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Letter to the Editor

Impaired Mitochondrial Functions in 22q11 Microdeletion Syndrome with Schizophrenia

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In a recent article Li *et al*., reported about a study on mitochondrial involvement in stem-cell derived neurons from patients with the 22q11 deletion syndrome and schizophrenia (22q11DSS) (Li, J. *et al*., 2019). In the patient group the authors found reduced activity of complexes I (C1) and IV (CIV) of the respiratory chain, reduced .ATP levels, and reduced amount of gene products from the 9 genes associated with mitochondrial functions which are deleted in 22q11DSS (Li, J. *et al*., 2019). It was concluded that reduced mitochondrial functions derive from the absent expression of the 9 mitochondrial genes deleted in 22q11DSS (Li, J. *et al*., 2019). We have the following comments and concerns.

The main shortcoming of the study that the integrity of mitochondrial DNA (mtDNA) was not investigated in neurons from patients and controls. Since a number of nDNA located genes secondarily causes multiple mtDNA deletions (e.g. POLG1, twinkle, OPA1) or even mtDNA depletion, it is crucial to know if any of the patients‘ cell lines revealed multiple mtDNA deletions or mtDNA depletion. It is also crucial to know if the mtDNA copy number was normal, increased or decreased in 22q11DSS neurons.

Another shortcoming of the study is that other causes than the 22p11 microdeletion were not considered as the cause of reduced ATP levels, or reduced C1 and CIV activity. ATP production may be reduced in association with multiple mtDNA deletions (Lodi, R. *et al*., 2011), and mtDNA depletion (Nile, D. L. *et al*., 2014) as well as acitivty of C1 and C4 respectively (Hargreaves, I. P. *et al*., 2002; Kopsidas, G. *et al*., 1998). Reduction of respiratory chain acitvity and oxidative phosphorylation may also result from increased oxidative stress, reduced mitochondrial biogenesis, abnormal mitochondrial dynamics, or increased apoptosis or mitophagy. Thus, it is crucial to know about the amount of oxidative stress within mitochondria from 22p11DSS neurons, about the capacity of mitochondrial biogenesis, mitochondrial dynamcis, and the activtiy of apotposis and mitophagy.

Missing in this study are also biochemical investigations of respiratory chain enzyme activity. Activity of the respiratoy chain should be quantified in 22q11DSS neurons as well as control cell lines in order to document suspected impaired functions of the respiratory chain, and to compare respiratory chain functions between the four cell lines. and to assess if mitochondrial functions were different between the 2 females and the 2 males oft he study.

Missing are also studies about the antioxidative capacity of 22q11DSS neruons, and whether it is normal, reduced, or increaed.

Overalll, this interesting study may profit form adressing the points raised above, particularly from a more thorough investigation of mitochondrial functions and the mtDNA. Understanding the relationship between mutations in nDNA located mitochondrial genes and mtDNA is crucial for interpretation of the genotype genotype correlation and lastly the treatment that can be offered to patients suffereing from impaired nuclear and mitochondrial crosstalk and interplay.

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