

# Mutation is Associated with Behavioral Variant Frontotemporal Dementia

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Handling Associate Editor: Beatrice Arosio

Accepted 23 August 2014

**Abstract.** Mutations in progranulin gene (*GRN*) are a common cause of autosomal dominant frontotemporal lobar degeneration and are associated with a wide phenotypic heterogeneity. Here, we describe two probands with behavioral variant frontotemporal dementia with a novel mutation in this gene (1159-1160delTG). Both had a positive family history for dementia and showed atypical features at imaging. Their progranulin plasma levels were undetectable, and the mutation was not present in cDNA, suggesting haploinsufficiency. Progranulin levels were low even in asymptomatic carriers of the variant. Results described enlarge current knowledge on genetic causes of the disease and clinical characteristics of carriers.

**Keywords:** Deletion, frontotemporal dementia, haploinsufficiency, mutation, progranulin (*GRN*)

## INTRODUCTION

Frontotemporal lobar degeneration (FTLD) is recognized as one of the more common type of presenile dementia, accounting for 8–10% of all dementia patients [1], with a prevalence of about 4–15 cases per 100,000 [2]. The disease manifests with different clinical syndromes: behavioral variant (bvFTD) and two syndromes affecting mainly the language, seman-

tic dementia (SD) and progressive non-fluent aphasia (PNFA). There is a familial history in nearly one third to a half of the cases, where it is possible to recognize an autosomal dominant pattern of inheritance [3]. To date, there are three main genetic causes of familial FTLD: Microtubule Associated Protein Tau gene (*MAPT*), progranulin (*GRN*), both located on chromosome 17, and the hexanucleotide repeat expansion in the Open Reading Frame 72 gene in chromosome 9 (*C9ORF72*). The pathology includes two main patterns: tau deposition (FTLD-Tau), which is typically found in subjects carrying *MAPT* mutations, and immunoreactivity for ubiquitin (FTLD-U). The latter is split in different entities depending on the major protein present. TAR DNA binding Protein (TDP)-43

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is found in the majority of the non-tau pathological pattern, including *GRN* and *C9ORF72* mutated subjects (see [4] for review).

*GRN* mutations are found in 5–20% of FTLD familial cases and 1–5% of sporadic cases [5]. The gene is located on chromosome 17q21 and is composed by 13 exons encoding for progranulin, a cysteine-rich growth factor which is secreted and cleaved in several fragments (granulins). It is expressed in multiple tissues of the body and it has pleiotropic actions, including functions related to neural proliferation, survival, and inflammation.

The majority of genetic defects in *GRN* are loss-of-function mutations, causing haploinsufficiency, and are associated with extremely low plasma progranulin levels [6, 7]. The penetrance of *GRN* mutations is incomplete and this condition is probably due to the presence of other genes influencing the manifestation of the disease. In this regard, TransMEMbrane (*TMEM*)106B, coding for a transmembrane protein that associate with progranulin in endo-lysosomes, has been recently identified as a disease modifier in *GRN* mutation carriers [8].

The clinical presentation associated with *GRN* mutations is extremely heterogeneous in terms of symptoms, disease duration, and age of onset. Patients usually present with any of the defined syndromes of FTLD, but in some cases there is prominent involvement of the extrapyramidal and motor systems, showing a clinical picture of a corticobasal syndrome, supranuclear palsy, or FTD with motor neuron disorders [9]. Typical neuroimaging in *GRN* mutation carriers consists of asymmetric brain atrophy with additional features such as asymmetric damage to white matter, severe cortical atrophy, and parietal lobe involvement. Here, we describe two families with a novel mutation in *GRN*. Probands, both with positive family history for dementia, developed FTD and showed very low plasma levels and atypical imaging features.

## CASE REPORTS

### Patient #1

According to his relatives, Patient #1 developed mild language deficits together with disinhibition and apathy at the age of 68. One year later, he showed cognitive decline, markedly altered behavior, and a reduced function in daily-working activities. In addition, he manifested sleep disturbances, visual disperseptions and falls, requiring access to the emergency department, from which he was directed to our Neurology unit.

