Reviewer’s report

Title: Whole exome sequencing in an Indian family links cerebroretinal microangiopathy with calcifications and cysts (CRMCC) and dextrocardia with a homozygous novel CTC1 and a rare HES7 variation

Version: 2
Date: 17 September 2014

Reviewer: Emma M Jenkinson

Reviewer’s report:

This is a very nice paper. The authors should be congratulated on submitting a well written and illustrated report. The clinical diagnosis and description of phenotype seems secure and well described. My main concern is the pathogenicity of the reported CTC1 variant. The authors provide good evidence in favour of causation (the rarity of the variant and predicted pathogenicity in silico). However, the EVS and 1000 genomes databases do not in my opinion include enough ‘controls’ from the same ethnic background as the family described here. As such I recommend that the authors screen a larger number of ethnically matched controls. I would also encourage the authors to comment on the fact that this is the only homozygous CTC1 variant identified in a Coats plus (CP) patient so far, and speculate as to why this might be. I also recommend that the authors comment in the conclusion section on the possible association of dextrocardia with CP.

At this point and with the recommended changes below I believe that this paper could be accepted. Given that this disease is so rare any new descriptions in the literature should be welcomed, and in particular cases such as these which may expand the phenotypic spectrum.

Major Compulsory revisions
1. Screen a larger number of ethnically matched control samples.
2. Comment on the fact that this is the only homozygous CTC1 variant identified in a case of CP, suggest reasons why

Minor Essential Revisions
1. In Figure 1 (V) image and legend, please clarify which parental sequence trace is shown. Carrier parent is not clear enough; please state either mother or father.
2. Clarify/comment on why homozygosity mapping was carried out in a non-consanguineous family
3. In Results and Discussion at the end of paragraph two, it would be more accurate to say that the observation of shortened telomere length in the DNA of affected individuals supports (rather than confirms) the speculation of conformational change and reduced capacity for binding to telomeric ends. I do not believe that this experiment alone confirms pathogenicity of the variant
described.
4. In Results and Discussion at the end of paragraph one, please correct the figure reference. The text refers to the CTC1 variation but Fig1. V shows traces for the HES7 variation.
5. In Abstract Results section, please correct the spelling of ‘leukocytes’.

Discretionary Revisions
1. Minor changes to text which are highlighted with comments on the attached pdf

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 that I have no competing interests