Understanding the Genetics of Autism

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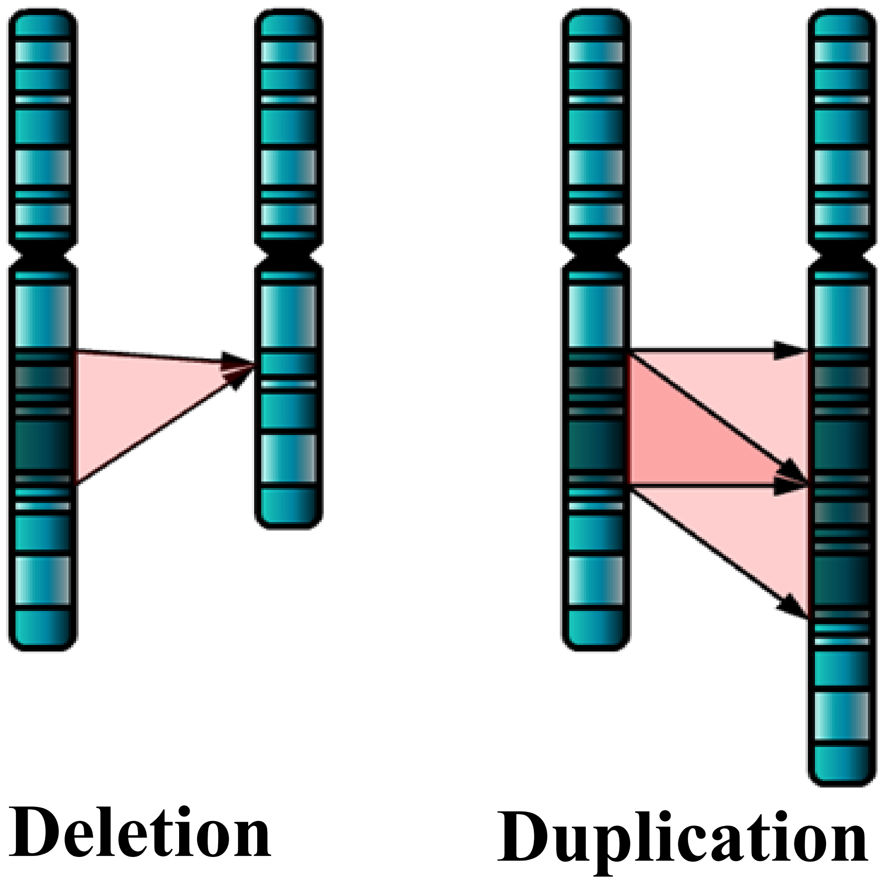
Autism

- Autism is a neurodevelopmental in origin and characterized by a triad of impairments—speech delay, impaired social interactions and repetitive behaviors
- Prevalence of 1 of 36 children (CDC)
- Autism is an umbrella term that has gotten larger over the years
- Significant comorbidity with intellectual disability, epilepsy and other neuropsychiatric conditions

Genetics of Autism

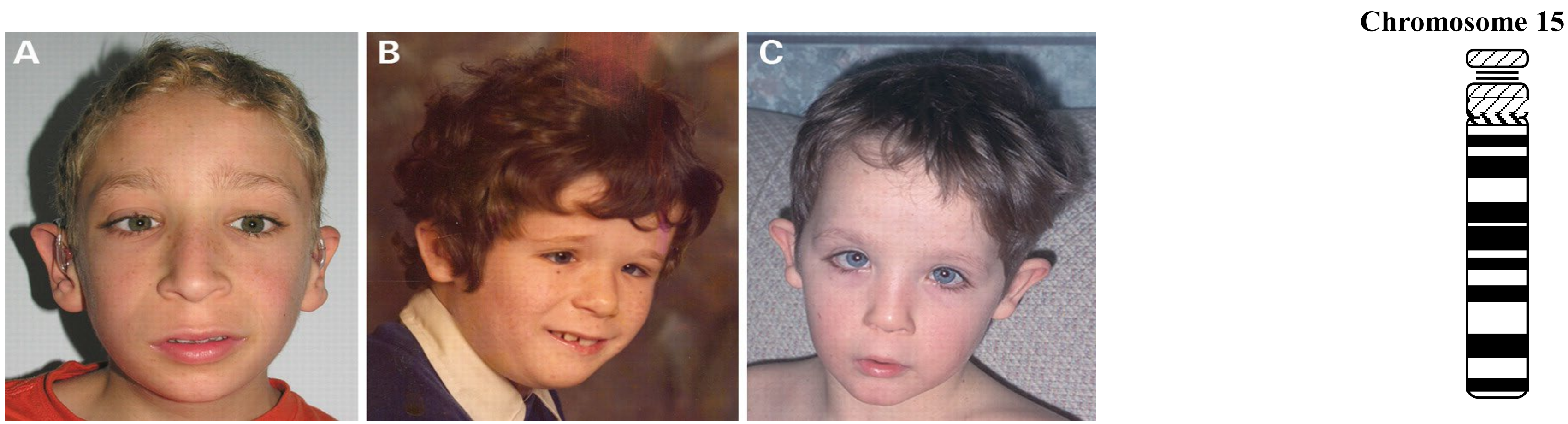
- Strong genetic component—>50%
- ~70-90% of identical twins are concordant for autism vs. 5-20% for sibs
- Sex bias:
  - Developmental delay ~1.4 male : female
  - **Autism (DSM-IV) ~4 male : female**
  - Asperger ~6 male : female
- Searches for common genetic variation uncovered few consistent genes
- Rare inherited forms account for 5-8%
- Where's the rest?

Excess of Large Copy Number Variants (CNVs) in Patients (~2005-2010)



