Reviewer's report

Title: Methylation status of SFRPs gene family in cutaneous squamous cell carcinomas

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Reviewer: Celine Pourreyron

Reviewer's report:

In this study, the authors investigated SFRP promoter methylation levels in cutaneous SCC, adjacent skin and normal epidermis. They reported a higher methylation rate in cutaneous SCC compared to adjacent and normal skin and suggested that the methylation level of SFRP1 promoter could be used as a cutaneous SCC marker.

Major compulsory revision:

- Please change the title as followed or to something similar to: SFRP promoters are hypermethylated in cutaneous squamous carcinoma compared to normal epidermis

- In background (line 51), the authors mentioned that there are no data on SFRP in cutaneous SCC. It looks that they have missed the paper by Pourreyron et al. (Plos One, 2012) where the authors showed dysregulation of SFRP1 and 2 gene expression in cutaneous SCC compared to normal skin. I suggest the authors to mention this study in the background section.

- Could the authors please add the body sites of the tumours and normal skin, the immune status of the cancer patients, as well as the number of poorly/moderately/well-differentiated tumours in the material and methods section?

- The authors suggest that SFRP1 promoter methylation could be used as a potential marker of cutaneous SCC early diagnosis (fig 2). I have two comments about these data. The first one is that I don’t find the ROC curve of SFRP1 CpG1.1 site very convincing and I would like to authors to calculate the area under the curve (AUROC) to determine the accuracy of the test. My second comment relates to the early diagnosis. Having not included any pre-cancerous skin lesions such as actinic keratosis in their study, I am not sure the authors can claim that SFRP1 promoter methylation could be used as a marker of early tumorigenesis. Could the authors please elaborate on this?

- In the discussion, the authors should discuss their results with Pourreyron et al. paper as well as with the data provided by the Human Protein Atlas on cutaneous SCC (www.proteinatlas.org).

Minor essential revision:

- Having worked on tumours from Chinese patients for this study, it would be interesting to include Chinese statistics in the background section, if such
numbers are available.
- The transition between paragraph 1 and 2 in the background is quite poor. I would delete lines 35-37.
- Line 45: please change leads for leading and contribute for contributing.
- Line 59: please add department after dermatology
- Could you please comment on how the adjacent skin specimens were checked for absence of tumour material?
- Line 101: aberrant methylation was detected in each tissue group compared to what?
- End of line 122 and 127: authors are requested to supplement some more references.
- Could you please comment on why you chose to study SFRP1 methylation as an SCC marker and not the other SFRP which according to your results are also hypermethylated in cancer?
- I feel that SFRP immunostaining on the samples used for the present study would strongly improve the manuscript and confirm the results. Since good antibodies are available for SFRP immunostaining on paraffin sections, I would recommend the authors to perform such staining on the tissues sent to pathology.
- line 175: am I right to think that the authors meant for cutaneous SCC diagnosis and not for melanoma diagnosis?
- Table 1: could you provide the age and mean age for both groups please (cases and controls)?
- Table 3: could you please define N and H and mention how many tumours there were for each stage
- Fig1A: isn't it SFRP1 and not SFRP2?

**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