Reviewer's report

Title: Copy Number Variants (CNVs) Analysis in a Deeply Phenotyped Cohort of Individuals with Intellectual Disability (ID)

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Reviewer: Alison Merikangas

Reviewer's report:

Qiao et al. present an interesting report examining the association between de novo, familial and common CNVs with phenotypic features in a cohort cases with intellectual disability. No differences emerged in the association between the types of CNVs and physical anomalies after correction for multiple comparisons. The authors highlight the need for standardization of measurements of phenotypic features in order to complete robust phenotype/genotype analyses. Systematic classification is a challenge in the field and the authors highlight this challenge, while suggesting a method for future work. This study makes an important contribution to the field, but it would benefit from some additional clarification and information before publication.

Major Compulsory Revisions

First, the authors should make a more clear statement regarding how this study advances the field beyond those cited in references #13 and #15. The text implies that the present study conducted a more systematic and comprehensive review of primary and secondary phenotypes, but this should be stated explicitly. Second, the lack of control patients should be cited as a limitation of this work. Third, no distinction is made between deletions and duplications that are likely to have differential impact on phenotypes. This is a critical comparison that should be presented. Fourth, because the phenotype data is based on clinical chart review, even though it was carefully standardized, a description of missing data and other limitations should also be included. More detailed suggestions are provided below.

Minor Essential Revisions

Abstract:
The results states that the present cohort had “a higher number of phenotypic abnormalities” but doesn’t state in comparison to what group. Please clarify.

Introduction:
As noted above, a more clear statement of how the present study differs from earlier studies would be helpful here. For example, what is an “array request form”? compared to a chart review vs. direct examination of affected patients. It would also be helpful if the authors would add more description of the de Vries checklist, the primary/secondary distinction, and norms that have been reported

Methods:
The experimental methods are generally well described. The motivation for excluding clinical features universally present or absent should be included in the materials and methods section, rather than later in the manuscript. Also, it is worth nothing whether all chromosomes or only autosomes were included in the analyses presented.

Results:
The results section would benefit from an additional column of all CNVs, as well as inclusion of the range of the CNV size (given that the mean is much larger than the median, I imagine that there are a few very large CNVs). A table detailing the phenotype classes and proportions by CNV type would be a useful addition to the manuscript - combining figures 2, 3, and 4. I believe that the Silfhout et al. reference for the de Vries score is incorrect and should be checked. I assume that the authors mean after correction for multiple comparisons, not after multiple corrections. In addition, when they refer to the correction, do the authors mean False Discovery Rate (FDR, Benjamini and Hochberg)? The description of the phenotype/genotype cluster analysis is unclear, and the results do not add much to the paper - this section could be removed.

Discussion:
In the discussion the authors should provide a more clear statement about how this report advances previous work of which the limitations were described in the introduction. The conclusions section can be included in the discussion, and should briefly reiterate the results of the current study.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.