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Symptomatic progression of FTD with the *TARDBP* I383V variant

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State of the Art:
The *TARDBP* I383V variant (NM_007375.3: c.1147A>G, p.Ile383Val) is increasingly recognized as a likely pathogenic cause of frontotemporal dementia (FTD) associated with bitemporal atrophy. We assessed cross-sectional and longitudinal neuropsychological characteristics of this variant in a cohort from the United States.

Methodology:
Clinical and genetic data shared by the ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration consortium (ALLFTD) was queried to identify participants with the *TARDBP* I383V variant. Five individuals were identified. All participants performed standardized comprehensive neuropsychological evaluations, and four had done so longitudinally over 1.0 to 3.9 years. Following baseline characterization, we evaluated subsequent changes in the Frontotemporal Lobar Degeneration Modified Clinical Dementia Rating Scale (FTLD-CDR), Montreal Cognitive Assessment (MoCA), Neuropsychiatric Inventory Questionnaire (NPI-Q), and the most abnormal baseline neuropsychological measures.

Results:
Average participant age was 69.8 years (SD 11.8) with an average age of onset of 62 (SD 12.7). 60% were male. Mean baseline FTLD-CDR sum of boxes was 8.8 (SD 3.9), MoCA was 19.4 (SD 9.9), and NPI-Q was 9.4 (SD 7.8). Across Z-scored neuropsychological assessments at baseline evaluation, the lowest Z-score was on the Multilingual Naming test (MINT, mean -7.8, SD 6.2). Mixed effects models confirm significant progression of MoCA (=-1.4, p=0.006, CI[-2.4; -0.4]) FTLD-CDR (=0.8, p=0.001, CI 0.3, 1.3]), and particularly the MINT (=-1.9, p<0.001, CI[-2.7;-1.2]).

Conclusion:
We contribute to the emerging picture of the *TARDBP* I383V variant in FTD, confirming a semantic pattern of deficits, losing around 2 points on the MINT annually. Further analyses in larger samples are warranted.

Conflicts of interest

N/A