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Identification of evolutionarily conserved gene networks mediating Neurodegenerative Dementia

Mutations causing the most common form of early onset dementia, frontotemporal dementia, have been identified, but the subsequent disease mechanisms are not well understood. Rather than focusing on a priori selected genes, we apply a multi-stage, systems biology approach, reasoning that defining transcriptional networks would significantly advance mechanistic understanding. By taking genetic background into consideration, representing a variety of causal mutations in our transcriptomic analyses, coupled with gene co-expression network analysis, and validation in a dozen independent data sets, we bridged the species divide and identify disease-relevant gene networks representing specific molecular pathways. These networks are dysregulated not only across a variety of FTD mouse models involving different mutations and genetic backgrounds, but also in FTD patient iPSC-lines and more importantly, post mortem human samples. We further validate network predictions via proteomic studies in human brain and show that a hub of a putative regulatory miRNA module, miR-203, re-capitulates mRNA co-expression patterns associated with disease state and induces neuronal cell death. Moreover, we use disease-associated co-expression modules to identify probe compounds and show that they have the predicted protective effect. Collectively, we identify conserved, disease relevant co-expression networks representing convergent changes in dementia, and validate miR-203 as a novel regulator of core network components and neurodegeneration.

Speaker Biography

Vivek Swarup completed his PhD from Laval University, Quebec, Canada. He is the assistant professor at the Department of Neurobiology and Behavior, University of California, Irvine, USA. He has over 20 publications that have been cited over 1100 times, and his publication H-index is 15.

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