Reviewer's report

Title: Deletion Xq27.3q28 in female patient with global developmental delays and nonrandom X inactivation

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Reviewer: Maria Giuseppina Miano

Reviewer's report:

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

The authors seem to have improved the MS in several points. However, in my mind several points appear still inaccurate in particular the mapping details of SNP analysis and the HUMARA data. I suggest them to read accurately my comments here listed and introduce appropriate improvements.

Major points:
- Figure 3 can be improved adding details already available at UCSC webpage (see chrX:146,000,000-155,270,560 9,270,561 bp. at http://genome.ucsc.edu/cgi-bin/hgTracks UCSC Genome Browser on Human Feb. 2009 (GRCh37/hg19) Assembly). The authors can easily refer to information and data annotated in this genome databank. Taken into account them they can also improve the discussion.

I wish underline that in literature there are several case reports describing Xq27-q28 deletion in female presenting similar or other type of diseases, such as those affecting reproductive functions, associated to incomplete penetrance due to the complexity of X-inactivation phenomena.

Here few examples of crucial papers missed in the MS:
- Severe phenotype in MPS II patients associated with a large deletion including contiguous genes.

Or

- I accept the justification of the authors about the missing data about the breakpoint identification. However, they can speculate on the origin of the
rearrangement given that this region is often involved in genomic
rearrangements. Several authors give an explanation for that.

- The authors have summarised the main results in a Table. In my opinion they
are still unclear. They can improve the description adding accurate information.

For the SNP ARRAY: specify the probes of the SNPs delimiting the deleted
segment: NCBI name, position, etc. In the table is reported a “generic” and non
specific data.

Because this is the only data demonstrating that the proband carries a terminal
deletion and not an interstitial deletion, I believe that it is important to describe
accurately the SNP array results and integrate them with an accurate map
analysis.

For the X-Inactivation: specify the genotype of the AR polymorphic repeats and
analyse the segregation along the family. Because the authors attribute to the
X-inactivation a crucial role to explain the proband phenotype, I believe that it is
necessary to complete this data.

On the other hand, based on their data, the authors have established that one
allele of the AR locus is fully inactive and the other one is fully active (see
TABLE). But they do not demonstrate if the inactive allele maps on the X
cromosome carrying the deletion or maps on the health X chromosome. Because
their main statement is that the deleted X chromosome is preferentially
inactivated, the authors must clarify this important point improving their analysis
with a segregation analysis including in the study the mother and other
individuals that can help to establish the cis or trans phase of the inactive AR
allele respect to the Xq27-q28 deletion.

- Of note the authors use the expression “non-random X inactivation” and
“skewed X-inactivation” to refer to the same genetic condition. The two
statements have different genetic values corresponding to different range of the
X-inactivation:

Given two alleles for the AR locus, A and B

RANDOM XCI 50 (A):50 (B)
NON-RANDOM XCI 30(A):70 (B) or 70 (A):30 (B)
SKEWED 0 (A):100 (B) or 100 (A):0 (B)

The authors must clarify this point along the MS, also in the title.

- In Materials and Methods is still unclear the methods applied to study XCI: by
standard PCR, or by fluorescent genotyping, type of oligos, allele size, etc.

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'