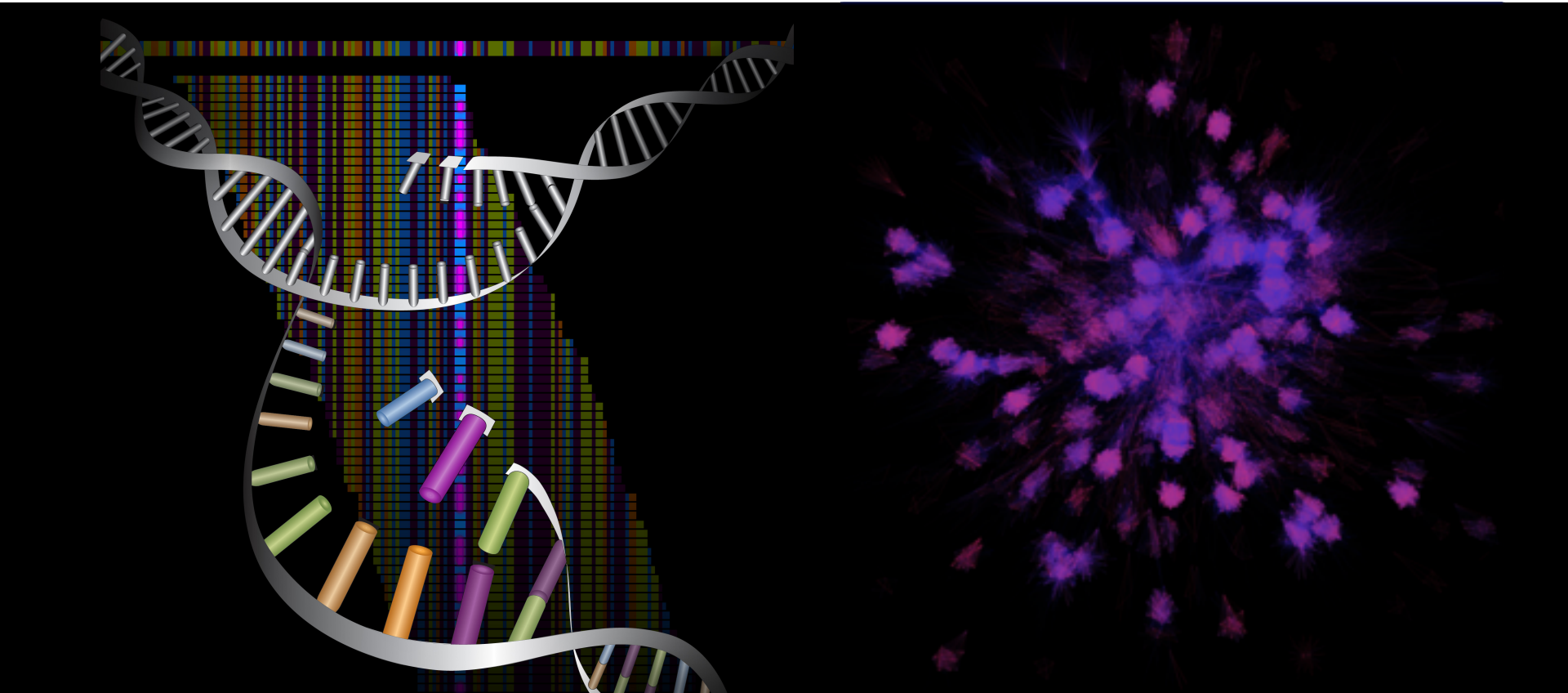
UCSF
University of California
San Francisco

Autism Spectrum Disorder Part III: Genetics and Autism



No conflicts of interest to declare

Funding sources:

Learning objectives

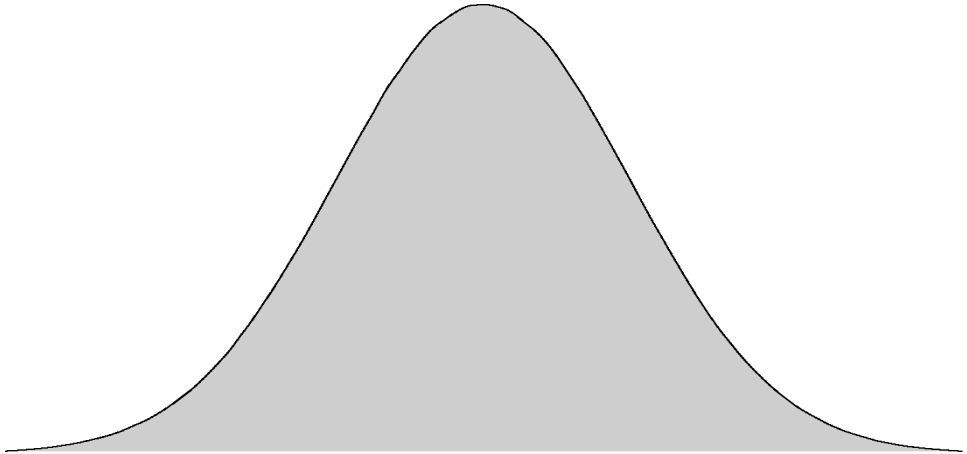
- Discuss the role of genetic and environmental factors that contribute to ASD
- Identify the wide range of genetic variation that is involved in ASD including gene-gene and gene-environment interactions
- Review the current status and key findings of genetics research in ASD

Autism Spectrum Disorder (ASD) is a developmental neurological impairment

- CDC estimates incidence of 1 in 60 (1.7%)
  - More common in males (2:1 to 4:1)
- Individuals with ASD have fewer children – Power *et al.* 2013

Genes vs. “The Environment”

- Trait: A characteristic of individuals in a population
  - E.g. milk production in cows
  - Height in humans
  - Sociability in humans
  - Autism spectrum disorder diagnosis



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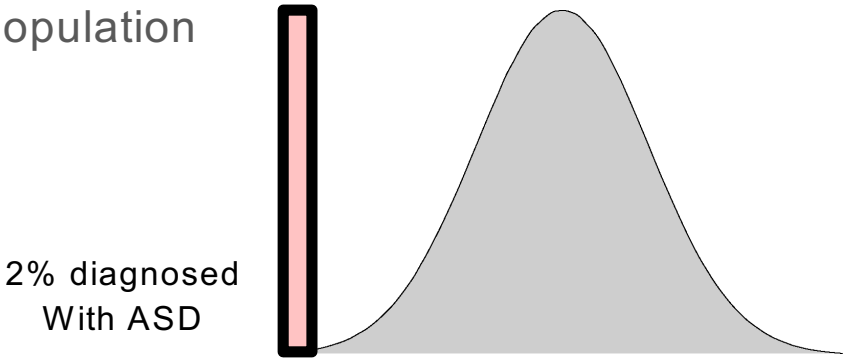
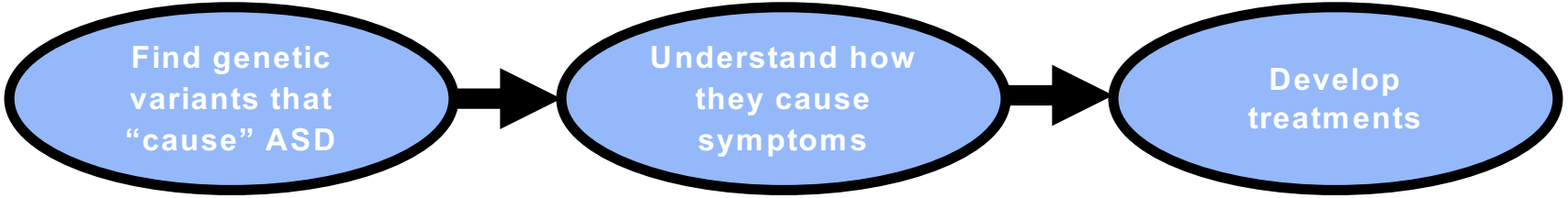


- Genes: The variance in a trait explained by heritable factors

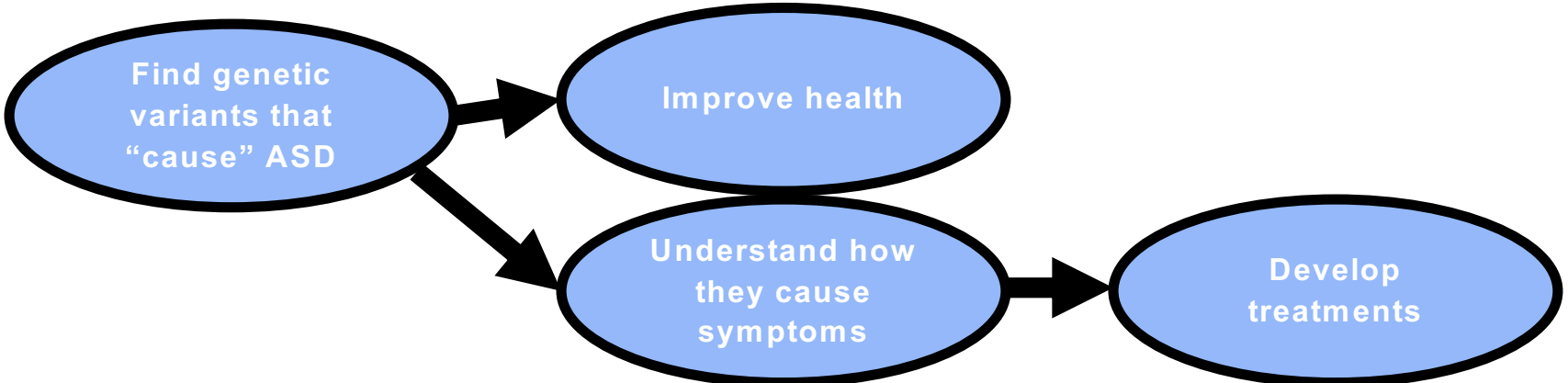
- Environment: The variance in a trait explained by everything else
  - ”Unaccounted” would be a better phrase
  - Environmental factors are one contributor to this term

What are researchers trying to achieve?

- **Genetics**



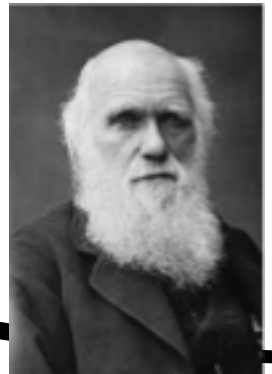
- **Environmental factors**



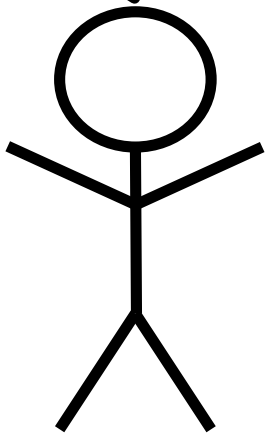
Genetics and heritability analyses assess the flow of information in biological systems

Mendel's laws of inheritance

Genotype

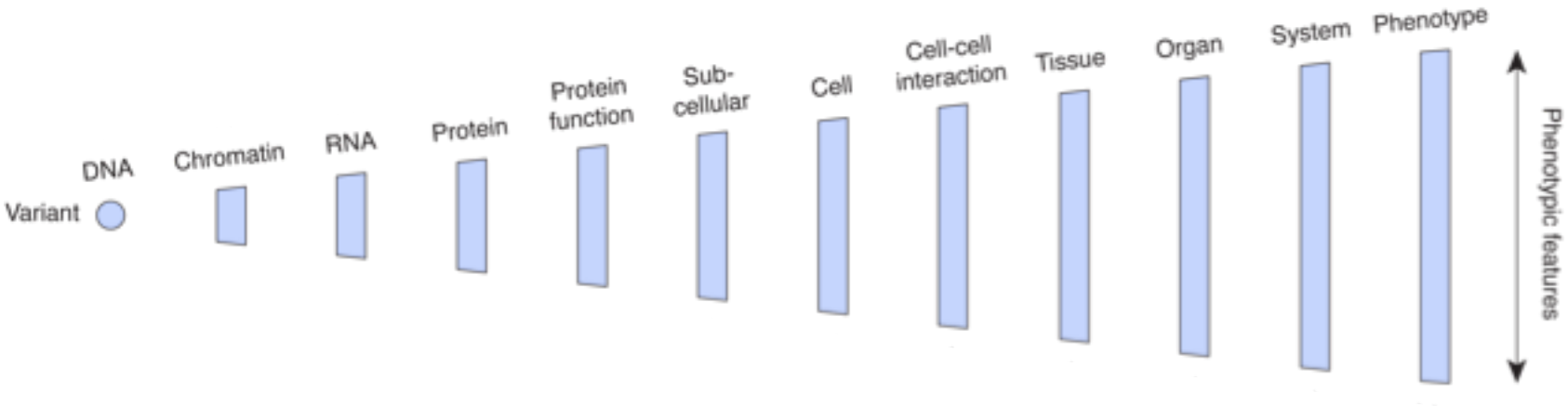


Darwin's theory of evolution by natural selection



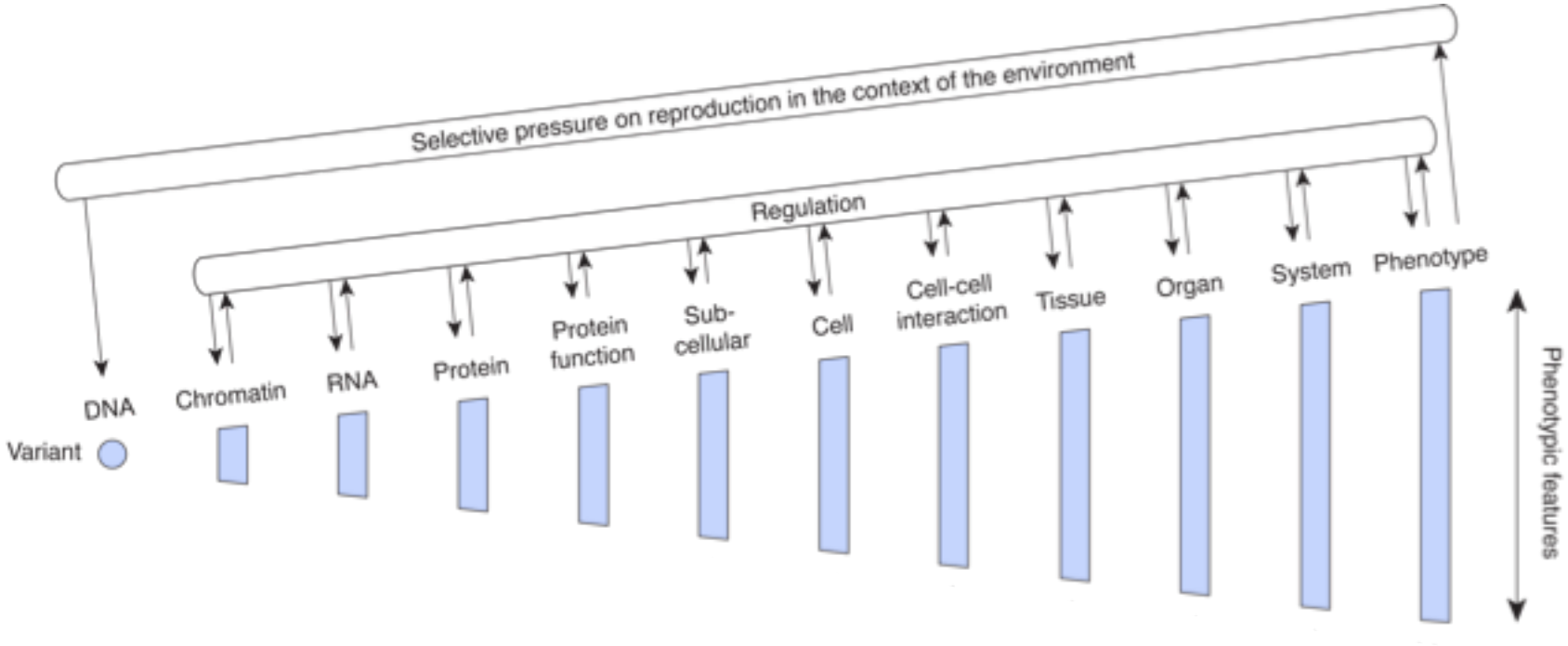
Phenotype

Genotypes are amplified to produce observable phenotypes



Sanders SJ, Curr Opin Genet Dev, 2015

Genotypes are amplified to produce observable phenotypes



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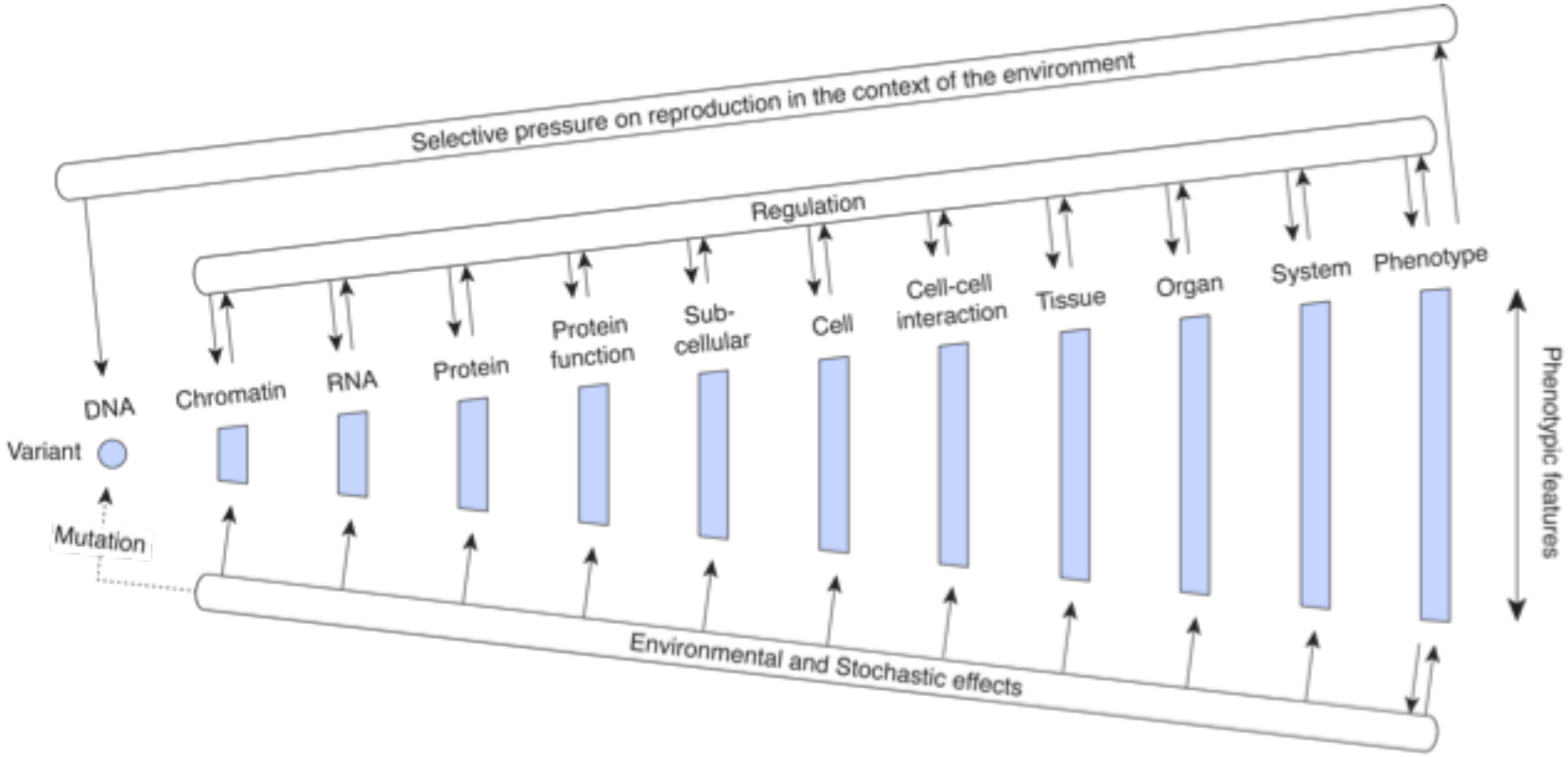