de Vries *et al.*, 2005; Sharp *et al.*, 2006; Sebat *et al.*, 2007……


A
B
C
D
Chromosome 17

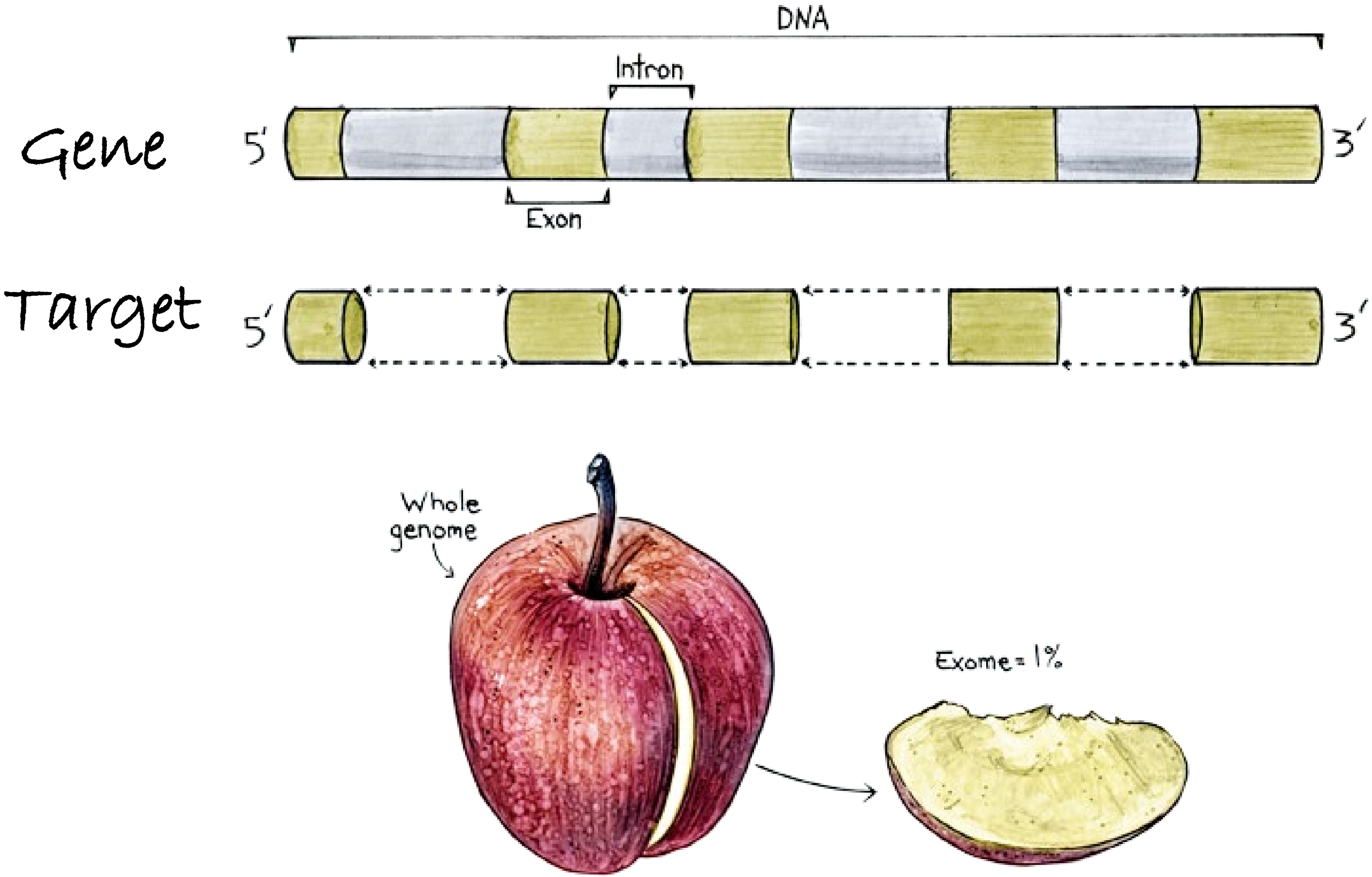

A
B
C
Chromosome 15


Chromosome 15

Lessons Learned from Large CNVs

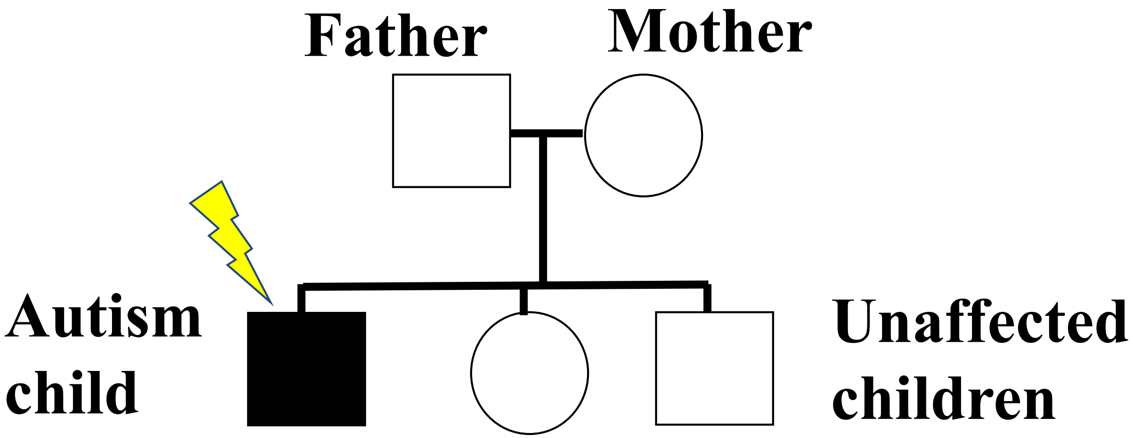
- Gene dosage imbalance and sporadic mutations
- Individually rare but collectively common (*de novo* and inherited)
- Large CNVs account for ~14-15 % intellectual disability—7-8% for autism spectrum disorders
- Problems
  - CNVs identify regions of genic imbalance but in most cases not specific genes
  - Most CNVs are of unknown significance

Targeting the Protein-Coding Sequence
“The Exome” (2010)



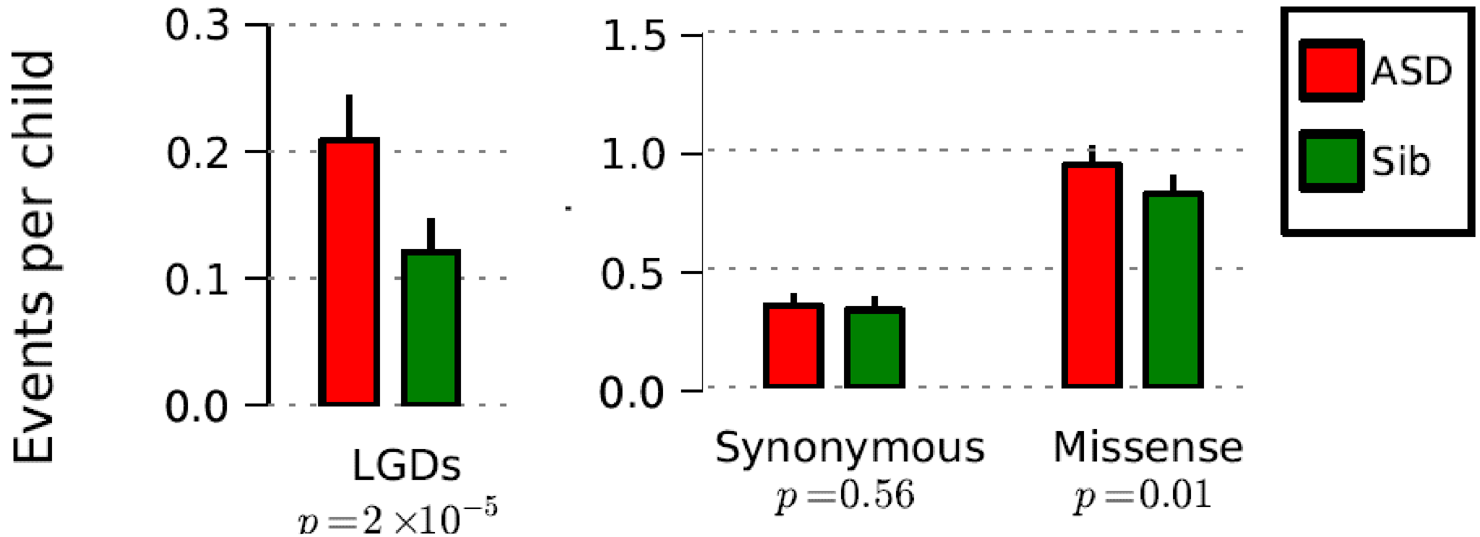
De novo Genetic Model

- Hypothesis: Excess of sporadic “gene-killing” mutations that only appear only in child with autism
- Exome sequence 2,517 autism families



- Goal: Discover genes and pathways that disrupt genes in autistic children but not parents.

