Reviewer's report

**Title:** Deletion Xq27.3q28 that includes IDS and FMR1 in female patient with global developmental delays and nonrandom X inactivation

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**Reviewer:** Maria Giuseppina Miano

**Reviewer's report:**

The manuscript “Deletion Xq27.3q28 that includes IDS and FMR1 in female patient with global developmental delays and nonrandom X inactivation” by Marshall et al. describes an interesting case with a deletion that covers a gene rich region including several disease genes involved in neurological defects. The authors map the deletion by BAC array, which has been estimated to be 10.6 MB long, and suppose that the deleted X chromosome is inactivated.

However, the authors need to improve their analysis because in my mind miss several important points, as here listed:

**Major Compulsory Revisions**

1) Add a detailed map with gene annotation, by using public databases (ENSEMBLE, NCBI, UCSC, et). Of note, within the 10.6 Mb involved in the deletion are present several disease genes that could be involved in the disease phenotype here described. Please check the appropriate references in the recent literature.

2) They could try to identify the breakpoints and propose a genetic mechanism that may trigger the rearrangement.

2) In Figure 2, the authors show the BAC array results. But neither the FMR1 results and nor the SNP array (for which gene?) results. Also the segregation in the family was missed.

3) It is not really accurate the statement about the X inactivation and its primary role in this disease presentation. The supposed inactivation of the deleted X chromosome is not clear on which data was established. HUMARA test or FMR1 alleles? The authors must show the results obtained and to discuss them accurately, as described in several other papers describing similar genetic conditions.

4) The authors must improve the discussion about the correlation genotype-phenotype. They have already considered the possibility that the deletion includes genes escaping the X inactivation but they miss to discuss in detail.

5) I’m not sure that this case represents the first described in the literature with a skewed inactivation of the mutant X chromosome. Please check accurately the literature describing both familial and sporadic rearrangement of X chromosome.

6) The authors carried out the Hunter assay. But the presenting phenotype is...
very different from the Hunter syndrome. I’m not sure that this approach is valid.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

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.