Reviewers report

Title: Clinical and genetic analyses of three Korean families with hereditary hemorrhagic telangiectasia

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Reviewer: LUISA-MARÍA Botella

Reviewers report:

Major compulsory revision: to make a protein analysis of endoglin in family 2, the reviewer recommends to measure it by flow cytometry on macrophages from the proband and a non affected HHT relative, just to prove that half of the protein is present in the mutant. This will reinforce the in vivo analysis of this new mutation.

Upon the additional experiment, the manuscript should be accepted.

No minor essential revisions
No discretionary revisions

The manuscript by Kim et al, on Clinical and genetic analyses of three korean families with hereditary hemorrhagic telangiectasia is interesting, well written and clear. The main original point is the finding of the first mutation introducing a new translation start codon in the gene Endoglin. The correlation between the mutation and the phenotype has been correctly assayed within the familiar pedigree, and also the molecular origin of the clinical symptoms has been approached by in vitro functional analyses. However, this referee thinks that the provision of protein data supporting the haploinsufficiency at protein level in the case of the new mutation will enrich considerably the paper. The suggestion would be to analyse the levels of Endoglin expression in macrophages from PBLs of the patient versus levels in a non HHT relative of the same family. The analysis could be done by either flow cytometry or by western blot. In this way, the functional proof of the new -127 ATG codon, could have the correlation with a reduced level of protein expression due to the premature stop of translation in the mutated mRNA.

1. The question of the paper is clearly defined, the molecular assessment of the HHT pathology in 3 families of Korean origin
2. The methods are extremely well written and described and are appropriate, although as stated before, the reviewer is missing protein analysis supporting the haploinsufficiency in family 2.
3. The manuscript is sound, it is extremely accurate in the sentences, introduction of the problem is very correct, and the discussion is appropriate. The authors know well the subject and all the details including clinical data, and familiar pedigrees to make a complete compilation of data in this kind of manuscripts.
4. Data are relevant, specially in family 2 since it is the first report on a type of mutation: new ATG created upstream the functional origin of translation in endoglin, giving rise to HHT.

5. The limitations are not clearly mentioned but they are implicit in the work by the time of in vitro functional approach performed by them.

6. They refer all the findings to previous database and previous papers of the same type, and make it clear the original findings.

7. Title and abstract are correct and adequate.

8. The manuscript is extremely well written

**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' below