Reviewer's report

Title: Genome-wide linkage and exome analyses identify variants of HMCN1 for splenic epidermoid cyst

Version: 1 Date: 20 May 2014

Reviewer: Elizabeth Blue

Reviewer's report:

Major Compulsory Revisions
None.

Minor Essential Revisions
(1) In the Background of the paper, the authors indicate that this phenotype is difficult to diagnose and cases are often asymptomatic (page 4 lines 78-79). In the Methods section of the paper, the authors describe the recruitment of the Japanese family (page 5 lines 95-107). Because the disease is often asymptomatic, I am curious to know how the "unaffected" relatives were evaluated. Were they merely asymptomatic, or were they evaluated by CT scan or ultrasound? It is important to know how affection status was determined, as the pedigree provided does not allow for missing or censored phenotypes. If the unaffected relatives are merely asymptomatic, it may provide answers regarding the imperfect cosegregation of the HMCN1 variant in the pedigree.

(2) The ascertainment of the patients from Kosovo needs to be more clear. The Background (page 5 line 90) and Methods (page 5 lines 102-107; page 6 lines 130-131) describe the number and origin of the Kosovo patients, but not why they were chosen for sequencing. Why were these four unrelated cases from Kosovo selected? Do they have familial forms of the disease? Were they the only available subjects also affected by this disease?

(3) Please explain why the functional significance of the DDHD1 variant was evaluated, but not the functional significance of the HMCN1 variants. The authors do a good job of explaining why the gene is a good candidate. It seems strange that they evaluated the function of a worse candidate variant, and did not do so for the HMCN1 variants.

(4) In Table 2, there are more novel INDELs reported than rare (<=2% in 1000 genomes). This is unusual, and in contrast to the SNV findings in the same table. Can the authors explain this discrepancy?

Discretionary Revisions
(1) The manuscript would benefit from copy editing to correct minor but numerous grammatical and vocabulary errors. For example, page 4 lines 70-71 "Accordingly, whole exons resequencing has increasingly been used as an
efficient way to identify disease causalities [2,3]." would be more clear if revised to "Accordingly, whole exome resequencing has increasingly been used as an efficient way to identify genetic causes of disease [2,3]." It is possible to understand the probable intent of the authors, but this copy editing would clarify the author's thoughts to the reader.

(2) Please clarify why the reported approach was chosen for evaluating the functional significance of the DDHD1 variant (page 8 lines 188-192).

(3) The authors propose a hypothesis to explain how HMNC1 could be involved in splenic epidermoid cyst in the Discussion section (page 10 lines 240-245; page 11 lines 246-248). Additional text detailing ways to test the hypothesis would be appreciated.

**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.