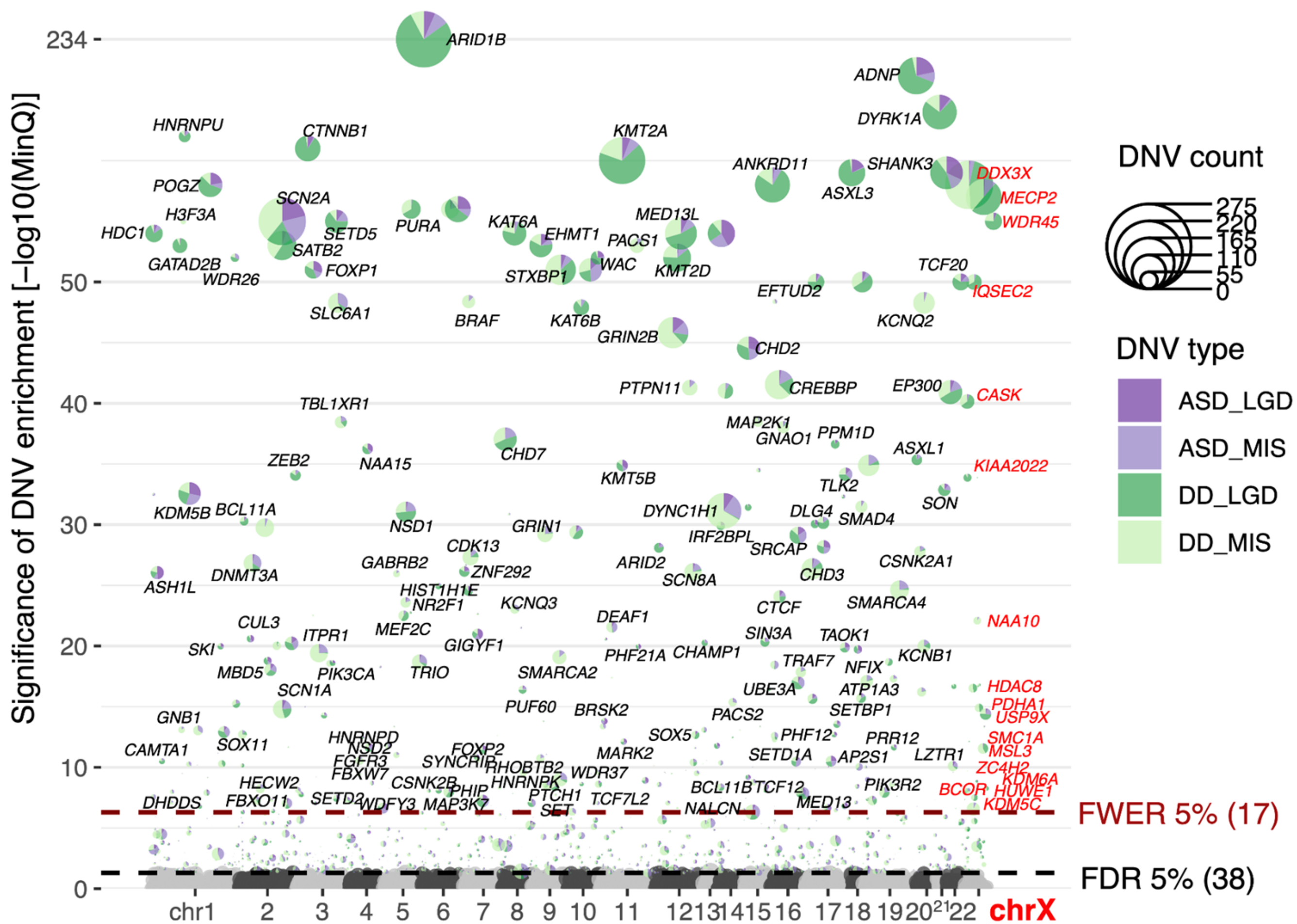
Types of New Mutations
Autism Probands vs. Unaffected Siblings



- **Good News**: >2-fold excess of *de novo* disruptive mutations when compared to unaffected siblings
- **Bad News**: Few genes hit recurrently; estimate 400-800 different genes cause autism but in each family it is a different gene or set of genes

Iossifov, O'Roak, Sanders et al., *Nature*, 2014; Krumm/Turner, *Nat Genet*, 2015

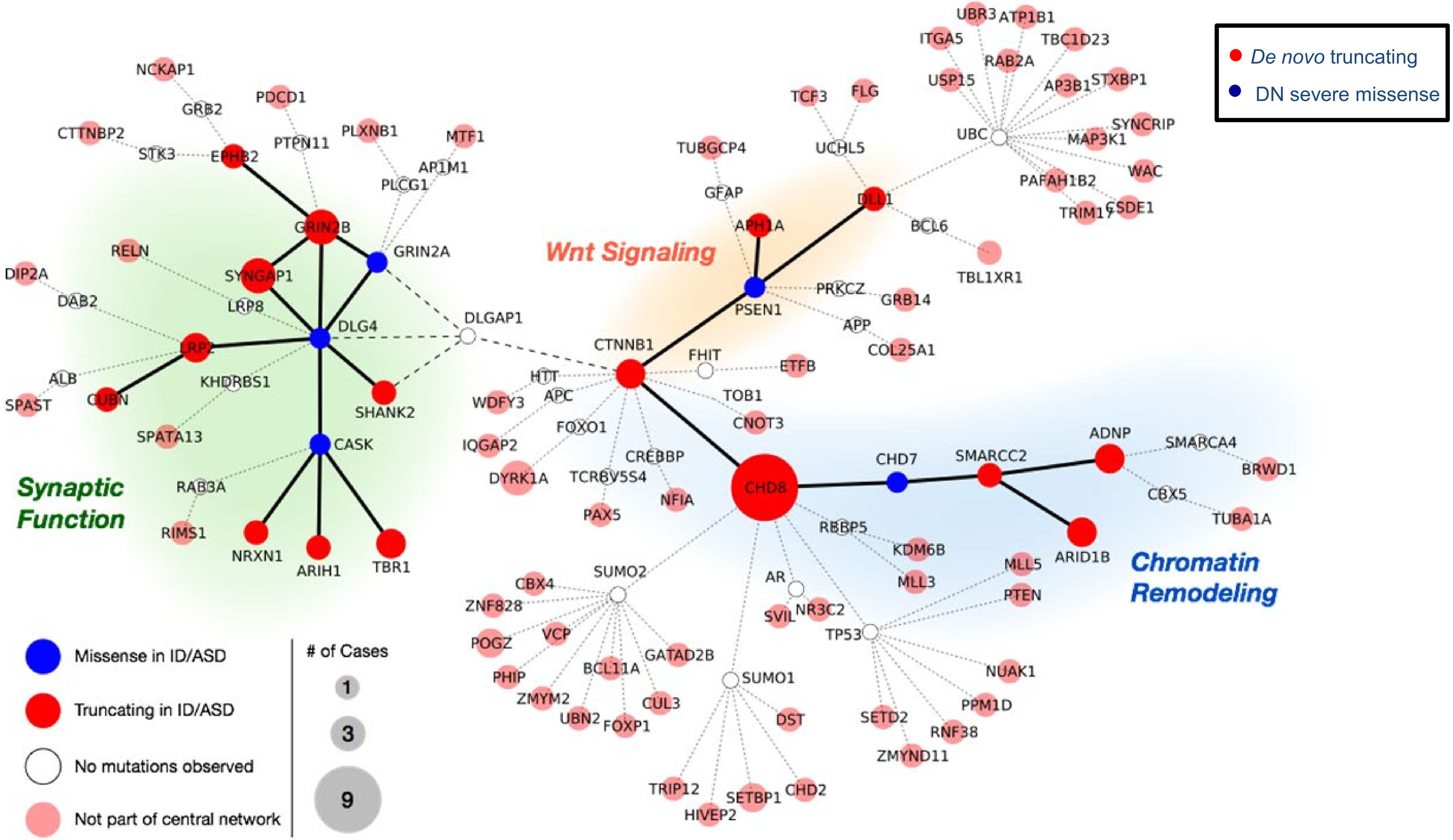
Autism/DD genes with excess of *de novo mutations*



- 61,121 families (15,065 ASD & 31,056 DD)
- 3 models
- 197 "autism" genes
- 612 candidate genes

