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Genetic characterization of patients with frontotemporal dementia and amyotrophic lateral sclerosis in the Nordic countries

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ABSTRACT

Frontotemporal dementia (FTD) is the second most common form of neurodegenerative disease affecting people under the age of 65 years. The general symptoms are dysfunctions in behavior and/or language. Up to 50 % of FTD patients have a positive family history for dementia and mutations in the progranulin (*GRN*) gene account for 13-25 % of the familial cases. In **Paper I**, the Swedish Karolinska family with FTD was shown to have a *GRN* mutation, p.Gly35GlufsX19, which segregated with the disease. The mutation resulted in an ~50 % reduction of the *GRN* transcript. Sequencing the *GRN* cDNA resulted in only wild type sequence indicating that the mutant allele had been degraded resulting in reduced *GRN* transcript levels.

GRN mutations have reduced penetrance which is shown e.g. in the Karolinska family where there is a 10 years range in age at onset. The single nucleotide polymorphism (SNP) rs1990622, in linkage disequilibrium with the transmembrane protein 106B (*TMEM106B*) gene, was suggested to modify age at onset in *GRN* mutations carriers. In **Paper II**, the effect of rs1990622 on age at onset in four *GRN* mutation families, including the Karolinska family was investigated. Patients homozygous for the A allele were shown to have a significantly earlier (13 years) median age at onset compared to patients with the GA or GG genotype. To investigate possible disease mechanisms of rs1990622, the GRN levels in plasma and the *TMEM106B* mRNA levels in brain tissue were measured. An effect of rs1990622 genotype on plasma-GRN levels was detected with AA carriers having the lowest GRN levels and GG carriers the highest levels. However, this effect was not shown to be mediated by the modulation of *TMEM106B* transcript levels.

In **Paper III**, 100 FTD patients from Sweden were screened for *GRN* mutations and four premature stop codon mutations were identified: p.Gly35GlufsX19, p.Cys416LeufsX30, p.Tyr294X and p.Cys404X. Furthermore, the p. Cys416LeufsX30 was shown to segregate in a family with clinical heterogeneity. The serum-GRN levels in carriers of the three first premature stop codons showed a more than 50 % reduction compared to non-carriers. GRN levels and age at onset in the patient cohort varied and were thus investigated for association with rs1990622, rs5848 (located in the 3'UTR of *GRN*) and apolipoprotein E (*APOE*). Patients with the TT genotype at rs5848 had significantly lower GRN levels compared to CT and CC genotypes. Moreover, *APOE* ε4 positive patients had a significantly later age at onset compared to ε4 negative patients.

FTD and amyotrophic lateral sclerosis (ALS) are part of the same disease spectrum. The identification of TAR DNA binding protein 43 (TDP-43) positive neuronal inclusions in the majority of ALS and FTD patients further supported the link. To investigate the importance of *TARDBP* (the gene encoding TDP-43) mutations in Nordic ALS patients, 177 patients were sequenced in **Paper IV**. Four missense variations in three familial ALS patients were detected: p.Ala90Val, p.Gly357Arg, p.Arg361Thr and p.Ser379Pro. The three last missense variations were concluded to be possibly pathogenic since they were predicted by *in silico* analysis to be pathogenic and were absent in 200 neurologically healthy controls. The mutation frequency of *TARDBP* in Nordic ALS patient was 1.7 %. Furthermore, the p.Arg361Thr was shown to be present in a family with both ALS and FTD-ALS which further strengthens the connection between FTD and ALS.

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