Reviewer's report

**Title:** Beta catenin and cytokine pathway dysregulation in PTEN hamartoma tumor syndrome patients

**Version:** 2  **Date:** 5 February 2012

**Reviewer:** Maurizio Genuardi

**Reviewer's report:**

The manuscript has been substantially improved. Most previous comments have been addressed satisfactorily.

**Minor essential revisions**

However, the clinical definition of patient PHTS2 and especially of patient PHTS3 is still non convincing. The authors point out that the histological characteristics observed in the patients are typical of “Cowden” polyps; these should be described, including appropriate references that mention a clear distinction between “Cowden” and juvenile polyps. Are these ganglioneuromas, the main distinctive type of polyp associated with constitutional PTEN mutations?

Anyhow, diagnostic criteria for PHTS would still not be satisfied (see: Pilarski and Eng 2004, J Med Genet 41:323-326.; and Tan et al. Am J Hum Genet. 2011, 88: 42–56). The authors state that “the diagnosis of PHTS is only made when a PTEN mutation is identified”; however, no mutation was identified in patients PHTS2 and PHTS3; the finding of reduced mRNA expression is suggestive of a mutation, but it could be due to other factors, possibly affecting other genes. Hence, the clinical condition of these patients is better defined as that of “patients with manifestations in the PHTS spectrum” or something alike. Likewise, the title should be changed into “Beta catenin and cytokine pathway dysregulation in patients with manifestations of the PTEN hamartoma tumor syndrome spectrum” or equivalent. The observation that PHTS2 and PHTS3 have less prominent manifestations could be related to a peculiar molecular mechanism, possibly not directly involving PTEN, but influencing its expression.

**Additional points**

- Fig. 1A is now redundant, since the authors have introduced histograms showing individual results from controls in Fig. 1B. Hence Fig. 1 should be composed of 2 insets (1A and 1B, corresponding to current 1B and 1C, respectively).

- Quantitative analysis for PTEN copy number variations has been performed for an additional fragment of the gene. This reinforces previous evidence against the presence of genomic rearrangements in PHTS2 and PHTS3, based on analysis of another genomic region as well as on cDNA analysis. However, though unlikely, such possibility, cannot be completely ruled out with the methods used;
this should be mentioned in the discussion.

- **PTEN** should be italicized throughout the text when referred to the gene.


- Page 5, Methods: the 4th and the 5th sentence (“In addition …”) are identical.

- Page 15, 2nd paragraph: “It is viable …” # replace with “It is reasonable …”

- Page 15, 3rd paragraph (“Although the relationship …. pathway [6]”): the concepts illustrated in this paragraph are not fully understandable; it is advisable that the whole paragraph be rewritten.

**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' below. If your reply is yes to any, please give details below