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ASSESSING THE ROLE OF *TUBA4A* GENE IN FRONTOTEMPORAL DEGENERATION

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Abstract

The Tubulin Alpha 4a (*TUBA4A*) gene has been recently associated with amyotrophic lateral sclerosis. Interestingly, some of the mutation carriers were also diagnosed with frontotemporal degeneration (FTD) or mild cognitive impairment. With the aim to investigate the role of *TUBA4A* in FTD, we screened *TUBA4A* in a series of 814 FTD patients from Spain. Our data did not disclose any nonsense or missense variant in the cohort, thus suggesting that *TUBA4A* mutations are not associated with FTD.

Introduction

Frontotemporal degeneration (FTD) represents a group of neurodegenerative disorders caused by frontal and/or temporal lobe atrophy and manifests with behavioral and/or language impairment (Neary et al., 2005). Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease, clinically characterized by progressive muscle weakness, atrophy, muscular fasciculations and spasticity. ALS and FTD are considered part of the same disease spectrum as demonstrated by overlapping clinical, pathological and genetic features (Kiernan et al., 2011). Recently, a case-control study found an excess of rare damaging variants in Tubulin Alpha 4a (*TUBA4A*) gene in familial ALS index cases using an exome-sequencing method (Smith et al. 2014). Importantly, among the seven ALS patients carrying rare variants in *TUBA4A*, two of them developed FTD and one had a first-degree relative affected by FTD. The involvement of *TUBA4A* in ALS has been recently replicated in a cohort of sporadic ALS patients (Pensato et al., 2015). Notably, one of the four mutation carriers had mild cognitive impairment. Overall, these data suggest that *TUBA4A* mutations might be particularly associated with the FTD-ALS disease continuum. Here we test this hypothesis in a large series of FTD patients from Spain.

Methods

FTD diagnosis was made according to international consensus criteria for the behavioural variant of frontotemporal dementia (bvFTD; Rascovsky et al., 2011) and for primary progressive aphasia (Gorno-Tempini et al., 2011). ALS diagnosis was made according to the *El Escorial* criteria (Brooks et al., 2000). A positive family history of ALS/FTD was defined as having at least a first or second-degree relative affected by FTD and/or ALS. A total of 814 DNA samples from Spanish FTD patients were collected from eight centres across the country. Among these patients, 51.8% were male and 45.2% had a positive family history. Mean age at onset was 64.4 ± 10.1 years (range 33-88). At onset, 585 patients (71.9%) presented with bvFTD, 161 (19.8%) with progressive non-fluent aphasia PPA (naPPA) and 68 (8.3%) with semantic variant PPA (svPPA). Thirty-one patients (3.8%), all with bvFTD, also suffered from ALS (FTD-ALS). Thirty-one subjects (3.8%) had a pathologically-confirmed frontotemporal lobar degeneration with TAR DNA-binding protein 43 inclusions (FTLD-TDP). Mean age at onset of this pathological series was 61.1 ± 11.6 years (range 42-78). All coding regions of *TUBA4A*, except the first exon (ENSE00001842398) which is solely composed by the start ATG codon, were PCR amplified and Sanger sequenced on an ABI 3100 automatic sequencer (Applied Biosystems, Foster City, CA). Resulting electropherograms were visually analysed using Sequencher software (Gene Codes Corp. Ann Arbor, MI).

Results

TUBA4A sequencing of 814 Spanish FTD patients revealed six synonymous rare genetic variants with frequencies below 1% in public databases, all of them located within exon

four (Supplementary table 1). Among the variants identified, p.Val182Val and p.Asn329Asn have not been previously reported in the European population from the 1000 Genomes Project (The 1000 Genomes Project Consortium., 2012), the non-Finnish European population from the Exome Aggregation Consortium (<http://exac.broadinstitute.org>) or the European Americans from the NHLBI Exome Sequencing Project (<http://evs.gs.washington.edu/EVS>).

Discussion

Our analysis in a comprehensive case series comprising 814 FTD patients did not reveal any potentially damaging rare genetic variant in *TUBA4A* gene. In fact, we only disclosed six rare genetic variants, all of them synonymous. Among them, two synonymous variants (p.Val303Val and p.Ala333Ala) have been already found in both controls and sporadic ALS patients from Italy (Pensato et al., 2015). Finally, p.Val182Val and p.Asn329Asn had not been previously reported in populations of European origin. Consequently, these data do not support a pathogenic role for *TUBA4A* in familial or sporadic FTD. Neither do our analysis support a relationship between *TUBA4A* and a concomitant presence of ALS in FTD, with the proviso that the limited subset of cases (n=31) available to us limits any firm conclusion and warrants further studies in larger cohorts of patients manifesting these two devastating disorders.

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Disclosure statement

The authors have nothing to disclose.

Table legend

Supplementary Table 1.

MAF= Minor allele frequency; 1KG = European population from 1000 genomes; ESP = European Americans from Exome Sequencing Project; ExAC = Non-Finnish Europeans from Exome Aggregation Consortium.

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