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Missense mutation in *GRN* gene affecting RNA splicing and plasma progranulin level in a family affected by frontotemporal lobar degeneration

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ABSTRACT

Gene coding for progranulin, *GRN*, is a major gene linked to frontotemporal lobar degeneration. While most of pathogenic *GRN* mutations are *null* mutations leading to haploinsufficiency, *GRN* missense mutations do not have an obvious pathogenicity, and only a few have been revealed to act through different pathogenetic mechanisms, such as cytoplasmic missorting, protein degradation, and abnormal cleavage by elastase. The aim of this study was to disclose the pathogenetic mechanisms of the *GRN* A199V missense mutation, which was previously reported not to alter physiological progranulin features but was associated with a reduced plasma progranulin level. After investigating the family pedigree, we performed genetic and biochemical analysis on its members and performed RNA expression studies. We found that the mutation segregates with the disease and discovered that its pathogenic feature is the alteration of *GRN* mRNA splicing, actually leading to haploinsufficiency. Thus, when facing with a missense *GRN* mutation, its pathogenetic effects should be investigated, especially if associated with low plasma progranulin levels, to determine its nature of either benign polymorphism or pathogenic mutation.

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1. Introduction

Frontotemporal lobar degeneration (FTLD), the third most common cause of presenile dementia (Vieira et al., 2013), is a group of neurodegenerative diseases clinically, genetically, and pathologically heterogeneous. The major genes linked to FTLD are the genes coding for microtubule-associated protein tau (*MAPT*), progranulin (*GRN*), and chromosome 9 open reading frame 72 (*C9ORF72*); a few additional genes account for a small number of cases (Bang et al., 2015).

Progranulin is a growth factor involved in the regulation of cell proliferation and migration, wound repair, inflammation, and cancer. It is expressed by many cell types and, in central nervous system, by both neurons and microglia (Toh et al., 2011). Neuroprotective and neurotrophic properties of progranulin or granulin peptides have been demonstrated (Van Damme et al., 2008; Xu et al., 2011).

Mutations in *GRN* cause a highly heterogeneous clinical phenotype with regards to symptoms, age of onset and disease duration, and lead to a neurodegeneration characterized by deposits of transactive response DNA binding protein 43 (Bang et al., 2015).

So far, about 150 *GRN* mutations have been described (http://www.molgen.ua.ac.be/admutations/; Cruts et al., 2012; Stenson et al., 2014), accounting for 5%–20% of familial cases and 1%–5% of sporadic cases of FTLD (Rademakers et al., 2012). Pathogenic mutations are mostly *null* mutations, that is, frame-shift, splicing, and nonsense mutations giving rise to a mRNA which is degraded as carrying an aberrant STOP codon, causing a condition of haploinsufficiency (Baker et al., 2006; Cruts et al., 2006). Reduced levels of plasma progranulin are optimal predictors of *null GRN* mutation (Ghidoni et al., 2012). A small number of missense mutations have been reported that determine different pathogenetic mechanisms: reduced levels of mutant mRNA, cytoplasmic missorting, protein degradation and reduced secretion, and abnormal protein cleavage

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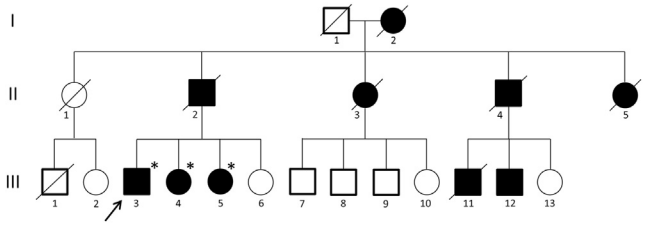

Fig. 1. Pedigree of the family. The proband is indicated by the arrow; black filled symbols represent subjects affected by FTLD; diagonal lines indicate the deceased; and asterisks represent the patients in whom the mutation has been demonstrated. Abbreviation: FTLD, frontotemporal lobar degeneration.

by elastase (Gass et al., 2006; Karch et al., 2016; Mukherjee et al., 2008; Shankaran et al., 2008; Wang et al., 2010). In the few cases investigated, reduced levels of plasma progranulin were found in association with some missense mutations: *GRN* C139R and R432C showed intermediate levels between normal and pathologic values (Bernardi et al., 2012; Finch et al., 2009; Sleegers et al., 2009), whereas A9D produced the values typical of *null* mutations (Wang et al., 2010). Thus, also in these cases decreased progranulin may be considered as a marker of pathology.

We previously reported the biochemical analysis of the *GRN* A199V missense mutation, found in a patient affected by FTLD, which showed no alteration of the physiological properties of progranulin (Karch et al., 2016). However, this mutation puzzled us because it was associated with low levels of plasma progranulin, similar to the levels of *null* mutations. Then, we decided to search for the family history of the patient carrying this mutation, to investigate the members of his pedigree and possibly to deepen the molecular study of the mutation.

