Reviewer's report

Title: Identification of a novel PAX8 gene sequence variant in four members of the same family: from congenital hypothyroidism with thyroid hypoplasia to mild subclinical hypothyroidism

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Reviewer: Seamus Sreenan

Reviewer's report:

General Comments

In this manuscript by Vincenzi et al, the authors present evidence of a novel PAX8 gene variant in four members of the same family that appears to be associated with a variety of thyroid abnormalities both structural and functional. The strength of the paper is that it presents a new heterozygous genetic variant in PAX8 and will be of interest to those working in the area. Unfortunately although there is clearly a genetic variation in the PAX 8 gene, functional studies don’t support a difference between the activity of the normal and variant genes under the conditions tested. While the authors recognise this limitation they interpret the clinical findings as being due to the genetic variant and speculate that the variant could lead to an abnormal interaction between Pax 8 and another transcription factor.

Discretionary revisions:

1. In the abstract the authors state that the aim of the study was to analyse the sequence of the PAX 8 gene in several members of the same family. From the methods it seems that several genes were studied in the proband and the authors focused on PAX 8 when the variant was discovered. I would suggest clarifying the aim to indicate this and make the question posed at the outset of the study clearer.

2. In the introduction I think the authors need to elaborate on the phenotype associated with previous PAX 8 mutations.

Minor essential revisions

1. There are several grammatical and linguistic errors in the manuscript. Careful proof reading of the paper should identify these as they are too many to list here. For example what does “Thyroid scintigraphy revealed weak fixation?”

2. The authors use PAX when referring to the gene and the transcription factor. The convention is that PAX refers to the gene and Pax to the gene product.

3. The authors say that the high TSH accounts for the nodules in three of the subjects with PAX 8 mutations. This is possible but they cannot be sure and so should qualify the comment. As thyroid nodules are such a common finding, how can the authors be sure that they are related to the genetic variant?
4. Why were all of the thyroid blood tests not done in the same laboratory (we can assume they were not since different reference ranges are provided)?

Major compulsory revisions

Subjects and methods

1. Given that the subject III-3 had a very subtle degree of thyroid dysfunction can the authors be certain that this was due to the genetic variant? There is no mention of an abnormal thyroid ultrasound in this case whereas the other three had some degree of agenesis of the gland. Was the thyroid function checked in that subject on more than occasion?

2. Likewise the other family members with normal thyroid function – were they checked on more than one occasion?

3. In the introduction the authors state that, at least in mice, Pax 8 has roles not only in the development of the thyroid but also in kidney and nervous system. What testing was done to ensure that neurological and renal functions were normal? Two of the subjects studied had ultrasound of the abdomen, presumably to look at renal size/structure but there is no other mention of further investigation. Some further comment is necessary.

Discussion:

4. While I accept that the authors indicate that PAX8 mutations may have a variable phenotype I think the authors need to soften their interpretation that the phenotype in the family studied is due to the genetic variant…at least to accept that given the very mild phenotype in the cousin that it is possible that the genetic variant and the clinical phenotype may not be related. Do we know for instance whether any of the family members who did not have the novel variant had thyroid nodules or any degree of thyroid dysplasia?

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

Quality of written English: Not suitable for publication unless extensively edited

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