

IDENTIFYING UNCONVENTIONAL ROLE OF MIRNAS IN ALZHEIMER'S DISEASE THROUGH CAUSE-AND-EFFECT MODEL

S. Bagewadi^{1,2}, E. Younesi¹, A. Tom Kodamullil^{1,2}, M. Hofmann-Apitius^{1,2}

¹*Department of Bioinformatics, Fraunhofer Institute for Algorithms and Scientific Computing (SCAI), Germany*

²*Bonn-Aachen International Center for IT, Rheinische Friedrich-Wilhelms-Universität Bonn, Germany*

shweta.bagewadi@scai.fraunhofer.de

Current drug discovery approaches to find novel therapeutics for Alzheimer's disease (AD) have focused on molecular events mainly around APP, Tau and BACE1; however AD is of multifactorial nature. Several direct and indirect mechanistic events underlying the disease etiology and pathophysiology are yet to be elucidated, posing a major challenge for identification of reliable biomarkers and efficient therapeutics. In the last decade, miRNAs have emerged as key regulators in several pathomechanisms. Here, we describe the construction of a cause-and-effect regulatory model using Biological Expression Language (BEL) to provide new mechanistic insights into the causal effects of miRNAs and their possible role in regulating pathological pathways in AD. We dissected and curated the existing knowledge related to miRNA regulation under AD conditions from literature (from abstracts using text-mining) and manually encoded the extracted causal relationships in BEL. Functional analysis on this model led to identification of a sub-network enriched with Toll-like receptor signaling pathway. Mechanistic validation of this sub-network provided new insights into in-direct regulation mechanism of APP and BACE1 by traversing different paths that lead to inflammatory responses through proteins targeted by miR-146a, miR-155, and miR-27b. Pharmacogenomics investigation revealed the association of miRNA-regulated targets with several approved drugs that could be proposed for repurposing and AD co-morbidities such as Heart Disease, Rheumatoid Arthritis, and Diabetes. Thus, we propose a holistic approach to identify causal patterns underlying miRNA regulated AD mechanism through interpretation of existing knowledge.