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# CHAIR SUMMIT

CME Outfitters

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# Genetic Testing in Autism Spectrum Disorder: Its Role in Clinical Management

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# Learning Objective

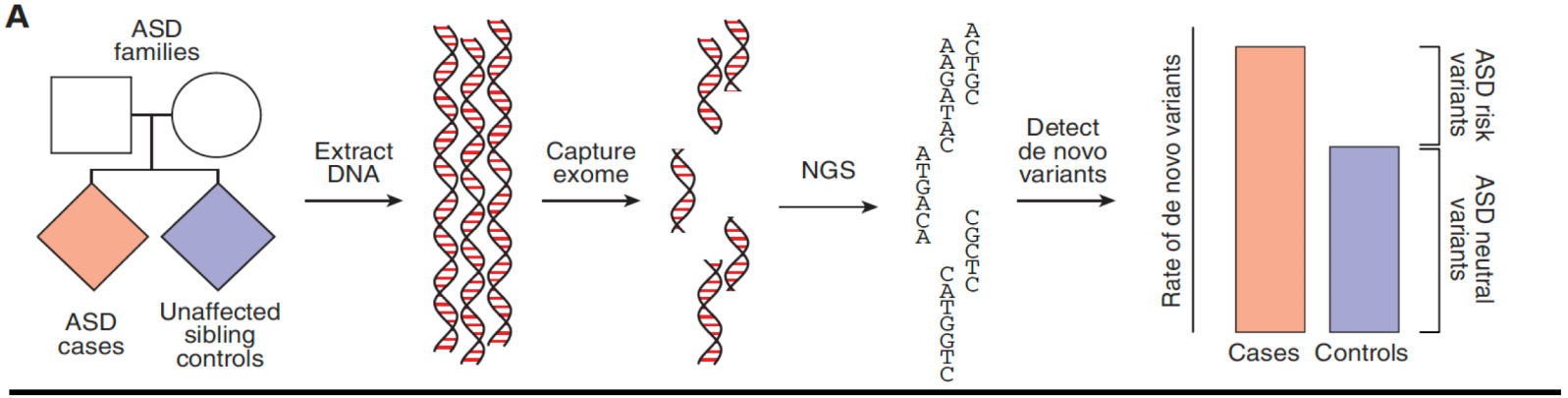
Integrate genetic testing into the clinical management of autism spectrum disorders.

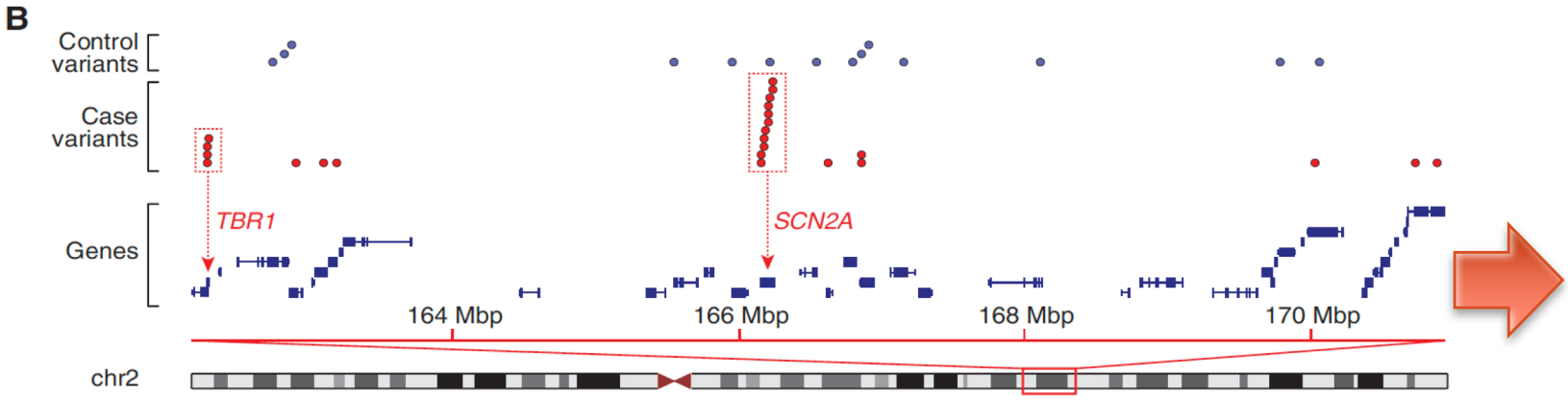
# Autism Genetics

- Greatest contribution from genetics of any psychiatric disorder
- Rapid progress in gene identification in last 5 *years*
- Various types of genetic variations in DNA contribute to ASD in the clinic
  - Three groups of variations: 1) Syndromic/Mendelian; 2) Rare variants; 3) Common alleles
  - Testing can help identify patients in first two groups and contribute to clinical management – predominantly via family counseling

Sestan N, et al. *Neuron.* 2018;100(2):406-423; Sanders SJ. *Cold Spring Harb Perspect Med.* 2018 Nov 12. [Epub].