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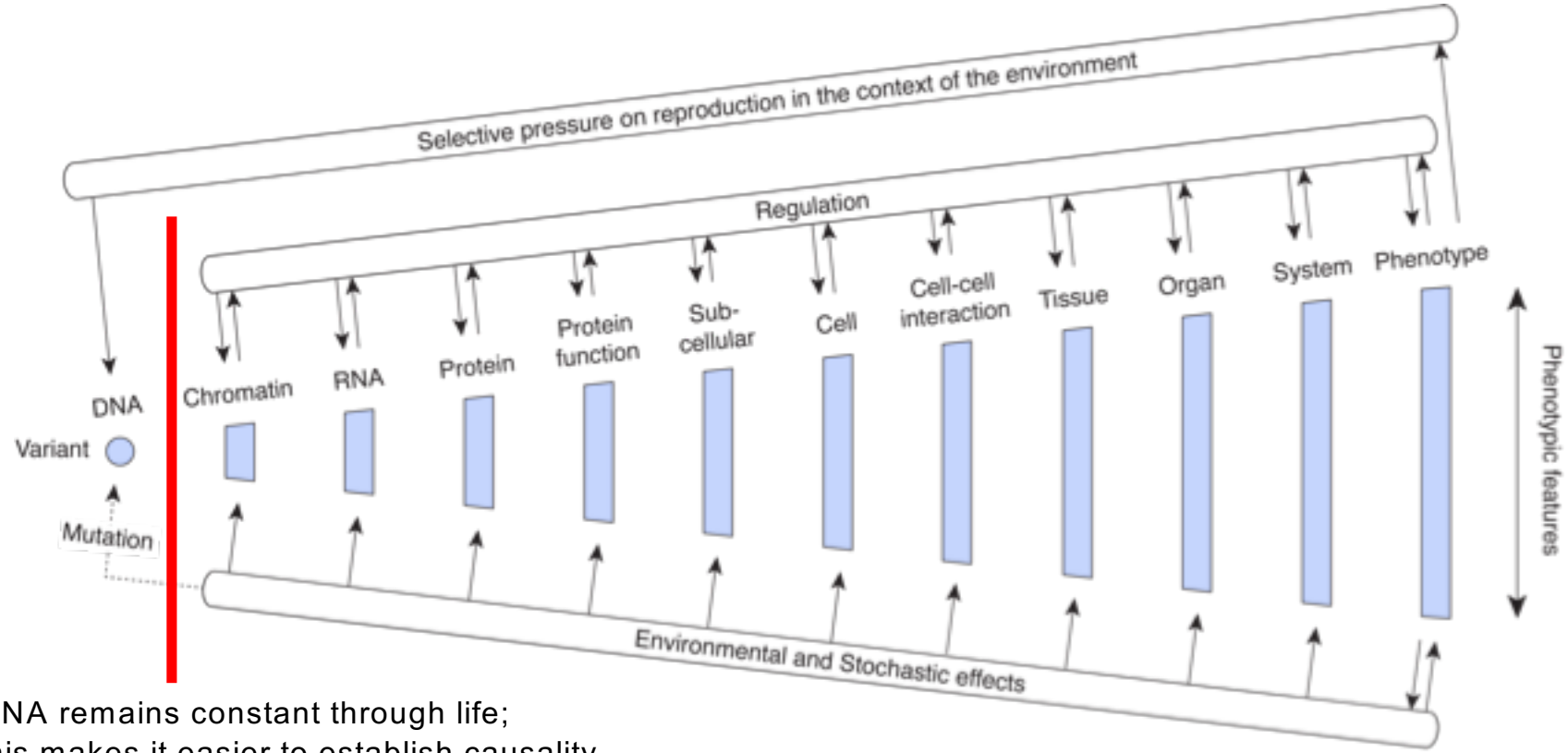
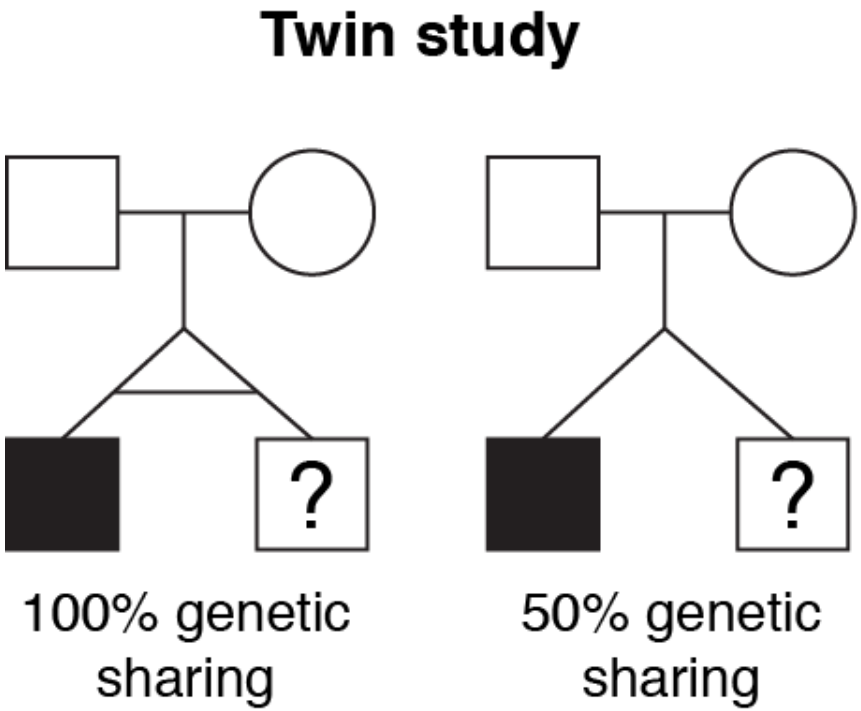


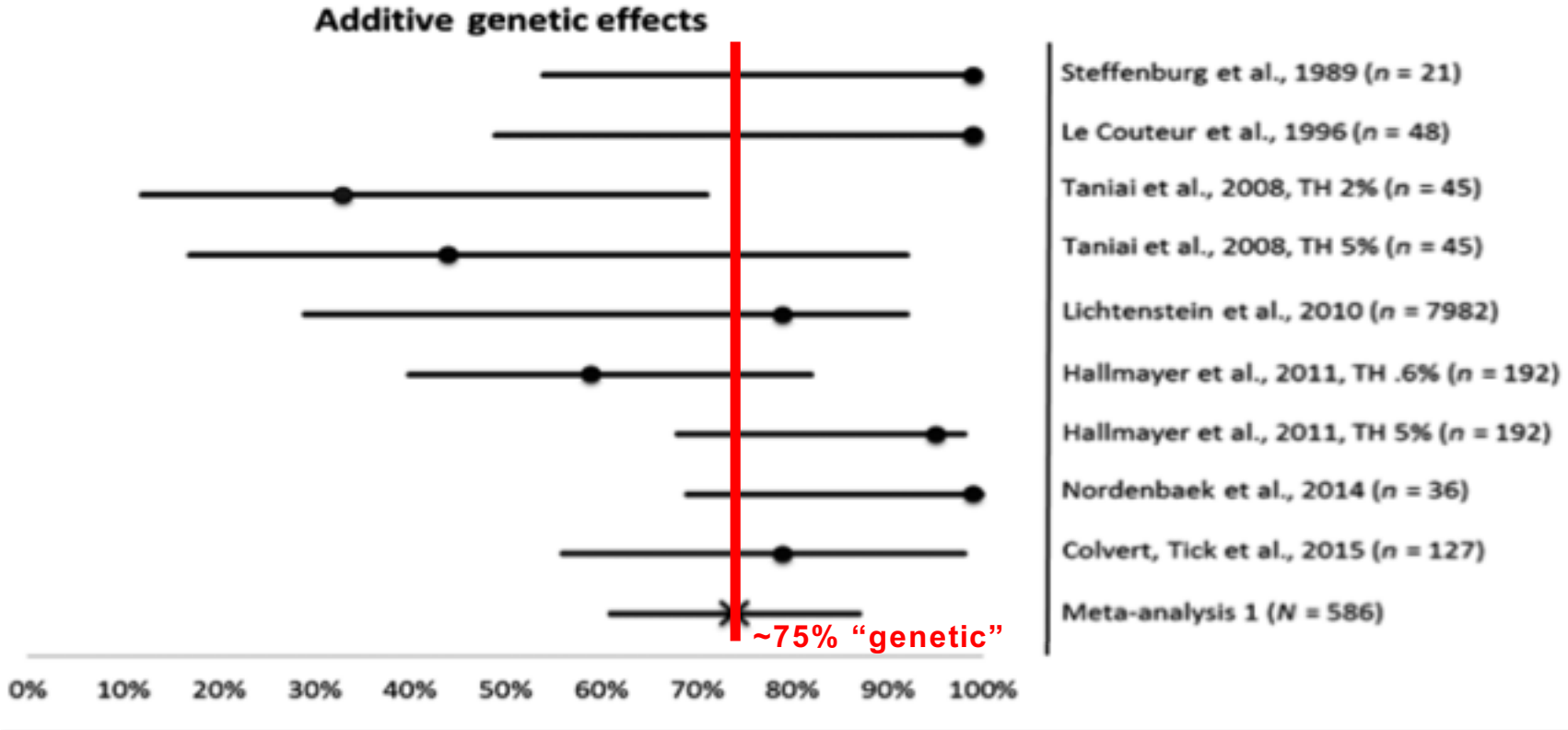
DNA remains constant through life;
this makes it easier to establish causality

Sanders SJ, Curr Opin Genet Dev, 2015

Twin studies compare identical (monozygotic) to non-identical (dizygotic) twins



Twin study: Combining data across 7 twin studies



Tick *et al. Journal of Child Psychology and Psychiatry* 2016

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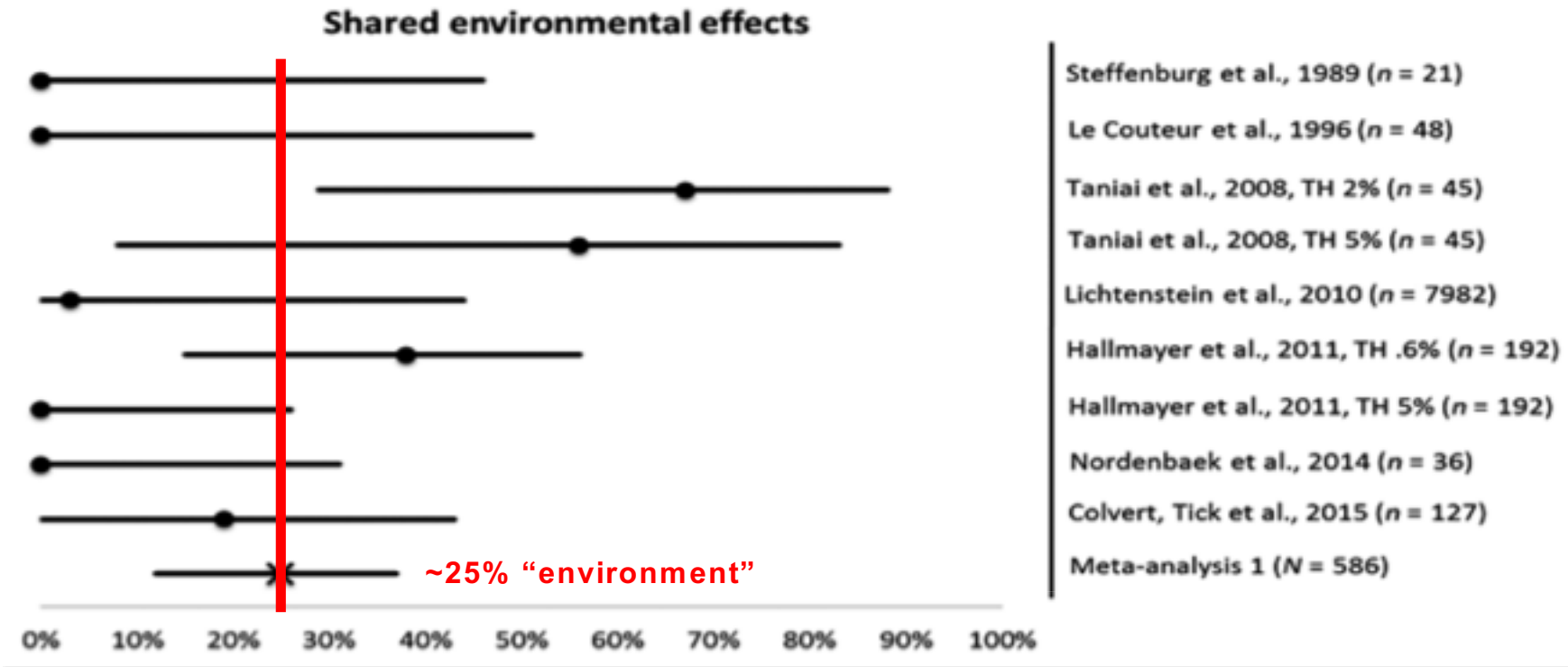
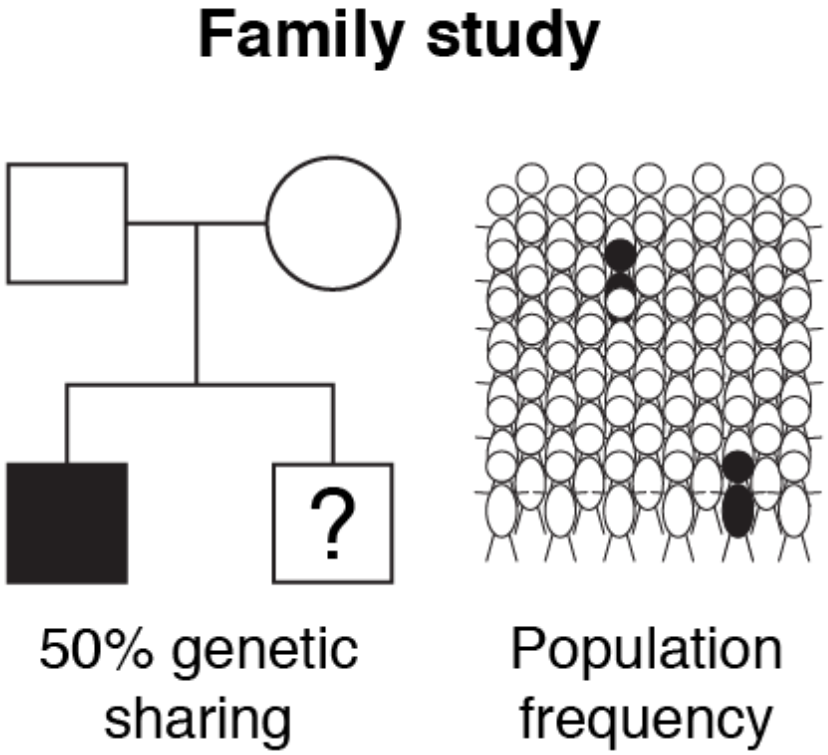
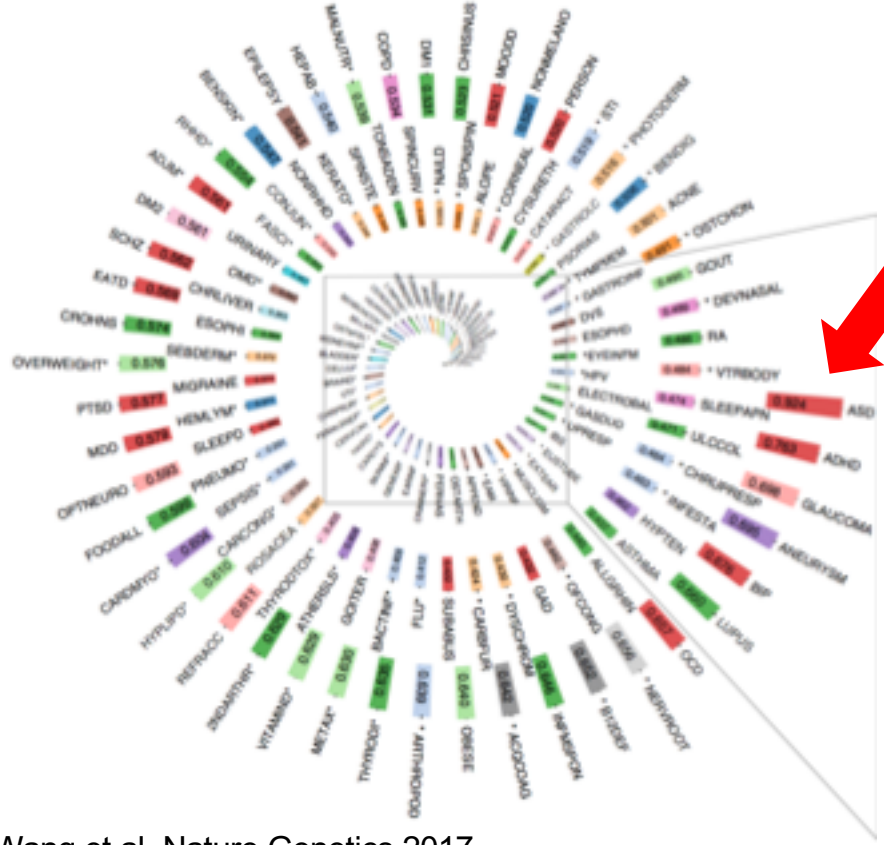


