Large-scale TUBB4A mutational screening in isolated dystonia and controls.

Abstract:
Mutations in TUBB4A have recently been implicated in two seemingly different disease entities, namely DYT4-isolated dystonia and hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC), a disorder characterized by considerable clinical variability. While several follow-up studies confirmed the importance of TUBB4A mutations in the development of H-ABC, their contribution to isolated dystonia remains uncertain. We screened the TUBB4A coding regions in a large population of 709 isolated dystonia patients of German/Austrian ancestry as well as in 376 ancestry-matched control subjects by means of Sanger sequencing and high-resolution melting. In addition, we assessed the overall frequency of rare non-synonymous TUBB4A genetic variation in the huge exome dataset released by the Exome Aggregation Consortium (ExAC). We were unable to identify any possibly pathogenic sequence alteration in either patients or controls. According to ExAC, the overall prevalence of rare missense and loss-of-function alleles in the TUBB4A gene can be estimated at ~1:706. In accordance with previous work, our data indicate that TUBB4A coding mutations do not play a critical role in the broad population of isolated dystonia patients. Rather, isolated dystonia as seen in DYT4 might be an
exceptional feature occurring in the heterogeneous phenotypic spectrum due to TUBB4A mutations.

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