Identification of Dysregulated Pathways Unifying Neurodegenerative Disease

Noori, Ayush (School: Phillips Exeter Academy)

Research and advances in medicine have dramatically increased human longevity, with an ensuing increase in the prevalence of geriatric conditions including Alzheimer's disease (AD), Lewy body dementia (LBD), amyotrophic lateral sclerosis and frontotemporal dementia disease spectrum (ALS-FTD), and other neurodegenerative disorders. Today, the global epidemic of neurodegenerative disease imposes a significant burden on patients, caregivers, and the health care system. Recognizing the commonalities between the molecular and symptomatic presentation of these neurodegenerative pathophysiologies, identifying common pathological processes across neurodegeneration is a compelling interdisciplinary approach which has unique potential to determine pathways most central to disease. Differential gene expression and subsequent pathway analysis of human gene expression data identified key molecular pathways dysregulated across AD, LBD, and ALS-FTD. 34 Affymetrix microarray patient-derived datasets were retrieved from the Gene Expression Omnibus database, categorized by both disease and brain region, and analyzed individually. A linear model was fitted to log-normalized data to compute the average expression value for each probe, and an empirical Bayesian moderated t-statistics test ranked genes by evidence for differential expression. After data filtration in R ($p < 0.05$), Bioconductor annotation packages mapped Affymetrix Probe IDs to ENTREZ IDs, which were passed to pathway enrichment functions against the Kyoto Encyclopedia of Genes and Genomes and Gene Ontology: Biological Processes databases. Results were validated via MSigDB GSEA Java and DAVID. The fundamental pathways identified suggest novel therapeutic targets for the unified treatment of neurodegenerative disease.