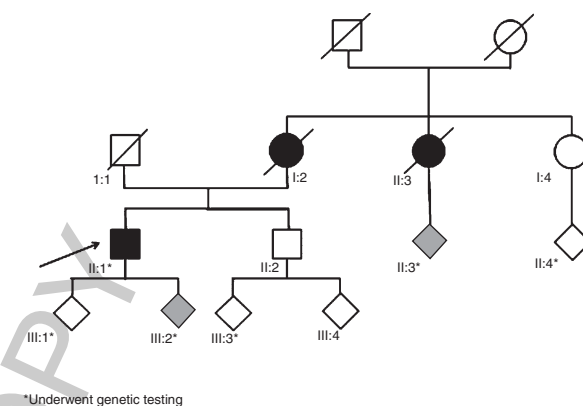


Fig. 1. Pedigree of patient #1 (arrow). Square indicate males, circles females; diamonds are used instead to avoid disclosing sex in non-affected individuals. Black indicates symptomatic subjects, gray presymptomatic, and white asymptomatic. Bars indicate deceased family members.

His family history was positive for dementia, as his mother and maternal aunt were diagnosed with dementia in their seventies (Alzheimer's disease and Lewy body dementia, respectively) (Fig. 1, I:2, I:3).

The collection of anamnestic information revealed arterial hypertension, arterial vasculopathy with femoral and carotid stenosis, dyslipidemia, obstruction sleep apnea syndrome, and prostatic hypertrophy. During the medical evaluation, he showed disinhibited behavior and lack of attention. In addition, sexual disinhibition and hyperorality were reported by his wife. The neurological examination was unremarkable, except for the evidence of primitive reflexes and an initial mild gait ataxia, whereas no language impairment was observed. At neuropsychological testing, the patient scored 28/30 on MMSE (normal memory, language, and visuo-spatial functions) showing global efficiency in cognition associated with behavioral disturbances, disinhibition, and poor social judgment. Furthermore, the patient history outlined an insufficient performance in daily self-care activities (ADL = 5/6, IADL = 2/8).

Axial T1-weighted scans at the magnetic resonance imaging (MRI) showed asymmetric frontal and temporal cortical atrophy (right > left) (Fig. 2A). The coronal T1-weighted scan documented asymmetric temporal atrophy (right > left) (Fig. 1C). [<sup>18</sup>F]-Fludeoxyglucose positron emission tomography (FDG-PET) showed bilateral frontal and temporal hypometabolism (Fig. 2B). Cerebrospinal fluid (CSF) biomarkers were normal (amyloid- $\beta$  = 731 pg/ml; tau = 181 pg/ml; Ptau = 29 pg/ml). As the patient did

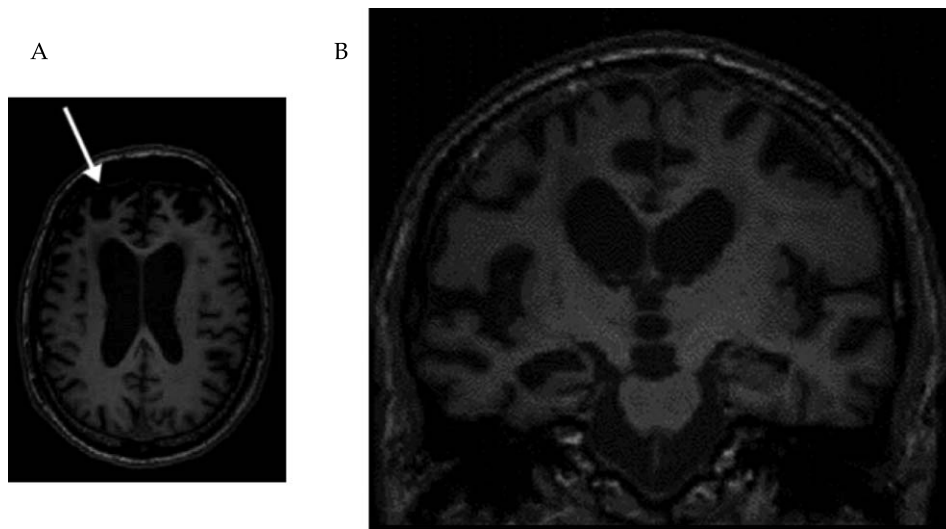


Fig. 2. MRI of patient #1. A) Axial T1-weighted MRI scan documenting asymmetric frontal cortical atrophy (arrow) and temporal cortical atrophy (right > left); B) coronal T1-weighted MRI scan documenting asymmetric temporal atrophy (right > left).