# Autism Genetics: Gene Discovery




8 copy number regions e.g. 16p11.2

102 genes e.g. *SCN2A*

Sanders SJ. *Cold Spring Harb Perspect Med*. 2018 Nov 12. [Epub].
Satterstrom FK, et al. *Biorxiv*. 2018 Dec 1. [Epub].

# Available Genetic Tests

- Mendelian disorders: specific testing for syndromes such as Fragile X (everyone), Rett/*MECP2* (regression in girls, static encephalopathy in boys), *PTEN* (macrocephaly), *NF1* (café-au-lait), *TSC1/2* (distinctive tumors, Wood's lamp)
- Large-scale rare mutations
  - Often *de novo* (new mutation in the child)
  - Variations in the structure of the DNA contribute to ASD. These are called copy number variants (CNVs) – e.g. 16p11.2 deletions
  - Detected by chromosomal microarray (CMA). Clinical geneticists consider this standard of care for initial evaluation in ASD and intellectual disability. Widely available, some reimbursement

Ho KS, et al. *Int J Mol Sci.* 2016;17(12):2070; Sanders SJ, et al. *Neuron*. 2015;87(6):1215-1233.

# Available Genetic Tests (cont.)

- Small-scale rare mutations
  - Often *de novo* (new mutation in the child)
  - Variation in the DNA sequence in the regions of genes that encode proteins (collectively the exome) called single nucleotide variants (SNVs) in insertions/deletions (indels). E.g. *SCN2A, CHD8*
  - Detected with whole-exome sequencing (WES). Increasingly available, but more limited acceptance and reimbursement
- Whole-genome sequencing (WGS): more expensive and more thorough way to capture coding mutations. Non-coding mutation detection is **research only.**
- Common variants: Genotyping array, e.g. 23andMe; **research only**

Fernandez BA, et al. *Dialogues Clin Neurosci.* 2017;9(4):353-371.

# Indications

- ACMG: Syndrome tests (e.g. Fragile X) and chromosomal microarray for any child who is being seen with ASD and intellectual disability who has not had genetic testing
  - Other guidelines (e.g. AACAP) recommend testing only in the presence of unusual features (e.g. regression, dysmorphic)
  - WES will be added to next round of guidelines
  - Often little impact on treatment, but may be important for family counseling and support groups
  - Families increasingly want to know
- Ascertainment dramatically impacts yield, increased by:
  - Severe developmental delay, seizures, dysmorphology, female sex

ACMG = American College of Medical Genetics; AACAP = American Academy of Child and Adolescent Psychiatry.

Barton KS, et al. *Genet Med*. 2018;20(7):737-744; Schaefer GB, et al. *Genet Med*. 2013;15(5):399-407; Volkmar F, et al. *J Am Acad Child Adolesc Psychiatry*. 2014;53(2):237-257.

# Results

- **Mendelian:**
  - "This is the cause of what is going on"
  - Referral to clinical geneticist and genetics counselor
- **Rare highly-penetrant mutations:**
  - "This is likely to be contributing in a significant way to what is going on"
  - Variants of unknown significance (VUS) can be vexing
  - Most primary providers will refer to geneticist/counseling
  - Future impact on research and treatment

# Results (cont.)

- While syndromic and rare mutations can provide some insight they are not predictive of ASD outcome
- **Common variants:**
  - No useful information for family counseling or management
  - Be extremely wary of commercial products claiming diagnostic accuracy
- **Biomarkers:**
  - None that predict diagnosis reliably before clinical manifestations

Grove J, et al. 2017. Available at https://www.biorxiv.org/content/biorxiv/early/2017/11/27/224774.full.pdf.

# Gene Therapies?

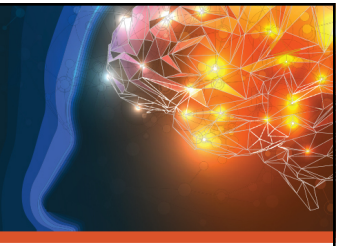
- Specific rare mutations offer an avenue to gene therapy
- First targets likely to be Mendelian: e.g. Angelman's syndrome, Rett syndrome, Fragile X
- **Significant obstacles:**
  - Targeting (deep) CNS: compared to Spinal Muscular Atrophy
  - When to intervene? At what age can ASD be reversed?
  - Regulatory hurdles: What level of severity? What outcome to measure?
- **Approaches:**
  - CRISPR-Cas9 editing; CRISPR activation (CRISPRa)
  - Antisense oligonucleotides (ASO)

# Conclusions

- Chromosomal microarrays and whole-exome sequencing can identify rare genetic contributors in ~20% of ASD cases
- Gene therapy trials are on the horizon for many of these
- Common variants found by commercial genotyping arrays have no current role in diagnosis or clinical management of ASD

# SMART Goals

## Specific, Measurable, Attainable, Relevant, Timely



- Over the next five years, all individuals with a diagnosis of ASD should receive chromosomal microarrays and whole-exome sequencing as a standard of practice to improve diagnosis, provide access to relevant support groups, and as a foundation for future therapies

# Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.