Genotype-Phenotype correlation in FTD: a rare GRN mutation identified in Italian Population

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Introduction

Frontotemporal lobar degeneration (FTLD) defines a group of neurodegenerative brain disorders with predominant degeneration of frontal and/or temporal lobes[1]. FTLD is remarkably heterogeneous in clinical, neuropathological and genetic features1. Since the first demonstration of FTLD-associated progranulin gene (GRN) mutation[2], over 150 GRN mutations were identified (82 pathogenic). We report the cases of two patients carrying the same frameshift mutation in exon 6 of GRN (c.468_474del), the first characterized by a behavioral clinical phenotype and the second one by a language disorder

Case reports:

#Patient 1
A right-handed 63-years-old man presented with a 1-year history of progressive attention deficit associated with apathy, loss of interest, and social regression. His mother and two aunts (maternal family line) received diagnosis of late onset Alzheimer Dementia. He had no significant medical history. The neuropsychological evaluation showed: Mini-Mental State Examination (MMSE) 23.53/23.8; Frontal Assessment battery (FAB) 11.98/12; Aachen Aphasia test (AAT) within the normal range (age- and education-corrected scores). At the neurological examination: no pathological signs. Brain magnetic resonance imaging (MRI) showed frontal lobar atrophy affecting the right side dominantly. Patient was diagnosed with Behavioral variant of Frontotemporal Dementia (BvFTD)[3]. Given his family history, we performed the genetic analyses for GRN and microtubule-associated protein tau gene (MAPT) mutations, identifying mutation (c.468_474del) of GRN.

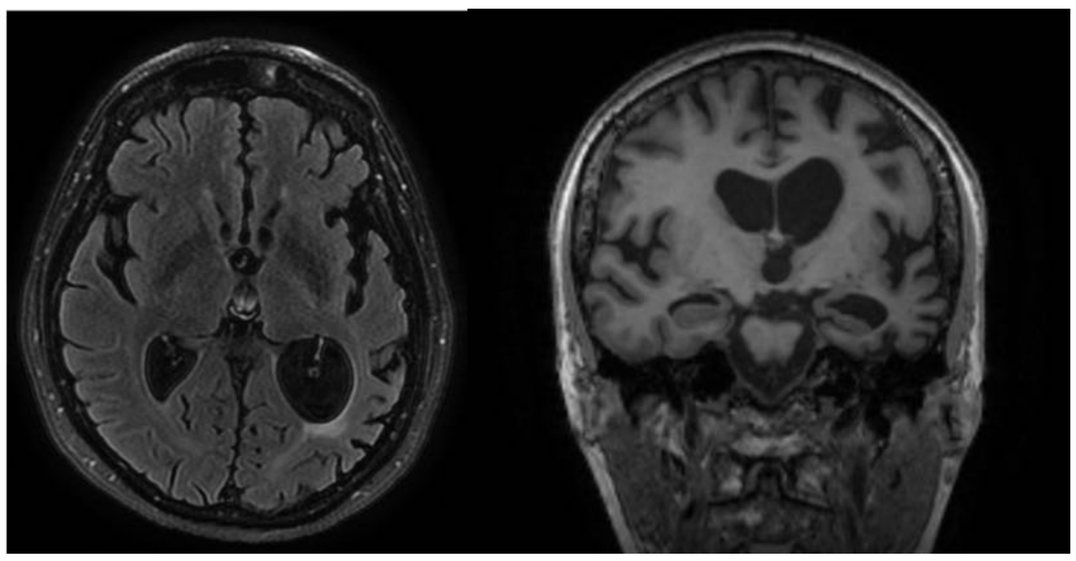

Fig.2 MRI showing cortical fronto-temporal atrophy (left>right) in Axial FLAIR and Coronal T1 sequences

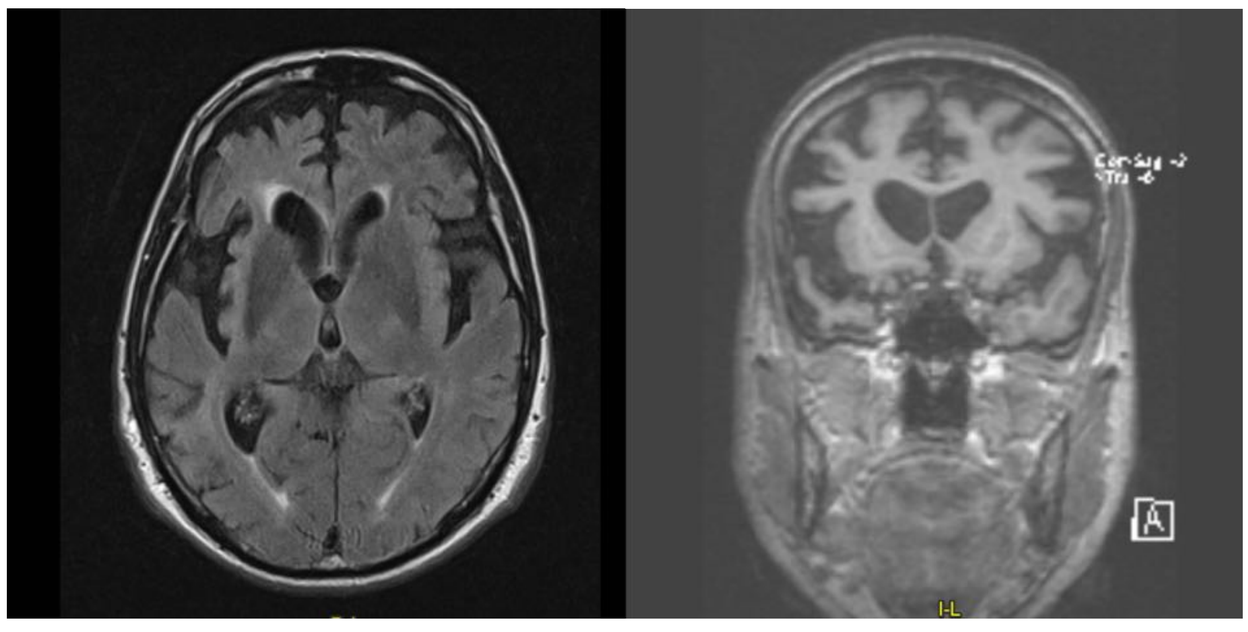

Fig.1 MRI showing cortical fronto-temporal atrophy (right>left) in Axial FLAIR and Coronal T1 sequences

#Patient 2
A right-handed 61-years-old woman presented with a 1-year history of a progressive speech impairment, characterized by a poor/slow production with phonemic and semantic paraphasia. She had no significant personal or familial medical history. The neuropsychological assessment showed: MMSE 20.46/23.8; FAB 13.01/12; AAT deficits in naming, writing, and repetition. Verbal comprehension and reading ability of words and short sentences were relatively preserved (age- and education-corrected scores). At the neurological examination: presence of frontal lobe signs such as Epstein sign. Brain MRI confirmed cerebral cortical atrophy affecting the left frontal and temporal lobes dominantly. According to clinical and imaging characteristics, the patient was diagnosed with Progressive Non Fluent Aphasia[3]. Given the early onset of symptoms, we performed the genetic examination (GRN and MAPT) and identified mutation (c.468_474del) of GRN.

Conclusions

To date, according to our knowledge, similar mutation associated with FTLD was not identified in the Italian population. Our cases highlight the heterogeneous spectrum of clinical presentations associated to mutation in GRN (c.468_474del), with and without evidence of familial history.

Bibliography

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