UNDERSTANDING THE LINK BETWEEN ALZHEIMER'S DISEASE AND TYPE 2 DIABETES IN TERMS OF METABOLIC ALTERATIONS

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ABSTRACT

Alzheimer's disease (AD) is a type of dementia that causes impairment in memory, reasoning, and thinking. Type 2 diabetes (T2D) is common in the general elderly population and is significantly associated with a higher risk of dementia. However, metabolic alterations responsible for this association are largely unknown. Genome-scale metabolic models (GEMs) computationally describe gene-protein-reaction associations for entire metabolic genes in an organism/tissue/a specific condition. Detection of active/inactive metabolic reactions by mapping gene expression levels of healthy and disease samples on GEMs provides crucial information about altered metabolic pathways.

In this study, we aim to predict metabolic alterations in the temporal lobe and hippocampus region of the brain by predicting the activation of the metabolic reactions based on the gene expression levels of control, AD, and T2D samples from human and *in vivo* disease models (*Mus musculus* and *Rattus norvegicus*). Microarray datasets, for *M. musculus* [1], *R.s norvegicus* [2], and human [3], were retrieved from Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/) and Robust Multi-array Average (RMA) normalization was performed for three datasets. The normalized data were mapped separately on genome-scale metabolic network models using the Integrative Metabolic Analysis Tool (iMAT) to create sample-specific metabolic networks. For each dataset, 25th percentile and 75th percentile were selected as thresholds to determine lowly and highly expressed genes for the iMAT analysis, respectively. Three rate constraints were introduced in the iMAT simulations of Human-GEM to ensure their activity in all samples: glucose and oxygen uptake rates and the active macromolecule synthesis rate have their minimum values set to 0.01, 0.01 and 0.0001, respectively, leaving all the other reaction rates unconstrained in the simulations. For each reaction in the *M. musculus* and *R. norvegicus* sample-specific metabolic networks, the active/inactive reaction ratio across disease and control samples was calculated instead of a statistical test because of the low number of samples. The active/inactive reaction ratio provides information about the affected reactions and their pathway associations. On the other hand, for reactions in the human sample-specific metabolic networks, significantly altered reactions/pathways were determined by the Fisher-Exact test (p-value < 0.05).

We predicted a set of relevant reactions/pathways to be affected between control-AD or control-T2D and commonly affected pathways in both diseases. Bile acids, fatty acids, cholesterol, glycosphingolipid, steroid, inositol phosphate metabolism, chondroitin sulfate, and keratan sulfate metabolisms are commonly affected pathways in both AD and T2D patients. In contrast, the glycolysis / gluconeogenesis pathway is only predicted as an altered pathway in *M. musculus* with T2D. Metabolic alterations indicate T2D to be a risk factor for AD. In conclusion, mapping transcriptome data on genome-scale metabolic networks to predict the condition-specific activity of reactions enabled genome-wide identification of metabolic relations between AD and T2D.

Keywords: Alzheimer's disease, Type 2 Diabetes, sample-specific metabolic networks, transcriptome.

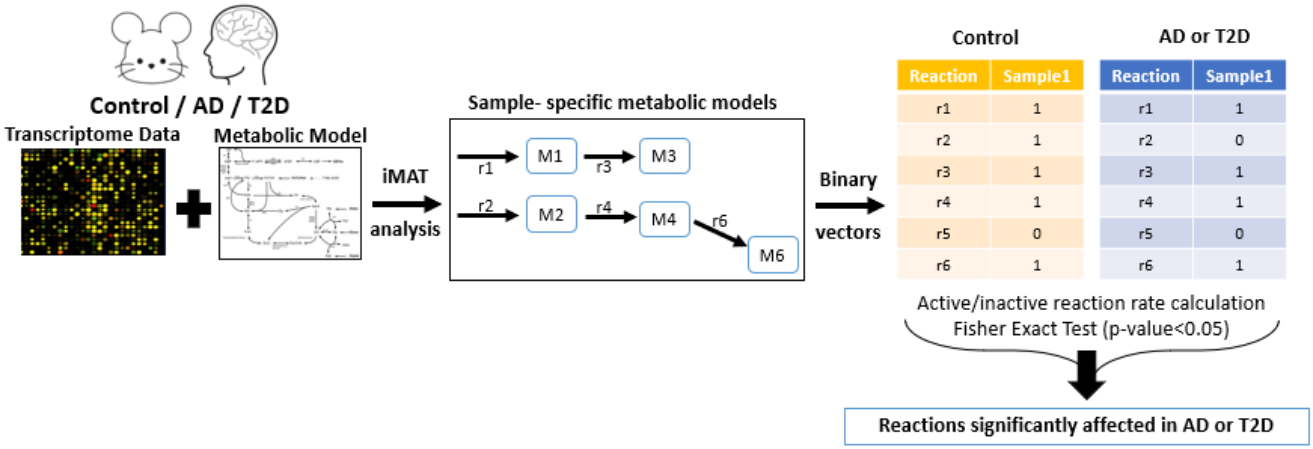

Figure 1. **Workflow for prediction of metabolic alterations.** Reaction activity is predicted for each sample in the datasets using the iMAT and represented in binary format. Each reaction is compared between control – AD , control - T2D cases to identify reactions significantly affected in AD and T2D.

References

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