Reviewer's report

Title: Serum levels of Pancreatic Stone Protein (PSP)/reg1A as an indicator of beta-cell apoptosis suggest an increased apoptosis rate in hepatocyte nuclear factor 1 alpha (HNF1A-MODY) carriers from the third decade of life onward

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Reviewer: katharine owen

Reviewer's report:

In this article the authors investigate PSP/reg1A as a marker of apoptosis in diabetes. In particular they hypothesise that PSP may be used as a marker of apoptosis in HNF1A-MODY and compare the levels seen in their group of HNF1A-MODY cases with a second monogenic subgroup (GCK-MODY) and type 1 diabetes.

I found the paper very interesting. A marker for # cell apoptosis could have wide use in both clinical practice and as a research tool. I have the following comments/concerns:

Major Compulsory Revisions

1. I have concerns over the 2 different control groups used in the study. While I can see the attraction of using family controls, the control group is on the small side and you say consists of “individuals who had both normal and impaired glucose tolerance”. This raises 2 questions: firstly that it must be incorrect to use controls with IGT when we are looking at a marker of # cell apoptosis/regeneration and secondly if there are non-mutation carrying family members with dysglycaemia, is there any doubt about the pathogenicity of the HNF1A mutations (i.e. are all novel non-truncating mutations co-segregating with diabetes). Were the sequencing results interpreted by a diagnostic genetics centre? I think you should use your larger, normally-distributed historical control group unless there is a good reason not too, especially as you use it to compare to the GCK/T1 cases.

2. Following on from this: it’s noticeable that the median value of PSP in the GCK group is quite similar to the HNF1A group. Was there any difference if the two MODY groups were directly compared? I think you have to be careful of concluding that there is a clear difference between the 2 groups and thus no evidence of apoptosis in the GCK group.

3. How does PSP correlate with duration of diabetes? Or with C-peptide? This might be a better way of looking at it than age of onset.

4. Statistics: please report results as either medians (IQR) if not normally distributed or means if normally distributed (or transformed). You seem to have used non-parametric stats mainly. The medians are different to the means except in the historic controls, suggesting PSP is not normally distributed.
5. General use of PSP as an apoptosis marker: Any biomarker needs to have adequate sensitivity and specificity. The differences between the diabetic groups and the controls are not huge, although the numbers are small and I see from other literature that PSP level can be elevated by several other liver/pancreas diseases and in chronic renal failure. It would be good to see a little of this context in the discussion in terms of the likely usefulness of this marker.

Minor Essential Revisions

1. The authors mention “reduced pancreatic volume” in the abstract, but then don’t refer to pancreatic volume again in the text.
2. Abstract results: I suggest giving the full p value rather than “p<0.05”
3. Background paragraph 2: It’s obvious that a somatic mutation is present from birth – rephrase.
4. Use of word “cohort” (multiple examples): Cohort has a specific epidemiological meaning in population or genetics studies - it would be better to use alternative terms such as “collection” or “group” in this context.
5. Subjects: for the MODY cases can you include the number of families the subjects were drawn from?
6. Methods: was the OGTT performed in all subjects including those with type 1 diabetes? This is implied.
7. Results: the results paragraphs contain both background and interpretation comments which should be deleted or moved elsewhere (e.g. first 2 sentences of 1st results paragraph could be deleted).
8. In Table 1: do you have incorrect units for C-peptide? Should it be ng/ml? Your type 1 group seems to have quite a high (mean? Median?) fasting C-peptide if so….what are PSP levels like in C-peptide negative type 1?
9. In Table 1: you give duration of diabetes for the GCK cases from the identification of hyperglycaemia….however strictly speaking hyperglycaemia is present from birth
10. The Figures and Table legends need to be edited to remove the interpretations – there should just be a description of what is illustrated. Table 1 - are medians or means being presented? What is being compared to what for the non-significant result

Discretionary Revisions

1. The abstract seems too long at 340 words and the heading for the Methods section is missing

**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'