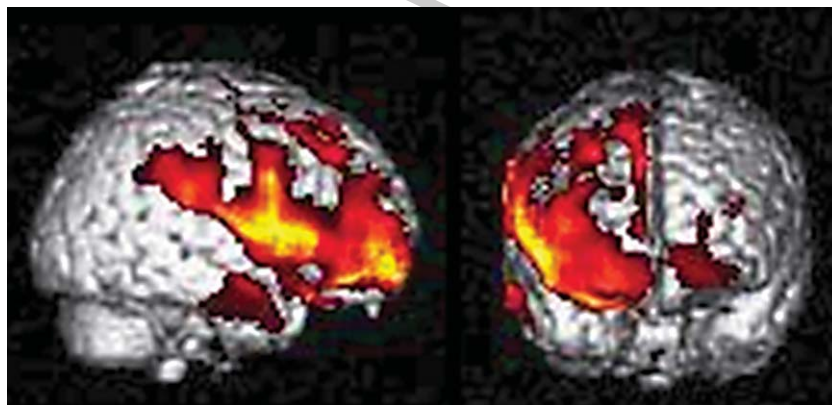


Fig. 3. FDG-PET of patient #2, showing areas of hypometabolism mainly on the right side in fronto-temporal regions and thalamus and frontal cortex and insula ( $p=0.001$ ).

not show clinical symptoms and signs suggesting motor neuron disease, the electromyography was not carried out.

#### Patient #2

Patient #2, a male, began presenting with loss of inhibitory control, relevant mood alterations related to emotional lability, anhedonia, apathy, depressive mood, anosognosia, and loss of hobbies and personal interests at the age of 66. The onset of symptoms started after retirement and they progressively worsened, with the addition of cognitive deficits of language (anomia, dysarthria, and stutter), memory and difficulties in

the spatial orientation. He also suffered from mild dysphagia both for solid and liquid foods. Neuropsychological assessment showed normal global cognitive profile (MMSE 28/30) with partially reduced daily-living activities (ADL 5/6, IADL 4/5) and scores under the normality threshold in praxis and attention. He suffered from hypertension and extrapyramidal signs lateralized on the left side. His family history was positive for FTD (father and sister). Electromyography and magnetic evoked potentials were normal, while brain CT showed bilateral temporal ventricular atrophy. The patient refused the lumbar puncture and MRI examination. Brain FDG-PET, using SPM5 software (Supplementary Materials), showed areas of

