Reviewer's report

Title: Linkage and exome analysis implicate multiple genes in non-syndromic intellectual disability in a large Swedish family

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Reviewer: Carla Rosenberg

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The authors report the investigation of a very large nine generations pedigree with individuals with intellectual disability (ID) in the two younger generations. These large family has been previously investigated and no obvious single cause of ID was identified; the present study confirms that the etiology of ID in this family is likely heterogeneous.

The authors performed a thorough investigation searching for CNVs and variants that would explain the phenotype. In the lack of a genetic alteration that could explain the phenotype in all individuals with ID, they looked for alterations in branches or individuals in the large pedigree. Although neither new genes nor a founding effect were identified, the results are interesting and deserve publication.

I have, however, few comments regarding the individual findings:

1. They identified a CNV (duplication) in individual 3 that includes the gene MAP3K4, possibly related to ID. However, by examining the DGV and "DDD case" x "DDD control" databases, the results suggest that only deletions, not duplications, would cause a phenotype. I wonder whether this variant should not be considered benign.

2. The authors identified a homozygous disease-causing variant at position chr6:g.74354306 G>A in the SLC17A5 gene in patients 829, 830 and 322. The mutation is known to cause Salla Disease. It would be interesting to know, if possible, if these individuals have a phenotype compatible with Salla Disease.

3. We found that individuals 301 (affected male) and 304 (affected female) carried a hemizygous/ heterozygous missense variant in FLNA gene, supposed to cause a disorder with dominant mode of inheritance. The problem is that these individuals are quite distantly related and, for a common origin, the variant would have to be transmitted without clinical manifestation in ~16 ancestors. It would be reasonable to assume that the variant is not disease-causing.
The text needs an extra revision for few small errors, such as "homozygous" variants on the X chromosome in males instead of hemizygous and "share" spelled wrongly.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
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Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

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Not relevant to this manuscript

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