Tick *et al. Journal of Child Psychology and Psychiatry* 2016

Family/sibling studies compare relatives (e.g. siblings) to the general population



Analysis of heritability across ~130 complex human disorders; ASD is the most heritable



ASD: 92% “genetic”

Many other family studies of ASD alone; most estimate ~75% heritability

Wang et al. Nature Genetics 2017

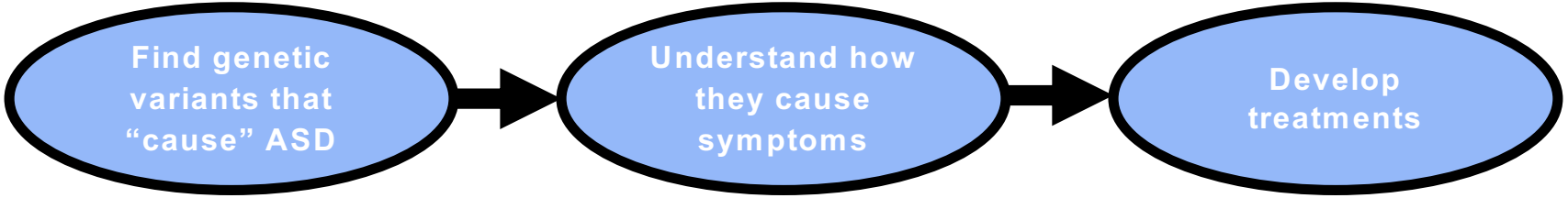
Neuropsychiatric disorders, like ASD, are frequently genetic

Disorder	Clinical utility	Heritability
ASD	Parental counseling	70 - 95%
Schizophrenia	None at present	60 - 90%
Alzheimer's	APOE4 testing?	60 - 80%
Height	Mid-parental height used to estimate expectation	55 - 81%
Multiple Sclerosis	None at present	64%
Migraine	Commonly assessed in the evaluation of headaches	53%
IQ	None at present	50%
Personality	None at present	50%
Breast cancer	Family history guides genetic testing and counseling	25 - 56%
Coronary Heart Disease	Used to inform models of cardiac risk	49%
Type 2 Diabetes	None at present	26%

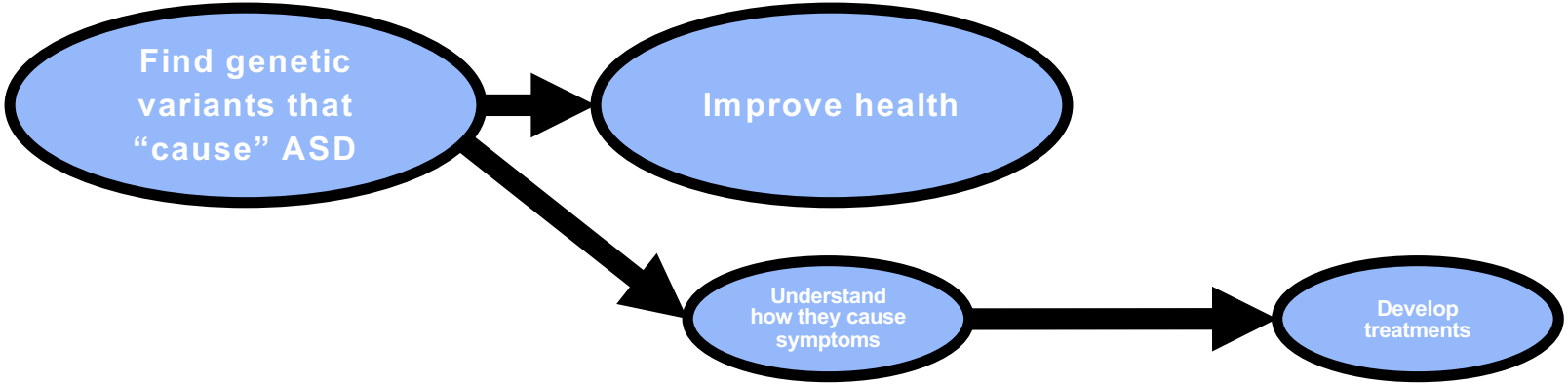
Source: SNPedia

What are we trying to achieve?

- **Genetics** – strong contributor, causality can be established; 20,000 genes



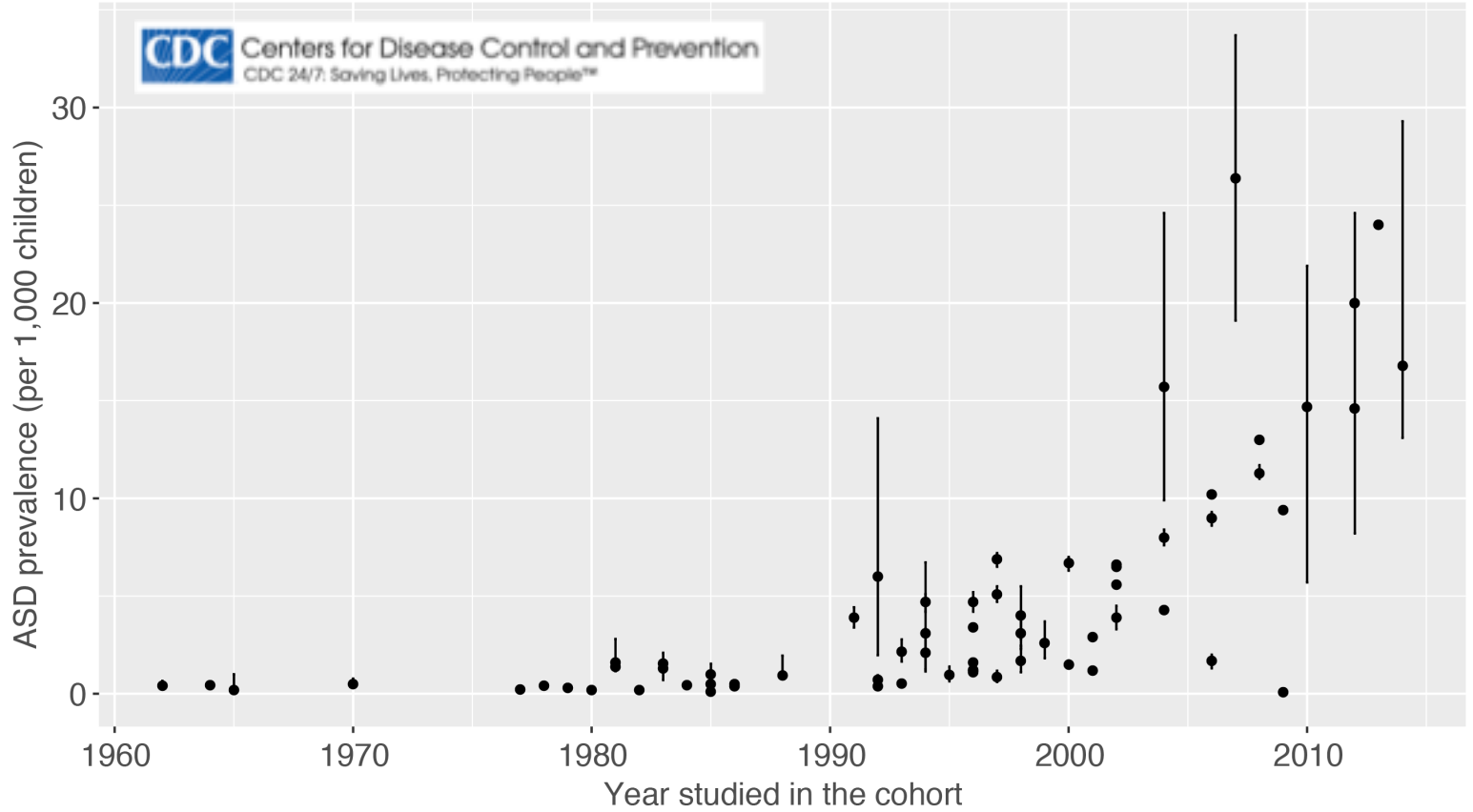
- **Environmental factors** – weaker contributor; causality is hard to establish; 100,000s of factors to assess



Environmental factors associated with ASD

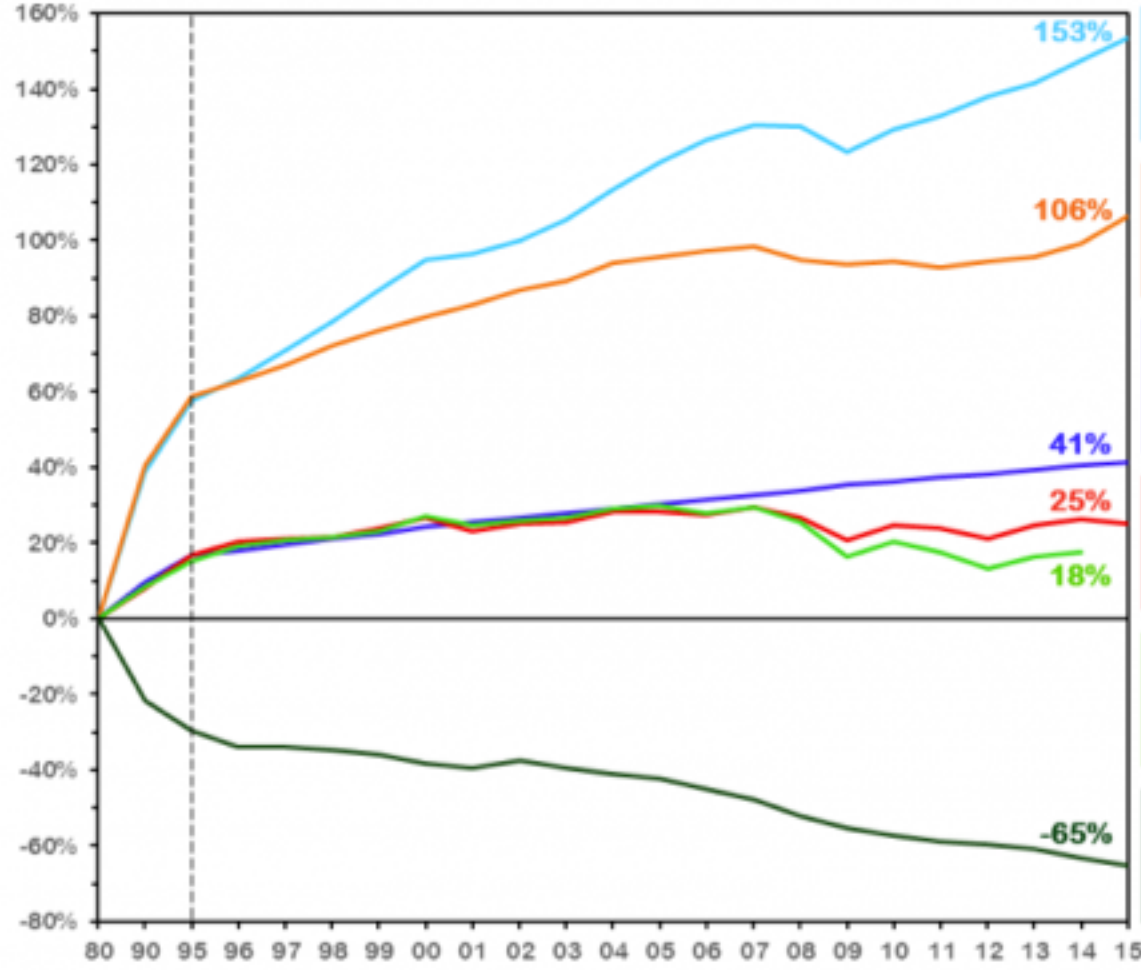
- Maternal valproate use for epilepsy during pregnancy
  - 2-fold increase in risk Christensen *et al. JAMA* 2013
  - Does epilepsy carry genetic risk for ASD, or valproate carry environmental risk?
    - 1,623 mothers with epilepsy (22 had children with ASD, 1.4%)
    - 388 mothers on valproate (12 had children with ASD, 3.1%)
    - But was there an additional reason the mothers were on valproate vs. other treatments?
  - Causality is hard to establish
- Many other factors considered, but few thoroughly assessed:
  - Congenital infection, pollutants, pesticides, heavy metals
- Very hard to “guess” what to study without knowing the biology

The prevalence of ASD has risen over the last few decades



Comparison of Growth Areas and Emissions, 1980-2015

EPA United States Environmental Protection Agency



Gross Domestic Product

Vehicle Miles Traveled

Population

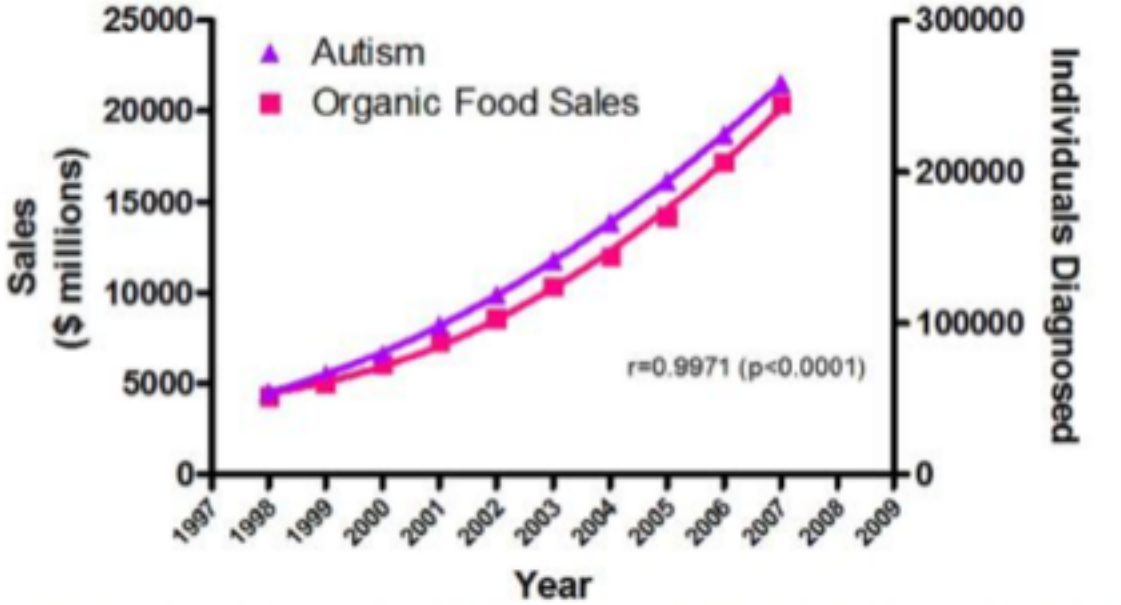
Energy Consumption

CO_2 Emissions

Aggregate Emissions (Six Common Pollutants)

There are many explanations for rising prevalence; simply looking for "new" factors is a risky strategy

- Changing diagnostic methods
- Replacing other diagnoses
  - Developmental delay
  - Intellectual disability
- Increased surveillance
- Rising parental age
- New ways to find a partner
- Environmental factors

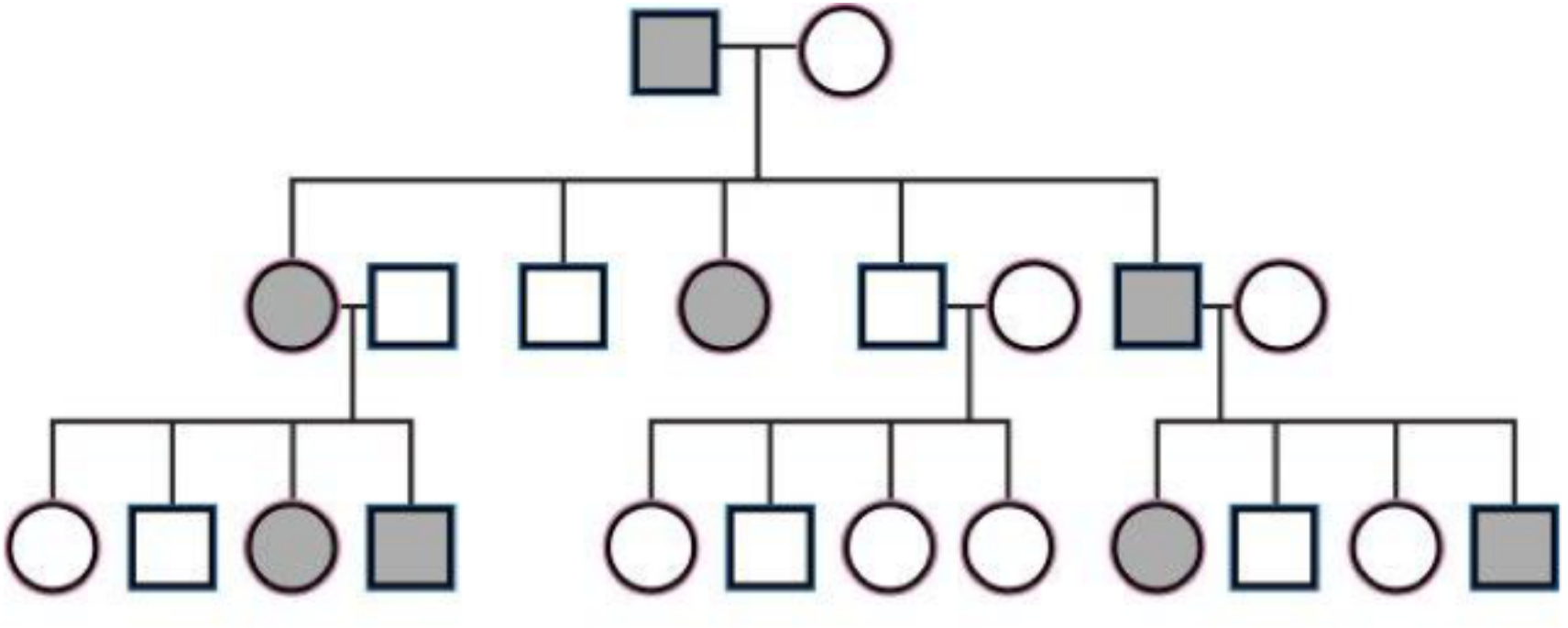


Sources: Organic Trade Association, 2011 Organic Industry Survey; U.S. Department of Education, Office of Special Education Programs, Data Analysis System (DANS), OMB# 1820-0043: "Children with Disabilities Receiving Special Education Under Part B of the Individuals with Disabilities Education Act

