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Topological Influence of Immediate-Early Genes in Brain Genetic Networks and their link to Alzheimer's Disease

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Immediate-early genes (IEGs), a subset of activity-regulated genes (ARGs), play a critical role in genetic networks, responding rapidly to neuronal activity without requiring de novo protein synthesis. This talk examines the network-level influence of IEGs in gene networks and their relevance to Alzheimer's disease (AD). Using a combination of network analysis and genome-wide association study (GWAS) summary statistics, we demonstrate that IEGs exert greater topological influence in human and mouse gene networks compared to other ARGs. Although ARGs are sparsely implicated in diseases and more mutationally constrained than non-ARGs, many AD-associated genetic variants are enriched in ARG regions.

Among these, **MARK4**, located near the IEG **FOSB**, emerges as a key factor. An AD risk expression quantitative trait locus (eQTL) increases MARK4 expression in cortical regions, while multi-omic network analysis identifies MARK4 as a central hub with notable druggability potential. These findings underscore the central role of genes in the IEGs in AD pathogenesis and suggest novel avenues for therapeutic intervention targeting their downstream dysregulation. This talk highlights how network science provides critical insights into the complex genetic underpinnings of Alzheimer's disease and highlights MARK4 as a promising target for future research.