Reviewer’s report

Title: Xp11.22 Duplications in Four Unrelated Chinese Families: Delineating the Genotype-phenotype Relationship for HSD17B10 and FGD1

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Reviewer: Orsetta Zuffardi

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BMC Medical Genomics
Xp11.22 Duplications in Four Unrelated Chinese Families: Delineate the Genotype-phenotype Relationship for HSD17B10 and FGD1

The manuscript reports on four unrelated male probands, who were ascertained for intellectual disability and/or other disorders, all carrying a CNV gain at Xp11.22. In each case, the authors define the genomic rearrangement through a deep molecular sequencing approach in order to delineate precise genotype-phenotype relationship. To this aim, they compare the duplication of each of their cases with those reported in the literature and in DECIPHER.

The main problem of the manuscript relies in the writing style that does not fit with the scientific English. It is therefore necessary for the manuscript to be reviewed by a native English speaker.

The following points are also problematic:

The Xp11.22 region contains a few inversion polymorphisms (see Database of Genomic Variants). The authors should discuss whether some of the CNVs could be mediated by these polymorphisms.

The authors propose that FGD1 "may be a potential dosage-sensitive gene responsible for hypogonadism observed in our patients." Indeed, "given that FGD1 gene is duplicated exclusively in the three unrelated patients who all displayed strikingly similar hypogonadism phenotype and other Xp11.22 duplication patients did not show this feature, it was reasonable to speculate that FGD1 was likely to be a dosage-sensitive gene and FGD1 duplication may be responsible for hypogonadism observed in our patients."

Based on the literature regarding the Rho family of small GTP-binding proteins similar to the FGD1 protein, the authors should speculate how the duplication of FGD1 may lead to a phenotype overlapping its LoF.

To strengthen their hypothesis that partial HUWE1 copy number gain does not contribute to ID and language delay that was observed in the proband of Family 1 and DECIPHER patient 263219, the authors state that a partial HUWE1 duplication was also reported in Database of Genomic Variants (esv3576879, chrX:53529972-53593214).

However, looking at gnomAD SVs v2.1, this variant is present in 2 out 21694 alleles, corresponding to a frequency of 0.00009219 and is only present in females. A recurrent rearrangement with these characteristics, is very likely pathogenetic in males.

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?**
If not, please specify which controls are required in your comments to the authors.

Unable to assess

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

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

**Quality of written English**
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

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