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PROGRANULIN GENE MUTATION IN BIPOLAR DISORDER AND FRONTOTEMPORAL DEMENTIA: A CASE REPORT

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Objective

Mutations in progranulin gene (GRN) are one of the major causes of familial frontotemporal lobar degeneration (FTLD), usually associated with psychiatric symptoms and parkinsonism. Here we describe a GRN mutation occurring in a patient who presented with bipolar disorder (BD) that later developed behavioral variant of frontotemporal dementia (bvFTD).

Case Report

A 70 years old Caucasian man was diagnosed with BD type I at age of 55, with depressive episodes since his young adulthood. Familial history revealed a sister affected by major depression, and a son suffering of panic attacks and anxiety disorder. In 2014, 15 years after the diagnosis of BD, he developed progressive cognitive impairment associated with apathy, perseverative behaviours, and hyperphagia. He was hospitalized in 2015 and underwent neurological and neuropsychological evaluations, brain neuroimaging, lumbar puncture, brain 18-FDG-PET, extensive laboratory assessment and molecular genetic analysis. Brain neuroimaging (CT scans performed in 2014 and 2015) showed temporal atrophy (fig. 1). Liquoral biomarkers were in range of normality, 18-FDG-PET scan highlighted marked bilateral hypometabolism in frontotemporal areas. The neuropsychological assessment showed mild cognitive impairment (22.4 MMSE score), deficit in selective attention, verbal memory and executive dysfunction. A diagnosis of bvFTD was made according to Rascovsky et al. criteria (1). Later the gait disorder with reduced arm swing progressed and mild features of parkinsonism appeared. The genetic evaluation showed a c.1639 C>T mutation in GRN gene at exon 12, resulting in a R547C substitution, thus leading to an aminoacidic change in the progranulin protein.

Discussion

The GRN c.1639 C>T mutation (fig. 2) has previously been described only in one case of bvFTD with parkinsonism and impulse control disorder (2).
This alteration has a deleterious effect according to computational software for predicting the effects of mutations (Polyphen, SNAP). It has never been reported in bipolar disorder, although a role for GRN in BD has been hypothesized. Previous studies found lowered plasma progranulin levels in bipolar disorder and have shown that GRN polymorphisms may contribute to the susceptibility to develop bipolar disorder, in particular BD type I (3).

Fig. 1: CT imaging of the patient, showing asymmetrical brain ventricles and temporal atrophy (2015).

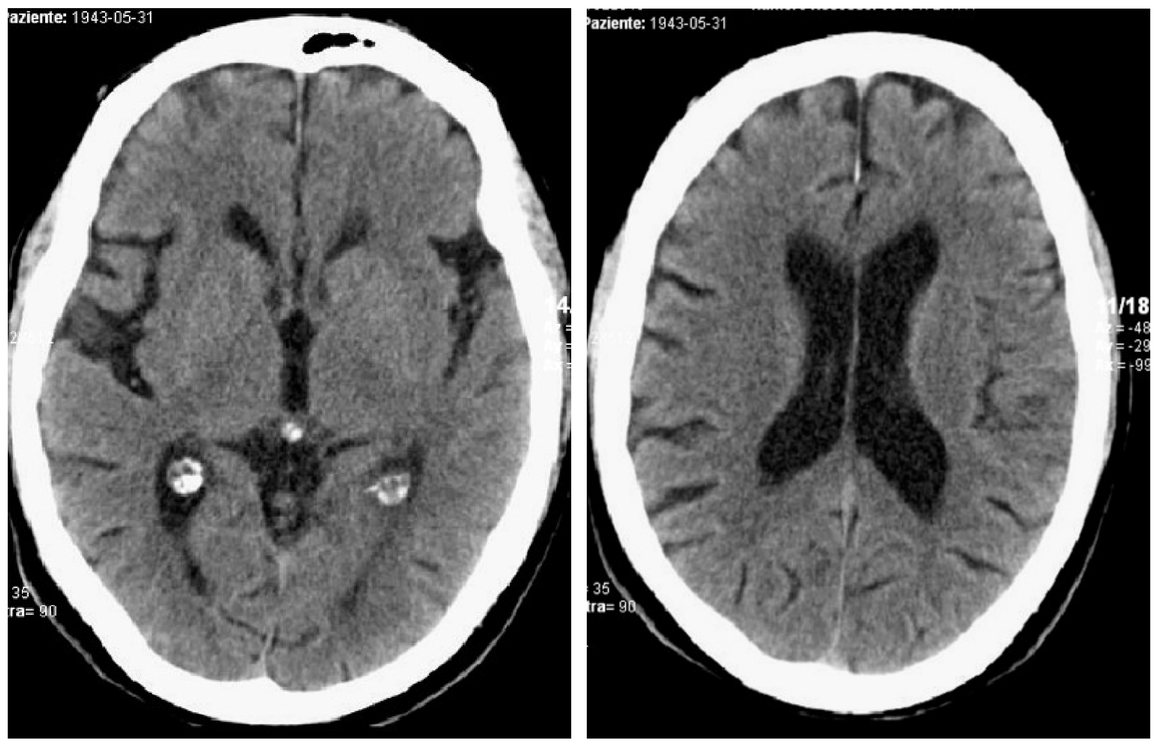


Fig. 2: Chromatogram of GRN gene sequencing with c.1639 C>T mutation.

