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Peer Review

Review of: "Chromosomal Microarray Analysis in Autism Spectrum Disorder: Diagnostic Yield, Deletion/Duplication Syndromes, and Clinical Utility"

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Peer-Review Report

Manuscript Title: *Chromosomal Microarray Analysis in Autism Spectrum Disorder: Diagnostic Yield, Deletion/Duplication Syndromes, and Clinical Utility*

General Comments

This manuscript provides a clinically oriented review of the role of chromosomal microarray analysis (CMA) in the diagnostic evaluation of autism spectrum disorder (ASD). The topic is timely and relevant, given the evolving landscape of genomic diagnostics and the increasing integration of exome and genome sequencing into clinical practice. The authors summarize current evidence regarding diagnostic yield, recurrent pathogenic copy number variants (CNVs), genotype-phenotype correlations, and the clinical utility of CMA in patients with ASD.

The manuscript is generally well-structured, clearly written, and accessible to clinicians involved in the care of patients with neurodevelopmental disorders. The discussion appropriately emphasizes that the diagnostic performance of CMA is strongly influenced by phenotypic complexity and that test interpretation should occur within a broader clinical context.

Major Strengths

1. **Clinical relevance**

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2. The review addresses an important clinical question and provides practical information for clinicians involved in the genetic evaluation of ASD. The distinction between syndromic/complex ASD and isolated ASD is particularly valuable.
3. **Balanced presentation of evidence**
4. The authors appropriately acknowledge both the strengths and limitations of CMA and avoid overstating its diagnostic capabilities. The discussion of how CMA complements, rather than replaces, next-generation sequencing approaches is well balanced.
5. **Focus on clinical utility**
6. Beyond reporting diagnostic yield, the manuscript discusses how genetic findings may influence downstream investigations, surveillance strategies, and genetic counseling, enhancing its practical value.
7. **Educational value**
8. The review provides a useful overview of recurrent microdeletion and microduplication syndromes associated with ASD and serves as a concise educational resource for non-genetic specialists.

Major Concerns

1. **Lack of quantitative synthesis**
2. Although the manuscript summarizes published evidence, it does not provide a formal meta-analysis or pooled estimates of diagnostic yield. Consequently, readers may find it difficult to appreciate the overall magnitude of effect across heterogeneous studies.
3. **Methodological transparency**
4. The review would benefit from a more detailed description of the literature search strategy, study selection process, and criteria used for inclusion of the additional studies discussed beyond the primary systematic review.
5. **Heterogeneity of included studies**
6. Considerable heterogeneity exists among the referenced cohorts, including differences in ASD definitions, patient phenotypes, CMA platforms, and CNV classification standards. The implications of this heterogeneity should be discussed in greater detail.
7. **Limited discussion of emerging genomic technologies**
8. While exome sequencing (ES) and genome sequencing (GS) are mentioned, a more contemporary comparison of diagnostic yield, cost-effectiveness, and diagnostic algorithms involving CMA, ES,

and GS would strengthen the manuscript.

Minor Comments

1. Consider adding a summary table comparing diagnostic yields reported across major studies.
2. A graphical diagnostic algorithm illustrating the current place of CMA within the genetic workup of ASD would improve readability.
3. The manuscript would benefit from a brief discussion regarding variants of uncertain significance (VUS) and their impact on clinical decision-making.
4. Some sections describing individual CNV syndromes could be condensed to improve overall focus and avoid repetition.

Scientific Quality

The article provides a useful narrative synthesis of the available literature and accurately reflects the current understanding of CMA in ASD. The conclusions are generally supported by the evidence reviewed and appropriately acknowledge the limitations of the available data.

Recommendation

Minor Revision

The manuscript addresses an important topic and offers clinically meaningful insights. The overall quality is good, and publication should be considered after revision. The main improvements should focus on strengthening methodological transparency, expanding the discussion of study heterogeneity, and providing a more detailed comparison of CMA with contemporary sequencing approaches.

Declarations

Potential competing interests: No potential competing interests to declare.