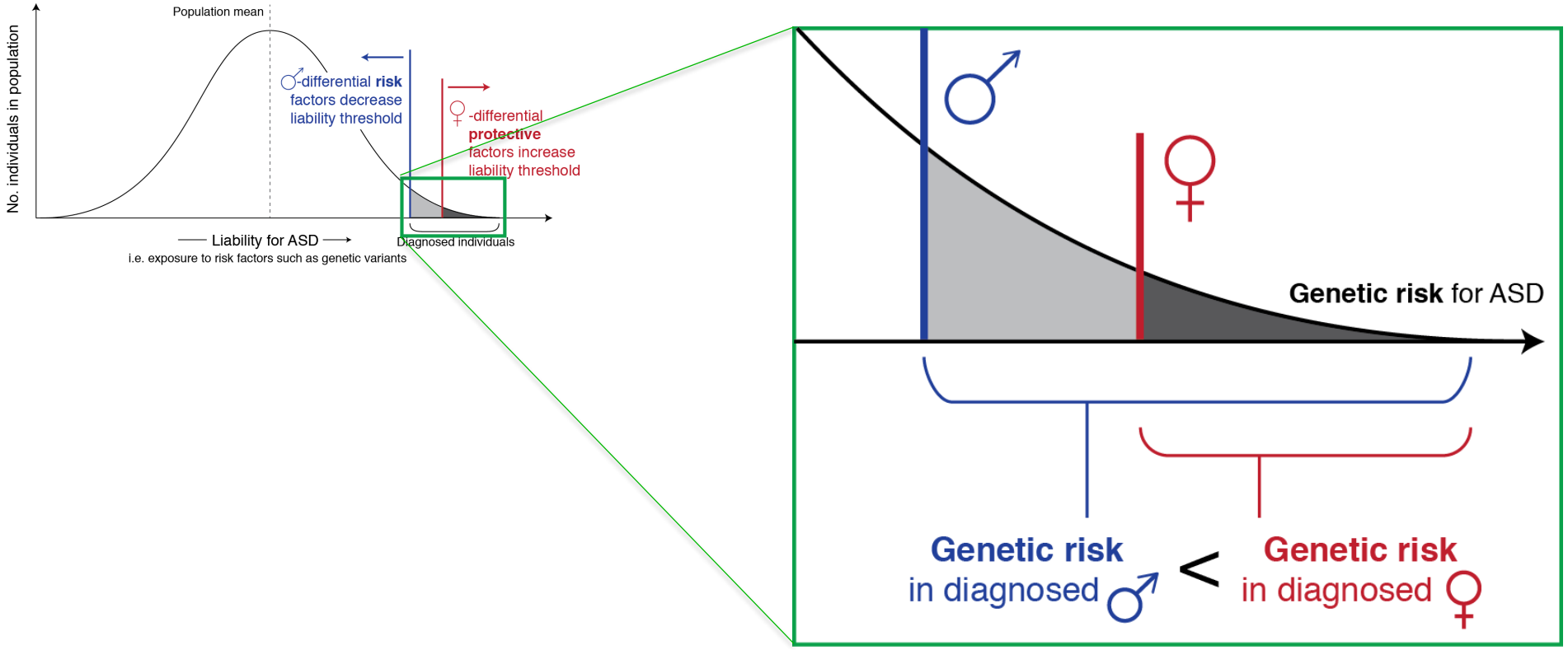

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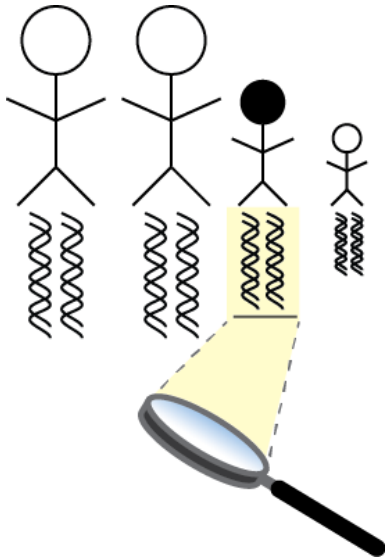

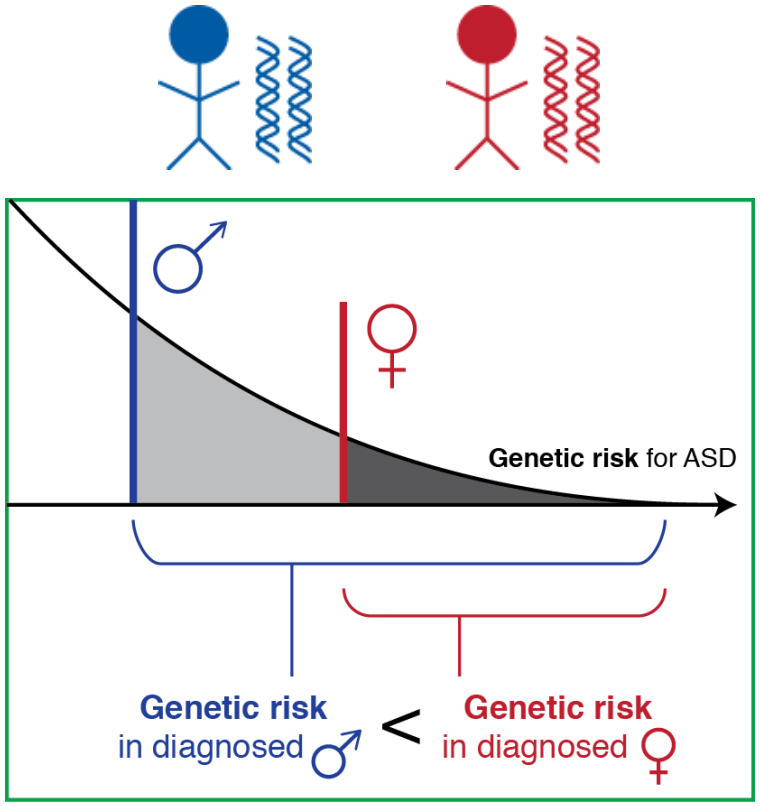

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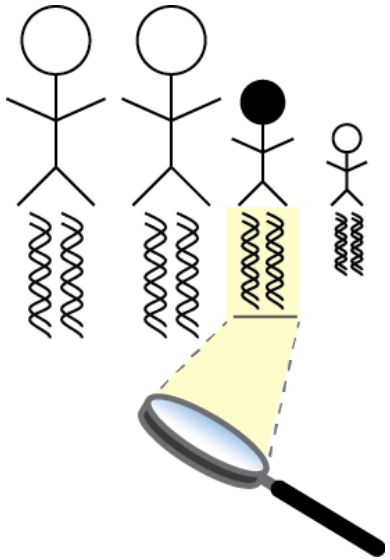