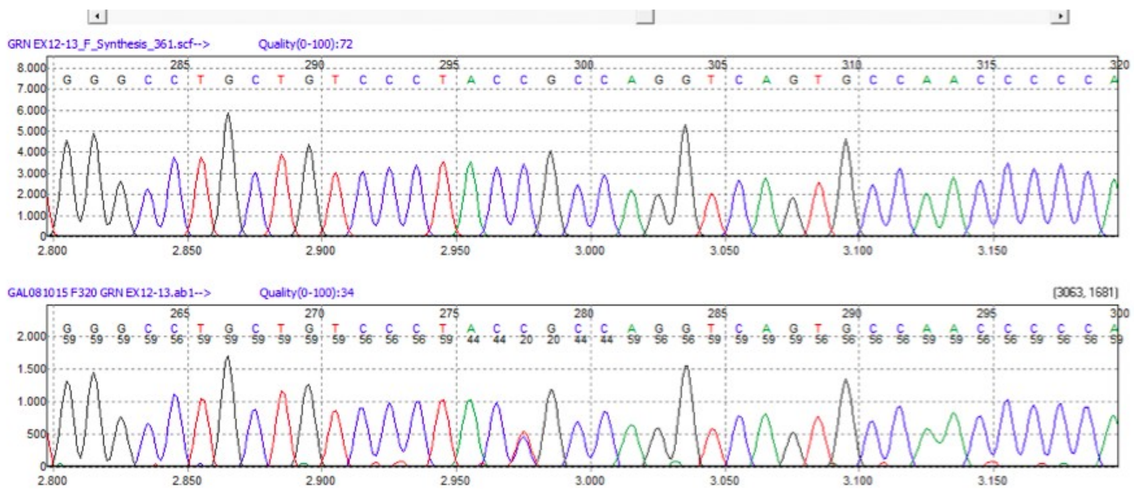
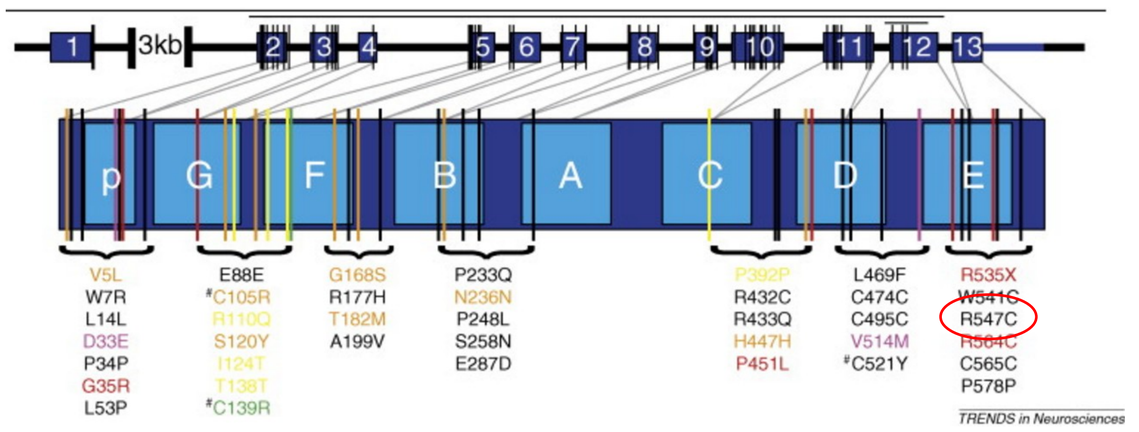


Fig. 3: Schematic representation of the genomic structure of GRN and the mRNA encoding the GRN protein (from Rademakers R, Rovelet-Lecrux A. Recent insights into the molecular genetics of dementia. Trends Neurosci. 2009;32(8):451-61).



Conclusion

Recent advances in genetic research have shed new light on the complex overlap between psychiatric and neurodegenerative diseases, in particular bvFTD and mood spectrum disorders, such as BD. Our observation further corroborates the assumption that GRN may be involved in both diseases, allowing to hypothesize that FTLD and BD could share a common etiopathological substrate involving the same cerebral regions.

References

1) Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011;134 (Pt 9):2456-77.

2) Galimberti D, Prunas C, Paoli RA, et al. Progranulin gene variability influences the risk for bipolar I disorder, but not bipolar II disorder. Bipolar Disord. 2014;16(7):769-72.

3) Wong SH, Lecky BR, Steiger MJ. Parkinsonism and impulse control disorder: presentation of a new progranulin gene mutation. Mov Disord. 2009;24(4):618-9.