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Letter to the Editor

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Expression Level of PGC1a, PARK2, and LC3B, Controlling Mitochondrial Functions, is Multiply Dependent and not Necessarily Disease-Associated

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LETTER TO THE EDITOR

We were interested to read the article by Chu *et al*. on the expression of PGC1a, PARK2 and LC3B in 20 previously untreated patients with a first episode of schizophrenia and 20 healthy controls [Chu, H. *et al*., 2024]. The gene expression levels of these genes were significantly lower in schizophrenia patients compared to controls [Chu, H. *et al*., 2024]. The expression level of PGC-1a correlated negatively with very low density lipoprotein levels and the expression level of PARK2 correlated negatively with uric acid levels in the patient group [Chu, H. *et al*., 2024]. It was concluded that these differentially expressed genes correlate with the metabolic abnormalities of the patients, suggesting that mitochondrial dysfunction may be related to the frequent occurrence of metabolic disorders in patients with schizophrenia [Chu, H. *et al*., 2024]. The study is noteworthy, but several points should be discussed.

The first point is that the level of gene expression depends on several influencing factors [Lovén, J. *et al*., 2012]. These include age, gender, genetic predisposition, penetrance, genomic imprinting, chromosome inactivation, exposure to toxins and other environmental factors [Lovén, J. *et al*., 2012]. Unless these factors influencing the level of gene expression are included in the analysis, the reported results are not reliable.

The second issue is that the reference limits for the over- or under-expression of genes have not been reported [Chu, H. *et al*., 2024]. Reduced expression does not necessarily mean that the gene product is dysfunctional, as long as the threshold for dysfunction is not exceeded. Therefore, we should know in how many of the included patients the expression levels of the genes of interest were actually reduced and in how many of the patients the gene expression levels were normal or increased.

The third point is that it was not reported whether the patients with reduced gene expression levels in the index genes also had clinical features of mitochondrial disorder (MID) other than schizophrenia. It was not reported whether the 20 schizophrenia patients were prospectively screened for multisystem disorders, which are common in MIDs [Di Donato, S, 2009]. Since reduced gene expression can influence the clinical picture [Choi, J. K. *et al*., 2007], it is essential to examine whether patients with reduced gene expression also manifest at the somatic level. This is of particular importance as psychosis can be a clinical manifestation of MID [Magner, M. *et al*., 2014].

The fourth issue is that the individual medical history was not reported. In how many of the included schizophrenia patients were the medical history positive for a previous somatic illness and what kind of medication were these patients taking regularly?

The fifth point is that no biochemical or functional studies have been performed to assess whether reduced expression of PARK2, PGC1a and LC3B actually affects mitochondrial functions or morphology. Until there is confirmation of mitochondrial dysfunction due to reduced expression of PARK2, PGC1a and LC3B, a causal relationship between low gene expression and schizophrenia remains unproven.

In summary, this interesting study has limitations that put the results and their interpretation into perspective. Removing these limitations could strengthen the conclusions and reinforce the message of the study. All unanswered questions need to be clarified before readers can uncritically accept the study's conclusions. Until there is evidence that reduced expression of PARK2, PGC1a and LC3B impairs mitochondrial function, the causality between reduced expression of the index genes and schizophrenia remains unproven.

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