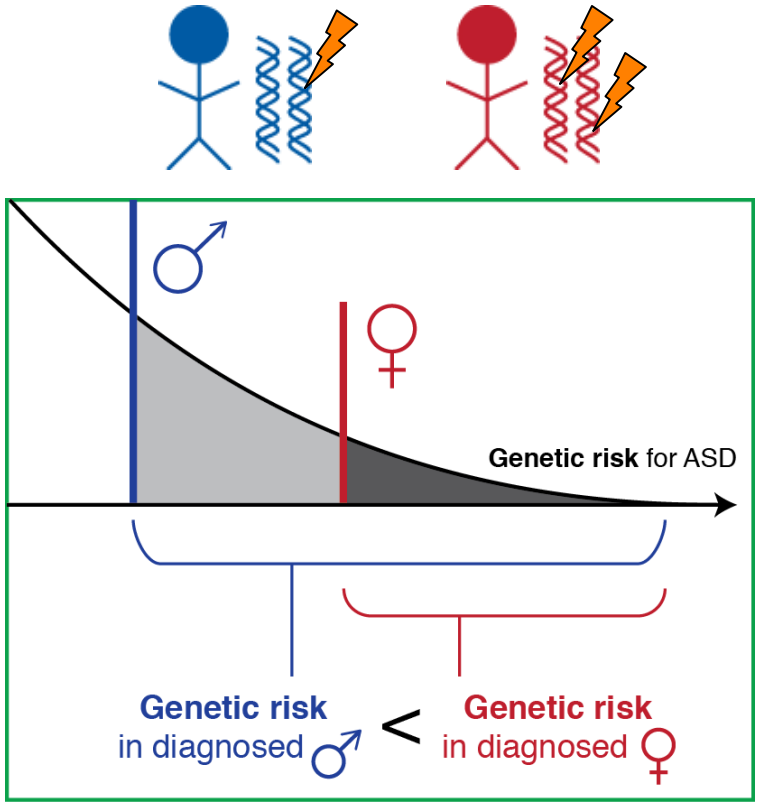

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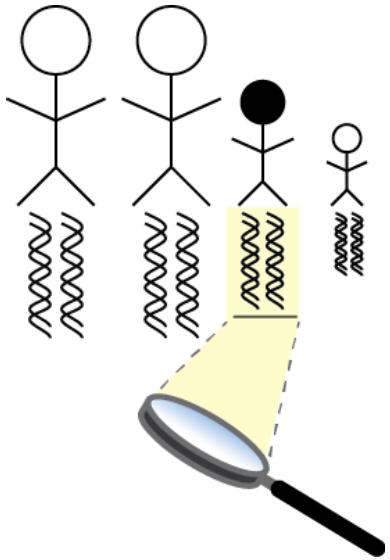
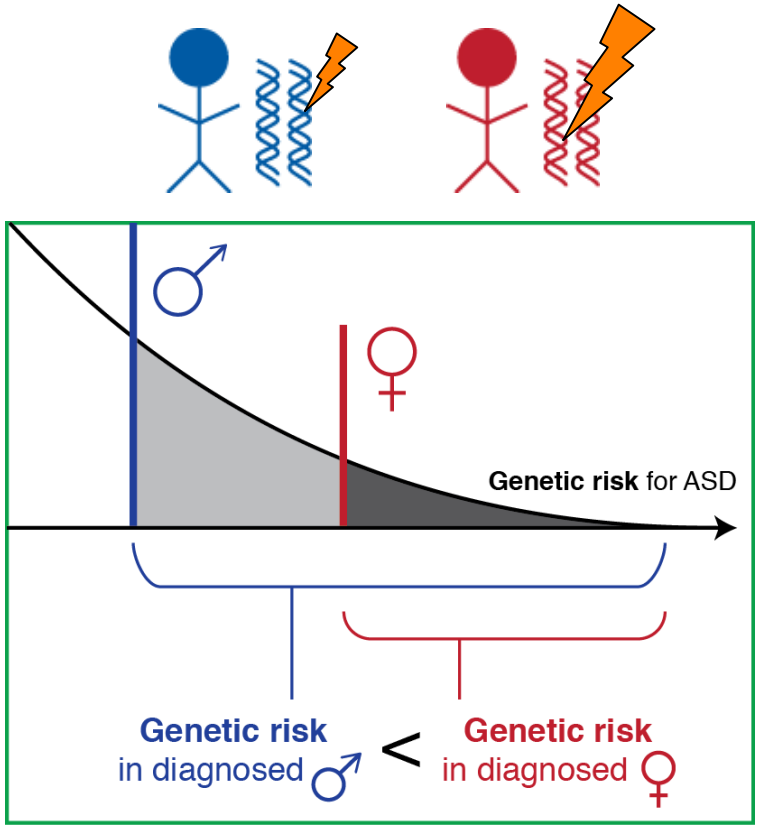
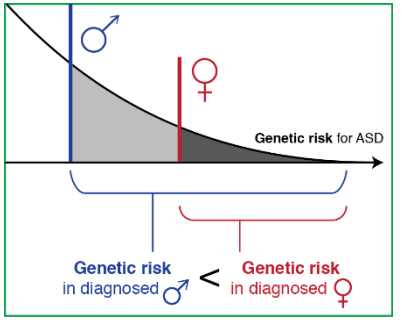
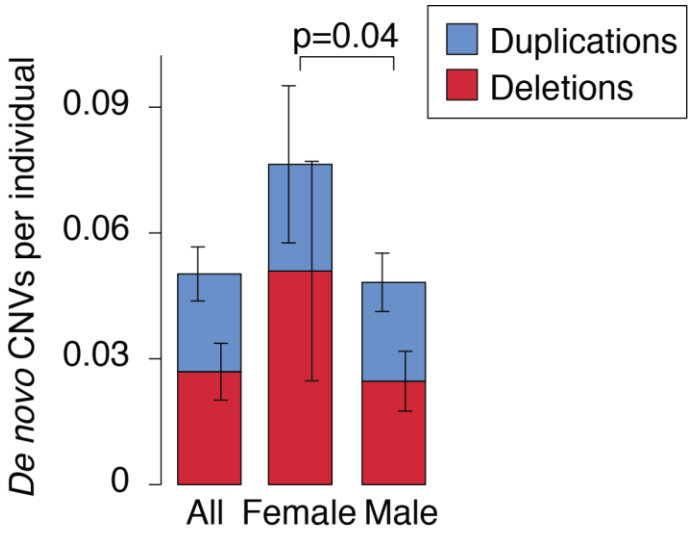




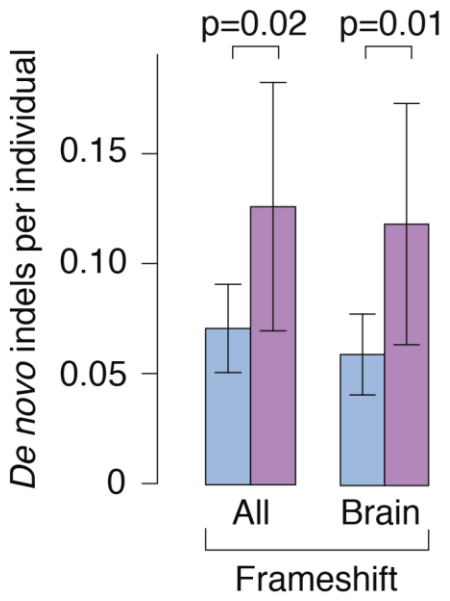
Higher incidence of disruptive, *de novo* variants in ASD females



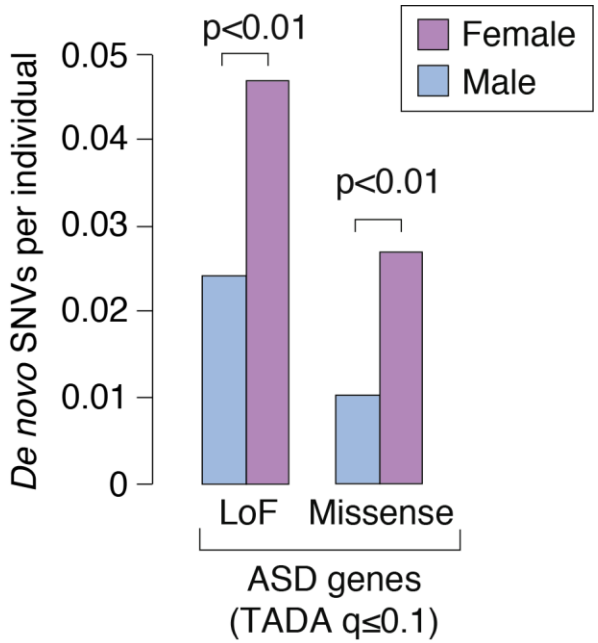
Copy number variants (CNVs)[1]



Insertion/Deletions (Indels)[2]

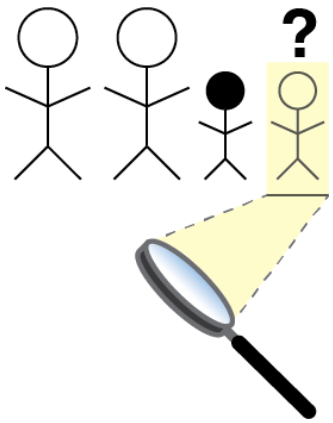


Single nucleotide variants (SNVs)[3]

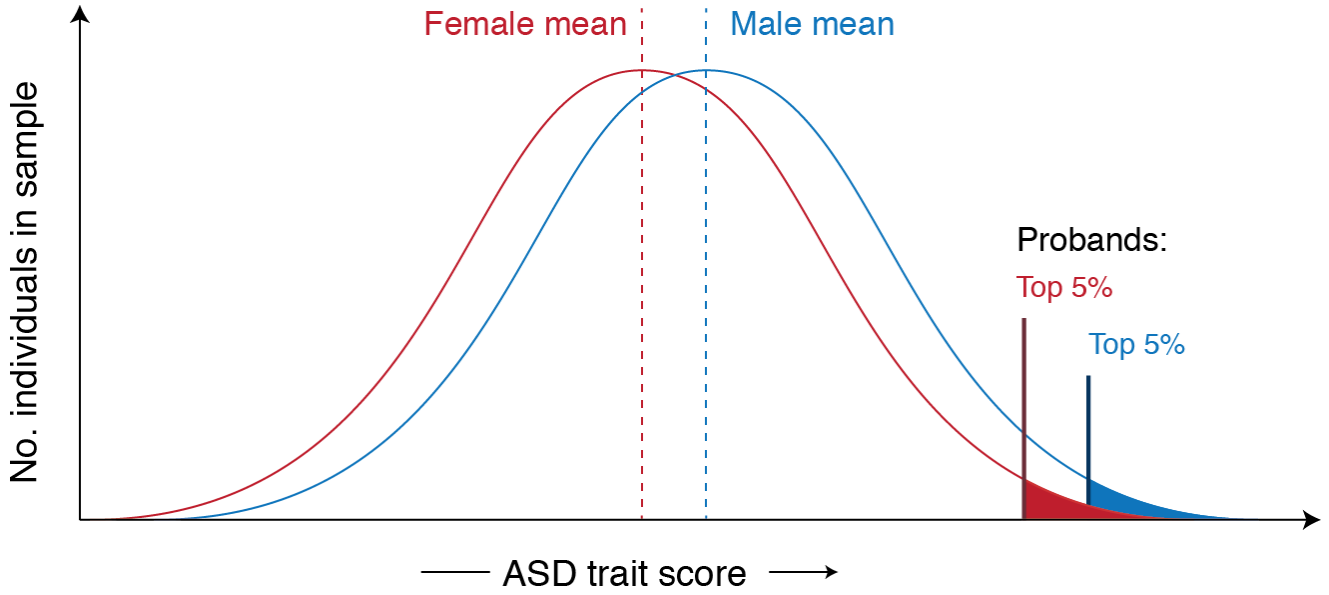


[1]Sanders et al, 2015, *Neuron.* [2]Dong et al, 2014, *Cell Rep.* [3]De Rubeis et al, 2014, *Nature.*

Siblings of female cases have higher ASD traits than siblings of male cases



Autistic traits in siblings?