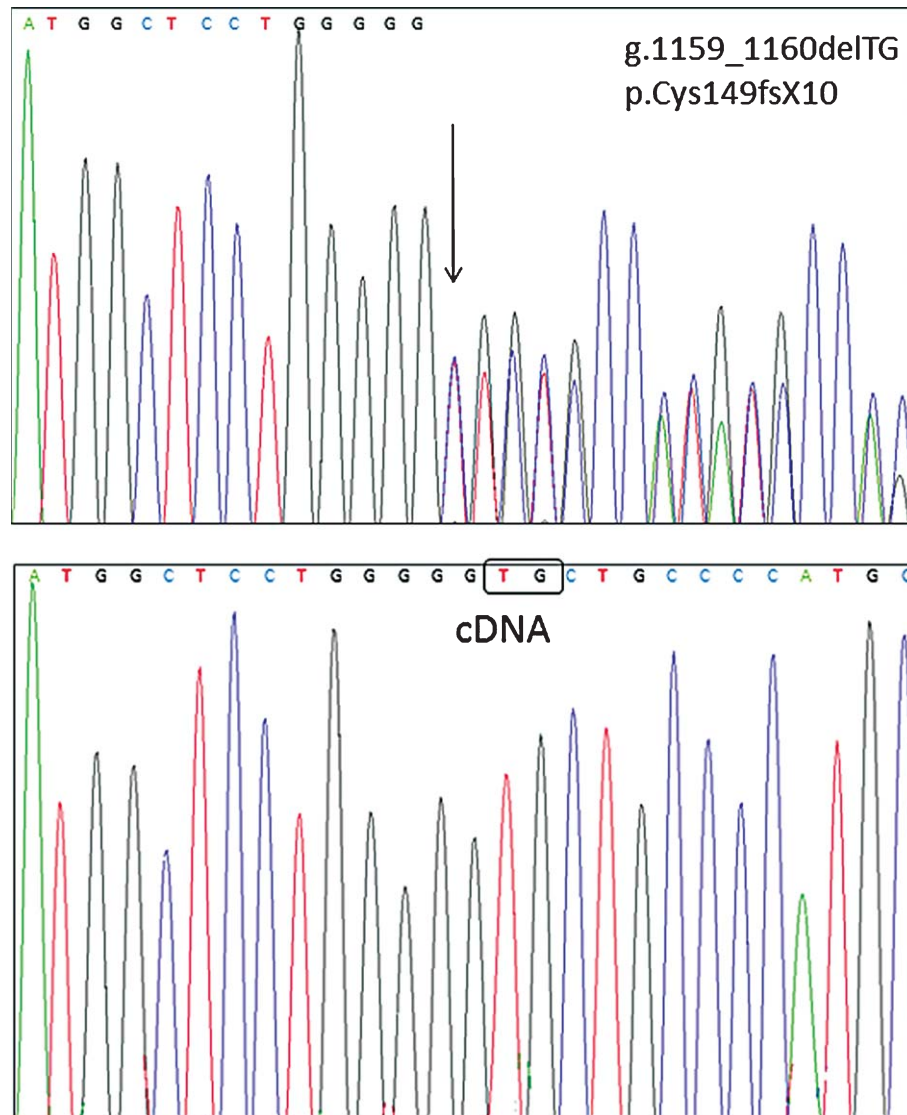


Fig. 4. Electropherogram of the DNA (top) and cDNA (bottom).

hypometabolism mainly on the right side in frontotemporal regions and thalamus, in bilateral superior frontal gyrus and left insula ( $p = 0.001$ ) (Fig. 3).

## METHODS AND RESULTS

Both patients met the criteria for bvFTD [10]. In both probands, progranulin plasma levels, evaluated through an ELISA kit (Adipogene, Korea) after the ethical committee approval and patients' consent, were below the detection threshold ( $<15$  ng/ml).

Therefore, we sequenced (*GRN*) and found a novel mutation in exon 5: g.1159\_1160delTG, that leads

to a frameshift, which in turn creates a stop codon (c.445\_446delTG, p.Cys 149fsX10).

The mutation was not observed in the cDNA isolated from peripheral blood cells, thus confirming that the aberrant mRNA is degraded through nonsense mediated decay (Fig. 4).

Additional family members of Patient #1 were asymptomatic carriers of the mutation (Fig. 1A, III:2 and II:3 age 37 and 50 years, respectively). Both of them had plasma progranulin levels under the detection threshold (61 pg/ml) [11], whereas subjects III:1 and II:4, who did not carry the mutation, had normal progranulin plasma levels. Relatives of patient #2 did not give informed consent for blood collection.

## DISCUSSION

Here, we described two patients with FTD carrying a novel mutation in *GRN*. Both families originate from the same region (central Italy), suggesting that they could derive from the same founder. Nevertheless, we did not have a large population to carry out a haplotype analysis.

So far, 69 different pathogenic mutations in *GRN* have been described, including about ten dinucleotide deletions (<http://www.molgen.vib-ua.be>). The most common associated clinical phenotype is FTD, although corticobasal syndrome has been reported as well [12]. Regarding patients we described, both of them showed a typical behavioral syndrome, but patient #1 developed, in addition, visual disperceptions and falls. Notably, his aunt was diagnosed with Lewy body dementia more than ten years before, due to the development of dementia, falls, and hallucinations, and died a few years later.

Progranulin plasma levels were undetectable, even in presymptomatic carriers, suggesting that biological changes associated with the mutation occur soon before clinical manifestations of the disease, and supporting the hypothesis that plasma progranulin evaluation could be a very good biomarker for identifying potential carriers. In accordance with MRI data on other *GRN* mutation carriers, this new variant showed asymmetrical atrophy (see [13] for review). In spite of the marked atrophy, CSF biomarkers were normal, including tau protein, which is supposed to reflect the degree of neurodegeneration. This observation is in line with previous data [14] and suggests cautiousness in the interpretation of an apparently normal CSF picture.

In conclusion, although further studied on other family members will be needed to demonstrate the segregation of the genetic defect with the disease, the evidence of very low plasma progranulin levels together with the mRNA nonsense mediated decay strongly support the hypothesis that the variant is pathogenic and cause haploinsufficiency.

## ACKNOWLEDGMENTS

This research was supported by Fondazione Monzino and Italian Ministry of Health (Ricerca Corrente to ES and Ricerca Finalizzata 2010-2311041 to PC).

Authors' disclosures available online (<http://www.jalz.com/disclosures/view.php?id=2519>).

## SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <http://dx.doi.org/10.3233/JAD-141380>

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