Negative results

No supportive evidence for TIA1 gene mutations in a European cohort of ALS-FTD spectrum patients

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We evaluated the genetic contribution of the T cell–restricted intracellular antigen-1 gene (TIA1) in a European cohort of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) patients. Exonic resequencing of TIA1 in 1120 patients (693 FTD, 341 ALS, 86 FTD-ALS) and 1039 controls identified in total 5 rare heterozygous missense variants, affecting the TIA1 low-complexity domain (LCD). Only 1 missense variant, p.Met290Thr, identified in a familial FTD patient with disease onset at 64 years, was absent from controls yet received a combined annotation-dependent depletion score of 11.42. By contrast, 3 of the 4 variants also detected in unaffected controls, p.Val294Glu, p.Gln318Arg, and p.Ala381Thr, had combined annotation-dependent depletion scores greater than 20. Our findings in a large European patient-control series indicate that variants in TIA1 are not a common cause of ALS and FTD. The observation of recurring TIA1 missense variants in unaffected individuals lead us to conclude that the exact genetic contribution of TIA1 to ALS and FTD pathogenesis remains to be further elucidated.

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pathology-confirmed TDP-43 pathology. In line with Mackenzie et al., we did not identify any variants outside the LCD region. Only 1 variant was present in patients only, the other 4 were also observed in unaffected controls.

The patient-specific variant p.Met290Thr was observed in 1 male familial FTD patient of 693 FTDS (0.14%) and absent from a well-characterized control cohort of 1039 individuals. The CADD score however was significantly less than 20, indicating it is less likely to have a deleterious effect on protein function and explain the disease phenotype of the patient. In the absence of supportive co-segregation and functional evidence, we propose to classify this variant as a variant of uncertain significance. We identified a female sporadic ALS patient with early disease onset of 34 years with a p.Val294Glu variant classified as deleterious by a CADD score of 20.9. However, we also detected the same variant in 1 male control individual of 58 years old. Of interest is that a different amino acid change at the same codon (p.Val294Met, CADD score 22.3) was reported in an ALS patient by Mackenzie et al. and proposed it to be pathogenic (Mackenzie et al., 2017). We detected an additional missense variant, suggested to be pathogenic by Mackenzie et al. (p.Ala381Thr, CADD score 22.4), in one of our investigated controls with inclusion age of 70 years. In total, 3 of the 4 missense variants identified in unaffected control subjects had a CADD score >20, including the p.Gln318Arg variant present in 29 of our tested controls (CADD score 23.5).

Despite ours and others’ ambiguous genetic observations (Van Der Spek et al., 2017), we acknowledge that TIA1 is a promising functional candidate gene for TDP-related ALS and FTD.

Similar to other ALS and ALS-FTD genes, it encodes an RNA-binding protein that assembles into stress granules. Mutant TIA1 was shown to alter these stress granule dynamics and, by this, promote TDP-43 accumulation and aggregation (Mackenzie et al., 2017).

Our findings in a large European patient-control cohort indicate that variants in TIA1 are not a common cause of ALS and FTD. Furthermore, the observation of recurring TIA1 LCD missense variants in unaffected individuals, including variants with estimated CADD scores >20, together with the lack of significant co-segregation in informative families, lead us to conclude that it is too early to attribute TIA1 genetic variation to ALS or FTD risk.

Disclosure statement

Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.neurobiolaging.2018.05.005.