Personalized analysis of metabolic changes in Alzheimer's disease with a systems biology approach

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Abstract

Alzheimer's disease (AD) is a multifactorial neurodegenerative disease without a cure. Metabolic changes are known to take place in the brains of patients. Metabolic reactions are catalysed by enzymes coded by genes. Therefore, genetic mutations can indirectly affect metabolic changes. Genome scale metabolic models (GEMs) are common tools used in systems biology to understand changes in metabolism. GEMs include all metabolic reactions and reaction-enzyme-gene relationships in the organism. Integrative Metabolic Analysis Tool (iMAT) [1] and Gene Inactivity Moderated by Metabolism and Expression (GIMME) [2] are bioinformatics tools used for integrating gene expression data into GEMs to leverage condition-specific metabolic models. In this study, individual-specific metabolic models were reconstructed by using gene-expression data from the brains of AD and healthy individuals obtained from ROSMAP [3] and Mayo Clinic [4] studies. Totally, 486 AD and 239 healthy samples were analysed separately. In addition, genomic variants were obtained from the transcriptome data for each sample. Among these variants, those that damage protein function was determined, and AD metabolic models were reconstructed by taking into account the effect of these variants. Finally, metabolic reactions whose activity is changed significantly between AD and healthy models were determined. Likewise, the models created by considering the effect of variants were also compared with healthy models. As a result, mechanisms such as fatty acid oxidation, sphingolipid metabolism, and bile acid biosynthesis were found to be affected pathways in both studies. It was also observed that the inclusion of the effect of variants enabled the capture of more AD-associated pathways. It is hoped that these results will be a step in understanding the metabolic changes in AD and will guide the treatment methods.

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References

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