Genetic factors associated with ASD

- Several genetic syndromes have ASD as a feature
  - Fragile X, Rett's, TSC1, TSC2, NF1, NF2, PTEN, CACNA1C

Example of a family with neurofibromatosis (NF1) and autosomal dominant inheritance



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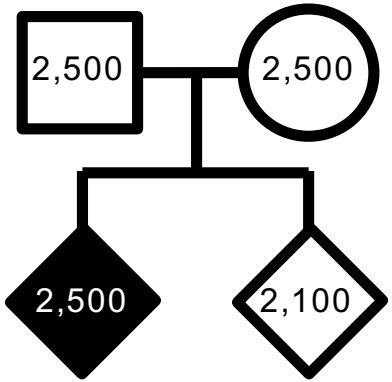
  - Sanders *et al. Nature* 2012, replicated in Iossifov *et al. Neuron* 2012, De Rubeis *et al. Nature* 2014, Iossifov *et al. Nature* 2014, Sanders *et al. Neuron* 2015, and many others

Large cohorts, new technologies, and new statistical approaches have revolutionized genetics

~2,500 ASD families in Simons Simplex Collection



SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

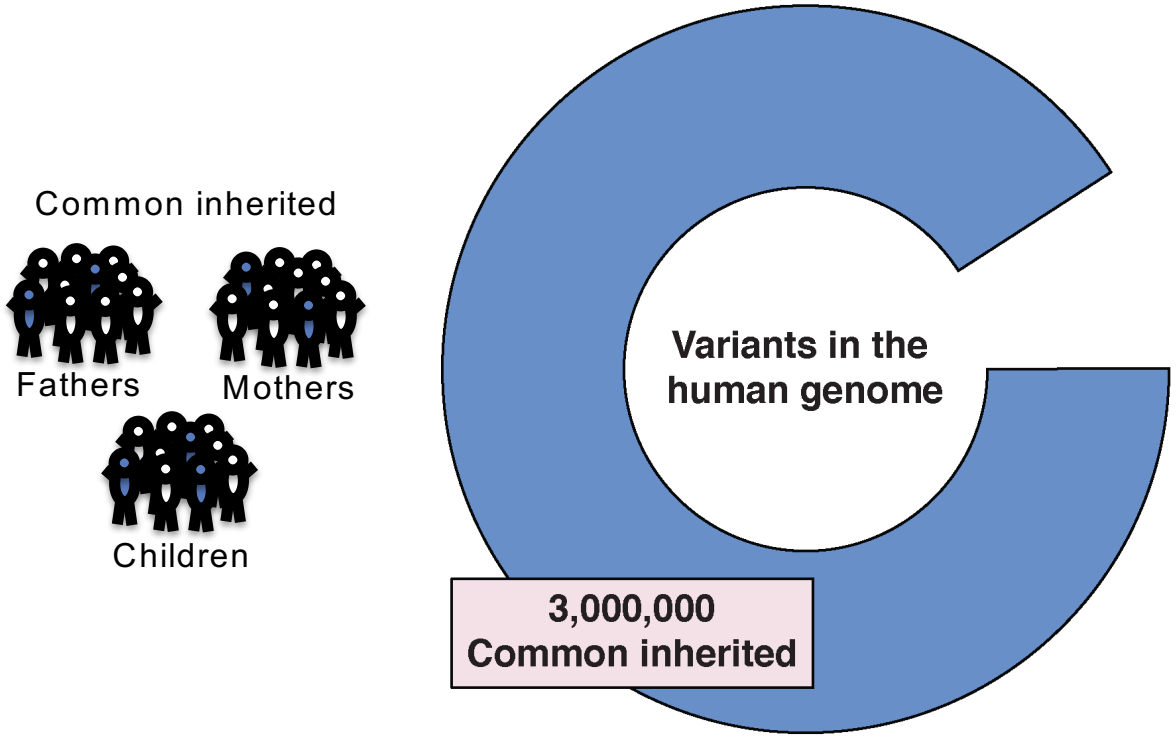
Microarray

illumina®

Exome sequencing

illumina®

The human genome has 3.2 billion base pairs and 3.3 million variants



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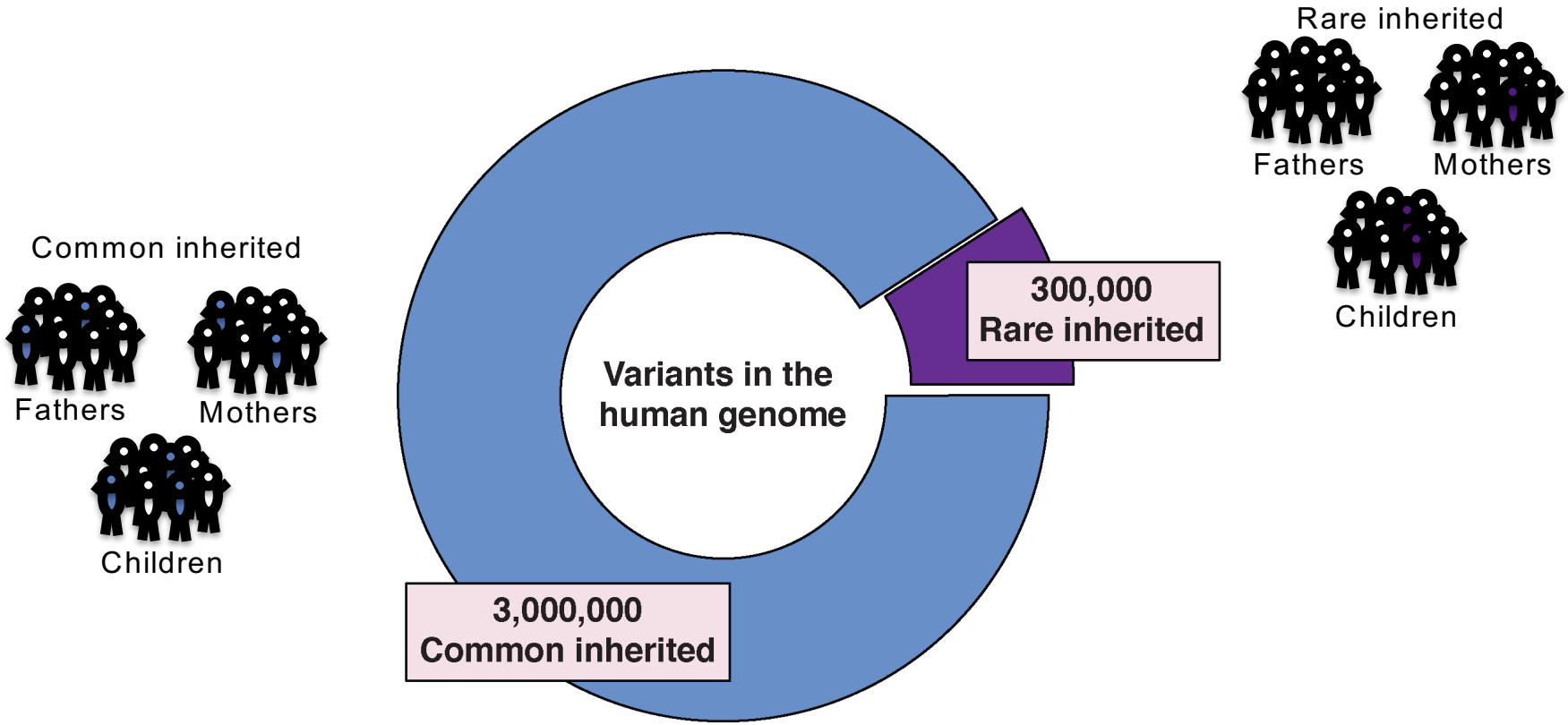

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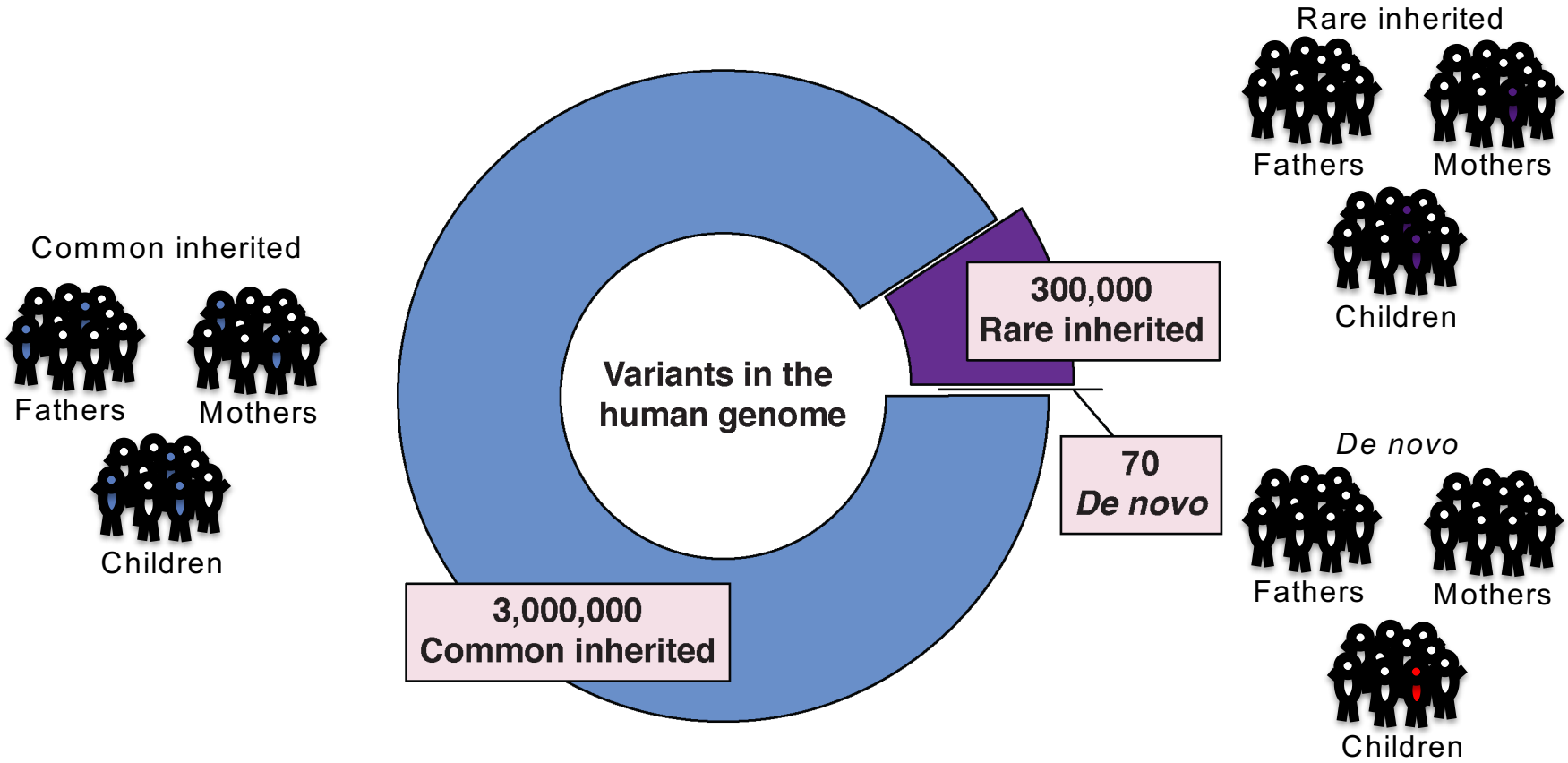
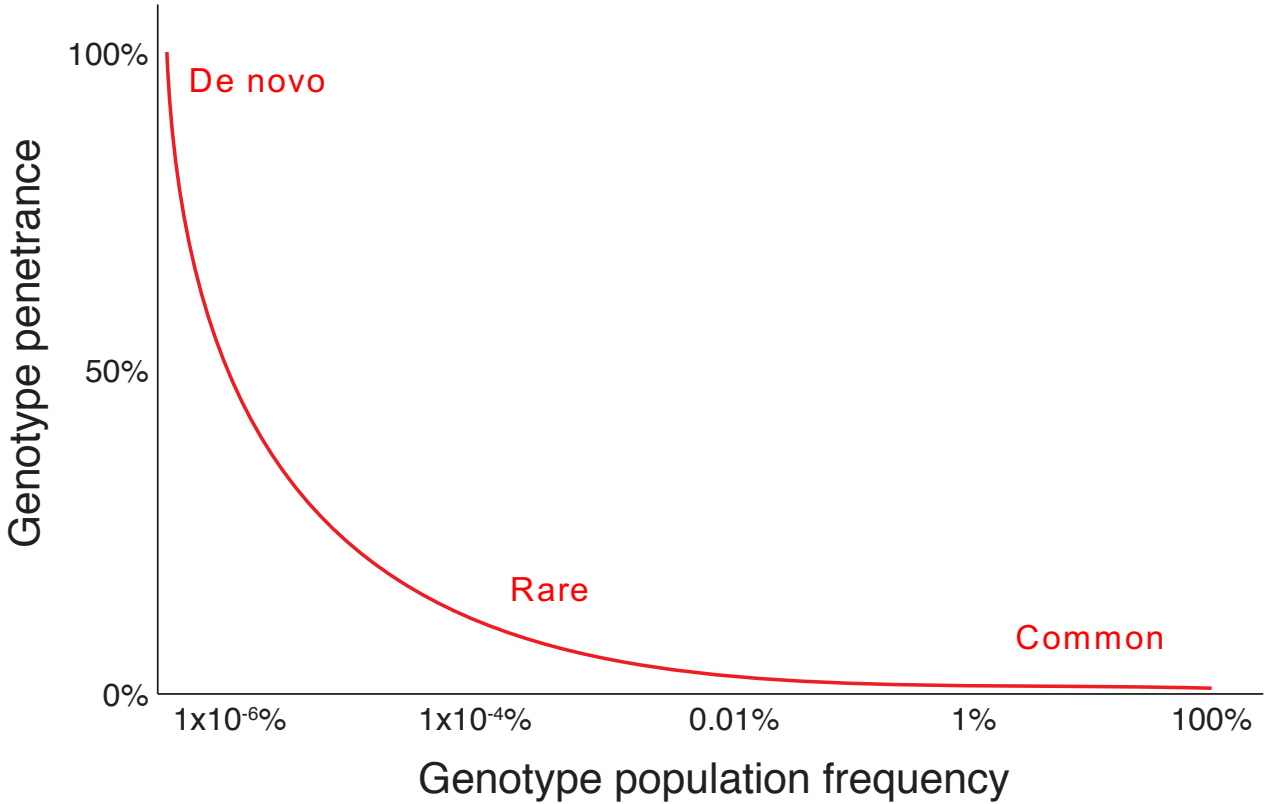
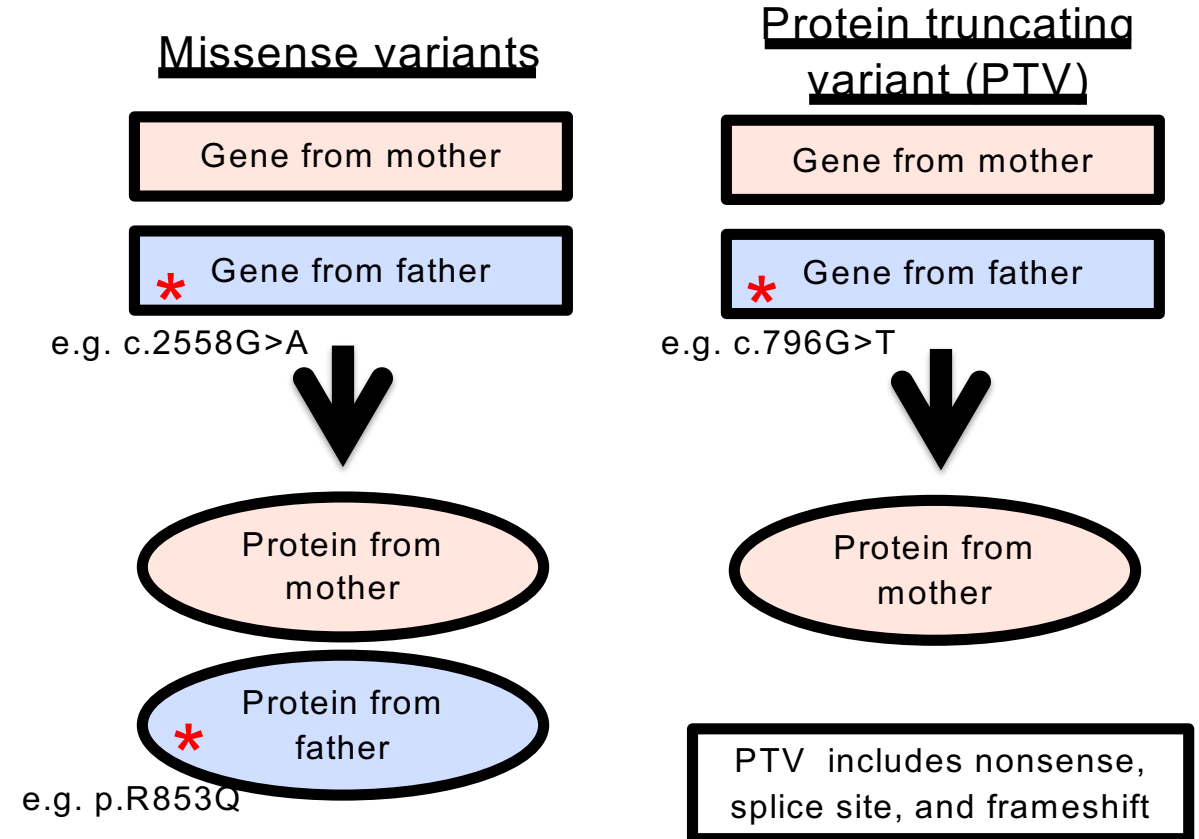


