

# Molecular genetic studies of progranulin regulators in FTLD and ALS

<https://www.neurodegenerationresearch.eu/survey/molecular-genetic-studies-of-progranulin-regulators-in-ftld-and-als-3/>

## Principal Investigators

RADEMAKERS, ROSA

## Institution

MAYO CLINIC JACKSONVILLE

## Contact information of lead PI Country

USA

## Title of project or programme

Molecular genetic studies of progranulin regulators in FTLD and ALS

## Source of funding information

NIH (NINDS)

## Total sum awarded (Euro)

314077.0642

## Start date of award

15/04/2013

## Total duration of award in years

1

## Keywords

PGRN gene, Frontotemporal Lobar Degenerations, Genetic study, Amyotrophic Lateral Sclerosis, Integral Membrane Protein

## Research Abstract

DESCRIPTION (provided by applicant): Mutations in the progranulin gene (GRN) cause frontotemporal lobar degeneration (FTLD). Individuals with GRN mutations have a 50% reduction in functional progranulin protein (PGRN) and also invariably display TDP-43 pathology (FTLD-TDP), indicating low PGRN levels as a potential initiator of TDP-43 dysfunction in FTLD. The identification of TDP-43 as the pathological protein, not only in patients with FTLD with

mutations in GRN, but also in the majority of patients with ALS further suggests a role for TDP-43 in a unifying neurodegenerative disease mechanism underlying these disorders. Consequently, determining how PGRN levels are regulated in brain may lead to novel treatments and therapies for a range of neurodegenerative diseases. In the last few years, we and others have identified two PGRN regulators through genome-wide association studies: the uncharacterized transmembrane protein 106B (TMEM106B) and the multiligand receptor sortilin (SORT1). TMEM106B was identified as a risk factor for FTL-D-TDP, with subsequent studies from our laboratory suggesting a role for TMEM106B in PGRN regulation. Of particular interest was the finding that a specific TMEM106B genetic variant (rs3173615 predicted to result in p.T185S) could significantly protect GRN mutation carriers from developing disease. We further identified SORT1 as a major regulator of PGRN levels in human plasma. Interestingly, SORT1 was independently identified as a neuronal receptor for PGRN. In preliminary data we now present an unpublished genome-wide quantitative trait locus analysis of GRN mRNA levels in human brain and identify TBC1 domain family, member 1 (TBC1D1) as yet another novel PGRN regulator. In this Project, we hypothesize that genetic variants in TMEM106B, SORT1 and TBC1D1 regulate PGRN levels and/or function in brain, thereby modifying disease risk, penetrance and presentation in TDP-43 proteinopathies. The Specific Aims are focused on 1) the functional characterization of the effect of the p.T185S protective variant on TMEM106B and PGRN using cell culture models, including primary cultures of mouse Pgrn knock-out and wild type hippocampal neurons, biochemical and molecular approaches and “somatic gene transfer” in mice using recombinant adeno-associated virus; 2) Systematic analyses of the role of genetic variants in TMEM106B, SORT1 and TBC1D1 in the development and presentation of FTL-D and ALS by performing genetic association studies in extensive FTL-D and ALS case-control populations using variants identified by whole-genome sequencing; and 3) determine the effect of newly identified TMEM106B, SORT1 and TBC1D1 variants on PGRN levels in vivo and in vitro. The proposed studies are relevant to fully appreciate the contribution of common and rare variants in TMEM106B, SORT1 and TBC1D1 to the development and presentation of FTL-D and ALS and will lead to a greater understanding of PGRN regulation.

**Further information available at:**

**Types:**

Investments < €500k

**Member States:**

United States of America

**Diseases:**

N/A

**Years:**

2016

**Database Categories:**

N/A

**Database Tags:**

N/A