Here, we report the results of this study, showing (1) the presence of 3 affected members carrying the mutation and having low plasma progranulin levels and (2) the effect of this missense mutation on mRNA levels, similar to that of previously described *GRN* splicing mutations. In conclusion, we think that a missense *GRN* mutation should be investigated for pathogenetic effects especially if associated with low plasma progranulin levels.

2. Materials and methods

2.1. Pedigree and clinical data

The family (Fig. 1) was native of a small village in the Marche region of Italy.

The proband, a 61-year-old man (III-3), came to our attention complaining motor impairment in his left upper limb. Neurologic examination revealed a mild asymmetrical extrapiramidal syndrome (bradikinesia, rigidity, ipokinesia, amimic facies, and festination of speech) and apraxia in his left hand. Neuropsychological examination revealed ideomotor apraxia in his left upper limb, left stereoagnosia and extinction (left hand) to the double sensitive stimulus, visuospatial impairment, and dysexecutive syndrome. A mild disinhibition was present during the examination, and rare myoclonic jerks were noticed in his left hand. Magnetic resonance imaging (MRI; Fig. 2A and B) revealed moderate brain atrophy involving frontal and parietal lobes. A diagnosis of corticobasal syndrome (CBS) was made.

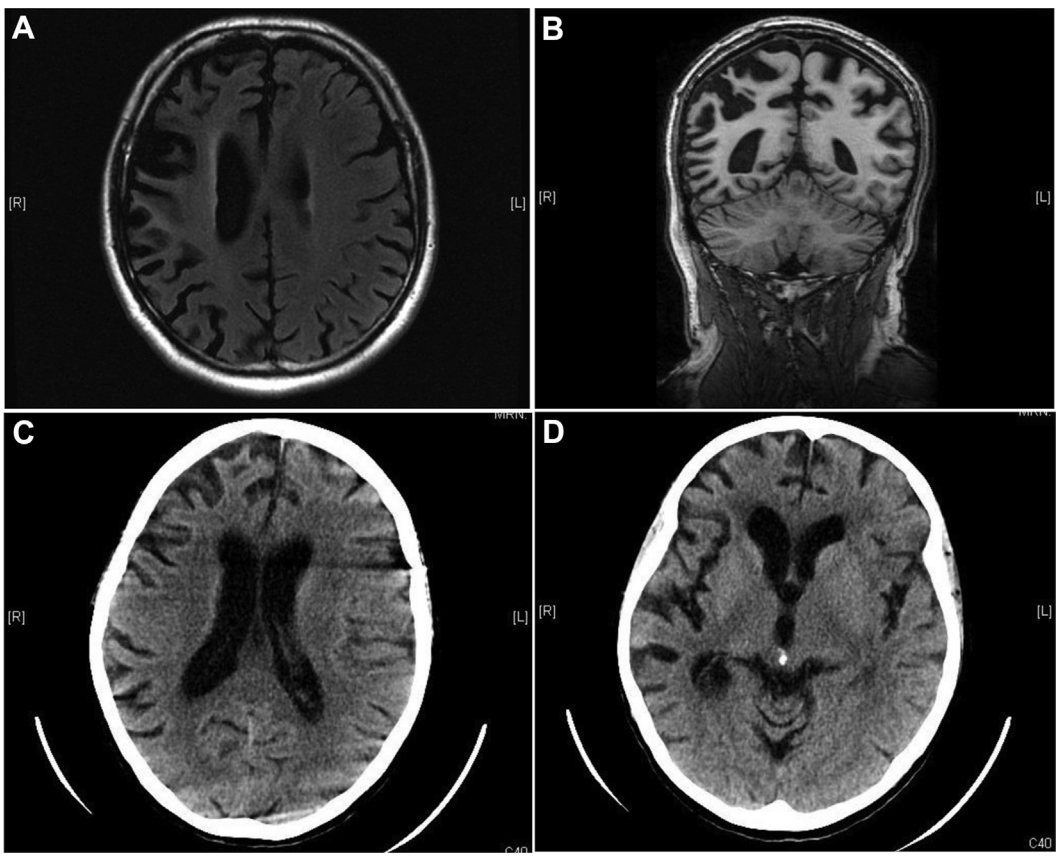

Fig. 2. Neuroradiologic findings of patients III-3 and III-5. (A, B) Magnetic resonance imaging of patient III-3. T1 axial and coronal images reveal a bilateral frontal and parietal cortical atrophy, frankly asymmetrical (right > left). (C, D) Computed tomographic scans of patient III-5 show frontotemporal cortical atrophy, with prominent involvement of the right frontal lobe. Some motion artifacts are present.

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