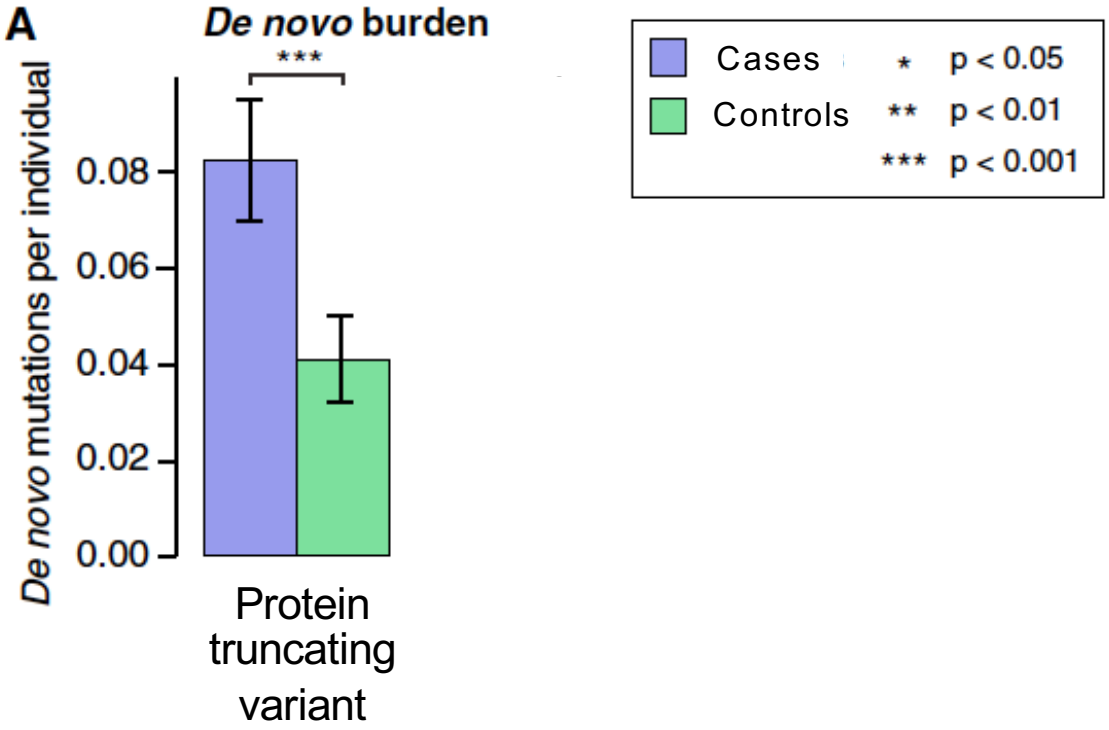
Rarer variants have greater potential to transmit ASD risk due to natural selection



Missense variants **alter** one copy of a protein, LoFs **disrupt** one copy of a protein



An excess of *de novo* protein truncating variants in ASD cases shows they contribute to ASD risk



Sanders et al, Neuron, 2015

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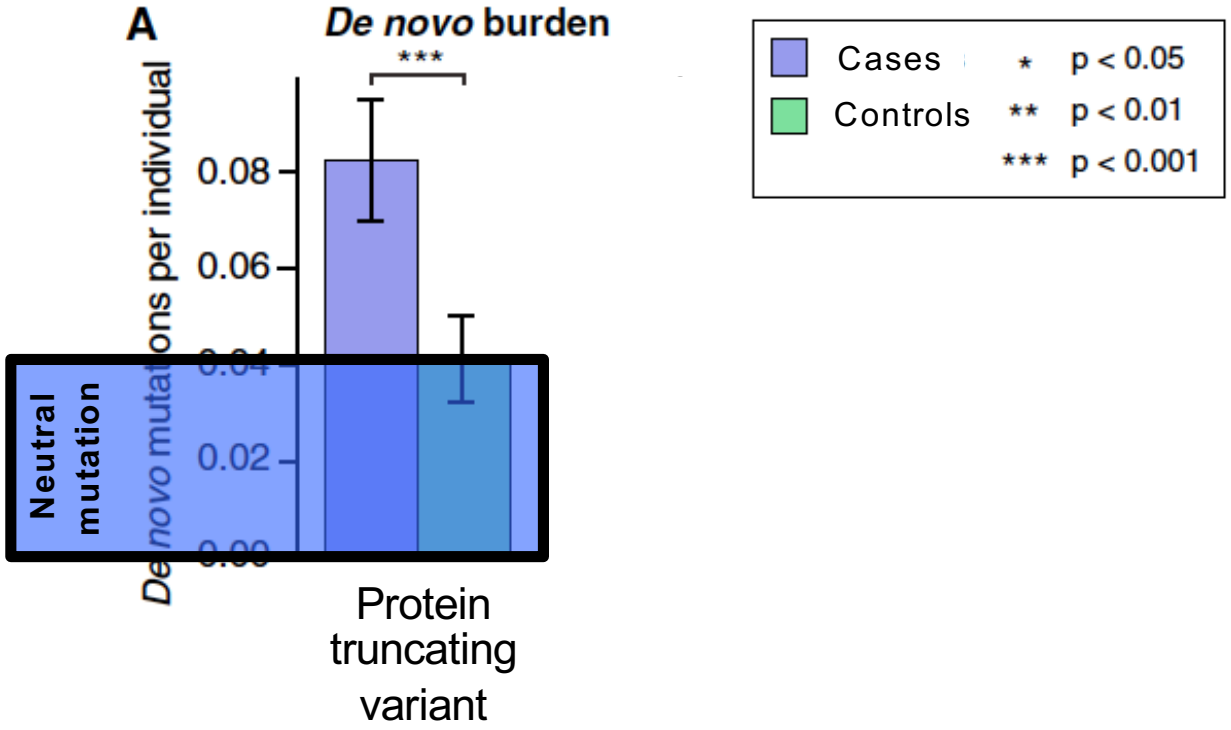

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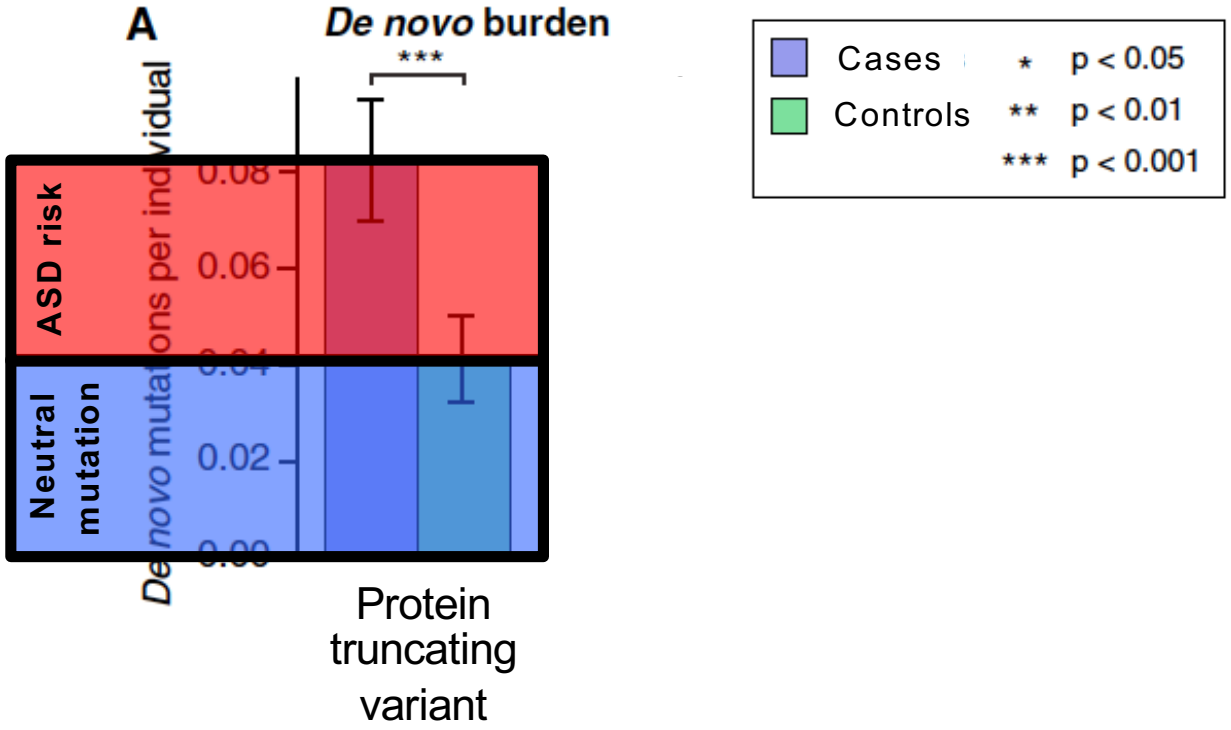

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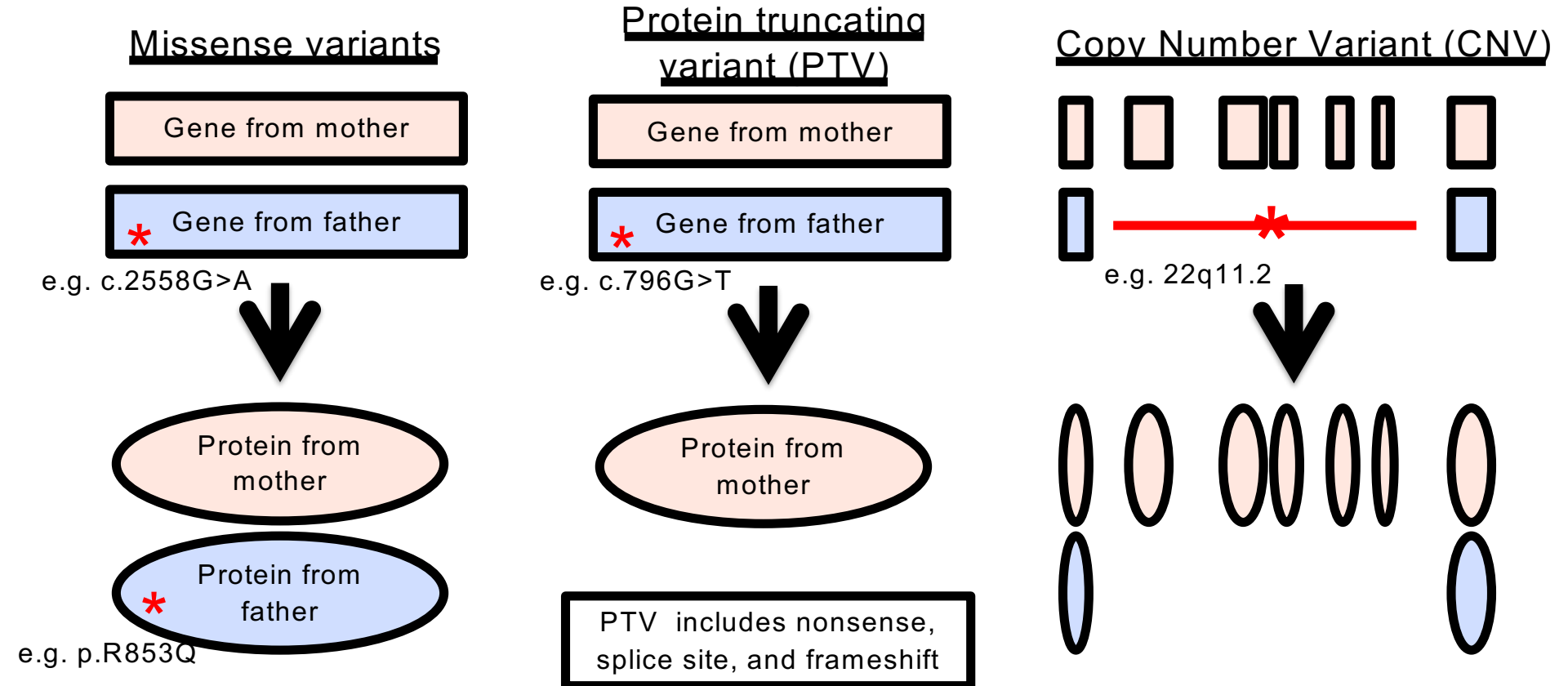
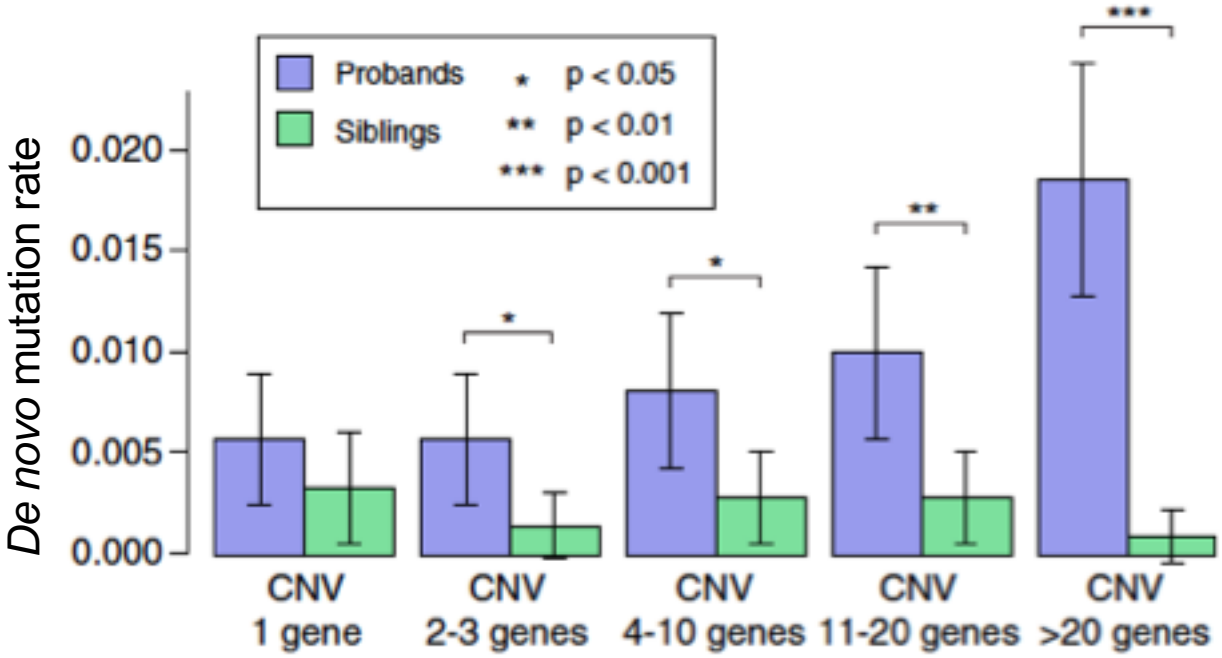
- Using gene microarrays, ASD-associated *de novo* CNVs are found in ~3% of children with ASD (>10-fold increase in risk)
  - Sebat *et al. Science* 2007, replicated in Pinto *et al. Nature* 2010, Sanders *et al. Neuron* 2011, Pinto *et al. AJHG* 2014, Sanders *et al. Neuron* 2015 (over 4,000 cases), and many others

Missense variants **alter** one copy of a protein, LoFs **disrupt** one copy of a protein, copy number variants (CNVs) **disrupt** one copy of multiple proteins



