Unsupervised Analysis of Gene Expression in Neurological Animal Models Reveals Spatiotemporal Differences between Developing Mouse and Human Brains

Hu, Kevin

Mouse models serve as a readily available base for experimentation in neurodegenerative drug development. However, less than 10% of drugs that have shown success in mouse-based preclinical trials show similar success in subsequent human clinical trials. Although previous studies found a high conservation between human-mouse expression, many such studies exclusively examined the late adult brain. A direct comparison of cerebral gene expression in the embryonic and early postnatal stages would require the existence of precise analogous timepoints. In this study, the developmental transcriptomes of mouse and human brains were indirectly compared with the assumption being that similar landscapes of expression would yield similar clusters in each organism. ISH and RNA-seq data were compiled into species-specific datasets containing expression matrices for 1,912 mouse-human orthologs. Correlation networks were constructed in each dataset, and a hierarchical method was applied to identify clusters of inter-correlated expression. A deep manifold projection model was further applied to assess the similarity between the two organisms through density-based clustering. Cross-organism adjusted rand index analysis revealed a high degree of divergence that was evident in the correlation clusterings, manifold projection results, and correlation networks. Furthermore, comparison of regulatory genes failed to identify a significant intersection of DNA-binding elements between the two organisms. Immediate applications of this study include justification for the low success of mouse-derived treatments, a method of validation for future transgenic mouse models, and a robust process for deep analysis and visualization of high-dimensional transcriptomic data.

Awards Won:
Third Award of $1,000