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

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Reviewer: Renato Borgatti

Reviewer's report:

The aim of the study is to describe a eight-year old boy with a complex phenotype characterized by CRMCC (cerebroretinal microangiopathy with calcifications), dextrocardia and situs inversus, in which a novel homozygous missense variation in the CTC1 gene and a rare known variation in the HES7 gene were detected by targeted resequencing and whole exome sequencing (WES).

As far as concerned the genetic findings, the reported association between a homozygous CTC1 missense mutation with CRMCC phenotype is not new, as widely recently described in several recent studies. Also the association between the HES7 gene and dextrocardia and situs inversus phenotype is known, as reported by Sparrow DB, et al. Am J Med Genet 2013, but it is the first time in which the two genetic defects are described in a same patient.

Despite the study describes the first genetically confirmed case of CRMCC from India, and an unusual association between two different syndromes usually each other independent, it is of poor interest because it lacks to discuss this association. Overall the paper is conducted with little care: the case is not well described and the language used is not always appropriate.

Major revisions:

The reported genetic defect of HES7 gene is a known rare variation in dbSNP so its real pathogenic role it is unclear. The Authors don’t discuss this issue.

The CTC1 and HES7 genes belong to the family of transcription factors regulating Notch signaling pathway. This data should be discussed as the possible clinical consequences of this.

Minor revisions:

In all the test, in figure legend check and add the term gene/genes after the gene symbol. Check that gene symbol CTC1 in all the text, in figure Legend and in references is written in italicus. Many typewrite error (space, full stop, commas, etc..) are present.

Abstract:

Line 2: the terms “Cerebroretinal microangiopathy with calcifications and cysts (CRMCC)” and “Coats plus syndrome” are used as synonymous. It is not correct,
and the Authors should preferably use the term CRMMC than Coats plus syndrome”. This problem is present in many part of the text.

Line 9: the sentence “Targeted sequencing of CTC1…conducted” should be corrected in “Targeted sequencing of the CTC1 gene…were conducted”

Line 14: the sentence “HES7 was identified as a plausible…” should be corrected in “HES7 was were identified as plausible…”

Background:

Page 5, Line 13: explain the sentence: “In all diseases…central phenotype”. It is uncorrected because in CRMCC phenotype DC and bone marrow failure are not major criteria.

Page 5, Line 17: The sentence “overlap …till date)” should be better explained with a major attention to the proper terminology to describe the clinical continuum observed among these pathologies.

Clinical presentation

Page 6, Line 16: “Coats disease of the eyes” edit in The eyes present …. compatible with the diagnosis of Coats Disease.

**Level of interest:** An article of limited interest

**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 have non competing interest