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CLINICAL MANIFESTATIONS

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NEUROPSYCHIATRY AND BEHAVIORAL NEUROLOGY

Genetic and Pathological Characteristics of Frontotemporal Dementia with Right Anterior Temporal Predominance: A Multicenter Retrospective Cohort Study

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Abstract

Background: Frontotemporal dementia (FTD) with right anterior temporal lobe (RATL) predominant atrophy is an emerging area of interest. Recent findings by the International Working Group (IWG) have identified this subtype as having a distinct clinical profile within the FTD spectrum (Ulugut et al., 2024, A&D). However, its genetic and pathological underpinnings remain unexplored in large, multicultural cohorts.

Methods: Retrospective analyses encompassing clinical, genetic, pathological, and neuroimaging data from 23 IWG sites across 13 countries in Asia, Middle East, Europe, North and South America were conducted. The study included 444 patients with FTD exhibiting predominant RATL atrophy.

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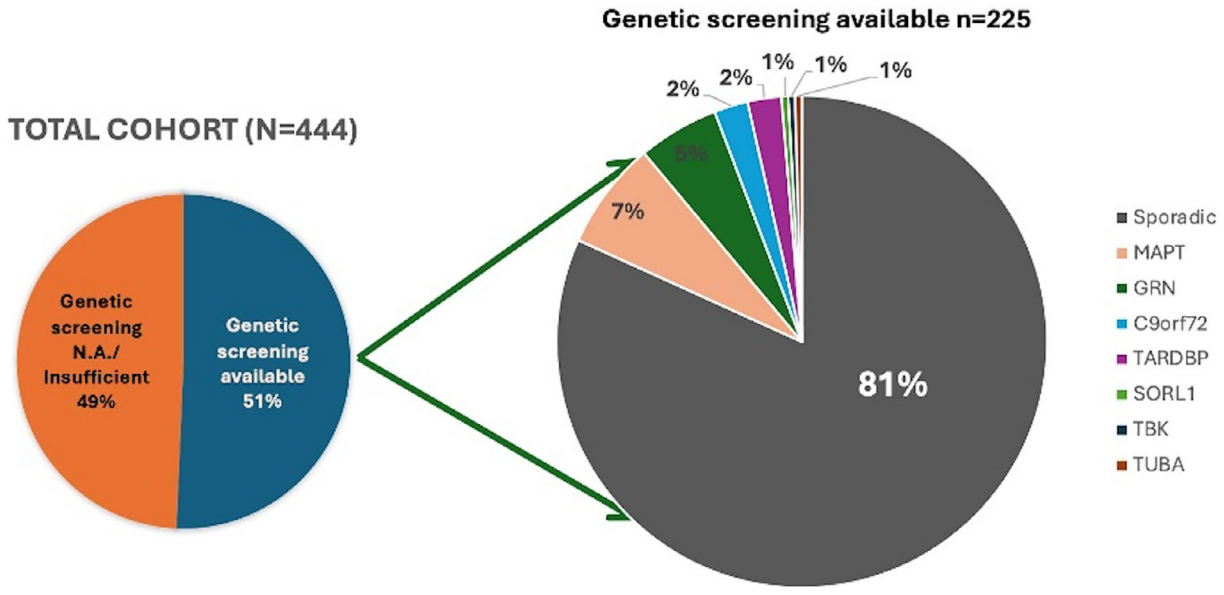
Results: Genetic screening was performed on 51% ($n = 225$) of the cohort for at least the major frontotemporal lobar degeneration (FTLD) mutations including microtubule-associated protein tau (*MAPT*), progranulin (*GRN*), and chromosome 9 open reading frame 72 (*C9orf72*), or dementia panels encompassing extended sets of genes. Of these, 81% were sporadic, showing negative results for the screened genes and a modified Goldman Score of ≥ 3, indicating a negative family history for dementia. The *MAPT* mutation was the most common genetic variant, identified in 7% of the screened cases (Figure 1). Pathological confirmation was available for 63 patients. Among the sporadic cases, transactive response DNA-binding protein 43 type C (TDP-C) pathology was most prevalent (60%, $n = 32$), while tau-MAPT pathology was most common in the genetic cases (38%, $n = 16$). Fifteen cases did not fit neatly into genetic or sporadic categories, displaying heterogeneous pathologies (Figure 2). At the initial visit, compared to genetic cases, patients with TDP-C pathology were older, and more frequently exhibited semantic deficits, with less frequent attention difficulties and executive dysfunction. No differences were observed in sex distribution, symptom duration or disease severity between genetic and sporadic TDP-C cases. However, left handedness was more common in TDP-C cases (14%) compared to genetic cases (5%).

Conclusion: While FTD with RATL atrophy primarily appears sporadic, a significant proportion of cases exhibit genetic variants. These sporadic and genetic subtypes display distinct neuropathological features and clinical manifestations. Given the implications for therapeutic strategies, precise clinical and molecular subtyping is critical for enhancing patient management and ensuring appropriate enrollment in clinical trials.



•N.A.: No screening available
•Insufficient: Only one or two genes were screened (e.g., only C9orf72)
•Sporadic: Screened at least for MAPT, GRN, C9orf72 and no mutation found, Goldman Score ≥ 3