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Pathway enrichment and FDA-approved drug repurposing analysis for the treatment of CTNNB1 Syndrome modeled in an SH-SY5Y cell line

John Vergis[1*], Robert E. McCullumsmith[2]

[1]College of Medicine and Life Sciences, 3000 Arlington Avenue, The University of Toledo, Toledo OH 43615
[2]Professor, Chair of Department of Neurosciences and Psychiatry, 3000 Arlington Avenue, The University of Toledo, Toledo OH 43615

Email: john.vergis@rockets.utoledo.edu

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Background or Introduction. CTNNB1 syndrome is a rare disorder involving the loss of function of the β-catenin protein following a mutation in the gene which encodes it with which primarily causes neurological deficits; management focuses on symptoms as there is no FDA-approved treatment.

Objectives. To identify enriched pathways in CTNNB1 syndrome and FDA-approved drug repurposing candidates.

Methods. We reused a transcriptomic signature generated from autonomic ganglion tissue (derived from an SH-SY5Y cell line) with *CTNNB1* knockdown from the integrative Library of Integrated Network-Based Cellular Signatures (iLINCS) portal. We performed pathway enrichment analysis separately on upregulated genes and downregulated genes (to respectively derive “upregulated” and “downregulated” pathways) utilizing EnrichR with KEGG 2021 Human pathway and Orphanet Augmented 2021 disease ontology databases. Drug repurposing analysis was performed through iLINCS to identify potential treatments for CTNNB1 syndrome.
Results. We identified 20 notable and significant enriched pathways and disease annotations (5 for up- and down-regulated terms, for a total of 10 per database). We also identified the top 10 drugs with the most discordant signatures to the CTNNB1 knockdown signature: 6 of the top 10 drugs are already FDA approved for the treatment of other disorders, including miltefosine, rolipram, amlodipine, topiroxostat, indapamide, and mefenamic acid.

Conclusion. Our analysis has successfully provided insights into which biological pathways can be affected by CTNNB1 knockdown as well as which orphan diseases display similar transcriptomic signatures to CTNNB1 syndrome. We have also identified several drugs which are already in use that are potential drugs for CTNNB1 syndrome which should be further studied, paving the way for additional research on the treatment and management of CTNNB1 syndrome.

Keywords: Bioinformatics, CTNNB1 Syndrome