Robinson et al, *PNAS*, 2013

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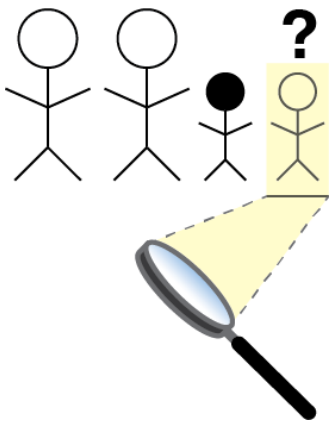

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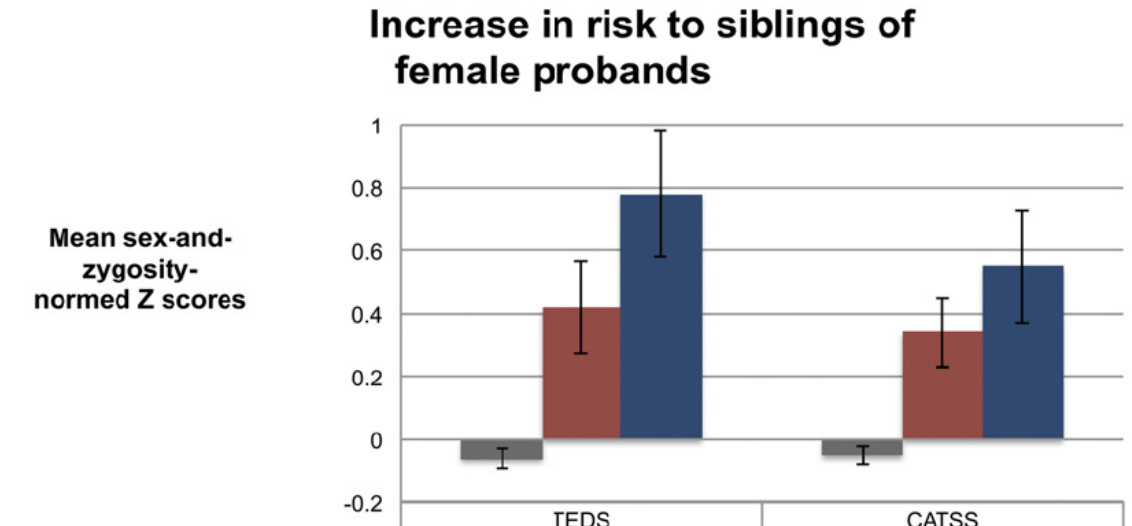
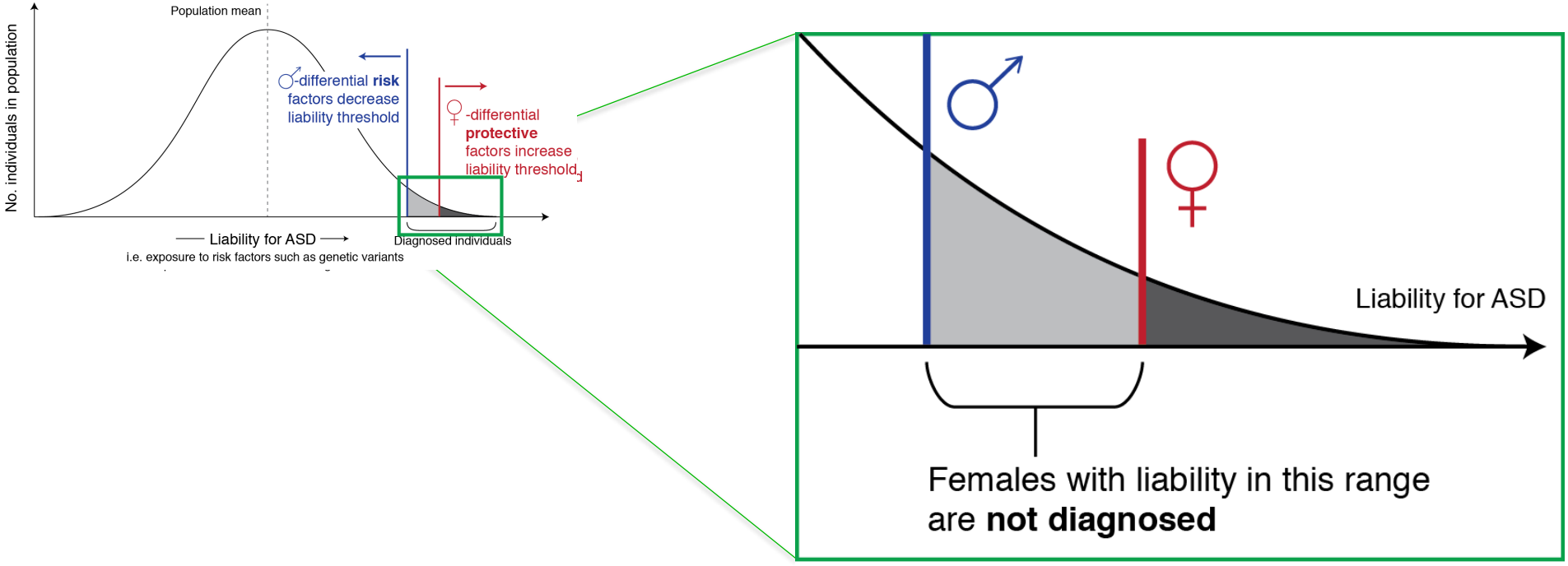


	TEDS	CATSS
Siblings of All Non-Probands N(TEDS) = 3,444 N(CATSS) = 5,340	-0.06 (p<0.0001 *§)	-0.05 (p<0.0001 *§)
Siblings of Male Probands N(TEDS) = 262 N(CATSS) = 470	0.42 (p=0.002 §)	0.34 (p=0.02 §)
Siblings of Female Probands N(TEDS) = 136 N(CATSS) = 230	0.78	0.55

Robinson et al, *PNAS*, 2013

FPE model predicts that females respond differently to liability that is sufficient for diagnosis in males



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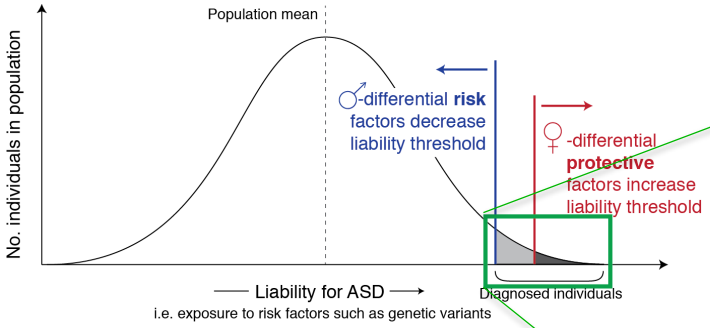

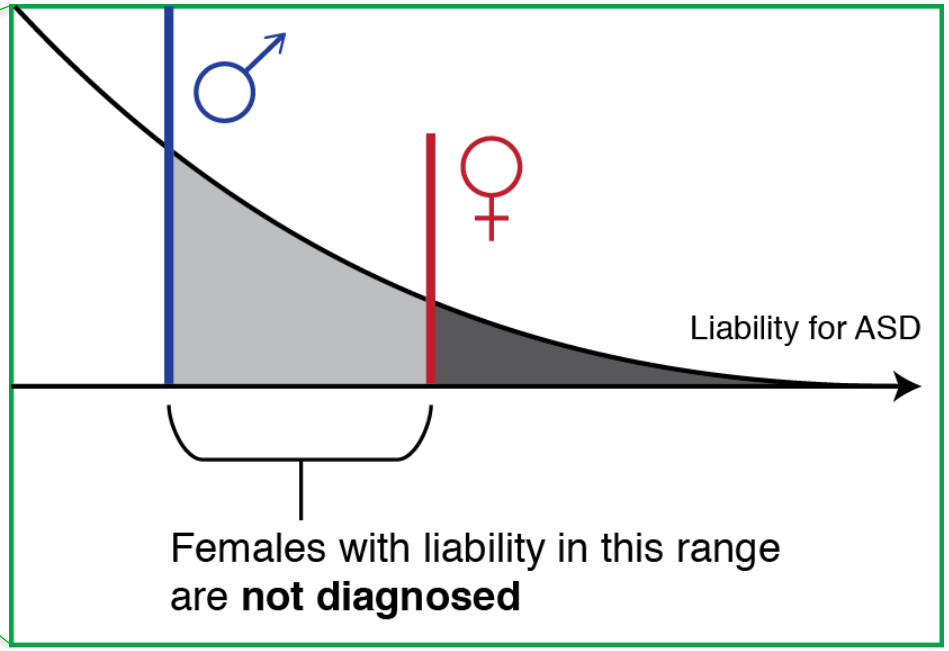

1. Quantitative:

   Females are protected and have neurotypical phenotype.

2. Qualitative:

   Females present symptoms differently than males, and are not diagnosed.

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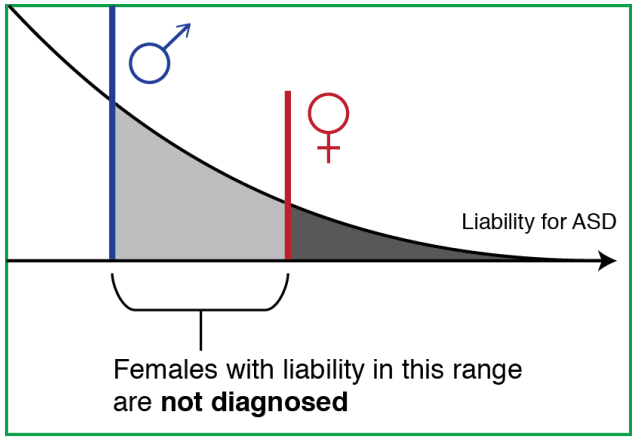

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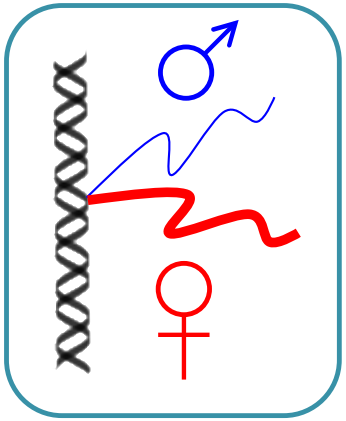
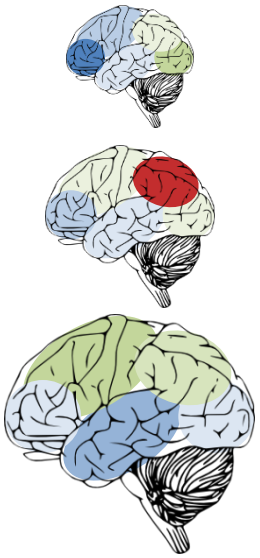
Hypothesis:

