



## PEER-REVIEW REPORT

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

**Manuscript NO:** 100214

**Title:** Integrative transcriptomic and proteomic analysis reveals that SERPING1 inhibits neuronal proliferation via the CaMKII-CREB-BDNF pathway in schizophrenia

**Provenance and peer review:** Unsolicited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 06128019

**Position:** Peer Reviewer

**Academic degree:** PhD

**Professional title:** Doctor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** China

**Manuscript submission date:** 2024-08-10

**Reviewer chosen by:** Jia-Lin Zhang

**Reviewer accepted review:** 2024-11-12 10:08

**Reviewer performed review:** 2024-11-13 10:42

**Review time:** 1 Day

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Novelty of this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
<b>Creativity or innovation of this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



<b>Scientific significance of the conclusion in this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

In this paper, the authors identified SERPING1 as a significant molecule in schizophrenia patients using PBMCs and explored associations with a part of pathway in the rat hippocampus. The exploration of biomarkers in blood for schizophrenia is indeed an important and valuable topic. However, there are several critical concerns, I have outlined my specific concerns below: ### 1 - Clarify the specific criteria used to select "The ten most significant DEGs." It is presumed to be fold change. ### 2 - Why are neural pathways emerging in blood sample analysis? ### 3 - The rich factor and the software used for analysis should be described in the methods. ##4 All the cases included in the study were patients with recurrent schizophrenia who had received long-term antipsychotic treatment. This may introduce confounding factors, affecting the accuracy and universality of the results of peripheral blood transcriptomics and proteomics analysis, and thus cannot well represent the entire schizophrenia patient population, especially the situation of first-episode patients or untreated patients. ##5 The study mainly focuses on the exploration of the basic mechanism. Although it has been found that the SERPING1 gene may be a potential therapeutic target, there is a lack



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of discussion on how to translate these basic research achievements into clinical applications. For example, it does not mention whether new diagnostic methods or therapeutic drugs can be developed based on the results of this study, as well as the possible challenges and solutions in clinical practice. ##6 Future studies may consider incorporating other sample types, such as cerebrospinal fluid or post-mortem brain tissue samples (if feasible), to explore the pathogenesis of schizophrenia from different perspectives more comprehensively and verify the reliability and relevance of the PBMCs research results. ##7 During the process of integrative analysis of transcriptomics and proteomics data, relying solely on correlation analysis of gene expression and protein expression (such as Spearman correlation coefficient analysis) may not fully reveal the complex regulatory relationships between genes and proteins. In addition, for the differentially expressed genes and proteins screened out, there may be some false positive or false negative results, and the study did not conduct more in-depth verification and screening optimization. Suggestion: Adopt multivariate statistical analysis methods, such as principal component analysis (PCA) or partial least squares discriminant analysis (PLS - DA), to further explore the hidden information in the data and improve the accuracy of analyzing the regulatory relationships between genes and proteins.



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**Reviewer's code:** 07352102

**Position:** Peer Reviewer

**Academic degree:** PhD

**Professional title:** Postdoctoral Fellow

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** China

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**Reviewer chosen by:** Jia-Lin Zhang

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<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Novelty of this manuscript</b>	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
<b>Creativity or innovation of this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



<b>Scientific significance of the conclusion in this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

The manuscript titled "Integrative transcriptomic and proteomic analysis reveals that SERPING1 inhibits neuronal proliferation via the CaMKII-CREB-BDNF pathway in schizophrenia" provides an integrative transcriptomic and proteomic analysis of PBMCs from patients with schizophrenia and identifies several DEGs and DEPs, including SERPING1. The authors also demonstrate that knockdown of SERPING1 in rat neurons increases the expression levels of CaMKII, CREB, and BDNF, all of which are important for neuronal survival and function, such as synaptic plasticity. 1. In the first part of this paper, SERPING1 is identified as a potential biomarker in PBMCs, which is interesting. However, SERPING1 is merely a marker in PBMCs, and its expression pattern in the brain is unknown. Therefore, the rationale for this study using rat neurons in the latter part of the paper is a bit unclear. In recent years with the advent of induced pluripotent stem (iPS) cell technology, it is recommended to utilize neurons derived from iPS cells for pathological research of psychiatric disorders. Considering the author's workload, the overall completion of the experiment is still acceptable. If the above requirements can be met, the logic will be more complete. 2. - Clarify if the WB results shown in Figure 6



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are derived from the same samples as those in Figure 4 or if they are independent. 3.- Indicate explicitly in the legend that only some samples' WB images are shown in Figure 6. If showing only a subset, consider adding images of all samples in the supplementary materials for greater credibility. Use "Normal" or "Disease" labels instead of in-house IDs for clarity. 4.- You have selectively examined the relationship between caMKII, CREB, and BDNF. Please explain why these particular molecules were of interest. 5.-Discussion - Consider discussing how events in the blood link to those in the brain. You can add some citations of high scoring literature



## RE-REVIEW REPORT OF REVISED MANUSCRIPT

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**Peer-review model:** Single blind

**Reviewer's code:** 06128019

**Position:** Peer Reviewer

**Academic degree:** PhD

**Professional title:** Doctor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** China

**Manuscript submission date:** 2024-08-10

**Reviewer chosen by:** Li Li

**Reviewer accepted review:** 2024-11-28 08:41

**Reviewer performed review:** 2024-11-28 08:53

**Review time:** 1 Hour

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Novelty of this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
<b>Creativity or innovation of this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



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<b>Scientific significance of the conclusion in this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## SPECIFIC COMMENTS TO AUTHORS

I am satisfied with the revisions made by the authors. They have addressed all the questions and suggestions raised thoroughly and satisfactorily. There are no further questions or concerns from my end at this moment.



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<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## SPECIFIC COMMENTS TO AUTHORS

I do not see a need for any corrections in the manuscript. I recommend that the manuscript be accepted.