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The case of two sisters carrying GRN p.R298H mutation

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Introduction: Progranulin (*PGRN*) is a secreted glycoprotein encoded in humans by the *GRN* gene, located on chromosome 17q21. Several nonsense and missense pathogenetic *GRN* mutations have been described [1]. To date, *GRN* p.R298H mutation was only reported in two papers and its pathogenetic role is still considered to be defined [2,3].

Objective: We herein present the case of two sisters carrying a *GRN* p.R298H mutation with extremely different clinical phenotypes and family history of dementia and behavioral disorders.

Methods: Patients underwent a multidimensional assessment including neurological and neuropsychological evaluation, structural and functional imaging, and genetic screening.

Results: The older sister presented at the age of 63 with severe depression of mood and apathy. She had a rapidly progressive and markedly asymmetrical parkinsonism and dementia. At the age of 65 years, she was anarthric and she developed severe dystonias prevalent in the left side of the body and in the cephalic district. She was bedridden at the age of 66 years. She was diagnosed with corticobasal syndrome. The younger sister presented at the age of 64 with dysphonia, dyspnea and inspiratory stridor. Soon afterward, she developed urinary urgency and sporadic episodes of urinary incontinence. The only clinical feature common to both sisters is frontal cognitive dysfunction. Their father died at 52 years due to diabetic complications. Two paternal aunts were diagnosed with dementia and behavioral disorders.

Conclusions: Our cases strongly support the pathogenicity of the *GRN* p.R298H mutation, which is first detected in two members from the same family, both with clinical manifestations. Our findings suggest that this mutation may be associated with an extremely variable phenotype. This wide clinical variability among the members of the same family has been frequently reported as features of *GRN* mutations [4]. More importantly, we report the first case of an *FTD-associated* mutation manifesting with inspiratory stridor.

References:

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