

Clinical and pathological heterogeneity in patients with the p.C139R missense mutation in Progranulin

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Frontotemporal lobar degeneration (FTLD) and Alzheimer's disease (AD) are two of the most common forms of dementia. AD usually affects individuals over 85 years of age and clinically those individuals present with memory and cognitive deficits. FTLD typically affects individuals in their early 60s and clinically presents with speech impairment, behavioral and personality changes before any memory and cognitive deficits are noticed. The majority of patients with FTLD have a positive family history of dementia indicating a strong genetic component to this disease. Recently, we identified loss-of-function mutations in the gene encoding the secreted growth factor progranulin (*GRN*) as a major novel cause of FTLD. Missense mutations in *GRN* have also been reported but their role in the development of neurodegenerative diseases still remains largely unknown. One particular missense mutation, p.C139R, showed evidence for a partial loss-of function. To further study the clinical, pathological and functional characteristics of p.C139R we screened a large cohort of neurodegenerative disease patients and controls for the presence of this missense mutation using a custom designed Taqman single-nucleotide polymorphism genotyping assay. Functional analyses were performed to determine the effect of p.C139R on *GRN* stability and secretion in a cell culture model. We identified three patients with the p.C139R missense mutation in our cohort, one patient with a clinical diagnosis of FTLD, one with a pathological diagnosis of FTLD and one patient with a pathological diagnosis of AD. Two research groups from Italy and Belgium also reported a clinical FTLD and AD patient with this mutation. Haplotype sharing analysis showed that the p.C139R mutation arose twice independently from two common founders. Western Blot analysis showed that expression of GRN p.C139R in cell culture after treatment with cyclohexamide resulted in more GRN in the pellet than in the media compared to cells transfected with wildtype GRN. A time-course experiment confirmed the delayed and reduced secretion of p.C139R GRN compared to wildtype GRN. Our data suggest that GRN p.C139R may cause a partial loss-of-function and that this may be a susceptibility factor for both FTLD and AD.