Reviewer's report

Title: Novel VPS13B Mutations in Three Large Pakistani Cohen Syndrome Families Suggests a Baloch Variant with Autistic-Like Features

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Reviewer: Irene Madrigal

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Major Compulsory Revisions

- Cohen syndrome is a rare genetic condition which, until now, has not been easily diagnosed, mainly because the size of the responsible gene (VPS13B). In fact there are less than 1000 diagnosed cases worldwide. Nevertheless, the authors state that this syndrome is one of the most common genetic syndromes, right after Fragile X with a frequency of 0.7%. The authors should provide a real incidence of this syndrome, since this 0.7% value was from a study of 670 patients to whom target sequencing was performed.

- The authors decided to perform a homozygosity mapping to interrogate samples even with highly inbred families. The expected number of homozygous regions must be huge. Can the authors provide this information? The final diagnosis is achieved by Whole Exome or Sanger sequencing. In families ANMR51 and RQMR10, did they sequence the VPS13B gene due to the findings of the homozygosity mapping?

- The authors mix the description of clinical findings from families RQMR10 and ANMR51, both in the material and methods and the results section. It would be easier to read if they separate the families.

- The authors state that most of the individuals with the 312 c.6879delT mutation in two of these families also present with autistic like traits, which suggests that this variant may lead to a distinct autistic-like COH1 subgroup. This conclusion seems too daring for me. Since these families are consanguineous, it cannot be discarded the presence of other homozygous mutations that could be responsible for the autistic features. Has this possibility been evaluated? In two members of the ATM02 family, they have performed whole exome sequencing; maybe they can extract some information from these data.

Minor Essential Revisions

- Authors could specify that the mutations are in homozygosis. e.g Sanger sequencing analysis of all PCR amplicons revealed a homozygous deletion of 1pb.

- In table 1, authors should provide data from the percentile and SD of the OFC (cm).
- Also in table 1, the abbreviation “n.k.” is not used in the table.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**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.