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**Telephone:** +1-925-399-1568
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# PEER-REVIEW REPORT

**Name of journal:** World Journal of Psychiatry

**Manuscript NO:** 64823

**Title:** Alternative models for transgenerational epigenetic inheritance: molecular psychiatry beyond mice and man

**Reviewer's code:** 05115904
**Position:** Peer Reviewer
**Academic degree:** PhD
**Professional title:** Assistant Professor
**Reviewer's Country/Territory:** India
**Author's Country/Territory:** Australia

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**Reviewer accepted review:** 2021-04-10 10:19
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**Review time:** 5 Days and 22 Hours

| | |
|---|---|
| **Scientific quality** | [ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good<br>[ ] Grade D: Fair [ ] Grade E: Do not publish |
| **Language quality** | [ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing<br>[ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection |
| **Conclusion** | [ ] Accept (High priority) [ ] Accept (General priority)<br>[ ] Minor revision [Y] Major revision [ ] Rejection |
| **Re-review** | [Y] Yes [ ] No |
| **Peer-reviewer statements** | Peer-Review: [Y] Anonymous [ ] Onymous<br>Conflicts-of-Interest: [ ] Yes [Y] No |

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**SPECIFIC COMMENTS TO AUTHORS**

Title: Alternative models for transgenerational epigenetic inheritance: molecular psychiatry beyond mice and man. Journal: World Journal of Psychiatry Manuscript id: 64823 Summary: The authors have selected a very interesting issue of using animal model to study transgenerational epigenetic inheritance. They argue that Drosophila melanogaster would be a better model due to its short life span. The authors are persuasive but it is hard to get convinced that one should only carry out such studies in Drosophila. • In the Introduction, reader gets a sense that every psychiatric disorder is inherited, there are non-heritable psychiatric disorders and I would advise authors to make that distinction clear in the introduction. • One cannot do away with mice as model organism, it would be great if both non mammalian model and mammalian models are used for psychiatric research. Authors would be aware that most preclinical drug testing is done is rodents, so one has to use rodents for those kinds of work. Its not clear whether authors mean Drosophila can be used for basic research/ primary screening of drugs or preclinical research. • The authors only give advantages of Drosophila as model organism. Granted a long of neuroscience concepts have been discovered from drosophila studies, but to study complex neuropsychiatric disorders such as Schizophrenia what are the limitations. • Authors cite an example of how temperature variations lead to changes in gene expression in Drosophila sperm and oocytes. And there is an increase in transposons during this stress. The authors claim that some disorders such as Bipolar disorder, schizophrenia (SZ) etc may be due to changes in transposon activity. If there are references, those should be cited to show association between transposons Bipolar disorder, schizophrenia (SZ). Unlike lower animals or plants, human do not have active transposons that contribute to variation or disease. And can Drosophila can be used to model Bipolar disorder, schizophrenia (SZ)

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has not been reported. Hence this argument is not persuasive at all. • On page 12 and 13, authors describe the mechanism of heat shock proteins and the associated histone H4 levels and with oxidative stress. Does this also affect neurons in Drosophila? Authors need to clarify. • Authors claim that PTSD leads to changes in miRNAs, these are associations and they may affect neuronal genes, but can this change be transmitted transgenerational? • Can the authors describe how SZ, bipolar disorder models are created in Drosophila, how are the flies verified that they exhibit characteristics of SZ/PTSD/bipolar disorder. Once these diseases can be modelled in Drosophila, only then can you study these diseased flies for generations. I would strongly advise authors to cite the paper that have shown SZ/PTSD/bipolar disorders successfully modelled in Drosophila. • As I understand in the Table 1 and Table 2, the last column shows the "Potentially relevant psychiatric conditions" in humans, but after the first two studies, the others are in mice or other animals. Since the aim of this review is highlighting use of Drosophila as model for Psychiatric conditions, they should restrict to relevant human conditions. Since many of these stresses may not induce "Potentially relevant psychiatric conditions", it would be best to remove these last two columns. The Table can just highlight the stresses that can cross over to F2, or F3 generations and have the epigenetics mechanism. • Epigenetic modifications identified by transgenerational studies of Caenorhabditis elegans relevant to psychiatry section illustrates several studies which show corelation between epigenetic changes and behavior, but it is not clear if these behaviours are transgenerational (Kim et al.,2016 and Heller et al., 2016). If C.elegans has proven to be efficient model, how is Drosophila model better than C.elegans needs to be explained. • Authors should also give limitations of using invertebrates for psychiatric disorder researcher and highlight gaps and experimental means by which the limitations can be overcome. The review should not just be literature review, but also critical analysis of current research along with its limitations.

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