Sex-differential biology contributes to male and female differences in ASD risk and/or symptom presentation

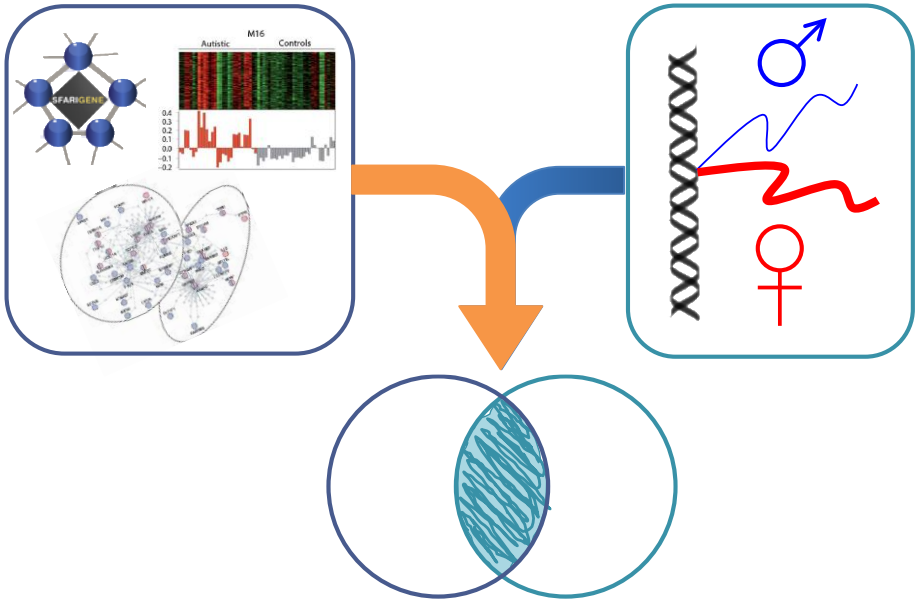
We can use gene expression analysis to identify sex differences that contribute to the FPE

1. Identify genes with sex-differential expression levels in the human brain





2. Characterize the relationship between sex-DEX genes and ASD biology



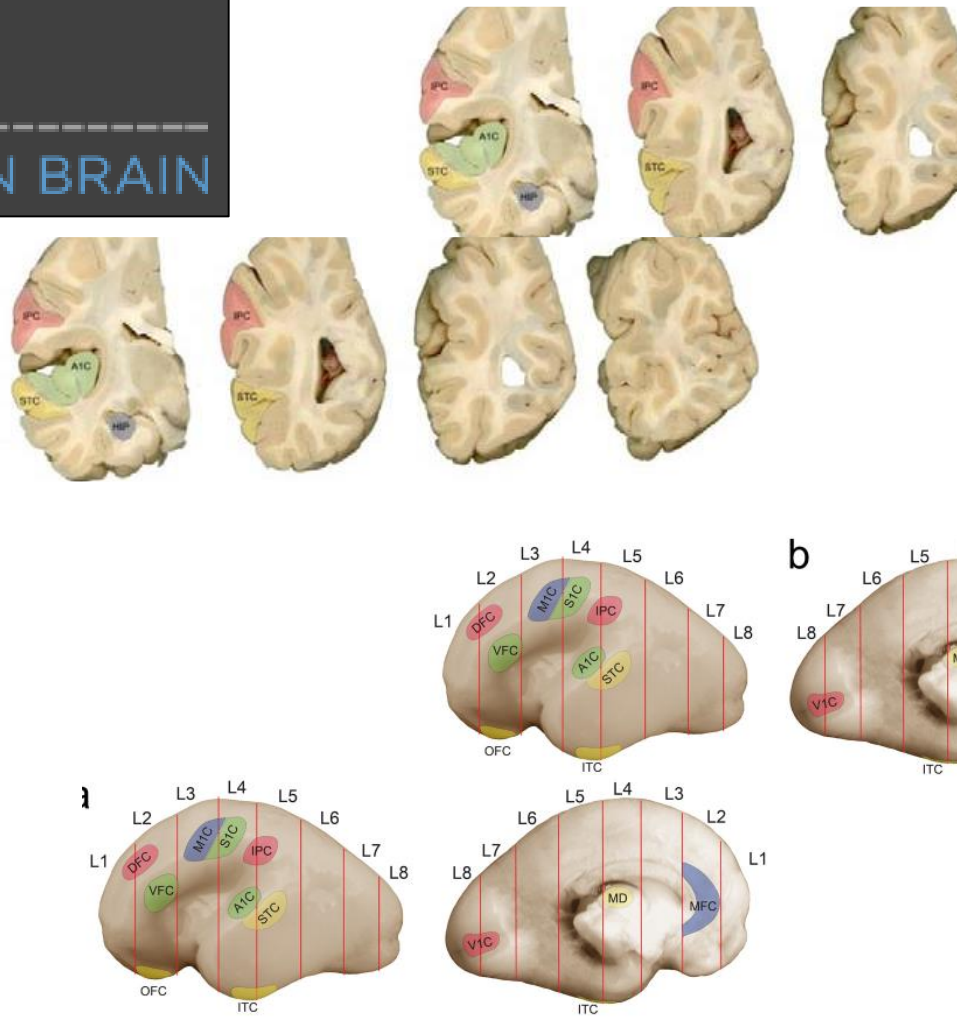
BRAINSPAN

ATLAS OF THE DEVELOPING HUMAN BRAIN

Table 1 | Periods of human development and adulthood as defined in this study

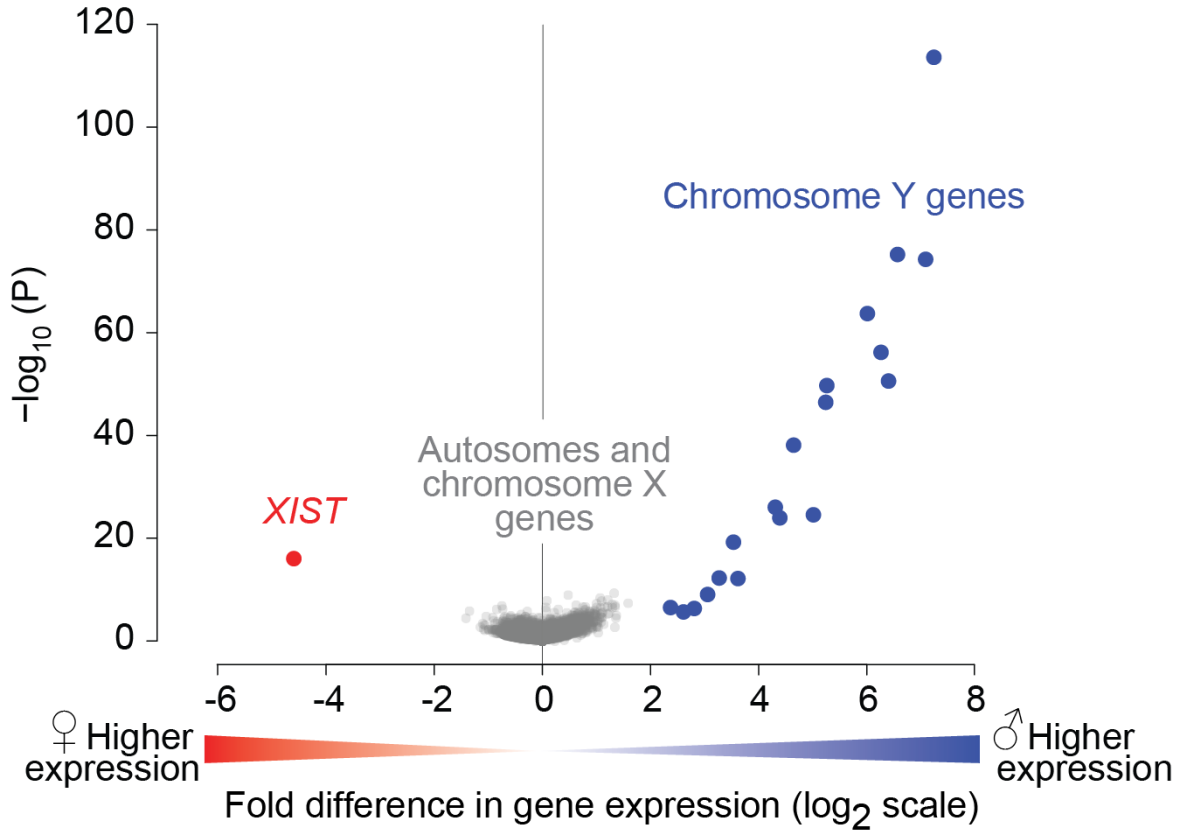
Period	Description	Age
1	Embryonic	4 PCW ≤ Age < 8 PCW
2	Early fetal	8 PCW ≤ Age < 10 PCW
3	Early fetal	10 PCW ≤ Age < 13 PCW
4	Early mid-fetal	13 PCW ≤ Age < 16 PCW
5	Early mid-fetal	16 PCW ≤ Age < 19 PCW
6	Late mid-fetal	19 PCW ≤ Age < 24 PCW
7	Late fetal	24 PCW ≤ Age <38 PCW
8	Neonatal and early infancy	0 M (birth) ≤ Age <6 M
9	Late infancy	6 M ≤ Age < 12 M
10	Early childhood	1 Y ≤ Age <6 Y
11	Middle and late childhood	6 Y ≤ Age < 12 Y
12	Adolescence	12 Y ≤ Age < 20 Y
13	Young adulthood	20 Y ≤ Age < 40 Y
14	Middle adulthood	40 Y ≤ Age < 60 Y
15	Late adulthood	60 Y ≤ Age

M, postnatal months; PCW, post-conceptional weeks; Y, postnatal years.



