Reviewer's report

Title: Genetic and protein characterization in symptomatic female DMD carriers: lack of correlation between X-inactivation, transcriptional DMD allele balancing and phenotype

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Reviewer: craig campbell

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Minor Essential Revisions:
1. Somewhat more detail on how were the patients actually recruited or identified would be helpful to the reader: were they part of a singular regular NM clinic and identified retrospectively if they had a biopsy available? Mutlple sites? Over what time period?

2. What is the expected test error in X inactivation studies and the dystrophin transcript studies. This is paramount to interpreting the degree of disagreement between the samples. This has not been touched on by the authors. Similarly what is the expected error rate in real time PCR for dystrophin transcript expression (figure 4 and 5). The authors have included standard deviation bars, why the SD is so different between the two markers (exon 12 vs 55) and how the potential variability impacts their conclusion.

3. Table 2 would be better expanded to include the information from figure 5 and 6. This would allow the reader to see all the methods used to understand dystrophin expression relative to X inactivation. As it stands now only the semi-quantitative analysis is included in that table.

4. I think the investigators have not used any correlation analysis and so the term correlation in their article and abstract should be changed to ‘no apparent relationship’ or some other such term which moves away from giving the reader the impression of a statistical test.

5. The opening sentences of the discussion are overly colloquial and could be changed.

6. In the second paragraph of the discussion it claims no correlation between ‘negative muscle fibres’ and phenotype but the investigators claim earlier that they did not do fibre counting(page 10). This statement should be clarified or removed.

7. Figure 2. The heading is wrong – it should be carrier 16 and 8 (not 2)

8. A different nomenclature for the subjects may be used ... in some cases they are called carriers (ie. Heading for figure 6) and it can be at first difficult to recall throughout the reading which are asymptomatic and which symptomatic

9. For case 3 it is almost impossible to say her symptoms came on at 14months of age. This is typically a time when children are not even necessarily walking
and it would be difficult to assess proximal weakness. Further, one would not necessarily even attribute weakness or motor delay to a dystrophinopathy at this age anyway. This child also has no dystrophic changes on her biopsy and is said to have non-progressive weakness. I might suggest this child has motor delay syndrome rather than a dystrophinopathy despite the mutation. The authors should comment on this.

10. Three of the children in the asymptomatic group were at such a young age at examination (6 or younger) that it is not confidently that one can yet consider them asymptomatic, and 4 children in the asymptomatic group are so young (under 6 years) at the time of biopsy that it is difficult to know if they would remain asymptomatic at an older age.

11. There is no limitation section to the paper and this should be added specifically addressing the problems in point 9 and 10.

**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:**

I declare I have no competing interests