Integrated Molecular Network Analysis Reveals MYC, EIF4EBP1, and NOS3 as Key Drivers of Cortical Abnormalities in PKD–TSC Overlap

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Abstract

Polycystic kidney disease (PKD) and tuberous sclerosis complex (TSC) are genetically distinct disorders that share overlapping molecular features, particularly in cases involving contiguous gene syndromes. While the neurological manifestations of TSC are well characterized, the contribution of PKD-associated molecular pathways to cortical brain abnormalities remains poorly understood. In this study, we employed a protein–protein interaction network–based approach to investigate the shared molecular landscape of PKD and TSC with specific emphasis on cortical development and neurological dysfunction.

Network analysis revealed a highly interconnected module centered on the hub proteins MYC, EIF4EBP1, and NOS3, indicating convergence of proliferative, translational, and neurovascular signaling pathways. Dysregulation of MYC was associated with altered neural progenitor proliferation and impaired neuronal differentiation, while persistent activation of EIF4EBP1 suggested abnormal mTOR-dependent translational control affecting synaptic maturation. Additionally, the identification of NOS3 as a central network node highlighted a previously underappreciated role of neurovascular and metabolic dysregulation in PKD–TSC–associated cortical pathology.

Collectively, these findings propose a unified mechanistic model in which structural cortical abnormalities, synaptic hyperexcitability, and metabolic stress act in concert to drive neurological phenotypes such as epilepsy and cognitive impairment. This study provides novel systems-level insight into the cortical involvement of PKD–TSC overlap and identifies potential molecular targets for future therapeutic and experimental validation.

Keywords

mTOR Signaling Pathway, MYC, EIF4EBP1, NOS3, Protein–Protein Interaction Network.