Reviewer’s report

Title: Similar gene expression profiles of sporadic, PGL2-, and SDHD-linked paragangliomas suggest mitochondrial complex II dysfunction in all three groups

Version: 1 Date: 6 December 2008

Reviewer: francesca schiavi

Reviewer’s report:

In this manuscript Dr Hensen and coworkers report on gene expression profile analysis of sporadic, PGL2- and SDHD-linked head and neck paragangliomas. The aim was to detect differences/similarities among these three paraganglioma subgroups, with the attempt to characterize PGL2 function and identity.

They performed gene expression profile in cDNA from frozen specimen of paraganglioma of different origin (PGL1, PGL2 and sporadic). Considering the rarity of these tumors, particularly PGL2, the sample size is acceptable even if limited.

No significant differential expression among sporadic, SDHD- and PGL2-linked paragangliomas was observed, suggesting a common tumor genesis in most head and neck paragangliomas, independently of their genetic background.

Major points

1. No clinical data are reported: more information should be included (at least gender, age of onset, malignancy, presence of multicentricity). These information could be added in table 1.

2. It is not clear which method had been used in the mutation scanning and which are the “known mutations”. Probably authors refer to SDHD founder mutations, but this need to be clarify.

About other genes, RET, VHL and NF1, I wonder if the authors are aware of any case of HNP only due to a mutation in one of these genes.

Particularly about NF1 gene, did the authors screen all its 60 exons?

3. Large deletion analysis should be performed in order to detect rearrangements in SDHB, SDHC and SDHD genes, representing 10% of the mutations affecting these genes.

4. The supervised analysis of chromosome 11 probe set did not find significant expression differences among sporadic, PGL2- and SDHD-linked tumors. Authors suppose that the loss of chromosome 11 could explain this similarity not only in the case of PGL2- and SDHD-linked paragangliomas but even in case of
sporadic ones.

This hypothesis should be easily verify performing LOH analysis on these samples.

By the way, in the paper of Dannenberg chromosome 11 loss was reported in few sporadic paragangliomas, but SDHB, SDHC and SDHD molecular screening was not performed and the definition of sporadic was bases on the absence of a positive family history.

Minor points

1. The definition of paraganglioma should be reviewed: parasympathetic paragangliomas located in the head and neck do not originate in chromaffin cells.

Moreover authors should consider as a manifestation in SDHB-, SDHC- and SDHD-linked syndromes not only pheochromocytomas arising in the adrenal medulla, but even functional paragangliomas arising in other sympathetic ganglia in thorax and retro-peritoneum.

2. In the discussion, authors affirm that the three subgroups share clinical characteristics, citing paper antecedent to the identification of SDHx-linked paraganglioma syndromes, they should refer to more recent reviews in which the clinical characteristics of these syndromes are described, highlighting the differences with sporadic paragangliomas (e.g. Neumann et al, Jama 2004; Benn DE et al, JCEM 2005).

3. I suggest to modify the title, with focus on the similarity in the expression profile, that is the original result of this work, as the mitochondrial complex II dysfunction has not been demonstrated here.

**Level of interest:** An article whose findings are important to those with closely related research interests

**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