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PEER-REVIEW REPORT

Name of journal: *World Journal of Psychiatry*

Manuscript NO: 80432

Title: Major depressive disorder is associated with the mitochondrial ND1 T3394C mutation in two Han Chinese families

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05906528
Position: Peer Reviewer
Academic degree: MD
Professional title: Assistant Professor, Staff Physician
Reviewer's Country/Territory: United States
Author's Country/Territory: China

Manuscript submission date: 2022-09-30

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-10-04 15:10

Reviewer performed review: 2022-10-10 14:21

Review time: 5 Days and 23 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty

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Creativity or innovation of this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation
Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

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

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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.

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Reviewer's code: 02445209
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Professor
Reviewer's Country/Territory: Czech Republic
Author's Country/Territory: China

Manuscript submission date: 2022-09-30

Reviewer chosen by: Dong-Mei Wang

Reviewer accepted review: 2022-11-14 07:39

Reviewer performed review: 2022-11-23 06:57

Review time: 8 Days and 23 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty

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Creativity or innovation of this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation
Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

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. The reviewer