Reviewer's report

Title: A multinodular goiter as the initial presentation of a renal cell carcinoma harbouring a novel VHL mutation.

Version: 1 Date: 13 September 2006

Reviewer: Christian Koch

Reviewer's report:

General
This is a well written and well presented paper. The English is excellent and the quality of the figures as well, although Fig 2A has some problems in terms of interpretation. However, the aim of this case study has not been reached and the conclusions cannot be drawn, as illustrated below.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
Why did the authors not instantly perform a CT of the abdomen/kidneys, if they already were thinking of renal cancer based on the result of clear-cell tumor on FNA? This would have established the anatomic site of origin right away. What are other primary clear-cell tumors? Please list these, since the readers would like to know about this.
Could the authors cite, based on the available data in the literature, how frequent somatic VHL mutations occur in patients with clear cell renal cancer? This, of course, impacts on the sensitivity and likelihood of finding such mutations in this setting.
How high do the authors estimate their rate of amplification errors based on their approach, i.e. subcloning?
Which primers did the authors use for analyzing the VHL gene (ref 14)? These should be reported. Except for exon 2, SSCP is a notoriously hard method to detect abnormalities in exons 1 and 3 of the VHL gene.
Why did the authors not perform immunohistochemical studies for the VHL gene product, especially in the tumor samples?
Why would the authors bring up the issue of hypermethylation on page 9 in their conclusion/discussion, if there was no germline mutation in the VHL gene? The Two-Hit model of Knudson does not refer to that but to the fact of a germline mutation in one allele and "second" hit in the remaining wild-type allele, i.e. by loss of heterozygosity, hypermethylation, etc.
How would the authors know which band to cut out for sequencing analysis when looking at Fig 2A? This reviewer sees one band in N (normal tissue) and 2 bands in T (tumor).

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
none

Discretionary Revisions (which the author can choose to ignore)
none

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 limited interest

Quality of written English: Acceptable

Statistical review: No

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