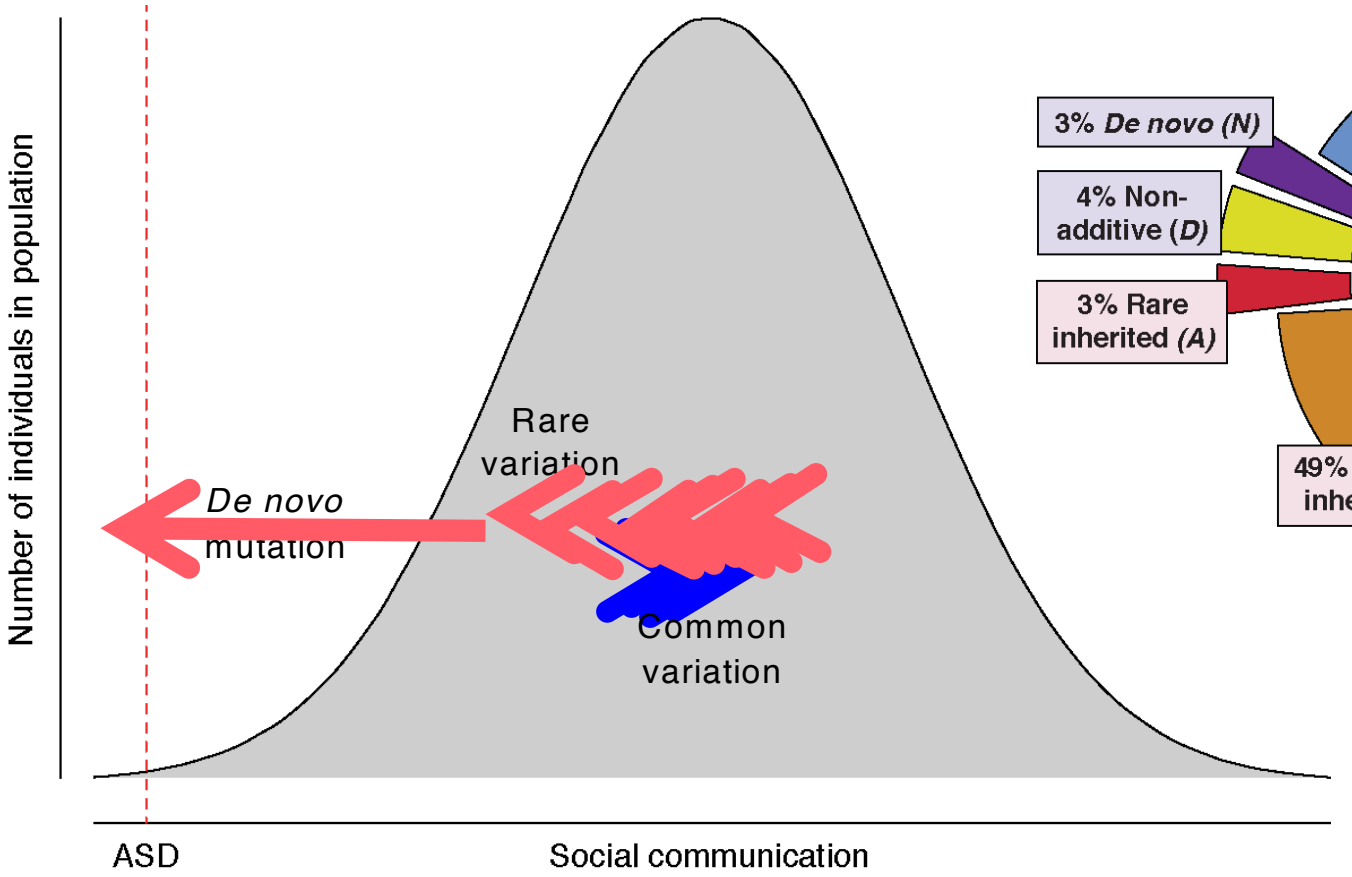
Individuals with a diagnosis of ASD have more *de novo* CNVs than unaffected controls

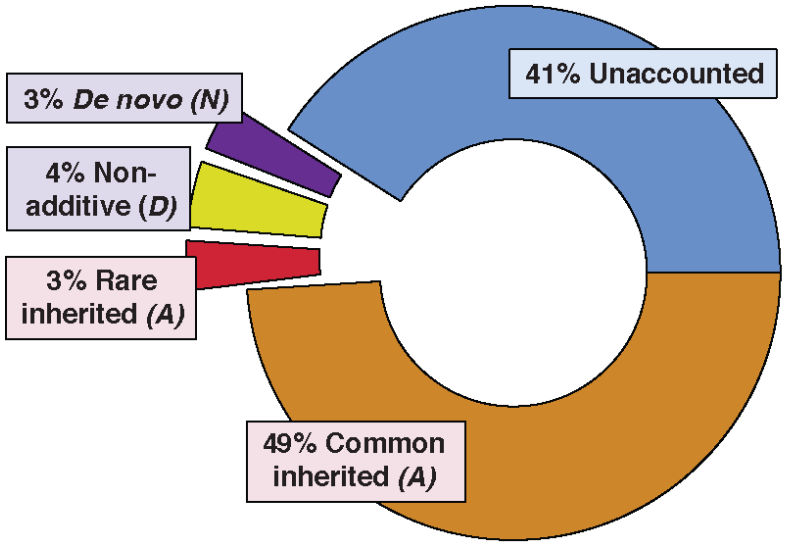
1,991 ASD cases and 1,991 unaffected sibling controls



Sanders *et al. Neuron* 2015

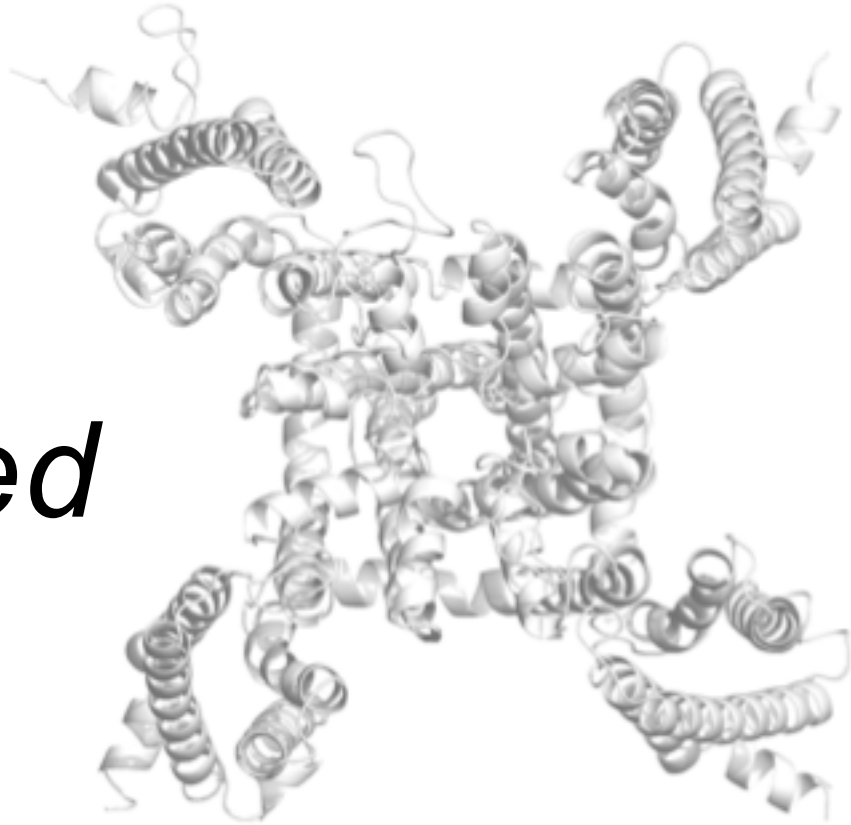
ASD is a frequently a combination of *de novo*, rare, and common variants





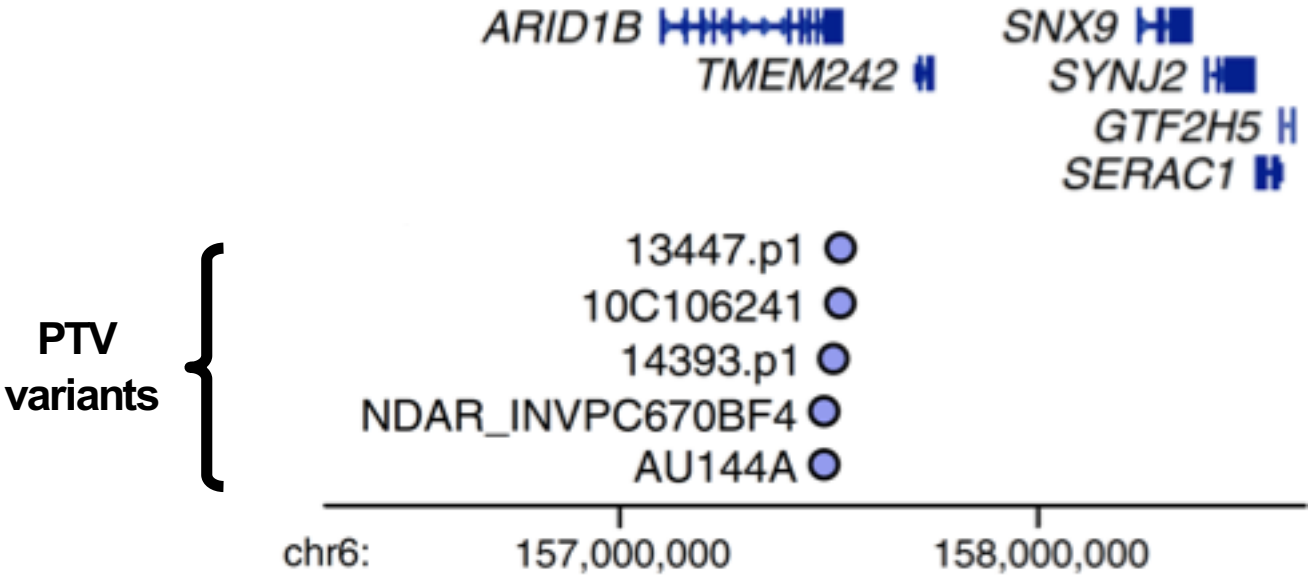
Gaulger *et al.* 2014

Finding genes linked to ASD



Nav1.2 structure from AJ Campbell, Broad

To distinguish risk mutations from neutral mutations, we identify genes with clusters of mutations



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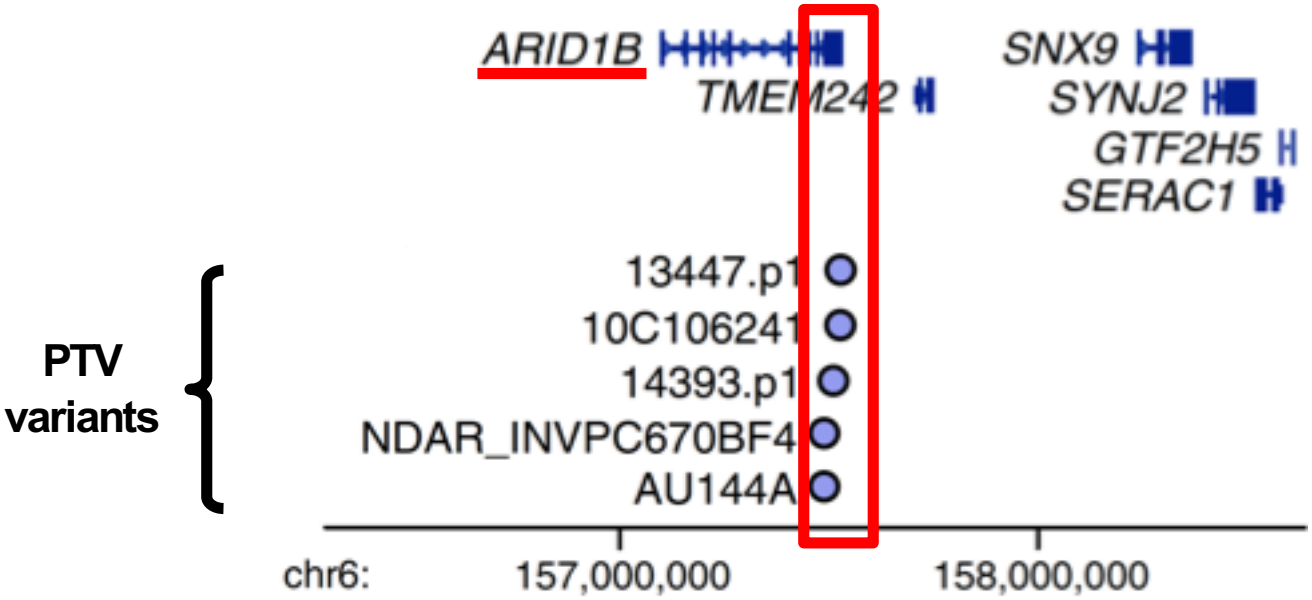

Sanders et al. *Neuron* 2015

Assessment of ~8,000 ASD cases has identified 65 ASD risk genes: a constellation of cryptic syndromes

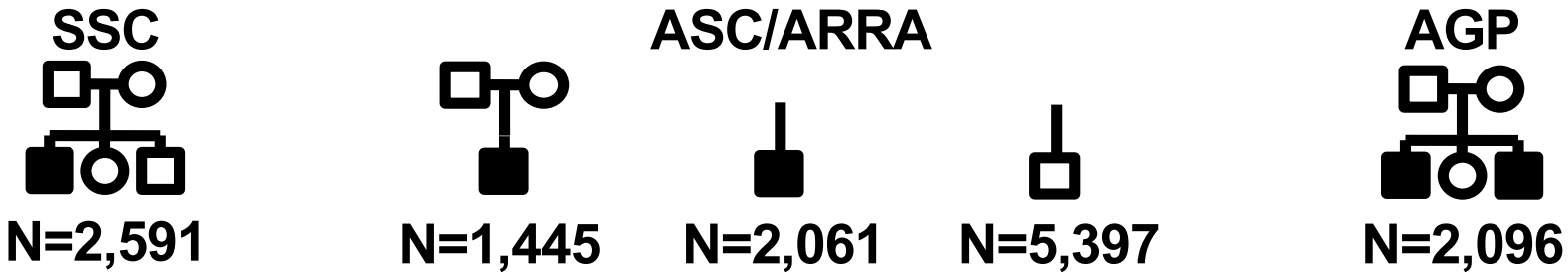

Table 4. Integrating Small De Novo Deletions in TADA Identified 65 ASD Genes

dnLoF Count	FDR ≤ 0.01	0.01 < FDR ≤ 0.05	0.05 < FDR ≤ 0.1
≥2	*ADNP, ANK2,* ***ARID1B****, ASH1L,* ***CHD2****, CHD8, CUL3, DSCAM, DYRK1A, GRIN2B, KATNAL2, KDM5B,* ***KMT2C****, NCKAP1, POGZ, SCN2A, SUV420H1,* ***SYNGAP1****, TBR1,* ***TCF7L2****,* ***TNRC6B****, WAC*	*BCL11A, FOXP1, GIGYF1, ILF2, KDM6B, PHF2, RANBP17, SPAST, WDFY3*	*DIP2A, KMT2E*
1	***NRXN1****, PTEN,* ***SETD5****,* ***SHANK2****,* ***SHANK3****,* ***TRIP12***	*DNMT3A, GABRB3,* ***KAT2B****, MFRP, MYT1L, P2RX5*	*AKAP9, APH1A, CTTNBP2, ERBB2IP, ETFB, INTS6, IRF2BPL,* ***MBD5****, NAA15, NINL, OR52M1, PTK7, TRIO, USP45*
0	–	*MIB1, SLC6A1, ZNF559*	*ACHE, CAPN12,* ***NLGN3***

Genes with a small de novo deletion are in bold. FDR, false discovery rate.

Sanders *et al.* Neuron, 2015

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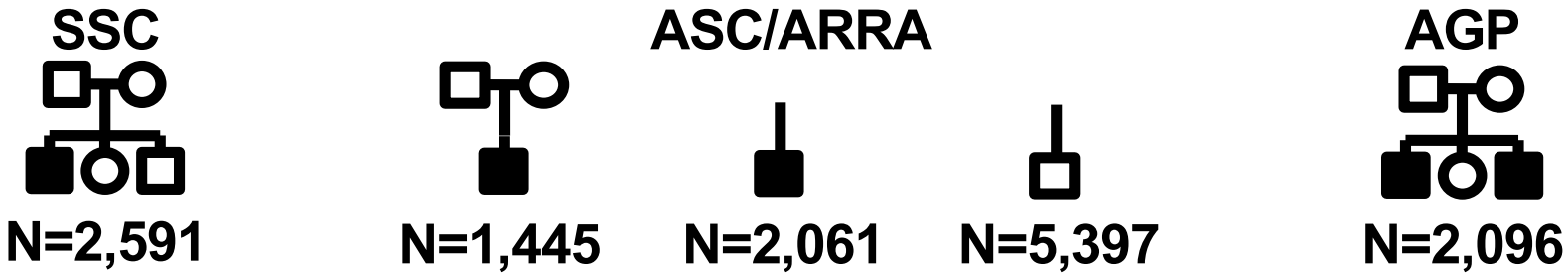

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1	***NRXN1****, PTEN,* ***SETD5****,* ***SHANK2****,* ***SHANK3****,* ***TRIP12***	*DNMT3A, GABRB3,* ***KAT2B****, MFRP, MYT1L, P2RX5*	*AKAP9, APH1A, CTTNBP2, ERBB2IP, ETFB, INTS6, IRF2BPL,* ***MBD5****, NAA15, NINL, OR52M1, PTK7, TRIO, USP45*
0	–	*MIB1, SLC6A1, ZNF559*	*ACHE, CAPN12,* ***NLGN3***

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Sanders *et al.* Neuron, 2015

Trends in
Neurosciences
Volume 41 Number 7
July 2018
ISSN 0166-2236

Review

Progress in Understanding and Treating *SCN2A*-Mediated Disorders

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SCN2A in Neurodevelopmental Disorders

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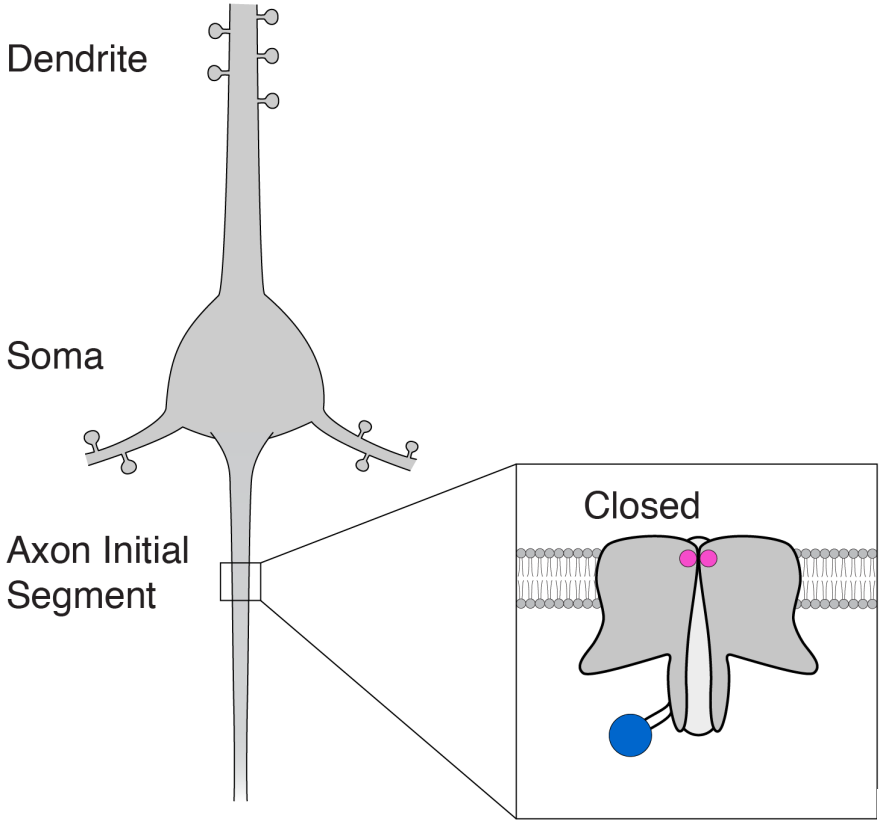
Simons Variation in Individuals Project

