Reviewer’s report

Title: Exome sequencing reveals a novel TTC19 mutation in an autosomal recessive spinocerebellar ataxia patient

Version: 2 Date: 8 October 2013

Reviewer: Daniele Ghezzi

Reviewer’s report:

The paper by Morino et al. reports the identification of a novel mutation in TTC19 in a Japanese patient presenting spinocerebellar ataxia.

Mutations in TTC19 seem to be extremely rare, and the one described in the present paper is the fourth mutation to be reported.

Although a functional validation of the identified variant is missing, the extensive genetic screening (exome sequencing) and the type of the mutation (nonsense mutation), together with the clinical presentation of the patient, strongly support the causative role of this variant.

Major revisions:

1- Interestingly all the identified mutations are nonsense mutations. In the previous papers on TTC19 no protein was detected in samples from TTC19 patients and the TTC19 transcript level was markedly reduced.

The authors suggest that the position of their substitution (more distal than the previous ones) could account for the milder clinical symptoms of the Japanese patient. If no biological material (fibroblasts?) is available for the detection of the protein, the authors should at least perform a quantitative PCR (using leukocytes for instance) to see if mRNA decay is present or if their mutation has a different behaviour compared to the other TTC19 mutations.

2- The four candidate genes remained after filtering have to be listed and a sentence should be added to explain why the other candidates were not taken into account. In consanguineous families we can’t exclude an unlikely but possible presence of two pathogenic mutations.

3- To be useful, the discussion needs to contain clear statements on the signs (i) that are common to all the TTC19 mutant patients described till now (for instance the involvement of the inferior olives at MRI) and that probably represent the hallmark for this genetic condition; (ii) that are typical of the Japanese patient and that could help to expand the phenotypic spectrum associated with TTC19 mutations.

In the first sentences of the discussion there are statements not clearly recognizable either on already published patients or on the Japanese case.

Minor points:
1. What type of relationship has the parents, reported as “consanguineous”? A pedigree of the family could be useful.
2. The exact values of lactate and pyruvate should be added, instead of saying normal and elevated levels.
3. The software for functional prediction, reported in the Methods section, are never cited in the Results and can be removed
4. Some info on the controls is missing: the origin of the “normal” control (are they Japanese?) and the meaning of “disease-controls”. What clinical presentation showed the heterozygous sample
5. How many controls of Japanese origin are present in the cited open databases? (for instance in ESP5400 there are only subjects with Afro-American or European origins)
6. How many genes are present in the regions identified by IBD?

Discretionary Revisions:
The meaning of some statements is not fully clear. Please modify, remove or improve the following sentences:
Page10: The therapeutic approach for mitochondrial disease is different from usual SCAs; therefore, we should carefully diagnose this disease.
What therapeutic approaches you refer to?
Page11: The clinical differences among mitochondrial abnormalities may be important to clarify
the pathogenesis of MRC dysfunction.
What mitochondrial abnormalities?
Pages11-12: …the mutation we identified may help to elucidate the pathology of mitochondrial disorders.
How?

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

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'