Wang *et al*, PNAS, 2022, Sui et al. unpublished

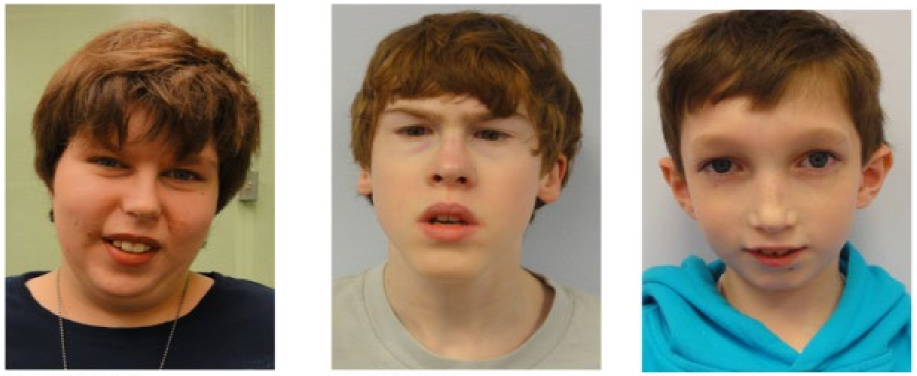
Autism Genes Group into Pathways



O'Roak et al., *Nature*, 2012; Krumm et al., *TINS*, 2014

DYRK1A Autism Subtype

Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A



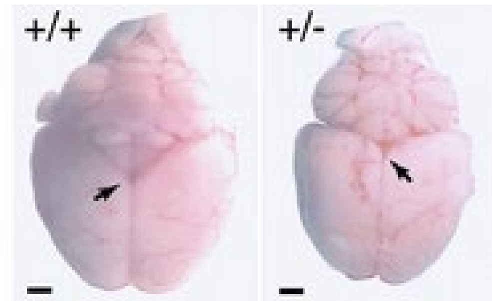
SSC13890 c.1098+1G>A

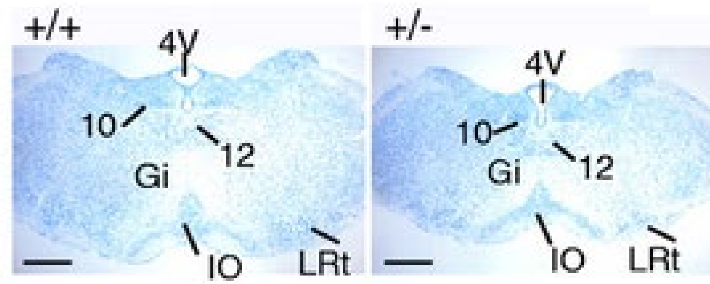
SSC12099 p.Ile48Lvsfs*2

SSC13552 p.Ala498Profs*94

- **98/ 61,121 families vs. 0/8,693 controls**
- **all are *de novo* and damaging($p<10^{-178}$)**
- 100% ID (mild to severe) & 100% microcephaly
- 89% late onset epilepsy; 75% anxiety
- 83% autism—severe impaired expressive language
- Typical facial features: pointed chin, high nasal bridge, foot abnormalities

Van Bon et al., *Mol Psych*, 2015 & unpublished

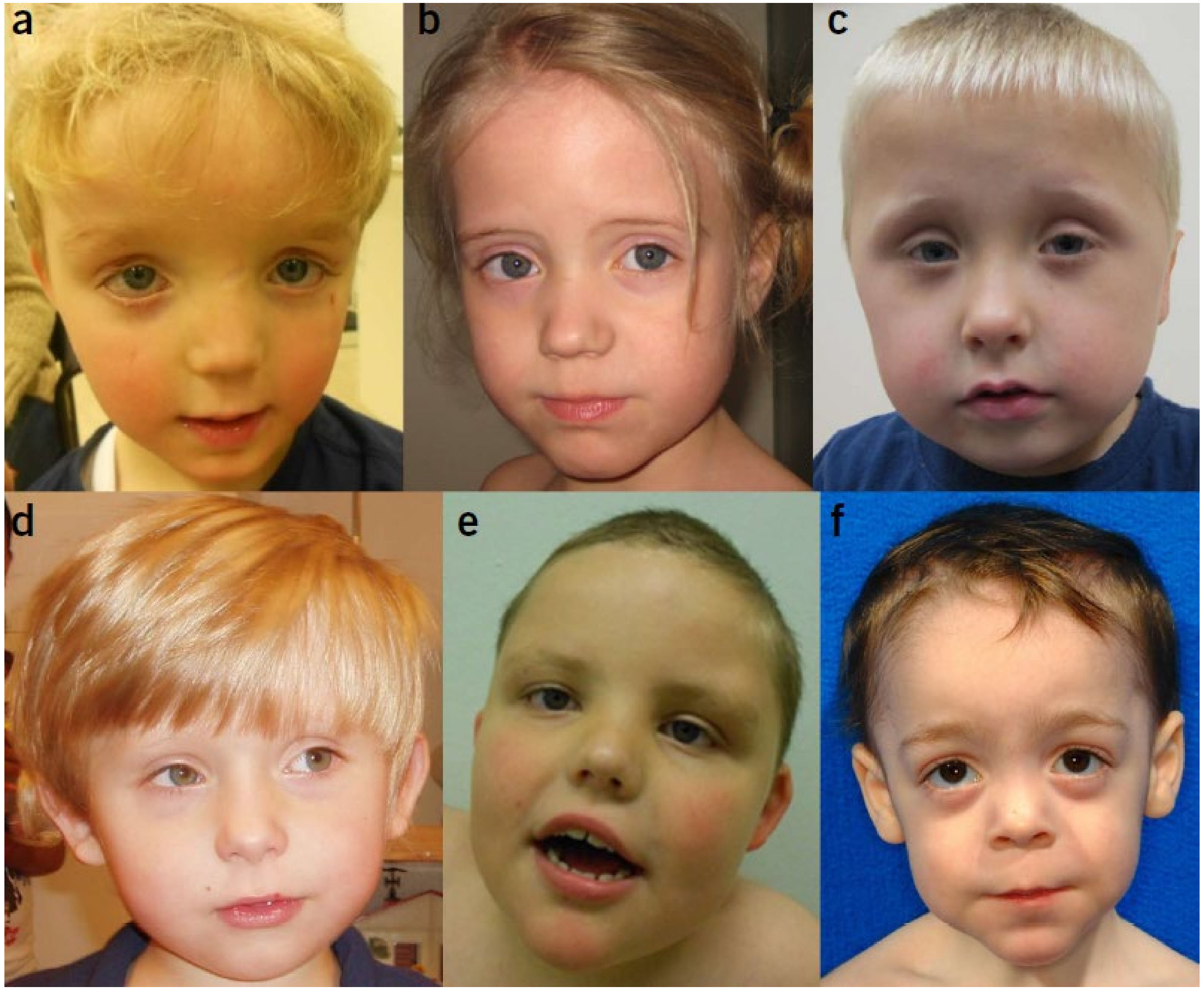




- Reduction in mesencephalic tectum and medulla oblongata
- Delay in preweaning behavior and reflexes; increased anxiety