Kang, *et al.*, *Nature*, 2011

There is no evidence of an autosomal gene with XY levels of sexual dimorphism in the brain



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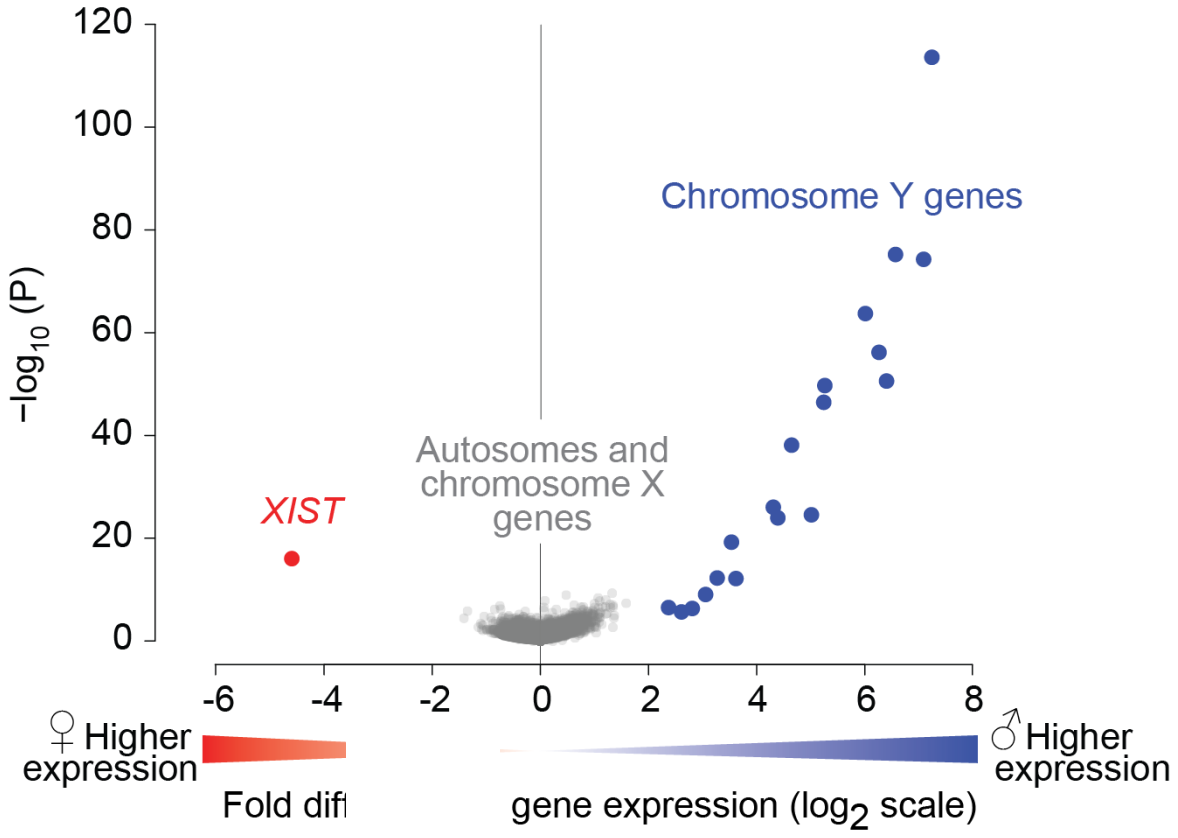
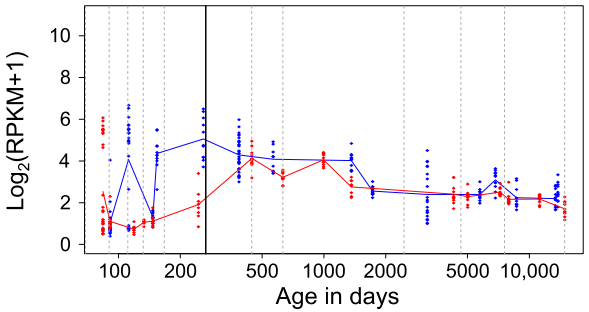
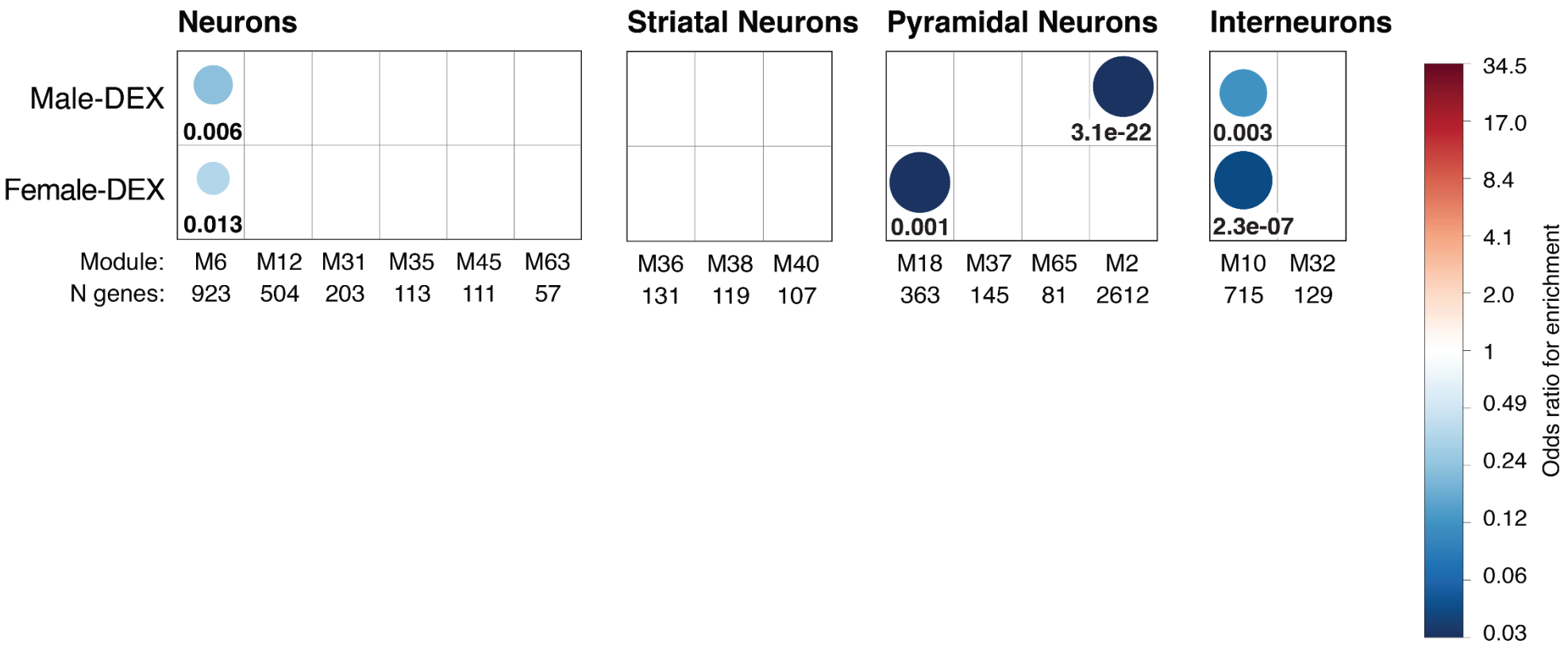


Sex-DEX genes identified by permutation approach (Q≤0.05; top-ranking sex-DEX in ≥2 consecutive developmental periods from same brain region):

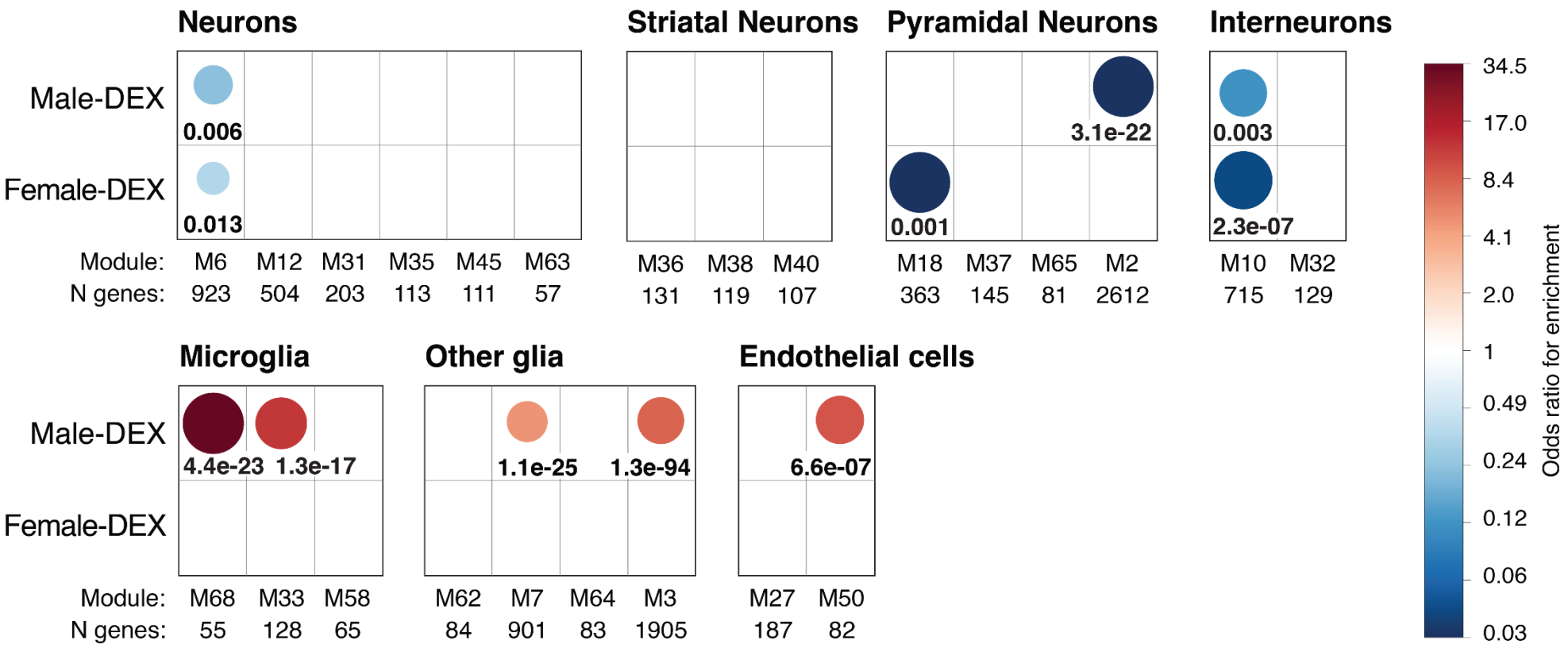
- Higher expression in males:
  - 505 protein-coding genes, 129 noncoding transcripts
- Higher expression in females:
  - 442 protein-coding genes, 466 noncoding transcripts



