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. Historically, chromosomal microarray (CMA) was the first-line genetic test recommended by the American College of Medical Genetics and Genomics (ACMG). In 2021, the ACMG issued updated recommendations for using exome sequencing (ES) as a first- or second-tier test in patients under 18 with DD/ID. While the new recommendations noted limited harms of updating practices to ordering ES first, it did not directly compare diagnostic outcomes between test methodologies.

Methods:

We performed a 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.

Results:

673 patients received a positive CMA report, defined as including at least one pathogenic (P) or likely pathogenic (LP) CNV. 59/673 (8.8%) additionally had ES with CNV analysis performed. 57/59 (96.6%) of P/LP CNVs reported on CMA were detected on ES. 30.5% (18/57) received one or more VUS on CMA, with an average of 0.4 VUS per patient. 8.8% (5/57) received one or more VUS on ES, with an average of 0.1 VUS per patient. ES detected diagnoses in 8.8% (5/57) that would have been missed by CMA alone. Based on ES reporting practices which incorporate phenotypic indication, 14.0% (8/57) of CNVs reported on CMA were not included on ES due to lack of clinical relevance.

Conclusion:

Our findings demonstrate that ES effectively detects CNVs and offers a higher diagnostic yield than CMA. ES results offered improved clarity, with fewer VUS and non-diagnostic CNVs. Overall, ES provides a superior test for identifying the genetic cause of DD/ID by enhancing the likelihood of a clinically relevant diagnostic finding.