Reviewer's report

Title: Somatic VHL gene alterations in MEN2-associated medullary thyroid carcinoma

Version: 2 Date: 1 April 2006

Reviewer: rossella elisei

Reviewer's report:

General

The authors studied allelic imbalance of RET, LOH and point mutations of the VHL gene in the tumoral tissue of a small series of 7 patients affected with hereditary medullary thyroid carcinoma. All patients carried a RET germline mutation. The analyses of allelic imbalance and LOH were performed using specific polymorphic markers. Mutational analysis of exons 1-3 of the VHL gene was performed by CSGE and direct sequence analysis.

Allelic imbalance between the mutant and wild type RET was demonstrated in 3 MTCs that showed also LOH of the VHL gene. One of these cases showed also a base pair deletion in exon 1 of the VHL gene leading to the formation of a stop codon at codon 66.

In summary they found that 3/7 cases showed allelic imbalance of RET and LOH of VHL gene, 1/5 cases (in 2 cases the authors could not receive sequencing analysis results) showed a VHL gene mutation. Their conclusion is that somatic VHL mutation and deletion are involved in tumor progression rather than tumor initiation of hereditary MTC.

The study is clearly written, the methods and results are well explained and the discussion is well balanced. The main criticism is about the small number of cases analyzed. This work could “clarify” some pathogenetic mechanism of tumor progression but these data must be confirmed in a larger series before driving any conclusion.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

The following points should be addressed:

1. Please, confirm these data in a larger series (at least 15 cases)
2. Two of the seven cases could not be analyzed by sequence analysis. The authors should find some genomic DNA to perform sequence analysis in order to complete the study at least on these 7 cases.
3. Fig 3 should include the normal sequence to highlight the alteration of the tumoral sequence.
4. The VHL gene deletion was found in the tumoral DNA. It is unclear if the authors looked for the mutation also in the blood DNA of this patient: please clarify.
5. Page 7, line 16: the sentence “Polymorphism G691S/S904S........” is incomplete because it has been reported that the G691S polymorphism is significantly associated to medullary thyroid cancer thus this polymorphisms not only affect the age of MTC onset but also its development (please cite Elisei R et al 2004 and Cebrian A et al 2005)

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
Minor points:

1. Page 6, line 5: “tumorinitiation” should be replaced with “tumor initiation”
2. Page 7, line 16: “effect” should be replaced with affect
3. Please carefully revise the spelling and typing mistakes.

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:
I declare that I have no competing interests