Fotaki et al., *Mol Cell*, 2002

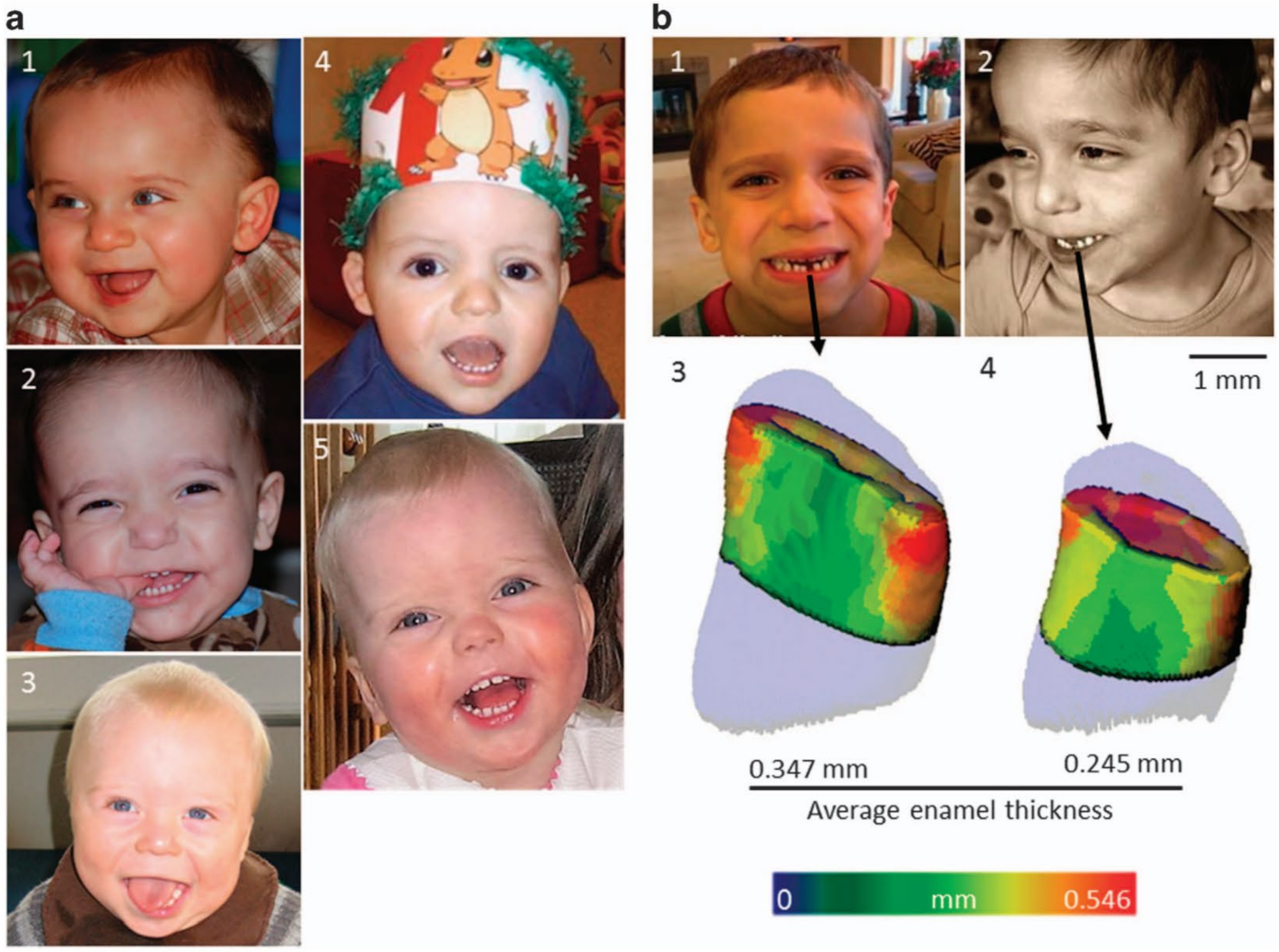
ADNP Autism Subtype
Activity dependent neuroprotective peptide



- **110 children /61,121 families**
- **all de novo damaging mutations ($p < 10^{-208}$)**
- 100% intellectual disability
- 100% autism
- 90% almost complete loss of expressive language
- 88% high hairline/frontal bossing
- 63% MRI abnormality

Helsmoortel et al., *Nat Genet*, 2014 & unpublished

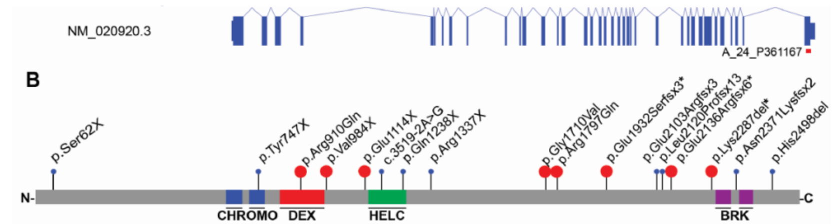
ADNP Kids:
Full Dental Eruption by 1 Year



Gozes et al., *Translational Pyschiatry*, 2017

CHD8 Autism Subtype

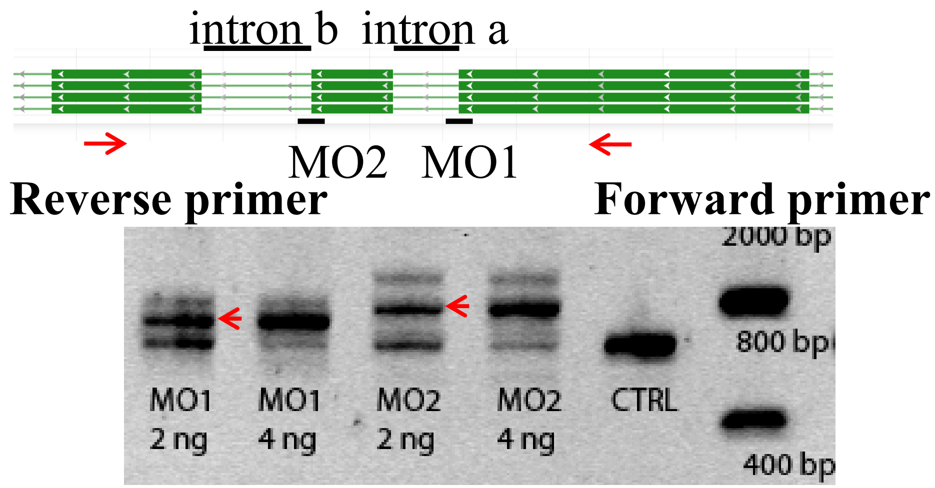
CHD8 Chromatin helicase DNA binding protein 8

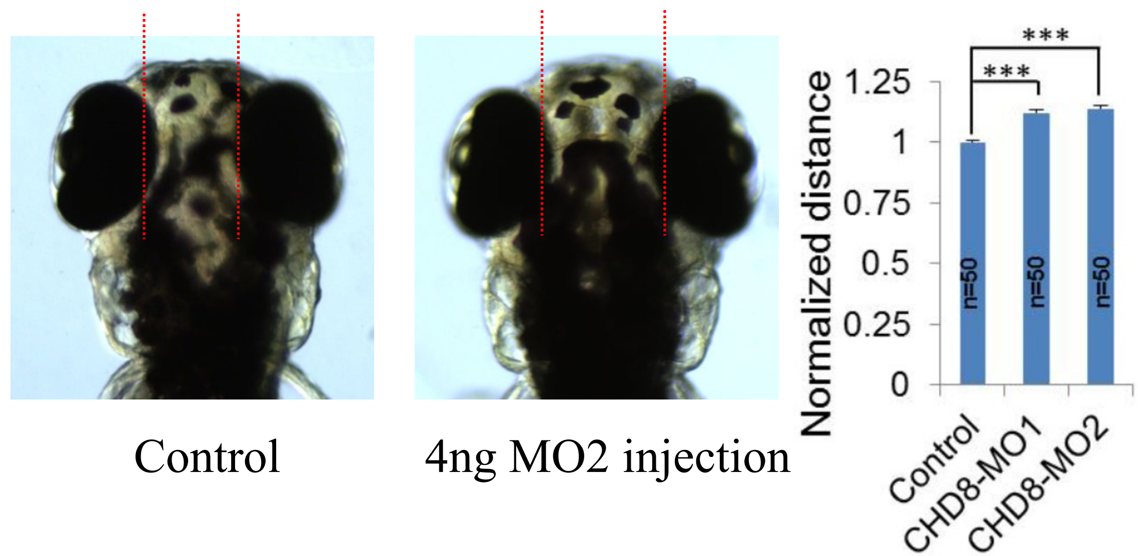


- 70 children /61,121 families
- All are de novo (OR=4.35-inf, $p<10^{-78}$)
- 87% autism
- 80% macrocephaly
- 73% gastrointestinal
- 67% sleep dysfunction