Sex-DEX genes are not enriched for neuronal markers



Male-DEX genes show enrichment for microglial and endothelial cell markers



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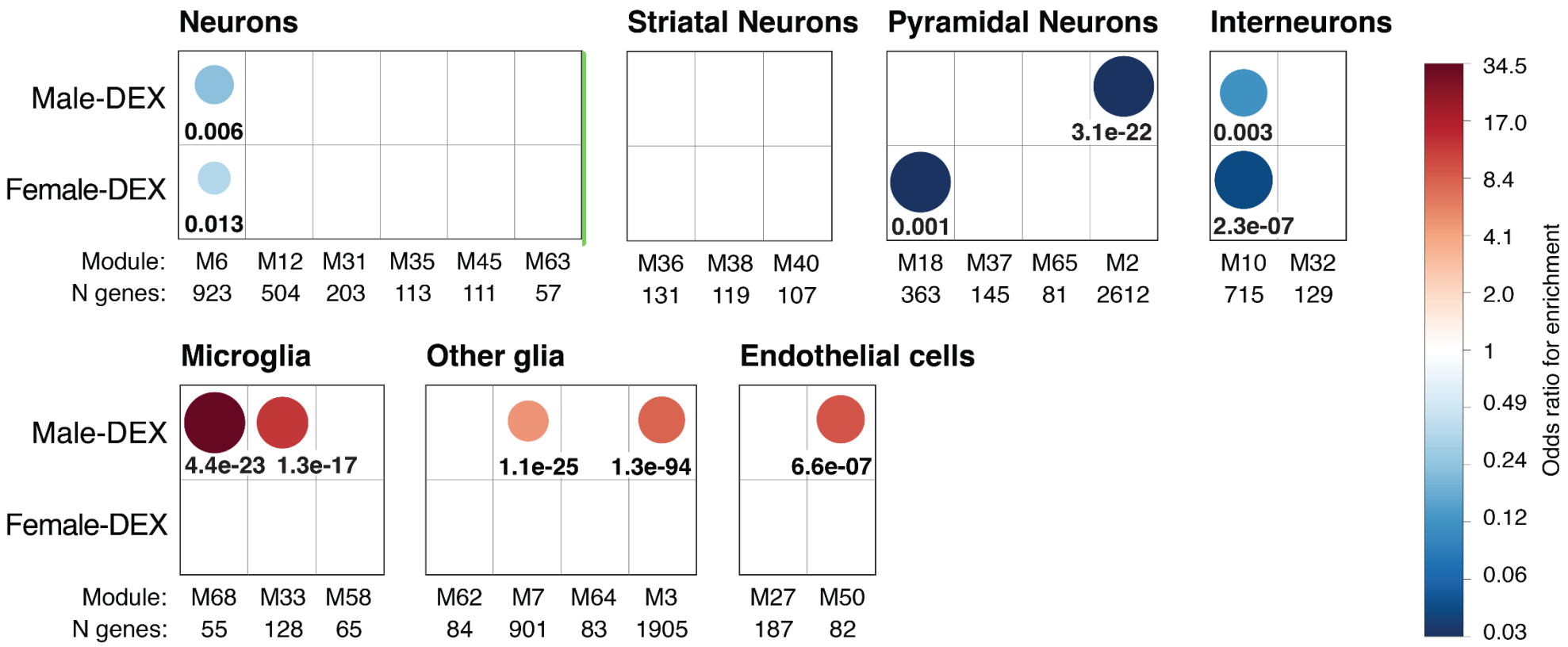

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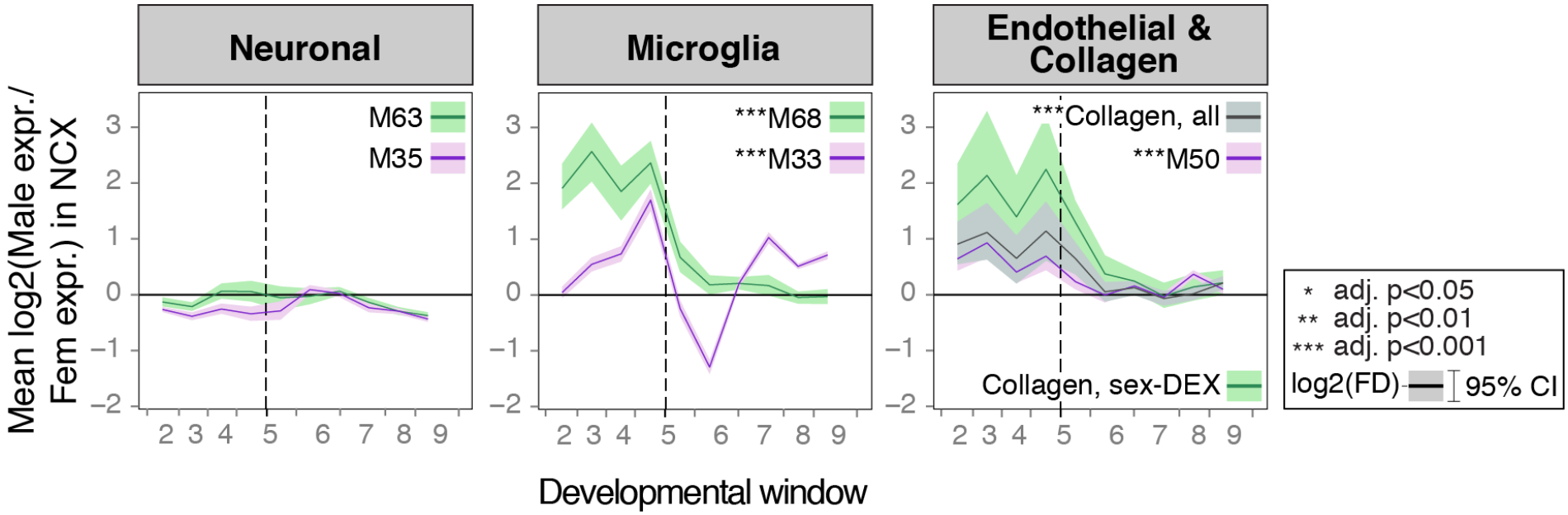
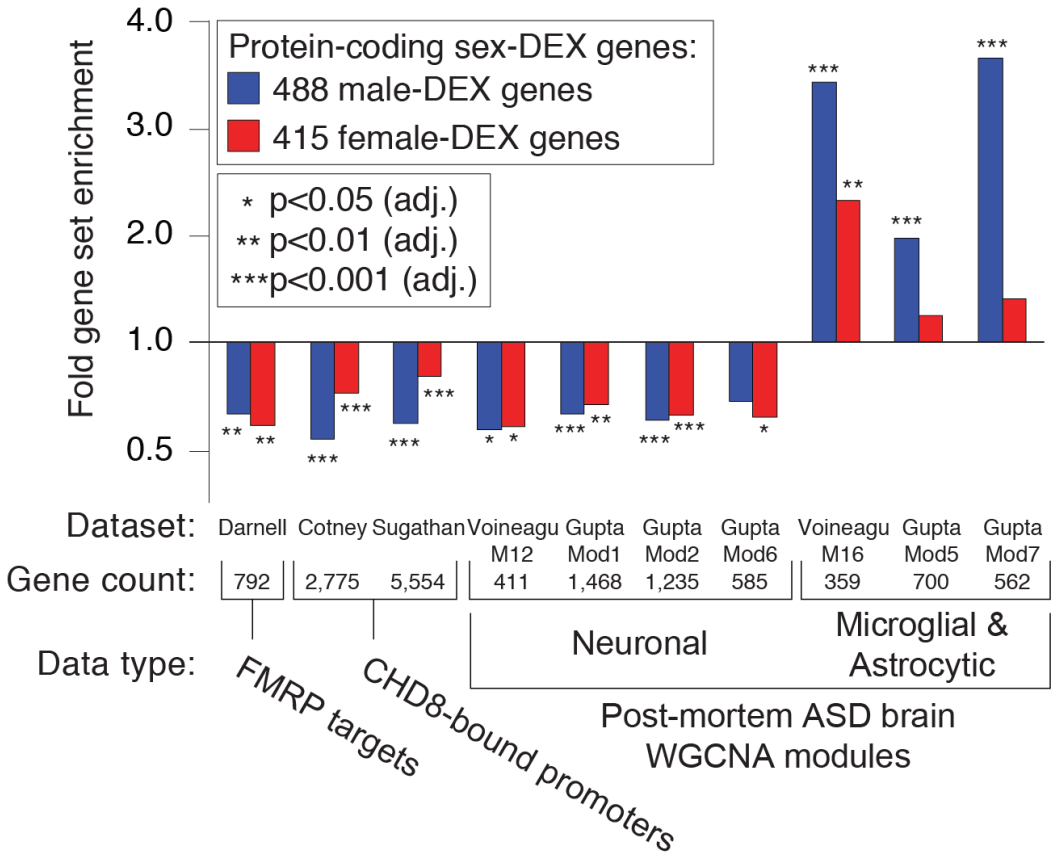


