Reviewer’s report

Title: A genomic copy number variant analysis implicates the MBD5 and HNRNPU genes in Chinese children with infantile spasms and expands the clinical spectrum of 2q23.1 deletion

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Reviewer: Joseph Glessner

Reviewer’s report:

“A genomic copy number variant analysis implicates the MBD5 and HNRNPU genes in Chinese children with infantile spasms and expands the clinical spectrum of 2q23.1 deletion” by Xiaonan Du et al. is not very good.

Major Compulsory Revisions
1. 14 CNVs in 47 IS cases is very low in the era of denser arrays CNVs should be detected in all samples.
2. Agilent 180K array CNVs sized 115 kb – 4.1 Mb
3. 4 pathogenic CNVs are found: HNRNPU (new), MBD5 (new), PAFAH1B1 (known), and CHD1L (known) are de novo.
4. Absence in DGV is also important: “The medical annotation was performed by reviewing the clinical reports related to each of the CNVs in PubMed, the candidate gene(s) in CNVs relevant to the OMIM entries, and the function of these genes in the evidence provided by other model organisms or experimental systems. Through these analyses, we determined the pathogenicity of the CNVs in IS based on a comprehensive assessment of the existing clinical data, the size of the CNV, the gene content of the CNV, and the inheritance of the CNV.”
5. Pathogenic CNVs section descriptions are very long.
6. Where is a recurrent de novo CNV to show the CNV is phenotype specific?
7. Absence of the great toes is interesting subphenotype correlation.
8. “conserved molecular mechanism leading to pathogenic CNVs across different ethnic backgrounds” is not clear as the molecular mechanism of most CNVs is non-allelic homologous recombination for both pathogenic and neutral CNVs.
9. The figures are good showing presence of CNV in proband and absence in parents.
10. The tables are good. Although Table 2 is unclear why 3 papers are being represented.
11. “distinct and more severe neurological presentations than other cases with similar sized deletions [20, 41, 42](Table 2).” May suggest additional variants play a role in this more complex phenotype.

Minor Essential Revisions
These sentences have grammar errors:
12. Abstract “We report herein the first genome-wide CNV analysis,” should be “We report herein the first genome-wide CNV analysis in children with ISS,”
13. “In particularly” should be “In particular”
14. “IS have been shown” should be “IS has been shown”
15. “20.2+9.7” should be “20.2+-9.7”
16. “However, no significant sequence variants were identified in the all coding exons of MBD5 and ORC4 genes.” Should be “in all”
17. “There are numerous reports suggesting that NRG3 contributes to the susceptibility of schizophrenia and other neuropsychiatric disorders [29, 36, 37]. In our case, because the duplication is inherited from the healthy parent, the role of this duplication in proband related to IS could not been determined with confidence .” should be “could not be”
18. “In the case S34, a 396 kb duplication in X chromosome containing NGFRAP1(NADE) gene in boy was inherited from the healthy mother. The similar duplication has not been reported before associate with disease in humans. The function of NGFRAP1 related to TSC1 suggested that the NGFRAP1 may be risk factor for the IS.” Should be “been reported before associated” and “may be a risk factor for IS.”
19. “Therefore, it is less likely that PMP22 related CNV found in proband is a risk factor for IS and additional investigation is warranted to search for other possible cause in this case.” Should be “and reported for the first time.”
20. “The finding of CNVs at 1q44, 2q23.1, and 1q21 in IS is novel and first time.” Should be “and reported for the first time.”
21. “These may simply due to the clinical information in these reports were typically extracted from limited medical records for the subjects in the studies.” Should be “These may simply be due to the”
22. “These results indicate that Mbd5 is important for brain development but the exact role of Mbd5 remains defined.” Should be “remains to be defined.”

Discretionary Revisions

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: Yes, and I have assessed the statistics in my report.

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