SCN2A/$Na_V1.2$ initiates the action potential at the axon initial segment



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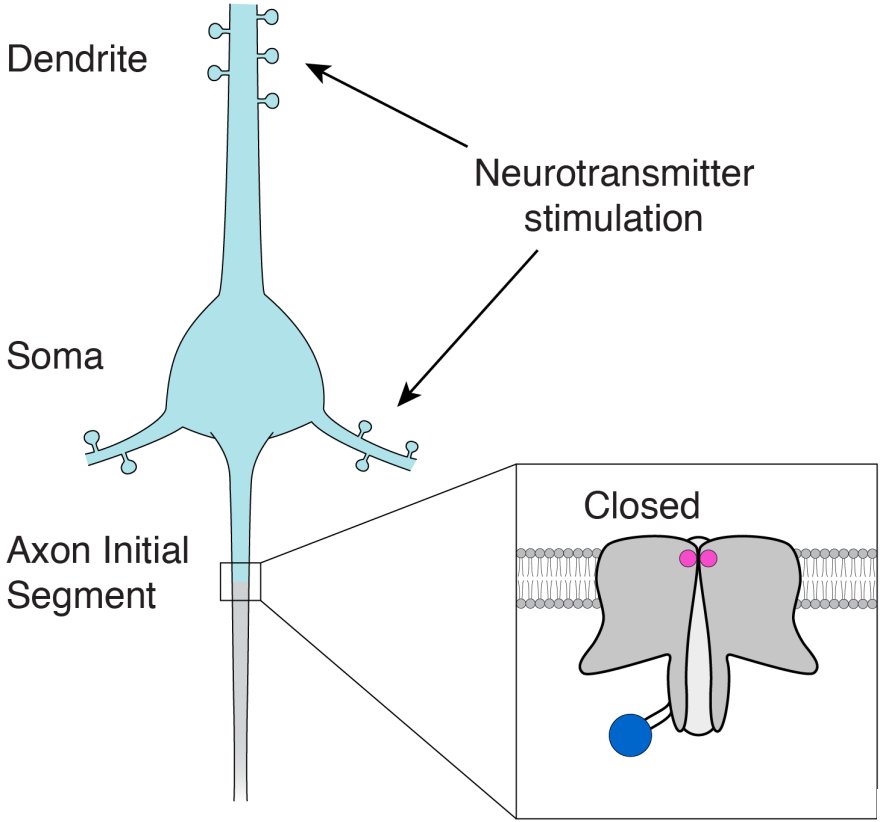

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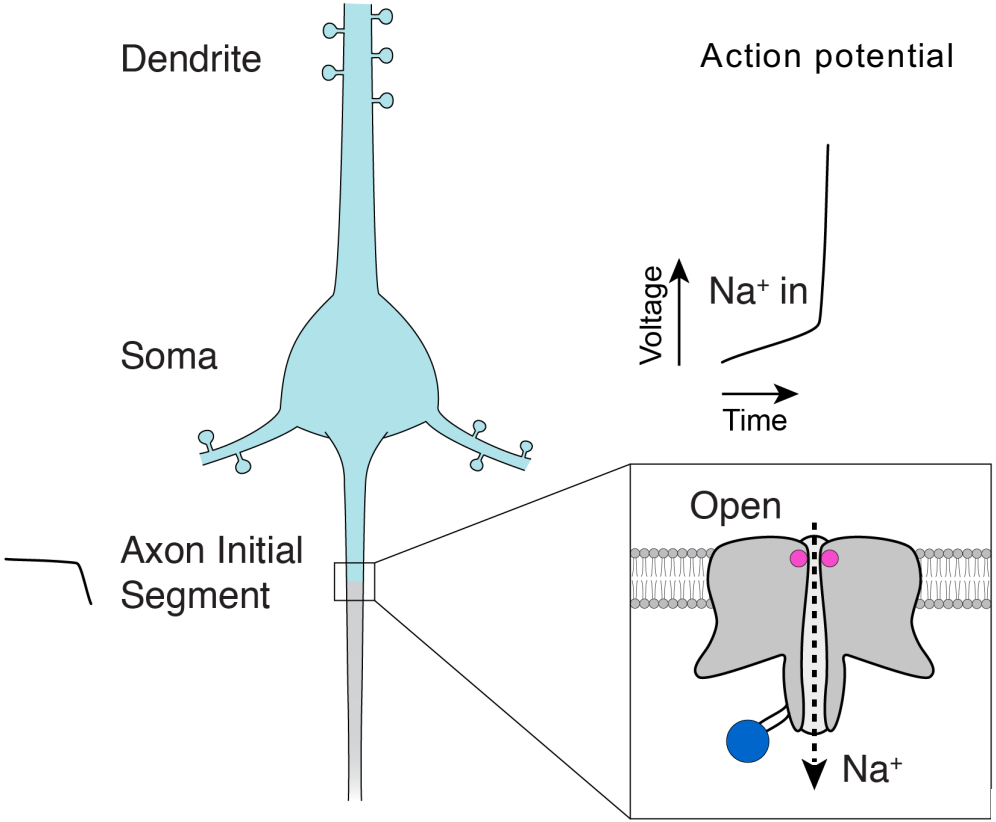

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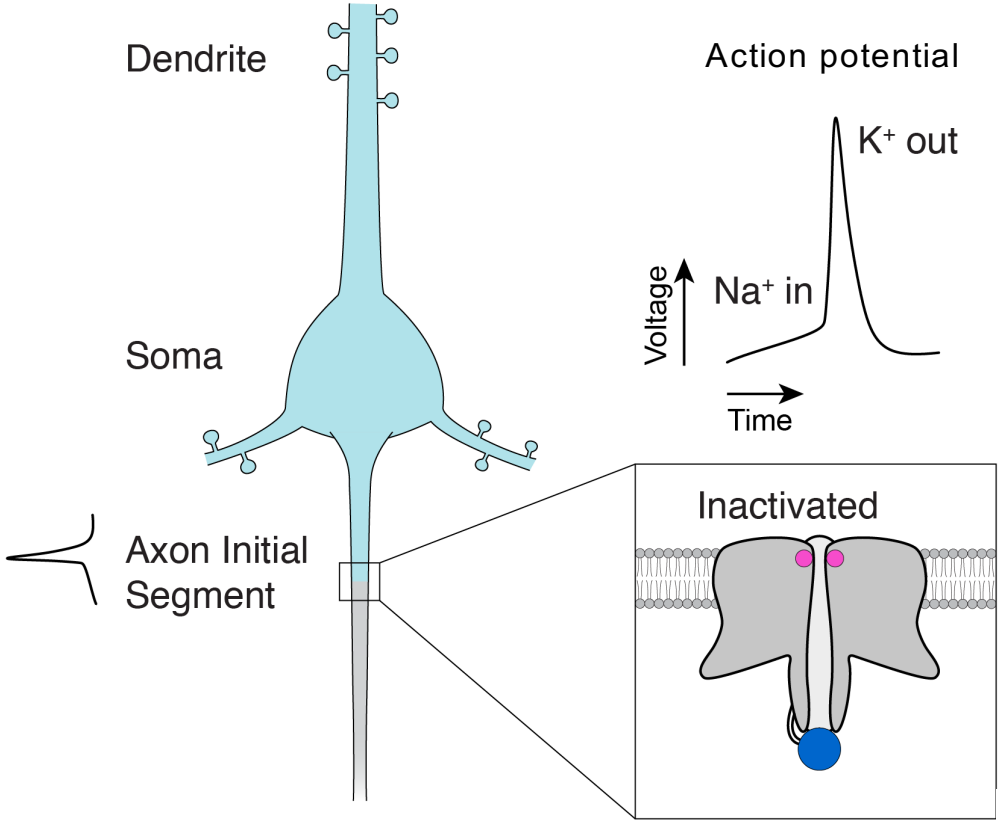

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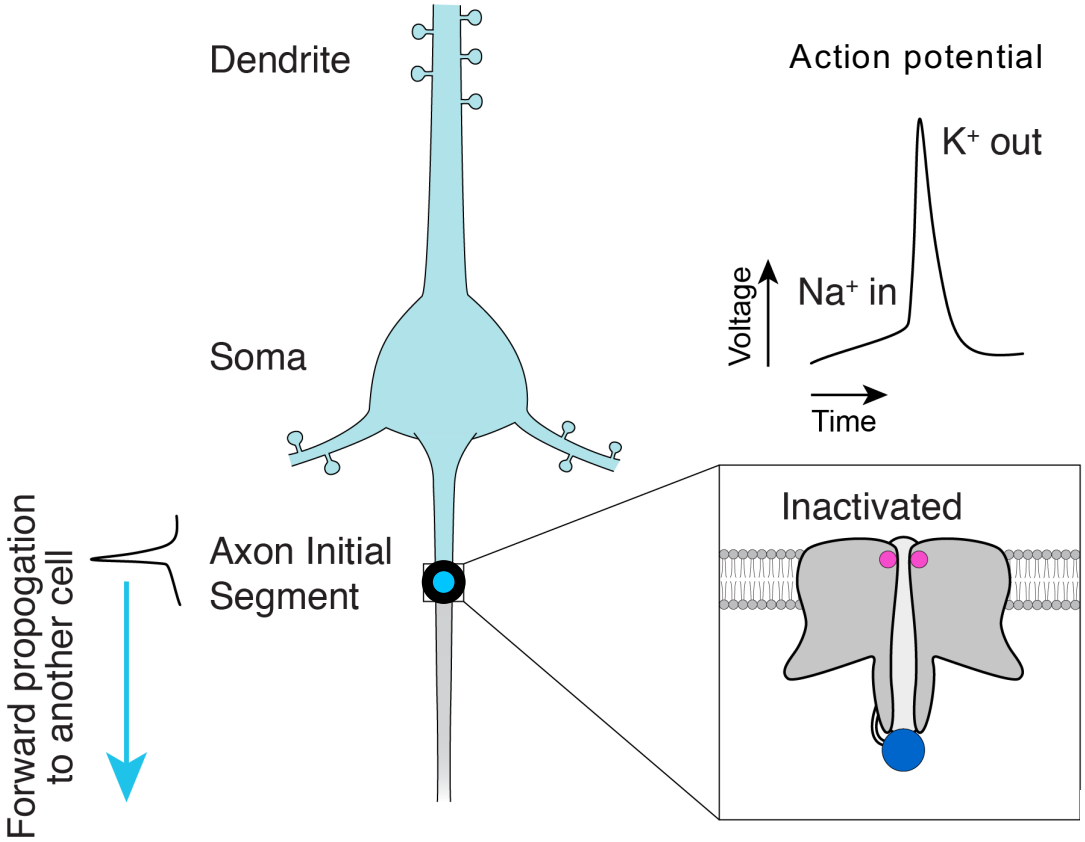

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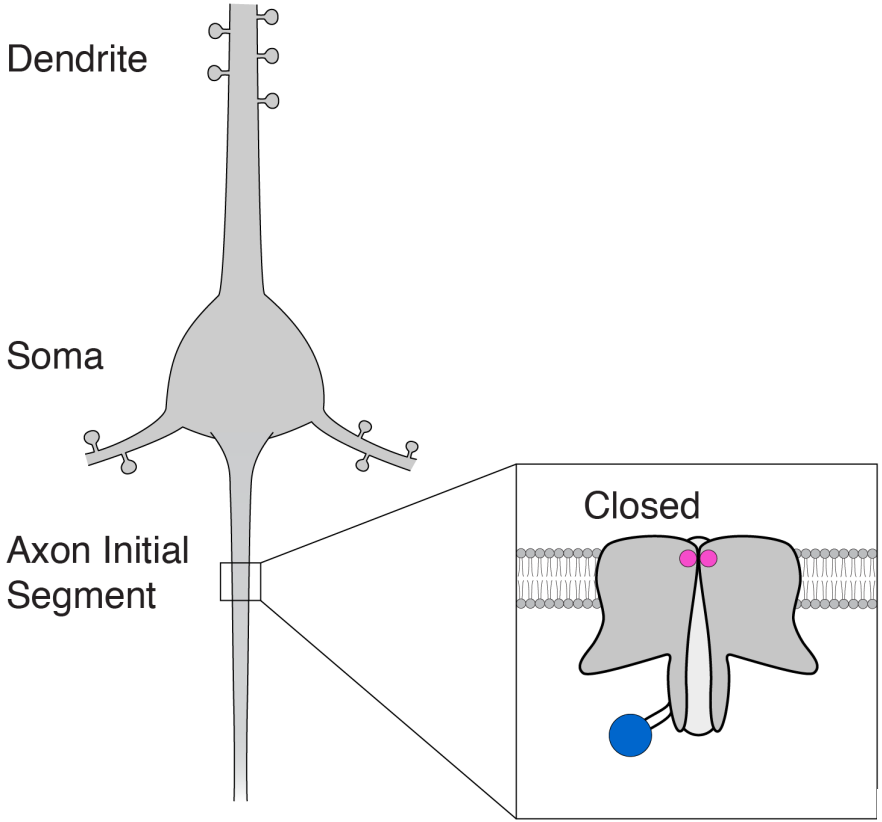

Along with ASD, genetic variants in *SCN2A* are associated with three disorders

	Disorder name	Infantile Seizures (<12mths)	Ongoing seizures (>2yrs)	Developmental delay
BIS	Benign (familial) infantile seizures	Y	N	N
IEE	Infantile epileptic encephalopathy	Y	Y	Y
ASD/ID	Autism Spectrum Disorder/ID	N	~25%	Y

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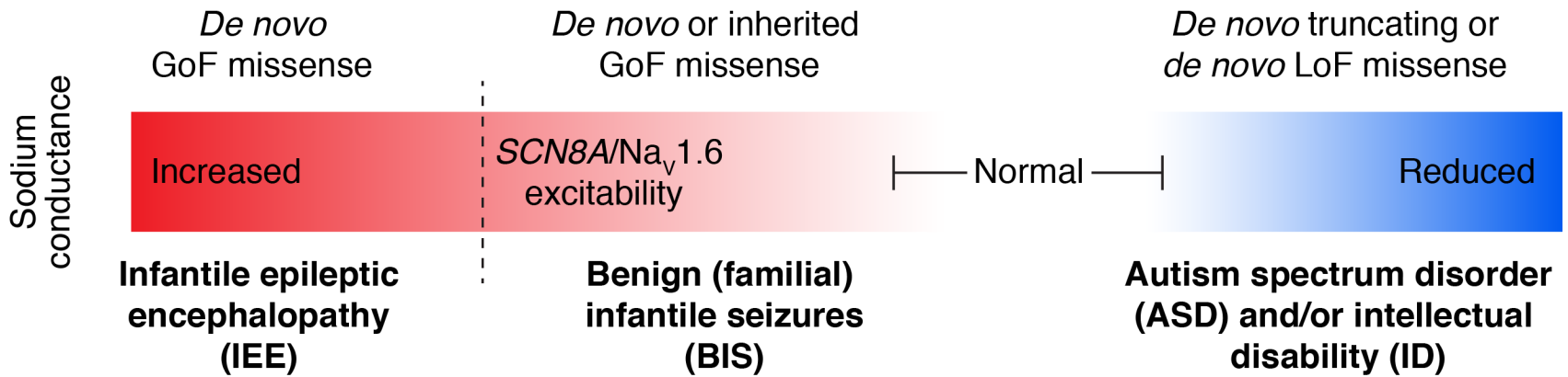
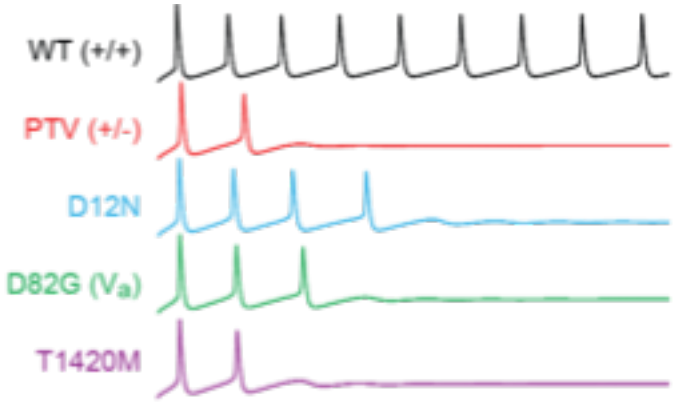
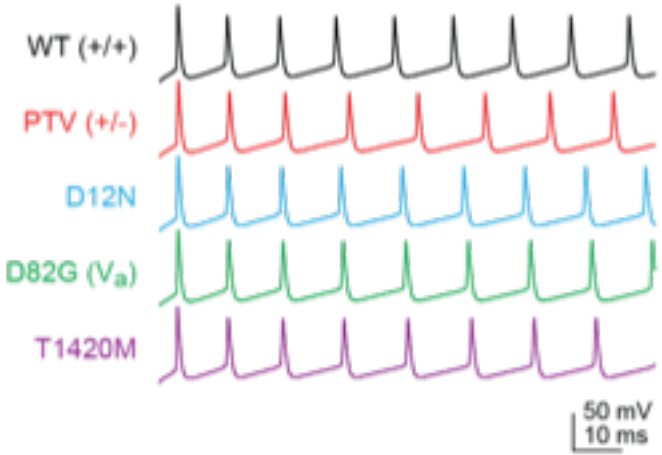


Loss of function in one copy of *SCN2A* makes excitatory neurons less excitable during development

Before 1yr of age



After 1yr of age

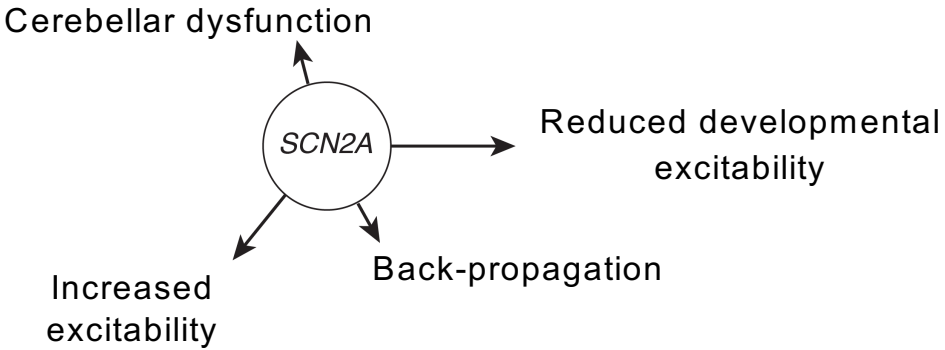


Ben-Shalom et al., 2017

Understanding the role of one gene provides some insight into when and how ASD occurs

- A 50% reduction in *SCN2A* function leads to ASD
- This implicates excitatory neurons in ASD
- It suggests that a reduction in neuron excitability may be involved
- It suggests that the “cause” of ASD occurs before 1yr of age

Since each gene has multiple functions, how do we know which functions lead to specific symptoms?