We observe a relationship between sex-DEX genes and ASD biology



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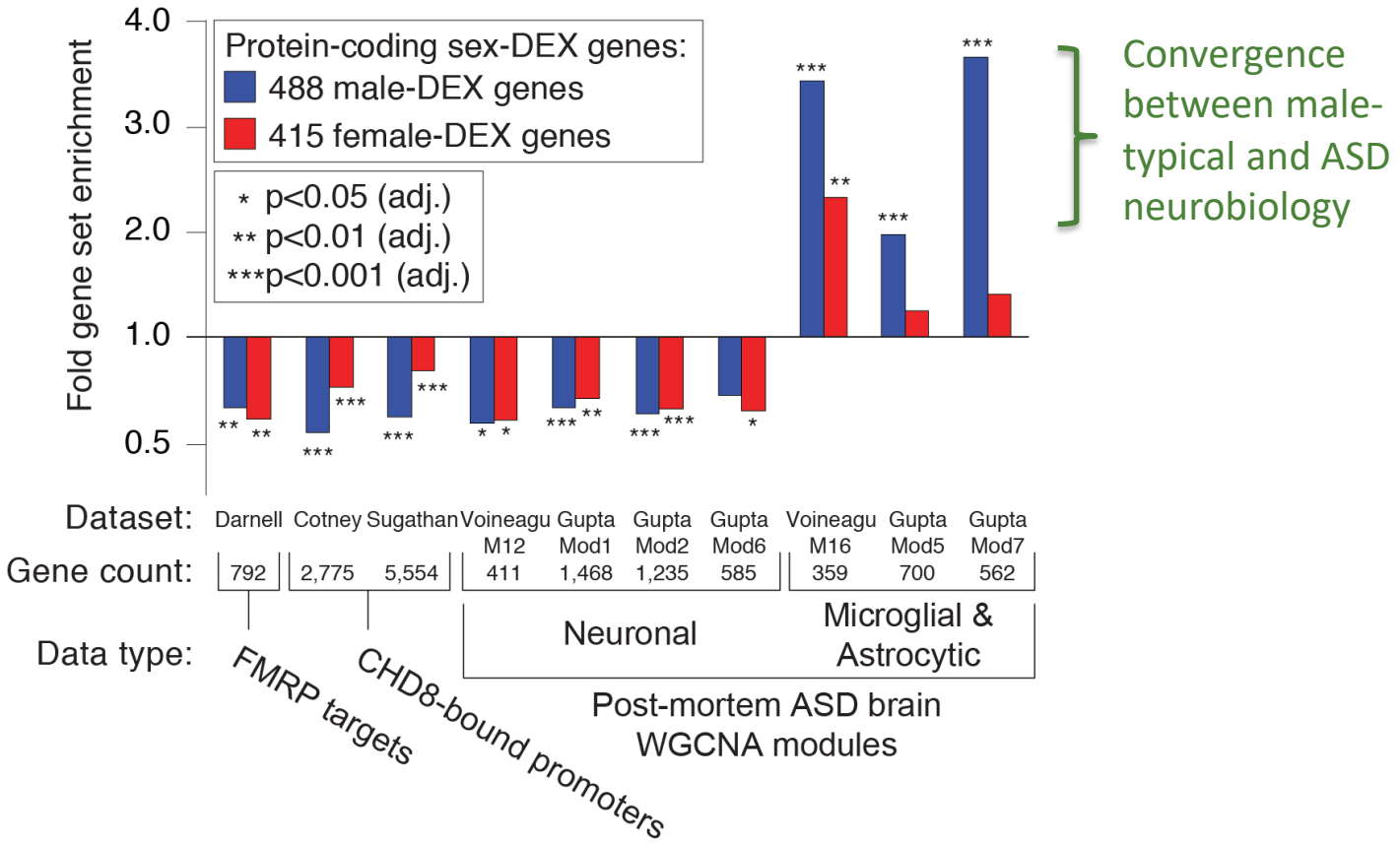
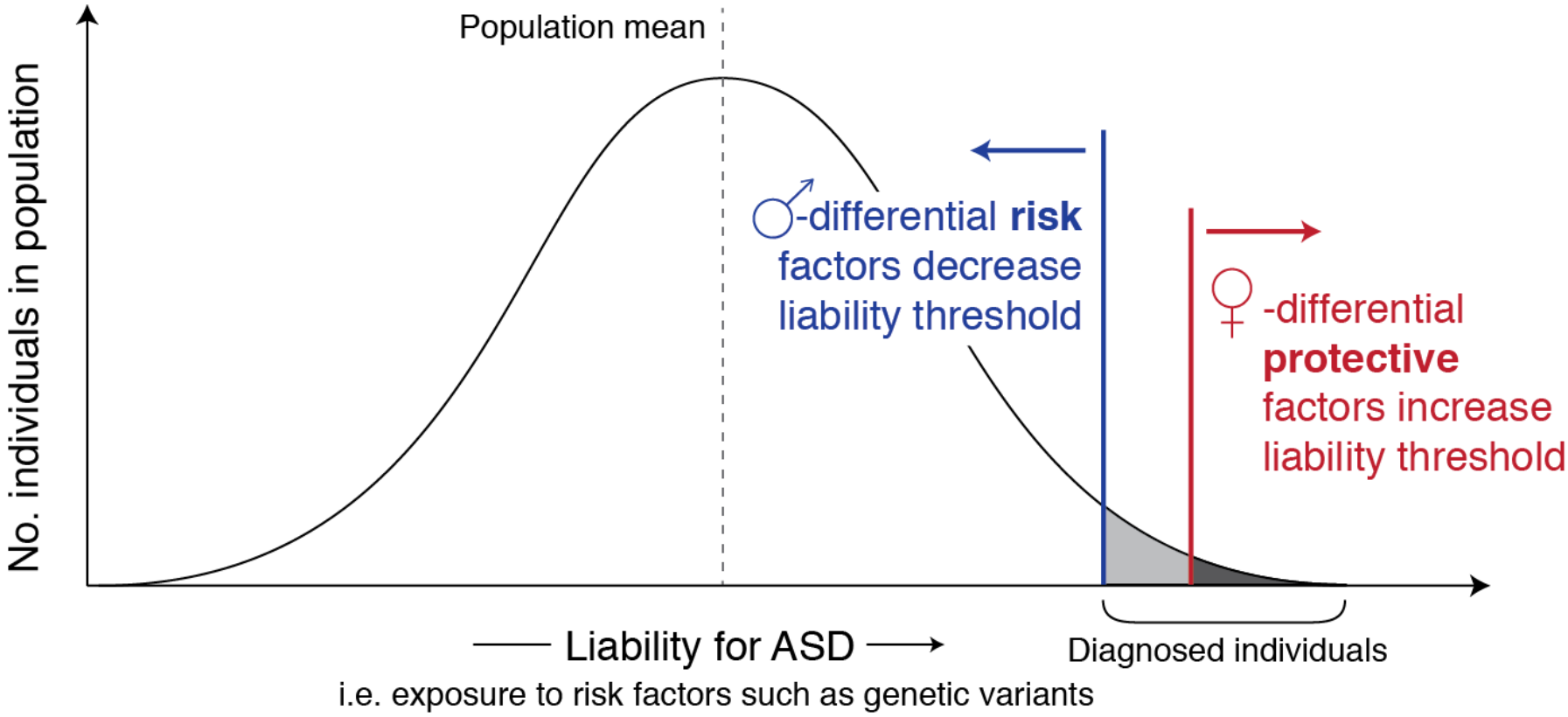


Enrichment evidence suggests a male sensitization model of ASD risk



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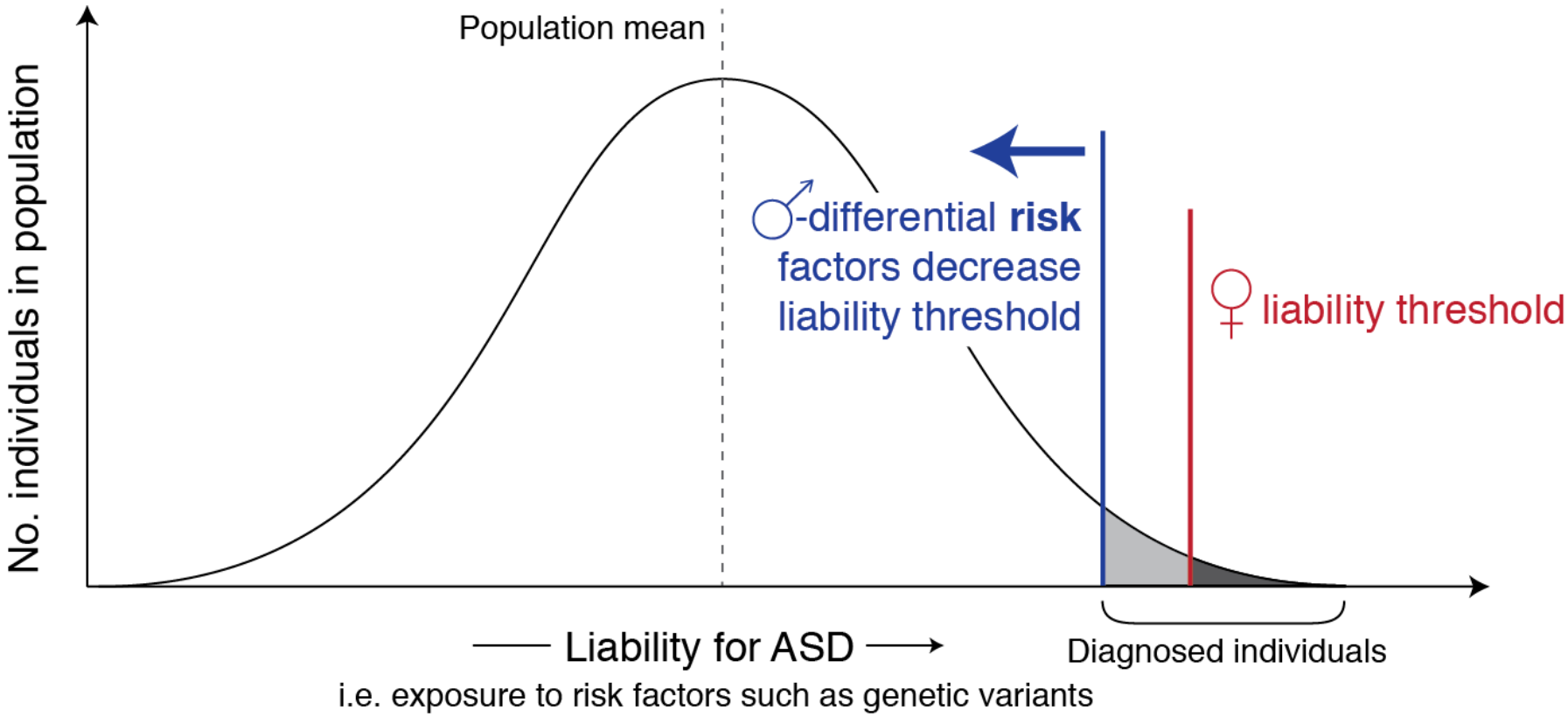