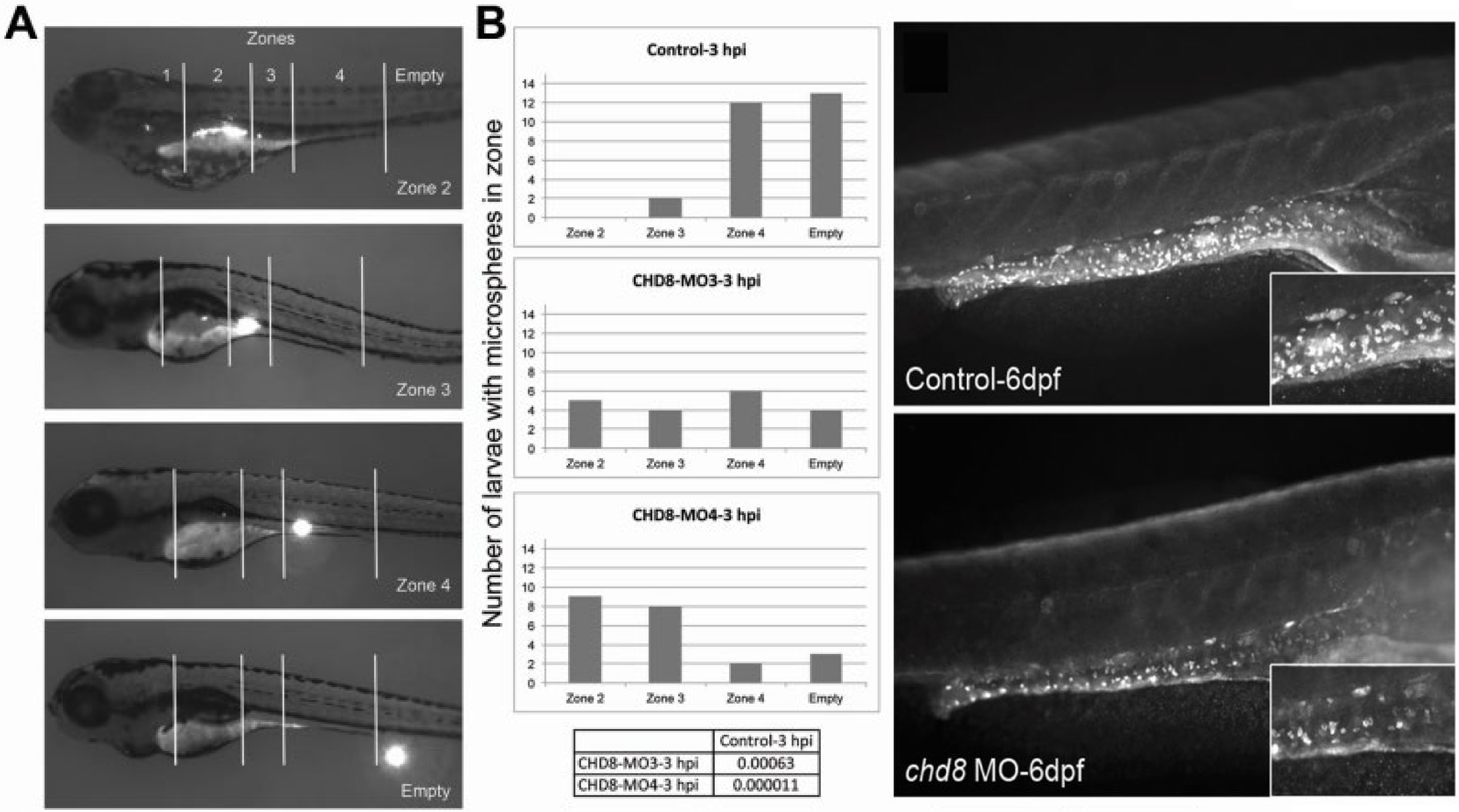
Bernier et al., ***Cell, 2014 & unpublished***

Modeling Autism Mutations





CHD8 Gastrointestinal Defects

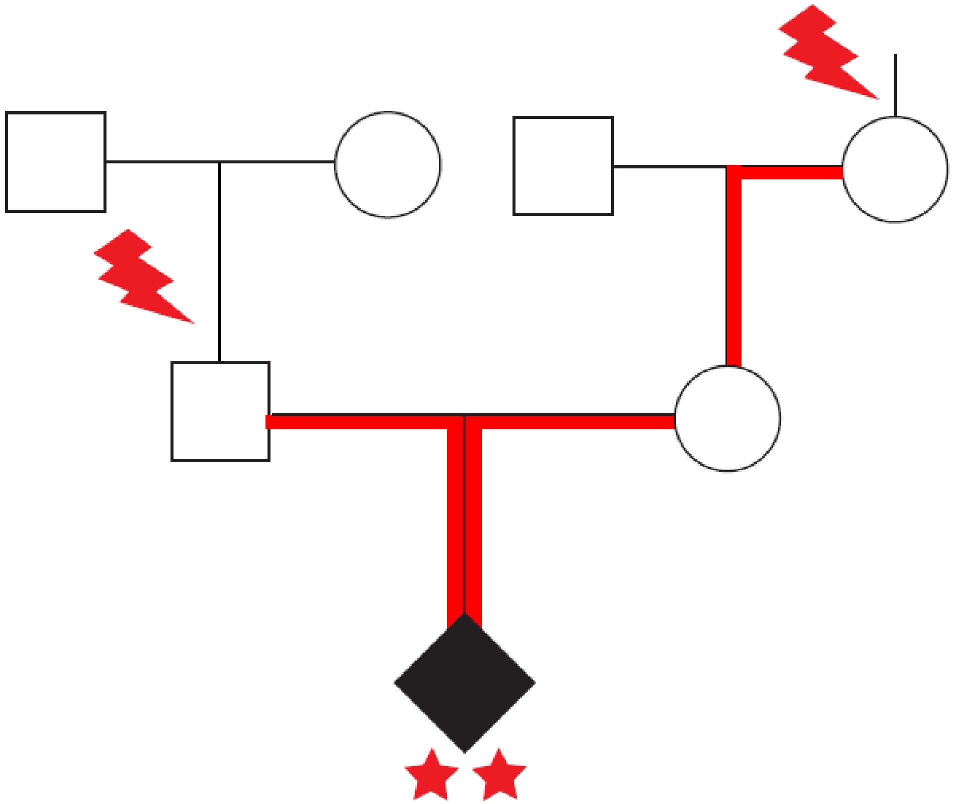


	Control-3 hpi
CHD8-MO3-3 hpi	0.00063
CHD8-MO4-3 hpi	0.000011

Estimate that ~25% of autism cases can be explained by large CNVs and *de novo* gene-disruptive mutation events.

Where's the rest?

