Author's response to reviews

Title: Systematic analysis of the clinical and biochemical characteristics of maternally inherited hypertension in Chinese Han families associated with mitochondrial genome mutations

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Author's response to reviews: see over
The authors have improved the manuscript, however, there are still some concerns.

1. In the abstract, the authors write about 74 maternal members from 9 hypertension families and 216 healthy controls. In the introduction, they speak of 140 hypertension patients and 124 healthy controls. The discussion starts with 108 hypertension individuals. These numbers do not match. In case they mean the previous study (references 11-15), they should not end the introduction with findings from that study but should rather describe how the new study (this manuscript) adds to that previous knowledge. In the methods part, the number of maternal members having been analyzed by sequencing is 69. Again, the numbers do not fit! Clinical data appears to having been available for 65 maternal members (results part).

All numbers need to be carefully revised!

The numbers were revised in the methods and discussion part.

2. The use of the term 'proband' is not clear. In line 22 on page 6, one might suspect that they used this term in the context of the 9 hypertension families. However, a proband is defined to denote a particular subject (individual/patient). Hence, it does not become clear what the authors mean when they state in line 10 on page 7: 'We sequenced the entire mitochondrial genome in 9 probands,...'. Did they sequence all maternal 64, 69, or 74 members or just 9 individuals? If indeed just those 9 patients had been sequenced from the maternal members cohort, how had the other members been analyzed (validation of mutations)? This is not explained in the methods part. The text in line 16 could be interpreted as if all 216 controls had been sequenced in order to generate a 'wildtype' reference sequence. Is this true?

The nomenclature of 'probands' and 'maternal members' needs to be clarified.

The probands here means that the 108 hypertension patients who were first involved in these study ascertained at the Institute of Geriatric Cardiology of Chinese PLA General Hospital. The maternal members means the families members from 9 probands who were proved to present with maternally inherited pattern.

As for the sequence analysis test, firstly we sequenced the entire mitochondrial genome in 9 probands, we found a total of 172 variants, including 151 variants identified located in the coding and control region. And then we indentified these 151 mutations in the other 65 maternal family (74 maternal members except 9 probands) members see more detail in the result part.

3. In rRNA/tRNA Mutation Analysis (p8) the authors first sequenced RNAs from 9 probands and then from 65 maternal family members. It does not become clear what the relation between probands and maternal family members is. The sentence 'We also identified 21 mutations in the 65 maternal family members' is not clear. Is this supposed to mean that they validated those 21 mutations they had identified in the 9 probands in the cohort of 65 maternal family members or are those 21 mutations unrelated?

The number of individuals having been sequenced (see also point 1) needs to be clearly specified. Also the kinds of mutations having been found in one or the other groups requires revision.
We first sequenced RNAs from 9 probands and identified 21 mutations, and then the 21 mutations were validated in the cohort of 65 maternal family members.

3. Instead of reproducing the exact kinds of mutations having been identified in the results and then again in the discussion part (lines 11-18 on page 10, they should rather restrict themselves to discussing the potential pathogenicity of these mutations. The text needs to be revised to remove redundancy.

Revised.

4. In the final paragraph of the discussion the authors state that their findings might provide valuable information for management and treatment of maternally inherited hypertension. They should add some ideas how their findings could be exploited to improve management and treatment.

Claims need to be backed up with explanations.

Claimed in the paragraph.

5. The grammar needs improvement. Sentences like 'The entire human mitochondrial DNA sequence has been mapped only 16k, including 13 encode proteins, 2 rRNAs, and 22 tRNAs' simply do not make sense. Hence, the manuscript must be carefully revised by a native speaker.

Revised

ADDITIONAL COMMENTS:

1. they need to better describe the source of their data. The GTEx consortium is not properly cited. Their reference 34 is neither a paper nor a database. There has indeed been a paper in Nature Genetics (2013 Jun;45(6):580-5. doi: 10.1038/ng.2653.) describing this consortium, however, this is not cited.

Revised.

2. along the same lines, the authors must include an ethics statement since human specimen have been sampled.

The ethics statement showed in the p4, line 13, 14.

3. where has the gene expression data been deposited - accession numbers should be provided 4. line numbers should be included in the manuscript.

http://www.mitomap.org/MITOMAP

5. In the results part, the expression profiles of more than 41,298 genes are said to having been analyzed. More than 41,298 would, for example, be 41,299. Why give an exact number and speak of more than? Furthermore, the human genome encodes much less than 40,000 genes. Hence, the statement does not make sense anyway.

Sorry, I did not understand what this issue means. This article not mentioned that.

A comment to the rationale (Background, first paragraph): It might be problematic to request tissue samples from athletes in sports events like the Olympic Games such that their age could be estimated based on the classifier the authors are out to generate.
In case the authors had some non-invasive way to obtain tissues (e.g., from 'sun exposed lower legs'), this should be described in more detail.

Not mentions the tissues in the article. We get DNA from the blood.

The first lines of the background sound anecdotal ('In an extreme case happened recently, a 16 year-old girl...'). This is not science language but newspaper style and should be changed.

I could not understand this issue. Could you please give more detail information about where the language style is more like newspaper. Thank you.