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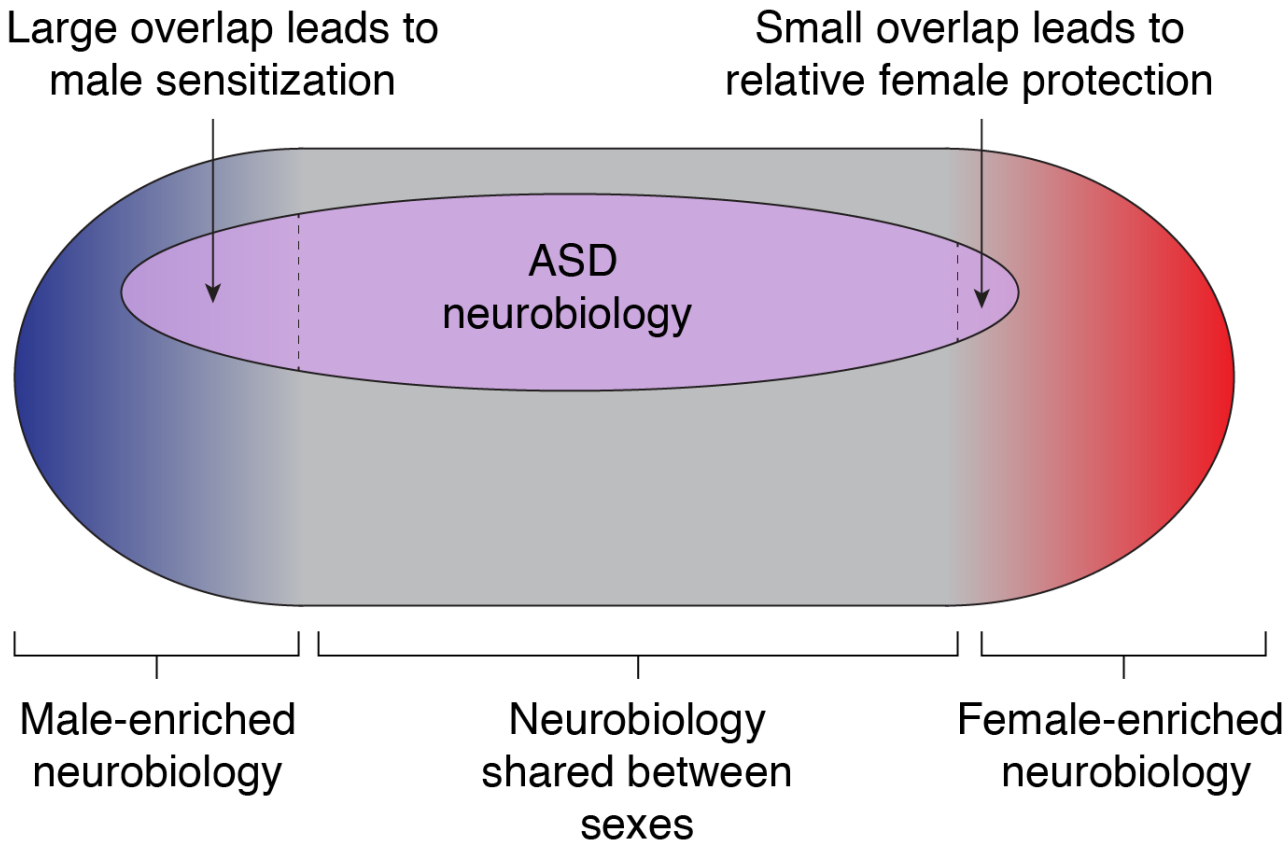

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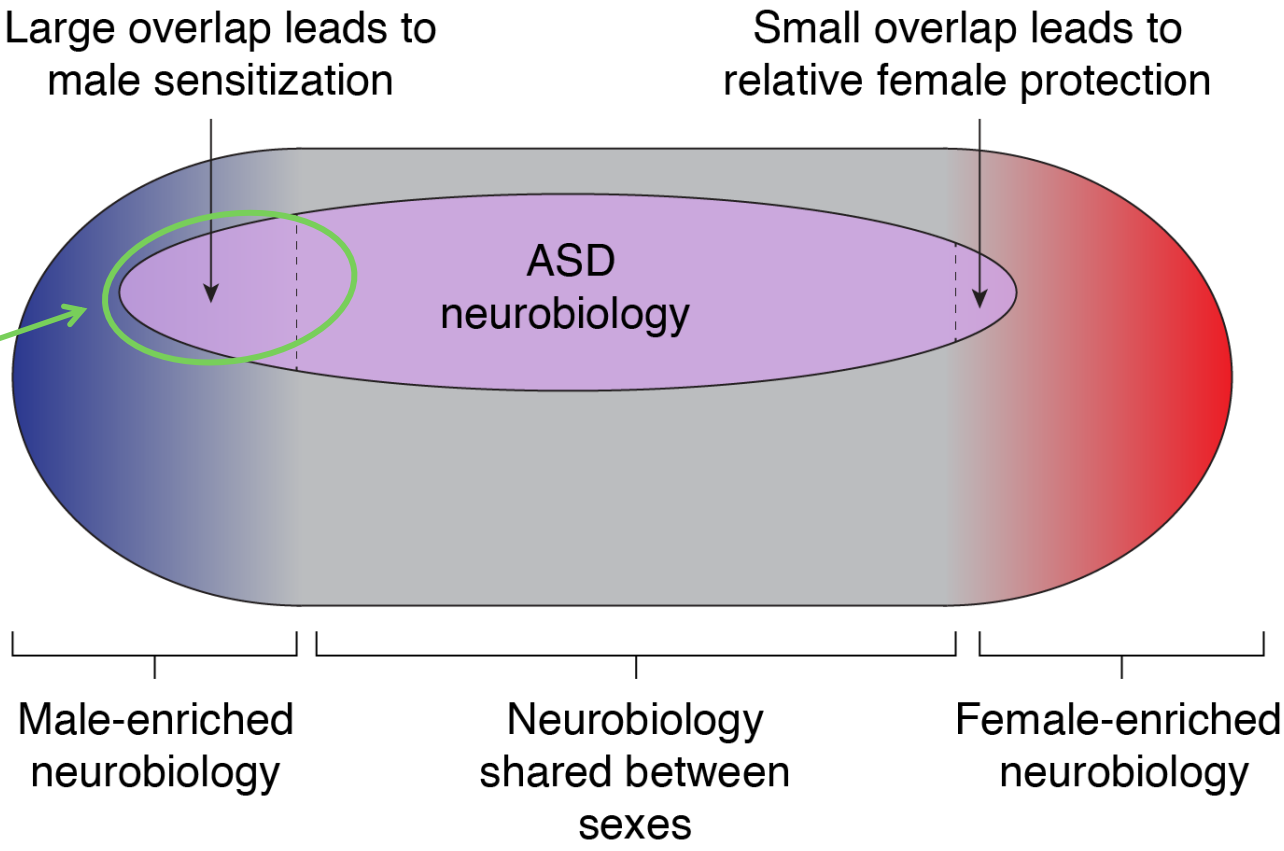

Summary

- Intersection of ASD neurobiology and sex-differential neurobiology provides an approach to understand sex bias

- Male-biased expression:
  - Microglial genes
  - Collagen genes and endothelial cell markers
  - Glial genes dysregulated in ASD brain, suggesting a male-sensitization effect

- Validation in independent samples is needed
  - Results are preliminary and based on analysis of a single data set

Looking forward

- Well powered, foundational data sets comparing males and females will be required for:
  - Rigorous validation of sex-differential patterns
  - Thorough investigation of relationships between sex-differential and ASD biology

Data types

- RNA sequencing for gene expression
- ChIP-seq for identifying gene targets of the estrogen and androgen receptors

2x2 design

Developmental stages

- Fetal
- Perinatal
- Early postnatal/childhood
- Puberty
- Adulthood

Cell types

- Neurons
- Microglia
- Astrocytes

Brain regions

- Neocortex
- Thalamus
- Striatum
- Cerebellum

Organisms

- Human
- Primate
- Mouse

Acknowledgements

Stephan Sanders
UCSF

Matt State
UCSF

Nenad Sestan
Yale

BRAINSPAN
ATLAS OF THE DEVELOPING HUMAN BRAIN

Yale
- Forrest Gulden
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- Xuming Xu
- Mingfeng Li
- Rob Kitchen

Allen Brain Institute
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- Jeremy Miller
- Trygve Bakken

USC
- Jim Knowles

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