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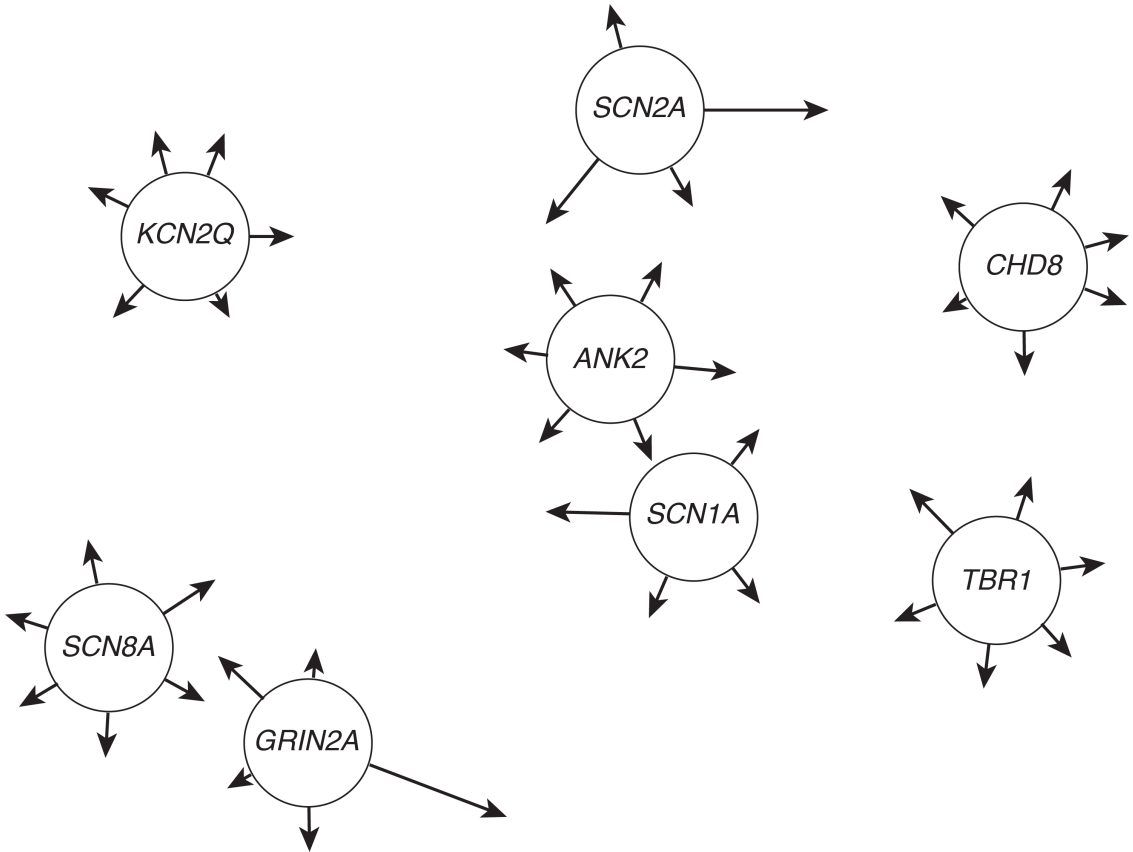

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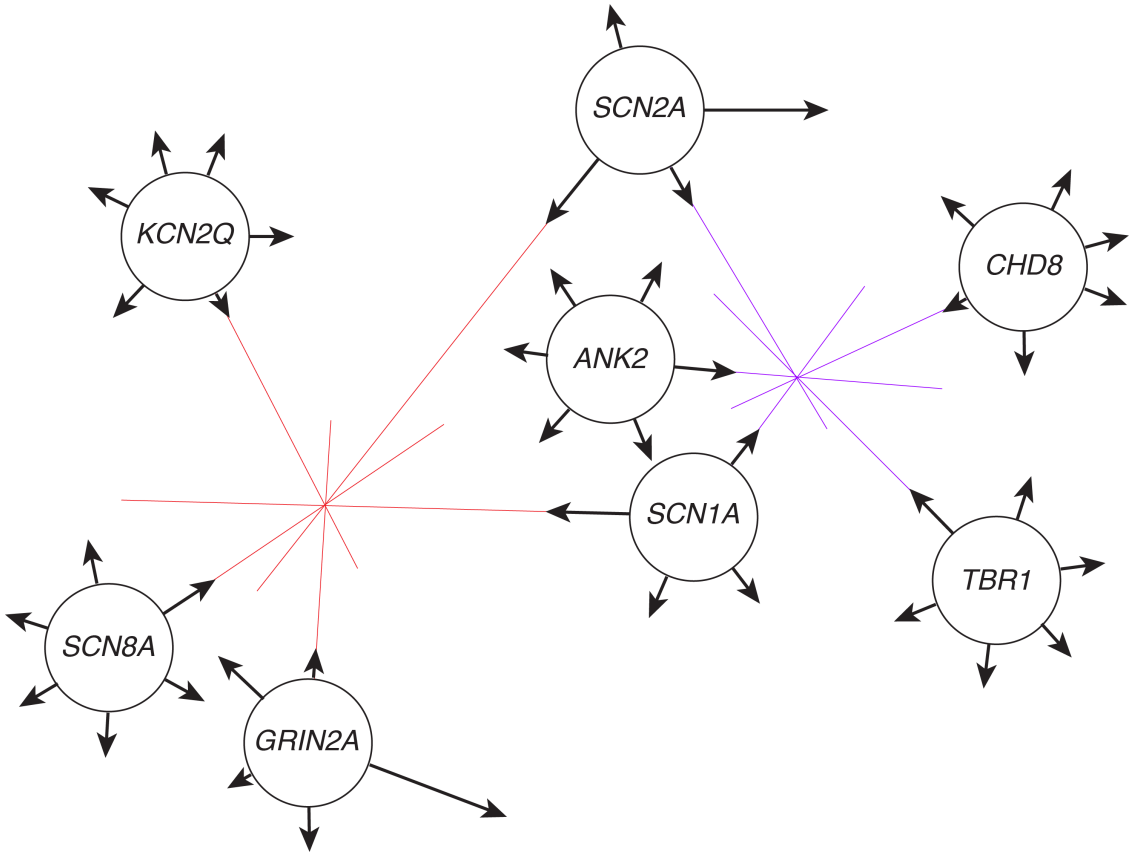

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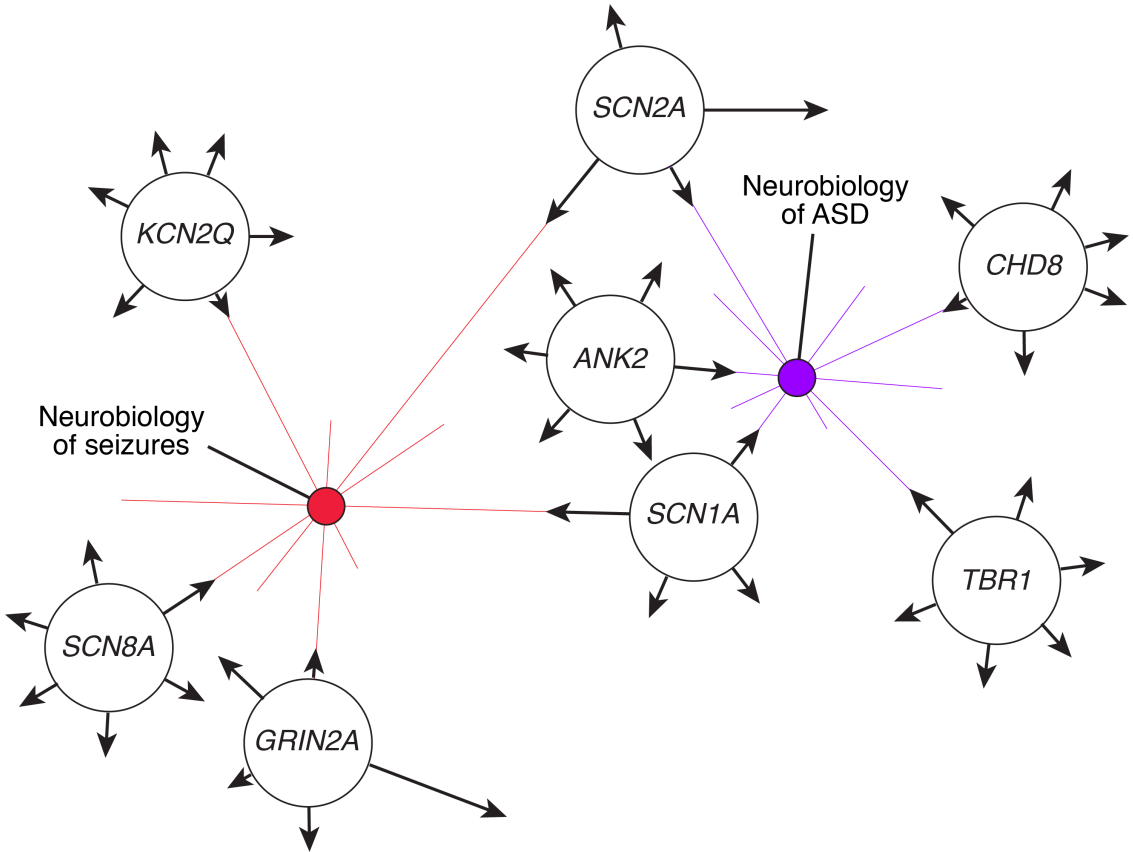
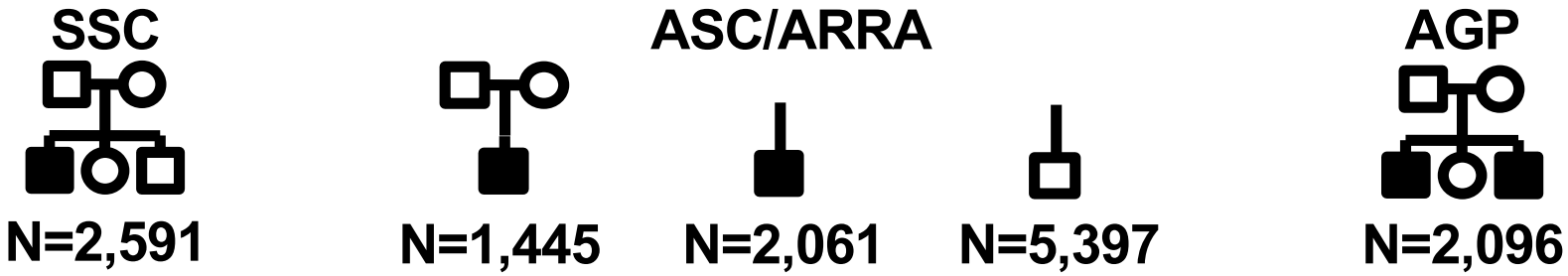


Assessment of ~8,000 ASD cases has identified 65 ASD risk genes: a constellation of cryptic syndromes



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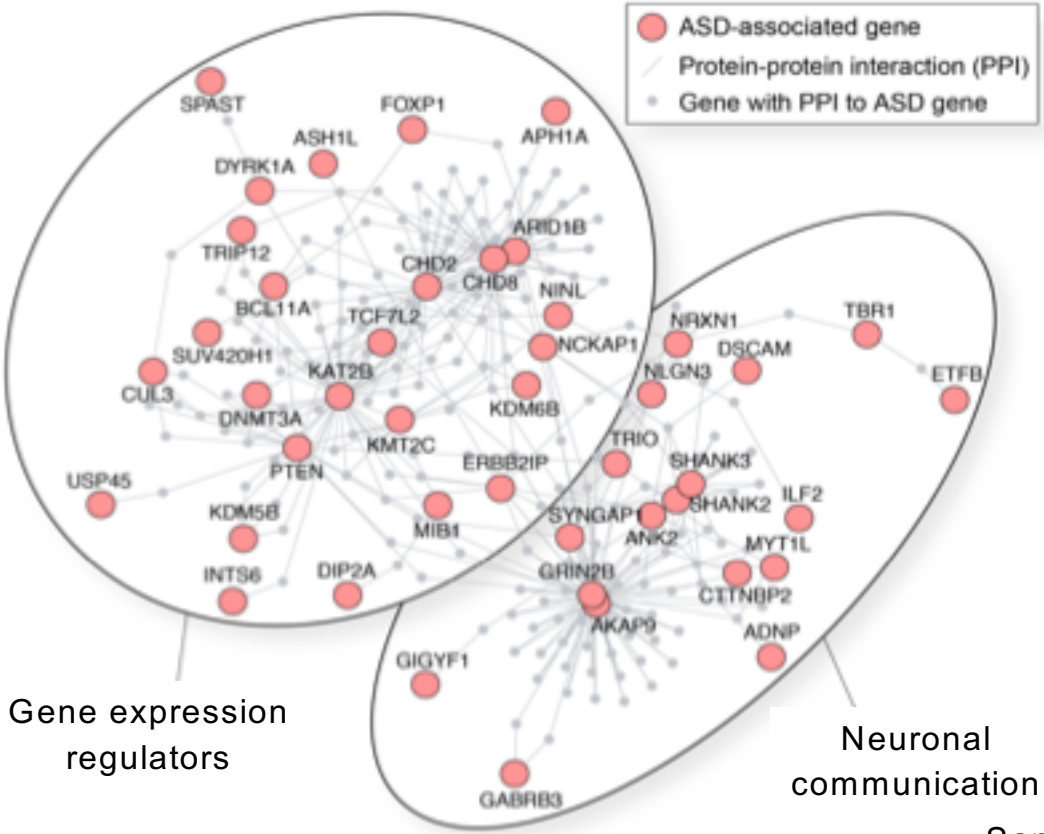
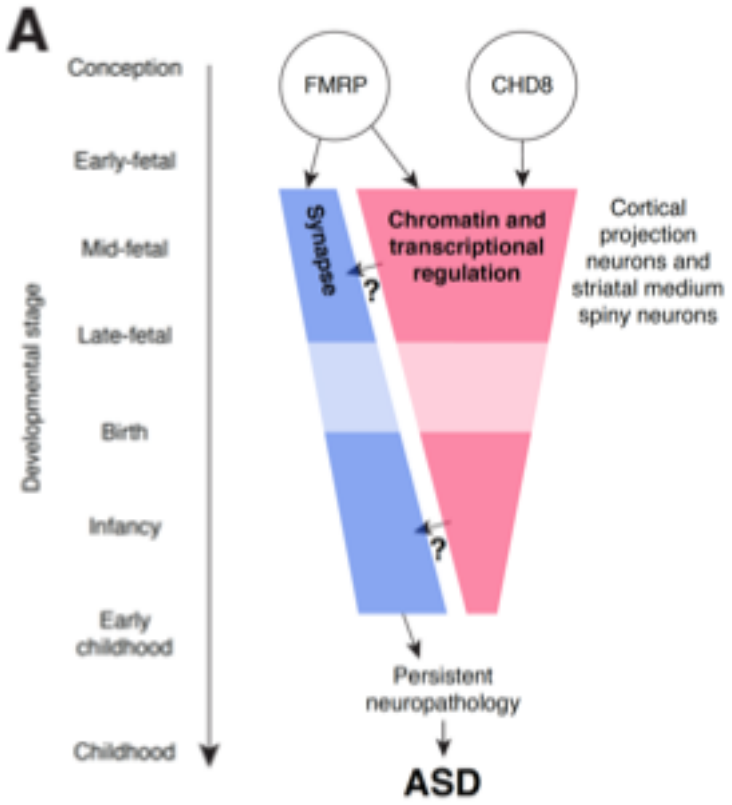
Sanders *et al.* Neuron, 2015

The 65 ASD risk genes converge on chromatin and synaptic networks



Sanders *et al.* Neuron, 2015

By considering the ASD-associated genes alongside other datasets, we can start to understand the 20,000ft view



BRAINSPAN
ATLAS OF THE DEVELOPING HUMAN BRAIN

PsychENCODE Knowledge Portal

GTEx Portal

ENCODE: Encyclopedia of DNA Elements

Sanders SJ *Curr Opin Genet Dev* 2015

Considering multiple genes in together also provides insight into when and how ASD occurs

- Two main groups of ASD-associated genes involved in:
  - Gene expression regulation
  - Neuronal communication
- Implicates prefrontal cortex in mid-fetal development
- Enriched for excitatory neurons and striatal neurons

Summary

- There is strong evidence that genetic factors play a role in ASD
  - Twin studies
  - Family studies
  - Syndromes
  - *De novo* mutations
- *De novo* mutations have identified ~65 genes associated with ASD
- These genes are providing insight into ASD etiology
  - Gene expression and neuronal communication
  - Early development (<1yr)
  - Excitatory neurons in the cortex
- Environmental factors are likely to be involved
  - Harder to search for than genetic factors

Useful information sources of ASD information

- Spectrum: https://www.spectrumnews.org
- Autism Science Foundation: https://autismsciencefoundation.org
- Autism Society: http://www.autism-society.org
- International Society for Autism Research: https://www.autism-insar.org