

Insights Into The Shared Genetic Architecture Of Alzheimer's Disease And Diabetes-related Metabolic Biomarkers

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Take away: Alzheimer's Disease and diabetes-related metabolic traits are genetically interconnected through shared genes and biological pathways, despite no evidence of direct causality.

Introduction

- Epidemiological studies consistently report an association between Alzheimer's disease (AD) and diabetes [1].
- Diabetes-related metabolic biomarkers, including glucose and insulin-related traits, have been implicated in AD susceptibility and progression [2-3].
- The genetic and biological mechanisms underlying the relationship between AD and metabolic dysfunction remain unclear [4].

Aim

Investigate the shared genetic architecture between AD and diabetes-related metabolic traits to uncover common biological mechanisms.

Methods

Figure 1: Study design and analytical workflow

Results

Global genetic correlation between AD and Metabolic Traits
(* p < 0.05, ** p < 0.05/57)

0.13	0.21*	0.26*	0.09	0.18*	0.22*
0.10	0.12	0.15*	0.07	0.10*	0.12*
-0.01	-0.20	-0.23*	-0.02	-0.18*	-0.21*
-0.08	-0.20*	-0.17	-0.08	-0.19*	-0.16*
-0.15	-0.34*	-0.42*	-0.11	-0.29*	-0.37*

AD GWAS (Jansen et al.) AD GWAS (Kunkle et al.) AD GWAS (Lambert et al.) AD GWAS (Jansen et al.) AD GWAS (Kunkle et al.) AD GWAS (Lambert et al.)

(+) APOE, MHC (-) APOE, MHC

2h Glucose (Chen et al.)
Random Glucose (Lagou et al.)
Fasting Insulin (Manning et al.)
HbA1c (Wheeler et al.)
Fasting Proinsulin (Strawbridge et al.)

Figure 2: Global genetic correlation between AD and diabetes-related metabolic traits by Linkage disequilibrium score regression (LDSC).

Local analysis of variant association (LAVA) between Metabolic traits and AD GWAS
Only Bonferroni-significant loci (p < 0.05/No of loci per study) are labeled

Figure 3: Loci contributing to the genetic correlation of AD with diabetes-related metabolic traits by local analysis of variant association (LAVA). Both positive and negative local genetic correlations were observed, indicating region-specific shared genetic influences between AD and metabolic traits.

Figure 4: Identification of genome-wide significant shared genes between AD and diabetes-related metabolic traits through gene overlap analysis.

Figure 5: Pathway enrichment network of shared genes between AD and diabetes-related metabolic traits. Major clusters correspond to lipid metabolism/lipoprotein particle pathways and MHC class II antigen presentation, highlighting interactions between metabolic and immune processes

Conclusion

- No evidence** for a causal relationship between AD and metabolic traits.
- Significant shared genetic** architecture was observed between AD and glucose-, insulin-, and HbA1c-related traits.
- Genome-wide significant shared genes suggest **common biological pathways**.
- Pathway enrichment implicated lipid metabolism and immune signalling/antigen presentation as key shared mechanisms.

Future Directions

- Validate findings in larger, independent cohorts.
- Explore functional and cell-specific mechanisms.
- Assess biomarkers for diagnostic and therapeutic potential.

References

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Acknowledgement

ECU Centre for Precision Health Strategic Research Centre
Australian Government Department of Education and Training
Curtin University Curtin Medical School
Collaborative Genomics and Translation Group (ECU)
Participants and Researchers of the Genome Wide Association Studies
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