The Genetic Regulation and Disease Function of the Frontotemporal Dementia Protei

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Country

USA

Title of project or programme

The Genetic Regulation and Disease Function of the Frontotemporal Dementia Protei

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NIH (NIA)

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15/07/2013

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5

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Proteus, Frontotemporal Lobar Degenerations, protein TDP-43, Frontotemporal Dementia, PGRN gene

Research Abstract
DESCRIPTION (provided by applicant): The Genetic Regulation and Disease Function of the

Frontotemporal Dementia Protein TMEM106B Frontotemporal dementia (FTD) is the second-most common cause of presenile dementia, characterized clinically by deterioration in language, behavioral control, or both. There are no effective treatments, and progressive neurodegeneration causes death within an average of 6-7 years. FTD is comprised of several neuropathological subgroups, likely representing different underlying pathophysiologies. The largest subgroup (~50% of FTD cases) is characterized by pathological inclusions of the HIV TAR DNA-binding protein of 43 kD (TDP-43) and accordingly named frontotemporal lobar degeneration with TDP-43 inclusions, or FTLD-TDP. FTLD-TDP can be either sporadic or familial, with a substantial proportion of cases (~10%) attributable to mutations in the progranulin gene (GRN). Inherited in an autosomal dominant manner, GRN mutations appear to cause FTLD-TDP through haploinsufficiency of progranulin, a secreted protein with trophic effects on neurons. Recently, we performed a genomewide association study (GWAS) in FTLD-TDP, identifying a 7p21 locus containing only the uncharacterized gene TMEM106B that confers increased risk of FTLD-TDP in both non-Mendelian and GRN mutation-associated FTLD-TDP. Carriers of risk-associated genetic variants and diseased individuals independently showed increased mRNA expression of TMEM106B, strongly implicating this gene as the cause of the GWAS signal. Beyond the fact that TMEM106B is the only risk factor for non- Mendelian cases of FTLD-TDP described to date, little is known about it. Preliminary data suggest, however, that TMEM106B expression is increased in FTLD-TDP~ that TMEM106B is regulated by the microRNAs miR- 132 and miR-212, which are both decreased in FTLD-TDP~ that increased TMEM106B expression leads to endosomal-lysosomal dysfunction~ and that increased TMEM106B expression leads to abnormalities in progranulin trafficking. These data lead to a working model in which genetic variants at TMEM106B confer increased risk of FTLD-TDP by increasing TMEM106B expression. Increased TMEM106B expression, in turn, alters endosomal-lysosomal function, which influences the proper sorting, internalization, or secretion of progranulin. The Specific Aims of the project, which will test the working model, are: AIM 1: Confirm the association of TMEM106B over-expression with disease states and with TMEM106B risk genotypes~ AIM 2: Investigate the precise cis-acting mechanism(s) by which TMEM106B gene expression is regulated~ AIM 3: Elucidate the normal and pathophysiological function of TMEM106B in endosomal-lysosomal pathways as well as in progranulin trafficking. The over-arching goal of this proposal is to move from a statistical association obtained by GWAS between TMEM106B and FTLD-TDP, to a mechanistic understanding of both the genetic regulation of TMEM106B and the normal and pathophysiological function of this protein. In the process, we will identify many potential avenues for therapy not otherwise in the landscape of research and drug discovery efforts for this currently untreatable disease.

Lay Summary

PUBLIC HEALTH RELEVANCE: Frontotemporal dementia (FTD), sometimes also called frontotemporal lobar degeneration, is an important cause of dementia which is currently untreatable. We have recently discovered a novel genetic risk factor for FTD by genomewide association. This risk factor, TMEM106B, is minimally characterized but modulates one’s risk of developing disease to a significant degree, with an odds ratio of 1.6. The proposed project will investigate the genetic regulation and pathophysiological function of TMEM106B and is likely to lead to new possibilities for treating this otherwise fatal disease.

Further information available at:

Types:

Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

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