

Inheritance Patterns and Genetic Mutations Frequency in a large cohort of the Frontotemporal Dementia Spectrum

P2-03

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INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERNCES
Frontotemporal dementia (FTD) is a heterogeneous group of progressive neurodegenerative disorders characterized by behavioral, language, executive, and/or motor dysfunction. The two main clinical variants are behavioral variant FTD (bvFTD) and the language variant – primary progressive aphasia (PPA). While more than half of cases are sporadic, 30–40% of patients have a positive family history. Up to one third of familial cases are associated with pathogenic mutations, most commonly in the <i>GRN</i> , <i>MAPT</i> , and <i>C9orf72</i> genes ¹ .	Objective: To determine inheritance patterns and the frequency of genetic mutations in a cohort of patients within the FTD spectrum. This study included 195 consecutive patients diagnosed with probable or definite FTD spectrum disorders at the Center for Memory Disorders, Clinic of Neurology, University Clinical Centre of Serbia, between October 2009 and October 2024. Family history was assessed using the modified Goldman score (1–4) ² . Molecular genetic testing included sequencing of the <i>MAPT</i> , <i>GRN</i> , and <i>C9ORF72</i> genes. Patients negative for these mutations underwent clinical exome panel analysis comprising 4,813 genes associated with neurodegenerative diseases.	A positive family history (Goldman score 1–3.5) was identified in 36.5% of patients, while 63.5% had no affected relatives. Pathogenic mutations were detected in 15 patients (7.7%): <i>C9orf72</i> in 11, <i>GRN</i> in 1, <i>OPTN</i> in 2, and <i>VCP</i> in 1. Mutations were most frequently observed in bvFTD (12 patients; 9.5% of bvFTD cases), including four patients with FTD–motor neuron disease overlap. <i>GRN</i> and <i>OPTN</i> mutations were identified in patients with PPA (4.9% of PPA cases). Mutations were more common in familial FTD (14.5%) than in sporadic cases (3.2%). Patients with genetic FTD were younger at disease onset (51.2 ± 7.7 vs. 62.5 ± 8.0 years; p < 0.001) and at evaluation (55.3 ± 8.4 vs. 59.3 ± 8.5 years; p < 0.001), and were more frequently female (73% vs. 44%; p < 0.05).	In this large Serbian FTD cohort, most cases were sporadic, while pathogenic genetic variants were identified in 7.7% of patients. The most frequent mutation was the hexanucleotide repeat expansion in the C9orf72 gene. Mutations were predominantly detected in patients with bvFTD, including four individuals with an FTD–MND overlap syndrome. Earlier age at disease onset and the presence of MND features emerged as the main clinical indicators warranting genetic testing. These findings are in line with previous studies showing that C9orf72 , together with GRN and MAPT , accounts for the majority of genetically determined FTD cases and that C9orf72 expansion is particularly associated with bvFTD, FTD–MND overlap. Although a positive family history remains one of the strongest predictors of an underlying genetic cause, pathogenic variants may also be identified in apparently sporadic cases, supporting broader access to genetic testing in clinically selected patients with FTD.	1. Moore KM, et al. Age at symptom onset and death and disease duration in genetic frontotemporal dementia: an international retrospective cohort study. The Lancet Neurology. 2020;19(2):145-156 2. Wood EM, et al. Development and validation of pedigree classification criteria for frontotemporal lobar degeneration. JAMA Neurol. 2013;70(11):1411-1417.
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