Reviewer’s report

Title: Exome sequencing identifies titin mutations causing hereditary myopathy with early respiratory failure (HMERF) in families of diverse ethnic origins

Version: 1 Date: 19 November 2012

Reviewer: Peter Hackman

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Major Compulsory Revisions
1. The segregation of the novel mutation with the disease should be verified both in the affected and unaffected members of family A by conventional Sanger sequencing, since whole exome sequencing gives some false positive results. The authors do not state whether they did this or not?
2. It could be good to check whether the Native American and Spanish patient share a common microsatellite or SNP haplotype since they have the same mutation. Speculations about the reason for these two individuals from different populations sharing the same mutation could be added to the Discussion part.
3. Even though it is unlikely that the CDC2 rare polymorphic variant detected rather than the TTN change would be responsible for HMERF it could be good to check by Sanger sequencing whether the CDC2 change is real, and whether it segregated in affected compared with unaffected members of the family A as well.

Minor Essential Revisions
1. In the beginning of the section Genetic Analysis the authors state that they identified the sequence variants in the results from the whole genome sequencing from all positions where there were high quality sequences bases. How was this defined, and what was the minimum and the mean coverage?
2. In the conclusion section of the abstract please correct a typing mistake: missense instead of "missence"
3. Why was the CDC2 Arg59Cys variant compared to exome data of European Americans while the p.Gly30150Asp change was compared to ClinSeq 1000 Genomes database and exome data of 6500 European and African Americans?
4. In Table 3 please use either single letters or three letters to describe amino acid changes, not mixed (i.e. Gly/Asp or G/D)
5. In two places in the manuscript on page 17 the mutation p.Gly30150Asp is wrongly written as p.Gly30150Ala. This should be corrected.

Level of interest: An article of importance in its field

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