Reviewer's report

Title: Familial imbalance in 16p13.11 leads to a dosage compensation rearrangement in an unaffected carrier

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Reviewer's report:

Delicado and colleagues describe an interesting family wherein the proband, his brother, maternal uncle, and maternal grandfather have a ~1.8 duplication of chromosome 16p13.11 whereas the mother of the proband had two copies of the region due to a deletion on the second copy of chromosome 16. The manuscript is well written and the authors for the most part are careful in the interpretation of their findings. I have some comments and suggestions.

Major Compulsory changes

The pathogenicity of the CNV is not the point of the manuscript as the authors acknowledge. The duplications of the region have been previously well described. Hence the only interesting thing in the manuscript is the mechanism for copy-neutrality in the mother. I think that this part is somewhat lost in the manuscript as the introduction starts of with 16p13.11 CNV and their role in disease. I would encourage the authors to reformat the manuscript in a way where one has to interpret a “familial” occurring rearrangement when none are found in one of the transmitting individual.

The authors state that the duplications are in “tandem”. Tandem is a specific term as duplication may have been in the same region though not tandem. I agree with the authors that the duplication is in the same region of 16p given that the metaphase FISH shows NO third signal but interphase FISH does – so the signals are likely close by. The authors however state that the signals being in close proximity on interphase FISH (fig 1C) as an argument for tandem duplication. I would ask the authors to perform a two-color FISH with another 16p flanking marker to show that the signals are indeed close to the region. This is more important given that the signals in the maternal FISH clearly appear farther than in the proband. Also, I would request the authors to delete the “16” labeled in red in the picture depicting maternal FISH. When the figure is condensed, the red 16 may look like a FISH signal confusing the readers.

The authors need to state whether the proband’s grandmother studied? Was she phenotypically normal? I realize that the chances of her carrying a constitutional deletion are minimal but she could have mosaicism? The post-zygotic hypothesis in the very early stage with preferential proliferation of only the copy-neutral cells is a hard sell.

Minor Essential revisions
The clinical report is rather brief and suboptimal. Authors do not describe the developmental milestones but just state that the development was normal. The authors should refrain from using the word “retardation” which is not the politically correct term to use. This is a minor point as I think the point of the paper is not phenotypic description.

Please cite appropriate manuscripts. For e.g.:


Feng Y, Walsh CA: Mitotic spindle regulation by Nde1 controls cerebral cortical size. Neuron 2004; 44: 279–293 when refereeing to the role of NDE1 and so forth

Figure 1 legend –Proband aCGH results showing 16p13.11 deletion; Mother aCGH results showing no 16p13.11 deletion. I am sure the authors meant duplication.

There are minor linguistic and syntactic changes that I would suggest:

Clinical features such as as cognitive impairment, behavior disorders, congenital heart defects, skeletal malformations and abnormal magnetic resonance imaging (MRI) findings have been associated with CNVs involving 16p13.11

Further examination at 37 weeks showed two interhemispheric cysts associated with corpus callosum agenesis and colpocephaly. Its is not clear what the authors intent to state here. Do they mean the cysts are due to ACC?

Perinatal period was uneventful and Apgar scores were 9 and 10 at 5 and 10 minutes, respectively.

…..subsequent increase in their size despite multiple drainage interventions granted the placement of a permanent ventriculoperitoneal shunt at 10 months of age. Please use mandated instead of granted.

This finding was interpreted as a CNV of uncertain significance since it had not been reported to show copy number variation in normal individuals, the region contained several MIM genes and there was an ongoing debate as to the exact clinical significance of the CNV.

There have been reports of those with “no obvious” phenotype with this CNV. Hence the authors need to be careful about the above statement.
I would recommend deleting the sentence “In line with this, it is tempting to suggest a somehow ‘deliberate’ postzygotic compensation mechanism of a genomic unbalance. That statement is speculative.

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

Quality of written English: Acceptable

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

Declaration of competing interests:

NONE