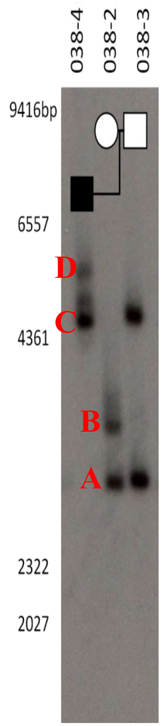
Multiple inherited mutations

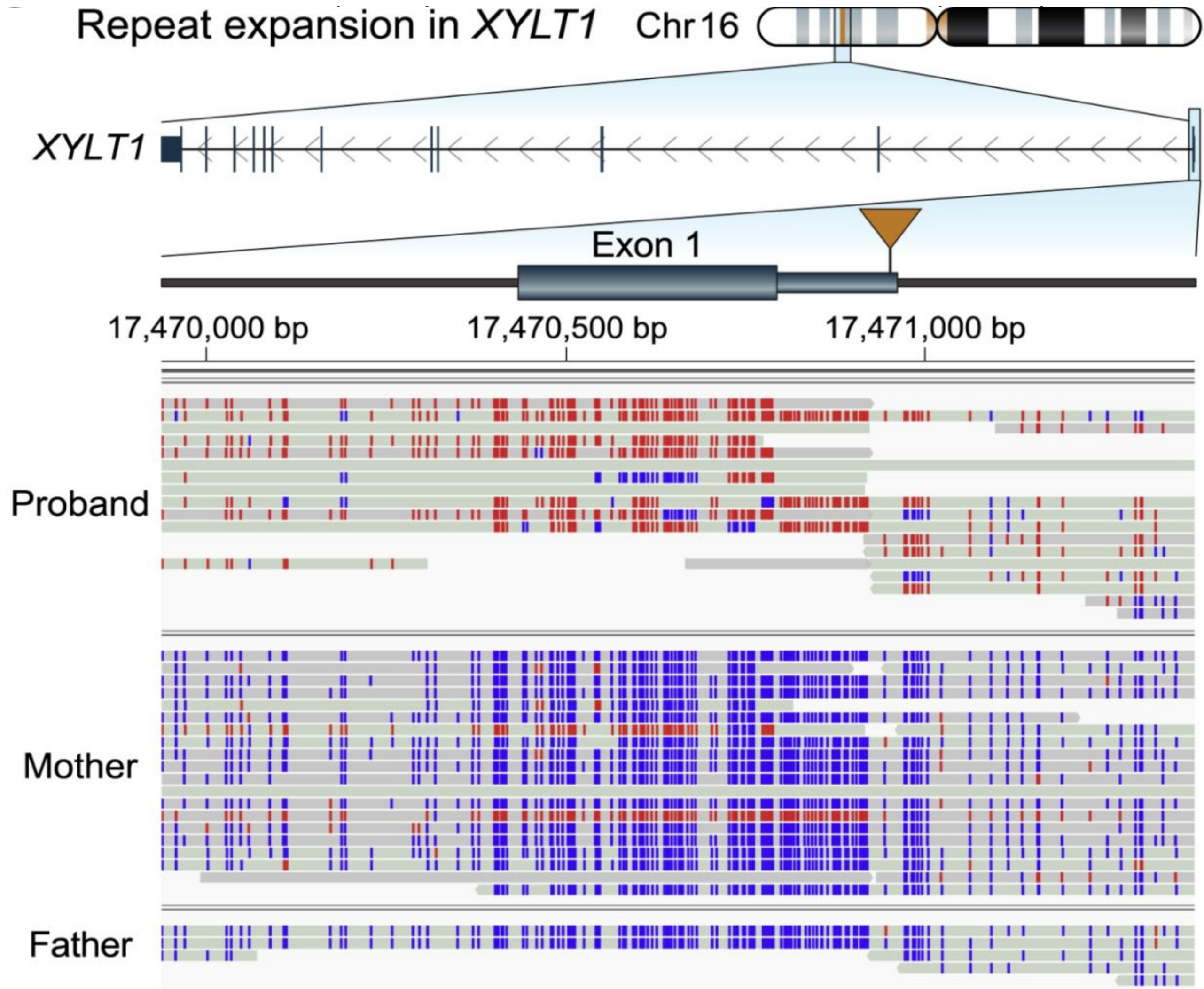


Excess of private inherited mutations in autists vs. unaffected sibs and effect gets stronger when consider two or more genes

Wilfert et al., Nat Genet, 2021, Wang et al, Trends in Genetics, 2022

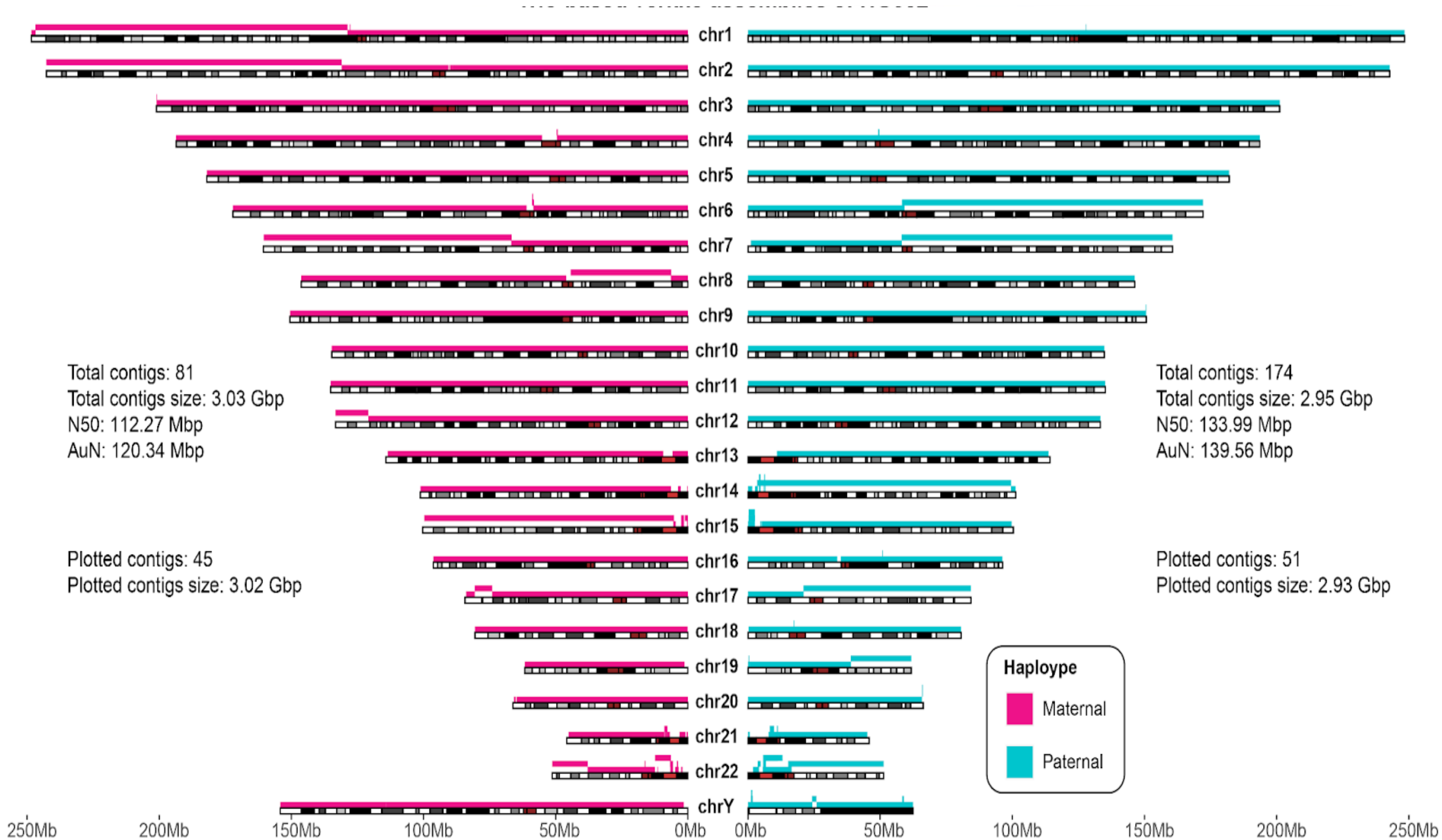
Regulatory mutations that disrupt expression





