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Mutation analysis of the GRN gene in Portuguese patients with Frontotemporal dementia

Heterozygous mutations in the progranulin (GRN) gene are a common cause of Frontotemporal dementia (FTD) with TDP-43 inclusions. Most pathogenic variants reported are loss-offunction mutations, leading to GRN haploinsufficiency. Herein, we aim to unveil the GRN mutation spectrum of 270 patients with FTD from the central region of Portugal and also to characterize the clinical and neuropsychological phenotype of the mutation carriers. The genetic analysis revealed 7 different pathogenic variants in 46 patients of our cohort. Behavioural variant of FTD was the most common clinical presentation among the GRN mutation patients, who showed a neuropsychological profile compatible with frontotemporoparietal deficits, with some charateristics resembling AD and other sporadic FTD. Interestingly, some of the variants identified were novel or had only been described in Portuguese patients. We detected the p.Ser301Cysfs*61 as the most frequent, followed by the p.Gln257Profs*27 variant. All of the patients harboring a pathogenic variant in GRN gene showed a significant reduction of serum progranulin levels, confirming the utility of serum prescreening test to predict GRN mutation status. The identification of pathogenic variants in GRN gene has been crucial for genetic counseling and also for the enrollment of patients in on-going clinical trials, which are essential to test new drugs for the disease.

Keywords: Progranulin gene, GRN, Frontotemporal dementia, Genetic analysis, haploinsufficiency

Biography:

Dr. Maria Rosário Almeida is a Clinical Laboratory Geneticist (CLG) and a Senior Investigator of the Center for Neuroscience and Cell Biology at University of Coimbra in Portugal. In 2001, she received her PhD in Human Genetics from the Faculty of Medicine of the University of Newcastle in UK, where she stayed as a post-doctoral fellow until 2003. Currently, her research focuses on the genetic basis of several brain diseases such as: AD, FTD, ALS, PD and SVD. Thus, she applies a variety of molecular techniques, including advanced genomic sequencing approaches, to identify causative variants that lead to disease, or potential future therapeutic targets.

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