What comes first, the exome or the array? A comparative study of results from chromosomal microarrays and exome sequencing

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INTRODUCTION

- Developmental delay (DD) and intellectual disability (ID) are common indications for genetic evaluation in children.
- Updated guidelines from the ACMG and AAP recommend genome or exome sequencing (ES) with sequential or concurrent chromosomal microarray (CMA) as first tier tests
- As these studies do not consistently compare diagnostic yield, there is uncertainty about what CMA can find and what ES may miss

RESULTS

Figure 1. ES detects CNVs identified by CMA and SNVs missed by CMA

673 Positive (P/LP) CMAs

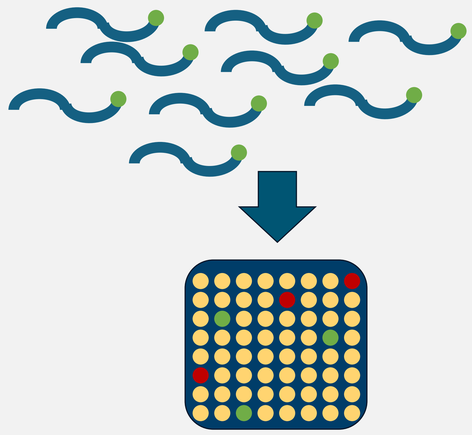
65 ES cases with CNV analysis

46 Positive	6 Likely Positive	1 Uncertain	12 Negative
37 CNV only 7 CNV + SNV 2 SNV only	5 CNV only 1 CNV + SNV	1 SNV only	5 CNV no clinical overlap 5 CNV failed 2 CNV under size

- 96.6% (58/60) of P/LP CNVs reported on CMA were detected on ES
- 32.3% (21/65) received one or more VUS on CMA, with an average of 0.4 VUS per patient.
- 7.7% (5/65) received one or more VUS on ES, with an average of 0.1 VUS per patient
- ES detected diagnoses in 16.9% (11/65) that would have been missed by CMA alone.
- 12.3% (8/65) of CNVs reported on CMA were not included on ES due to lack of clinical relevance.

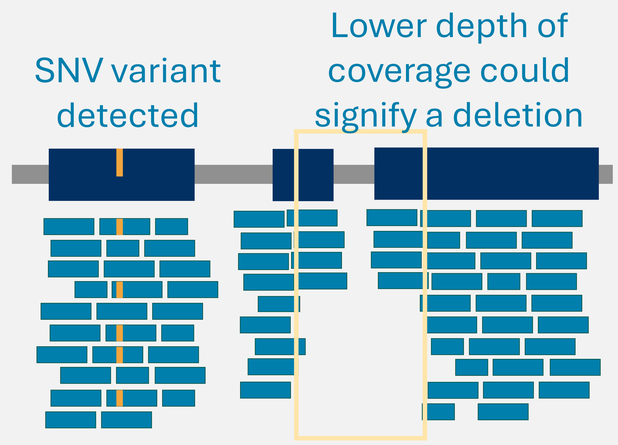
BACKGROUND

Chromosomal Microarray



- Shears DNA and labels specific points (SNPs) throughout the genome
- Adheres to chip and measures the intensity of probe signals to signify deletions or duplications
- Can also detect regions of homozygosity (ROH)

Exome Sequencing



- Targets protein-coding regions throughout the genome
- Single nucleotide variants (SNVs) are identified through comparing with reference sequencing data
- Copy number variants (CNVs) are identified through quantitative differences in sequencing depth

METHODS

Retrospective review of pediatric patients who underwent both ES and CMA over a five-year period at one commercial laboratory. The overall copy number variant (CNV) detection between CMA and ES were compared. Additional diagnostic outcomes of both tests and the prevalence of variants of uncertain significance (VUS) were assessed.

KEY TAKEAWAYS

- ES offers a higher diagnostic yield over CMA
- ES results offer improved clarity, fewer VUS and non-diagnostic CNVs
- Overall, ES is a superior test for identifying clinically relevant genetic causes of DD/ID

REFERENCES

1. Rodan, Lance H., et al. "Genetic Evaluation of the Child With Intellectual Disability or Global Developmental Delay: Clinical Report." *Pediatrics* 156.1 (2025): e2025072219.
2. Manickam, Kandamurugu, et al. "Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG)." *Genetics in Medicine* 23.11 (2021): 2029-2037.