Author's response to reviews

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

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Author's response to reviews: see over
August 30, 2011

RE: MS # 9286819105268473

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

Dear Dr. Tregouet:

We are submitting the second revision of manuscript 9286819105268473. The first reviewer accepted our previous revision satisfactory; while the second reviewer raised a concern and asked us to perform one additional experiment.

Fundamental issue was that the reviewer thought that ENG mutant patient may have elevated Eng transcript level, which might be linked to pathogenesis in this case. The reviewer’s reasoning was based on the restriction enzyme digestion of RT-PCR amplified band shown in Figure 4A (right panel). The reviewer said “We understand that the picture shows a qualitative result, and therefore the intensity of the bands we should not be taken into account.” As the reviewer noted, this experiment was to compare relative intensities of wild-type and mutant bands within each lane, not to compare the intensities between lanes. Nonetheless, the reviewer concerned that there may be elevated wild-type transcripts in the affected sample, as said “We understand that the bands which should correspond to the mutant allele, are hardly visible, then the interpretation of early mediated decay of the mutant RNA is correct. But, what is worrying is the increase in the wild type RNA in the affected sample. If this was the real case, instead of having haploinsufficiency of ENG as a cause of the pathology, we would have an “excess” of RNA (the result of a kind of compensatory mechanism operating on the mutated sample).“

The reviewer asked us to perform quantitative RT-PCR analysis to compare the level of Eng transcripts between normal and affected individuals. We performed the quantitative RT-PCR experiments. The results are summarized in Figure 4C. The level of Eng transcripts in the affected individuals was NOT more but significantly less compared to those in unaffected control samples. This result supports the interpretation of nonsense-mediated mRNA decay of Eng transcripts from the mutant allele.

All changes made during the second revision are marked by blue fonts.

We hope you find this revised manuscript acceptable for the publication in BMC Medical Genetics. I look forward to hearing from you soon. Thank you very much for your consideration.

Sincerely,
S. Paul Oh, Ph.D.
Associate Professor of Physiology