# IDENTIFICATION OF A NOVEL MUTATION IN GRN GENE ASSOCIATED WITH FRONTOTEMPORAL DEMENTIA

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## BACKGROUND

**Mutations in progranulin gene (GRN) are a common cause of autosomal dominant frontotemporal degeneration syndromes and are associated with a wide phenotypic heterogeneity[1]. The majority of genetic defects in GRN consists of loss-of-function mutations, causing haploinsufficiency[2].**

## CASE DESCRIPTION

**Herein, we present the case of a 67-year-old right-handed man with a 6-year history of gradually progressive behavioural disturbances with irritability and sometimes aggressiveness, social withdrawal and obsessive repetitive behaviours. In the family history, we found an uncle from the paternal line affected by dementia with behavioural disorders and progressive language difficulties. The patient performed a 3T MR imaging examination (Figure 1). Considering the early onset and the positive family history, a genetic analysis was carried out**

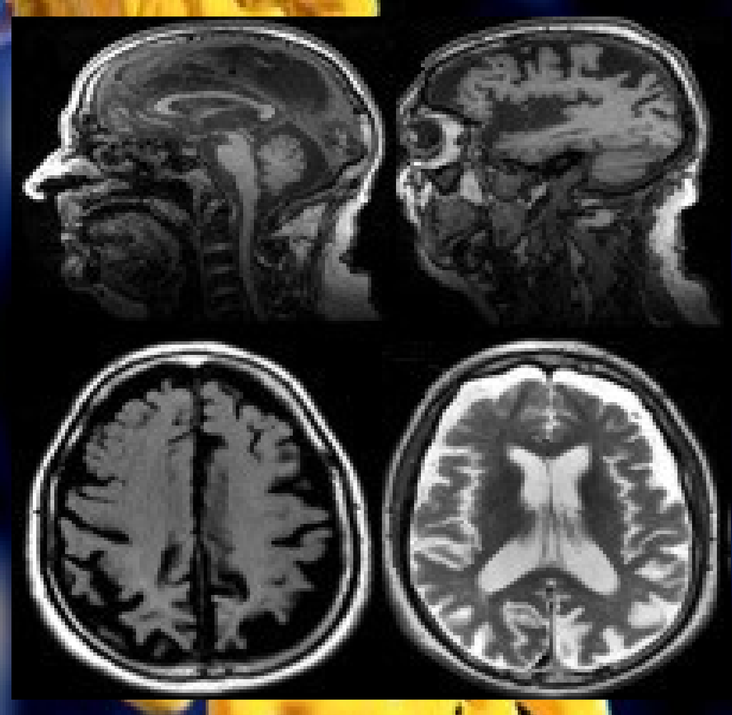

Figure 1. 3T MR imaging sequences of the brain showed severe atrophy in the frontal and temporal lobes

## RESULTS

**In our FTD patient, direct sequencing of DNA showing the presence of a novel heterozygous missense mutation c.53C>T in the GRN gene (Figure 2). The heterozygous C to T transition resulted in a threonine (ACG) to methionine (ATG) substitution (p.Thr18Met).**
**This GRN missense mutation was predicted to be probably damaging by the PolyPhen2 software (with a score of 0.995, sensitivity 0.68 and specifitcity 0.97), and deleterious by the SIFT software (with a score of 0.01). GRN c.53C>T was not found in 150 control subjects, but was detected in the ExAC browser with a very low minor allele frequency (MAF=4.5 x 10-5).**

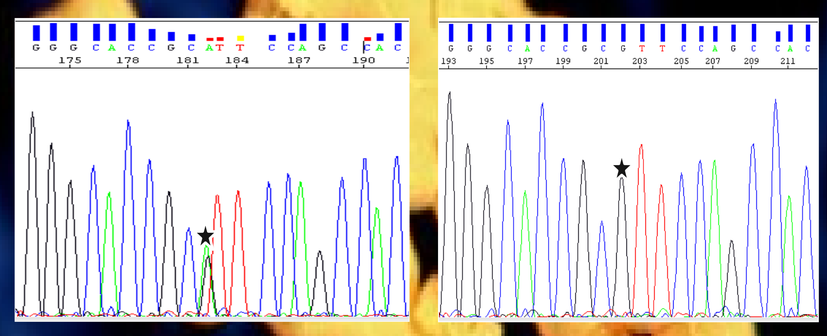

Figure 2. DNA sequencing chromatogram: the star indicates mutated (G/A) and wt sequence (reverse strand).

## DISCUSSION AND CONCLUSION

**Our findings suggesting that rare coding variability in GRN may influence the susceptibility to FTD and highlight the importance of genetic analysis also in sporadic forms of FTD. In conclusion, our result enlarges the spectrum of clinical phenotypes requiring genetic analysis in search of mutations of progranulin gene.**

**References**

[1]Van Swieten JC, Heutink P. Mutations in progranulin (GNR) within the spectrum of clinical and pathological phenotypes of frontotemporal dementia. Lancet Neurol 2008; 7: 965- 974.

[2]Le Ber I, Camuzat A, Hannequin D et al. Phenotype variability in progranulin mutation carriers: a clinical, neuropsychological, imaging and genetic study. Brain 2008; 131: 732-746.

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