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Featured Article

Conserved brain myelination networks are altered in Alzheimer's and other neurodegenerative diseases

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Abstract

Introduction: Comparative transcriptome analyses in Alzheimer's disease (AD) and other neurodegenerative proteinopathies can uncover both shared and distinct disease pathways.
Methods: We analyzed 940 brain transcriptomes including patients with AD, progressive supranuclear palsy (PSP; a primary tauopathy), and control subjects.
Results: We identified transcriptional coexpression networks implicated in myelination, which were *lower* in PSP temporal cortex (TCX) compared with AD. Some of these associations were retained even after adjustments for brain cell population changes. These TCX myelination network structures were preserved in cerebellum but they were not differentially expressed in cerebellum between AD and PSP. Myelination networks were *downregulated* in *both* AD and PSP, when compared with control TCX samples.
Discussion: Downregulation of myelination networks may underlie both PSP and AD pathophysiology, but may be more pronounced in PSP. These data also highlight conservation of transcriptional networks across brain regions and the influence of cell type changes on these networks.

Keywords: Proteinopathies; Alzheimer's disease; Progressive supranuclear palsy; Myelination; Coexpression networks; Transcriptome; Temporal cortex; Cerebellum

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1. Introduction

Many neurodegenerative diseases, including Alzheimer's disease (AD), are proteinopathies with common features including abnormal deposits of endogenous proteins, which propagate through the central nervous system (CNS) and culminate in cellular dysfunction and death, leading to clinical syndromes of dementia and/or movement disorders (reviewed [1]). Despite their commonalities, key differences are thought to exist in the events that trigger one proteinopathy versus another and in the downstream pathophysiological pathways that distinguish these neurodegenerative diseases. Gene expression profiling studies may discover genes implicated in neurodegenerative diseases and uncover the complex molecular pathways leading to these disorders [2,3]. With few exceptions [4–8], previous studies have investigated differential gene expression (DGE) in relatively small cohorts and were limited to comparison of individual gene transcripts rather than systems-level analysis. Furthermore, most studies assessed one disease group against control subjects rather than pursuing comparison between different diseases.

We postulate that comparison of brain gene expression levels in different neurodegenerative proteinopathies can uncover molecular pathways that are common to and those that are distinct for these diseases. Discovery of brain transcriptional networks with differential expression between different proteinopathies may uncover molecular pathways that may differentially influence these conditions. In contrast, networks that have similar expression changes in different diseases in comparison to control subjects may point to common dysregulated molecular pathways.

To test this hypothesis, we focused on two distinct proteinopathies, AD [9,10] and progressive supranuclear palsy (PSP) [11,12]. Although brain tau protein accumulation is a neuropathologic hallmark in both, these conditions are distinguished by different predominant tau isoform aggregates [13], and the unique presence in AD [9], of senile plaques composed predominantly of amyloid β (Aβ). They also have distinct clinical presentations. AD is the most common type of dementia [10], whereas PSP is a relatively rare parkinsonian movement disorder [12].

To identify genes and networks that are differentially altered in these conditions, we performed DGE and coexpression network analysis [14], in brain transcriptome [15–17], of subjects with AD or PSP. To determine whether observed network differences are driven by changes in AD versus PSP or different extent of change in both, we also compared each diagnostic group with elderly control samples without any neurodegenerative diagnoses. All coexpression modules (CEMs) were tested for enrichment of CNS cell types [18], to identify altered networks that may be indicative of selectively vulnerable cell populations. Furthermore, to determine the contribution of cell population changes to our findings [19], we performed all network analyses using two models: comprehensive model, which adjusted for levels of five CNS cell-specific transcripts, and simple model, which was not thus adjusted. Finally, we validated these results by protein analysis in brain tissue.

Our findings reveal conserved brain myelination networks that are altered in both AD and PSP, but to a greater extent in the latter. These results have implications for the role of myelin metabolism in the pathophysiology of these distinct neurodegenerative proteinopathies and ultimately for identification of novel therapeutic targets and biomarkers. Furthermore, our large-scale transcriptome data, which we made available to the research community [16], provide information regarding brain region conservation and CNS cell-enrichment of transcriptional networks, as well as the influence of cell population changes on their expression patterns.

2. Methods

Please also refer to Supplementary Methods for details.

2.1. Subjects and samples

In a two-stage design, Mayo Clinic brain expression genome-wide association study (eGWAS) was used as the discovery cohort and Mayo Clinic RNA sequencing (RNA-seq) samples were used as the replication cohort. The discovery cohort [15,16] had whole genome complementary DNA-mediated annealing, selection, extension, and ligation (WG-DASL) array-based transcriptome measurements, whereas the replication cohort [16,17] had RNAseq data obtained with 101 base pairs, paired-end sequencing on Illumina HiSeq2000 instruments, as previously published. The discovery cohort had whole genome genotypes from the Illumina HumanHap300-Duo Genotyping BeadChips [20], and the replication cohort from the Illumina Infinium HumanOmni2.5-8 BeadChip, which were used in quality control (QC).

2.2. Analyses

2.2.1. Differential gene expression

DGE analyses of brain tissue from subjects of two diagnostic categories were conducted with multivariable linear regression conducted in R. Discovery cohort DGE analyses used normalized gene expression measures as dependent variable, diagnosis as independent variable of primary interest and included age at death, gender, number of *APOE* ε4 alleles, plate, RNA integrity number (RIN), and $(\text{RIN} - \text{RINmean})^2$ as biological and technical covariates. Replication cohort DGE analyses used conditional quantile normalized [21] gene expression measures as dependent variable, diagnosis as independent variable of primary interest, and included age at death, gender, RIN, brain tissue source, and flow cell as biological and technical covariates. We