Dear Editor,

Thank you for your great effort in handling our submission (No: 80432, entitled Major depressive disorder is associated with the mitochondrial ND1 T3394C mutation in two Han Chinese families). We also thank the reviewer for his/her comments. In response to the comments and suggestions made by the referees, we have made a number of changes and additions to the manuscript. We believe that these changes, together with the detailed response to the reports given below, clarify all the points made by the referees. We would like to resubmit it to World Journal of Psychiatry. Thank you in advance for your further consideration of our contribution. We look forwards to your response in due course.

Sincerely yours,
Pan Jing, Xiaobin Zhang

Response to Reviewers:

Reviewer 1: Dear authors, I have a few comments on your manuscript: - I do not understand why you write that "the diagnosis of MDD is unreliable" (Abstract, Introduction). Is it specifically relevant for your manuscript? - In Discussion, you should mention whether epigenetics is relevant for mitochondrial DNA. Epigenetic mechanisms may also influence the phenotypic expression of mtDNA mutations.

Revision

1. I do not understand why you write that "the diagnosis of MDD is unreliable" (Abstract, Introduction). Is it specifically relevant for your manuscript?

   According to the advice, we modified the sentence as “However, the diagnosis of MDD is mainly based on clinical symptoms.” in paragraph of Abstract section. We also modified the sentence as “In spite of its high prevalence and morbidity, the diagnosis of MDD is mainly based on clinical symptoms, and there is little evidence at the molecular level [2].” in paragraph 1 of Introduction section.

2. In Discussion, you should mention whether epigenetics is relevant for mitochondrial DNA. Epigenetic mechanisms may also influence the phenotypic expression of mtDNA mutations.

   According to the advice, we modified the sentence as “Moreover, mtDNA epigenetics may be involved in the occurrence of MDD, but research on the role of mtDNA epigenetics in diseases and therapeutic targets is insufficient.” in the last paragraph of Discussion section.

Reviewer 2: Literature shows evidence that mitochondral DNA (mtDNA) is particularly susceptible to a higher rate of somatic deletions because mtDNA is not protected by histones and lacks the complete set of DNA repair machinery associated with nuclear DNA. Several studies indicate that oxidative stress and accumulation of reactive oxygen species have also been observed

in bipolar disorder and schizophrenia, suggesting a role for mitochondrial dysfunction in those disorders. There is limited literature depicting the role of mtDNA defects being the underlying molecular cause of major depressive disorder (MDD).In this case report, the authors discovered that the distinct sets of mtDNA polymorphisms, in addition to the identical T3394C mutation in the ND1 gene seems liked a plausible underlying basis for MDD. The authors have a done a good job in explaining the methods section. MDD being found as the only clinical phenotype in the maternal lineage of the pedigrees in the study was an interesting finding. As the authors rightfully noted, the penetrance of MDD was low in the studied families and the identified mitochondrial mutation T3394C mutation is not sufficient to explain the MDD presentations in the 2 subjects. This highlights the role of other environmental factors as being responsible for the manifestation of MDD. Overall the case report is well-written. This case report adds to the literature base of putative molecular basis of psychiatric disorders and signifies the need for further studies and investigation in this area.

Revision

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