Author’s response to reviews

Title: Clinical and genetic analysis of two Wolfram syndrome families with high occurrence of Wolfram syndrome and Diabetes type II: a case report

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Response to comments
Ana Gorostidi, Dr (Reviewer 1):
This work is interesting for the clinical-genetic aspect of the syndrome analysed, Wolfram. It is friendly and easy to read and should be published as it is an interesting contribution to the research of this rare syndrome.
The following are some minor suggestions:
Page 5, Lane 27: The term "Touch down" should be specified or described, with a reference or in supplementary material, as well as marker amplification M&M.
Response: We added a reference for Touch down PCR and explained the issue. We also added a reference for marker amplification.
Page 5, Lane 49: Reference to Figure 1 should be done before, when first referred to pedigrees.
Response: We corrected the point.
Page 8, Lane 45: "to be" is duplicated
Response: We corrected the point.
Page 9, lane 5: Detail of pathogenic analysis should be given, with results of each simulation analysis performed. Could be done in supplementary material.
Response: We added detail of pathogenic analysis in Supplementary material.
Page 9, lane 54: Sentence grammar should be revised
Response: We corrected the mentioned sentence.
I find information about molecular analysis in page 5 and afterwards, in page 8, you are back with "Molecular study". If the work is not described with M&M and results sections, the
information given in page 8, should be integrated with the introduction given before. I think this will help in the reading.
Response: We edited the structure of the manuscript adding subtitles to help in reading.

Anlu Chen, Ph.D. (Reviewer 2): Sobhani and colleagues studied extended consanguineous families and identified a novel mutation in a highly disease-associated gene, WFS1. This manuscript would be interested to researchers in this rare disease field and in general overlaps with the journal's interest. I only have some minor suggestions below.

1. In general, high-resolution images are required. Some contexts are unreadable, especially in Figure 1.
Response: We improved the quality of figures.
2. On page 3, the authors mentioned 'a second locus containing a gene designated as WFS2'. It might be reasonable to specify the WFS1 locus first.
Response: We specified the WFS1 locus first.
3. On page 3, WFS2 is an alias for CISD2.
Response: We added this point.
4. Please add a table to compare the clinic presentations among all patients.
Response: We added this Table.
5. Please confirm that if 'DM' mentioned in the clinic presentations all referred to 'T2DM'?
Response: Yes. We used T2DM in all situations.
6. Is there any special reasons to keep the family name as 'Family IR-WS-18' and 'Family IR_WS_25'? If not, change to Family I and Family II, respectively.
Response: We change the name of families.
7. It's confusing when referring to family members. For example, please use I-III-8 to represent case 1.
Response: We used the mentioned nomenclature.
8. In Figure 1, please double check if all consanguineous marriages have been marked as double lines.
Response: All consanguineous marriages have been marked as double lines.
9. In Figure 1, male partner can be put to left of female partner on relationship line. (Bennett RL. et al., J Genet Counsel, 2008)
Response: Based on the consanguineous marriages, the figure was adopted to be less complex.
10. In Figure 1, please double check the color indications.
Response: We corrected the mistakes.
11. In Figure 2, there's no V-9 in Family I. I assumed it's III-9 in Family I.
Response: We corrected the mistake.
12. In Figure 4, there's no VI-1 or V-1 in Family I. I would assume it's IV-1 and III-1, respectively.
Response: We corrected the mistakes.
13. In Figures 5 and 6, please add reference genome sequence and fully mark the chromat of the patients. For example, C/G indicates heterozygous at certain position. Please align the panels A and B if possible.
Response: We edited the Figures. However, we do not have the reference genome sequence chromate.
14. In Figures 5 and 6, please specify the ID of individuals represented in these figures.
Response: We added the note.