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Letter to the Editor

Maternal transmission of *CNTN6* copy number variation suggests mitochondrial disorder☆

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Letter to the Editor

With interest we read the article by Juan-Perez et al. about a 27yo female with schizophrenia, being attributed to a copy number variation (CNV) of the *CNTN6* gene (Juan-Perez et al., 2018). The patient carried a deletion of at least exon 21 and exon 22 of the *CNTN6* gene (Juan-Perez et al., 2018). We have the following comments and concerns.

The *CNTN6* gene is localised on the nuclear DNA (GeneCards, 2018). However, the title indicates that the genetic defect was transmitted via a maternal trait of inheritance, indicating that the genetic defect was localised on the mitochondrial DNA (mtDNA) (Juan-Perez et al., 2018). This is contradictory. To clarify if there was indeed a maternal transmission, provision of an extensive family tree covering several generations would be helpful. If there was indeed a maternal transmission, it is recommended to sequence the entire mtDNA, to see if an additional variant can be found in one of the mtDNA located genes. Is it conceivable that the CNV of the *CNTN6* gene was not pathogenic but that the patient had indeed a mitochondrial disorder (MID)? MIDs occasionally manifest with psychosis (Kytövuori et al., 2017), autism (Samanta et al., 2018), mood disorder (Cozart et al., 2018), or intellectual disability (Isohanni et al., 2018). Even the reduced number of mtDNA copies is associated with psychosis, as has been recently shown (Kumar et al., 2018). Thus, it is recommended to determine the amount of mtDNA within a mitochondrion, to see if there is depletion of mtDNA or not.

CNV of the *CNTN6* gene has been reported in association with Tourette syndrome (Huang et al., 2017), intellectual disability (Lopatkina et al., 2016), autism spectrum disorder (Mercati et al., 2017), seizures (Hu et al., 2015), attention deficit hyperkinetic disorder (Hu et al., 2015), or developmental delay (Hu et al., 2015). Additionally, *CNTN6* variants were reported in association with neoplasms of the autonomic nervous system and the peripheral nervous system (GeneCards, 2018). Were there any indications for such abnormalities in the described patient? Was the EEG normal?

Since the genetic diagnosis was uncertain ("…at least exon 21 and 22 were deleted"), it would be interesting to know if other exons were deleted as well. Did the authors attempt to clarify the exact amount of CNV in the index case? Were alternative techniques applied to quantify the exact size of the CNV?

We do not agree with the statement that the reported patient is the first in whom schizophrenia was associated with a *CNTN6* CNV (Juan-Perez et al., 2018). In an US American cohort study of 3724 patients screened for the 3p26.3 deletion, the *CNTN6* CNV was found in 14 patients. At least in one of these patients the family history was positive for schizophrenia.

In summary, this interesting case requires further diagnostic work-up for mtDNA mutations and mtDNA depletion and an extensive family tree to clarify if there was maternal transmission or not. Additionally, clinically affected first-degree family members should be investigated for the *CNTN6* variant and for the presence or absence of other clinical features indicative of a MID. Whether psychosis is truly a manifestation of CNV in the *CNTN6* gene needs to be assessed by future, prospective studies.

Author contribution

JF: design, literature search, discussion, first draft, FAS and CAS: literature search, discussion, critical comments.

Conflict of interest

None of the authors declares any conflict of interest.

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