TTR and C9ORF72 in ALS and related disorders

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Principal Investigators

VAN BLITTERSWIJK, MARKA

Institution

MAYO CLINIC JACKSONVILLE

Contact information of lead PI
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C9orf72, Prealbumin, Amyotrophic Lateral Sclerosis, Frontotemporal Dementia, Cerebrospinal Fluid

Research Abstract

? DESCRIPTION (provided by applicant): We seek to determine the role of transthyretin (TTR) in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) linked to a repeat expansion in chromosome 9 open reading frame 72 (C9ORF72), and whether TTR may serve as a much needed biomarker for C9ORF72-related diseases. Although emerging evidence suggests loss of C9ORF72 expression, the formation of RNA foci, and the generation of

dipeptide-repeat proteins contribute to C9ORF72-related diseases, much remains unknown about the pathogenic mechanisms underlying these fatal neurodegenerative diseases. More important, the substantial clinical variability described in patients carrying the expansion points to the involvement of other genes functioning to accelerate or mitigate disease progression. To elucidate which genes may be driving the pathogenic heterogeneity in ALS and FTD phenotypes and to identify potential biomarkers, we first performed a genome-wide brain expression analysis focusing on C9ORF72 expansion carriers. Our exciting preliminary data show a cerebellar up-regulation of TTR and multiple homeobox (HOX) genes, in expansion carriers as compared to disease controls (i.e. ALS and FTD patients without C9ORF72 repeat expansions) and to controls without neurological diseases. The identification of genes involved in developmental processes sheds light on potential compensatory mechanisms influencing the occurrence, presentation and/or progression of C9ORF72- related diseases. Moreover, we show that TTR protein levels in plasma are also increased in expansion carriers, thus reflecting the increase in cerebellar TTR expression. Given that TTR has neuroprotective effects, is involved in neurodegenerative diseases, and is detectable in both plasma and cerebrospinal fluid (CSF), we hypothesize that TTR may serve as a biomarker for C9ORF72-related diseases. To address the lack of validated biomarkers for C9ORF72-related diseases that have been described for diagnostic purposes, as prognostic indicators, or to monitor drug effects, we aim to characterize the up- regulation of TTR in C9ORF72 expansion carriers and to determine whether TTR could be a suitable biomarker. Our thorough assessment of TTR in C9ORF72-related diseases will include investigating TTR protein levels (plasma and CSF) in a unique cohort of symptomatic and presymptomatic C9ORF72 expansion carriers, disease controls, and controls without neurological diseases, which will allow comparisons among groups, disease subgroups (e.g. FTD, FTD/ALS, and ALS), and over time (Aim 1). Moreover, we will characterize the up-regulation of TTR in a range of neuroanatomical regions, evaluate the histopathological context, and examine which post-translational modifications are present (Aim 2). Taken together, these studies will enable us to determine whether TTR is a suitable biomarker for C9ORF72-related diseases, which may aid the identification of biomarker profiles for the entire ALS and FTD spectrum, and point towards novel therapies for these devastating neurodegenerative diseases.

Further information available at:

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