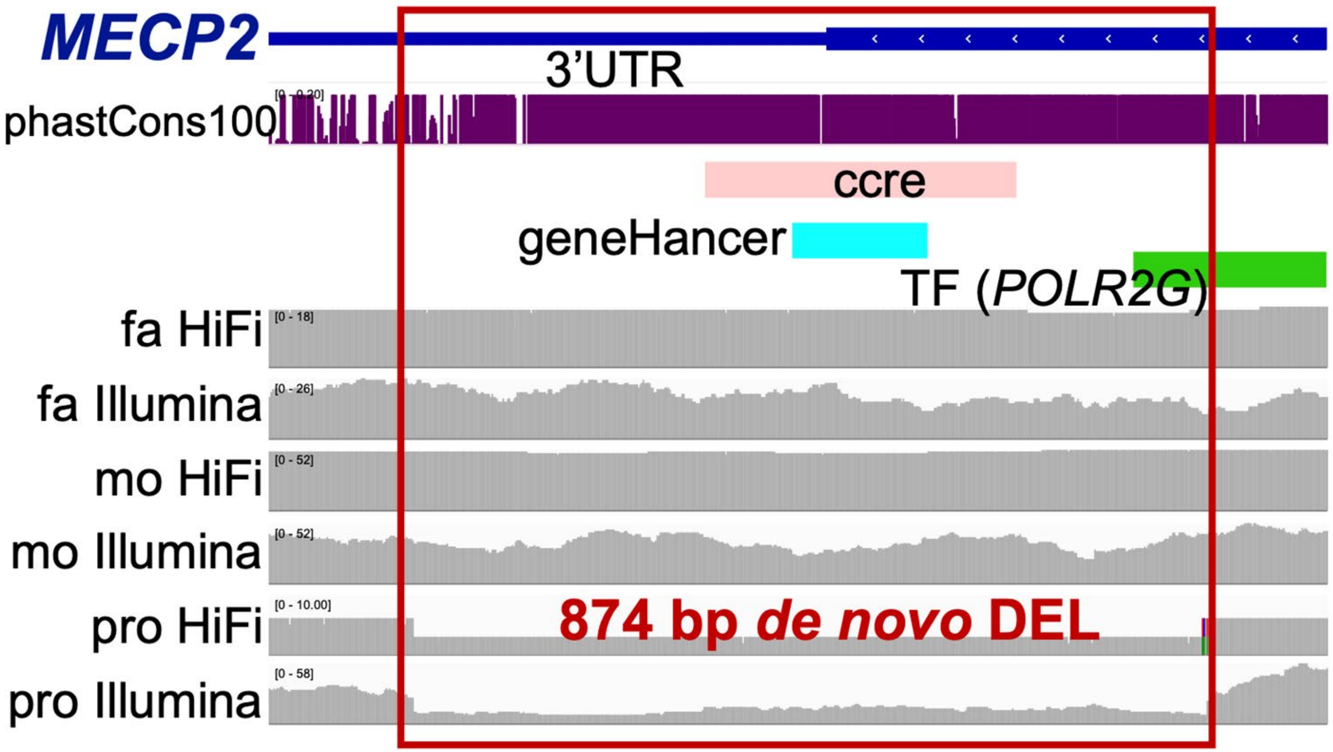
	38_2 (mom)	**38_4 (proband)**
Haplotype 1	237 A	1,609 C
Haplotype 2	674 B	2,546 D

Long-read whole-genome sequencing



Every unsolved case deserves complete sequencing!

Pathogenic variant "missed" in a girl with Rett-like Syndrome by WES screening at Ambry Genetics



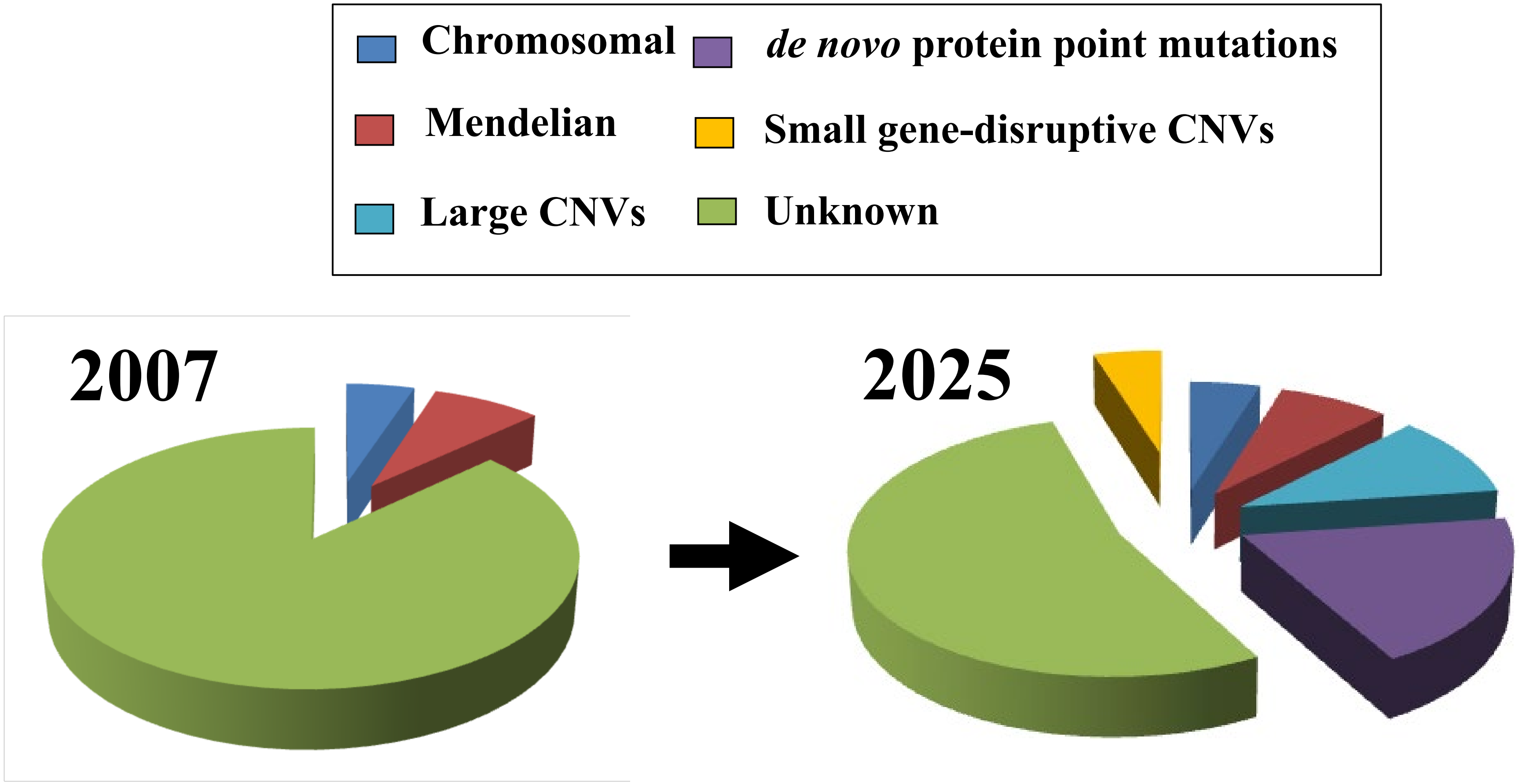
DEL from paternal germline.

Sui, Zoghbi et al, unpublished

Summary

- Large CNVs are enriched—7-8% of cases with autism and ~15% pediatric cases with developmental delay
- Sequencing of protein-coding regions reveals an excess of sporadic or new mutations in autism children
  - ~197/809 genes proven and can be used for diagnostics
- Genotype-first: Specific genes allow us to identify different subtypes of autism—allowing us to breakdown the heterogeneity of the disease at the molecular level (e.g., *CHD8*, *ADNP*, etc. subtypes)
- CNVs and sporadic mutations (~25%)—good evidence of regulatory and inherited mutation
- Discovery tightly linked to advances in genomics technology

Understanding Genetic Basis of Autism



Global ASID Networking

- Advances in genetic technology are allowing us to chip away at the genetic causes of autism piece by piece.
- Since there are >500 genetic "causes" of autism, it is critical that we network researchers, clinicians and families globally in order to begin to identify and subgroup patients.

Prospects and Promises

Mutations

Genes

Diagnostics

Proteins

Therapeutics

Networks

Type 1, 2, 3, 4……

……100,101,102

Genetic Subtypes

Acknowledgements

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