Supplementary Material

Aβ-dependent and independent genetic pathways regulating CSF tau biomarkers in Alzheimer's disease

Atul Kumar, PhD[1]; Shorena Janelidze[1]; Erik Stomrud, MD, PhD[1, 2]; Sebastian Palmqvist, MD, PhD[1, 2]; Oskar Hansson, MD, PhD[1, 2, #]; Niklas Mattsson-Carlgren, MD, PhD[1, 3, 4, #]

[1]Clinical Memory Research Unit, Department of Clinical Sciences, Lund University, Malmö, Sweden

[2]Memory Clinic, Skåne University Hospital, Malmö, Sweden

[3]Department of Neurology, Skåne University Hospital, Lund, Sweden

[4]Wallenberg Centre for Molecular Medicine, Lund University, Lund, Sweden

Shared Senior Authors

Email Addresses

Atul Kumar: atul.kumar@med.lu.se

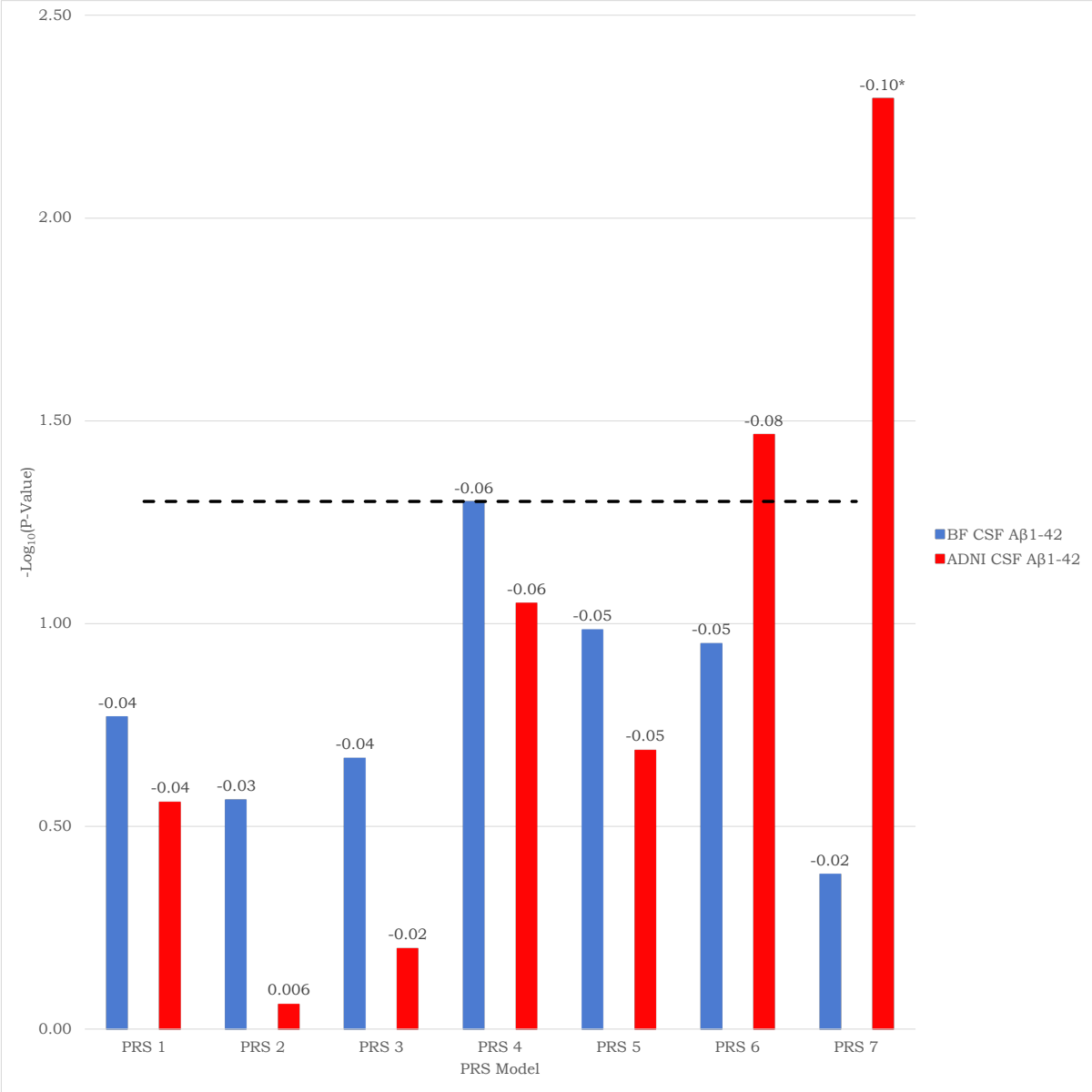
Shorena Janelidze: shorena.janelidze@med.lu.se

Sebastian Palmqvist: sebastian.palmqvist@med.lu.se

Erik Stomrud: erik.stomrud@med.lu.se

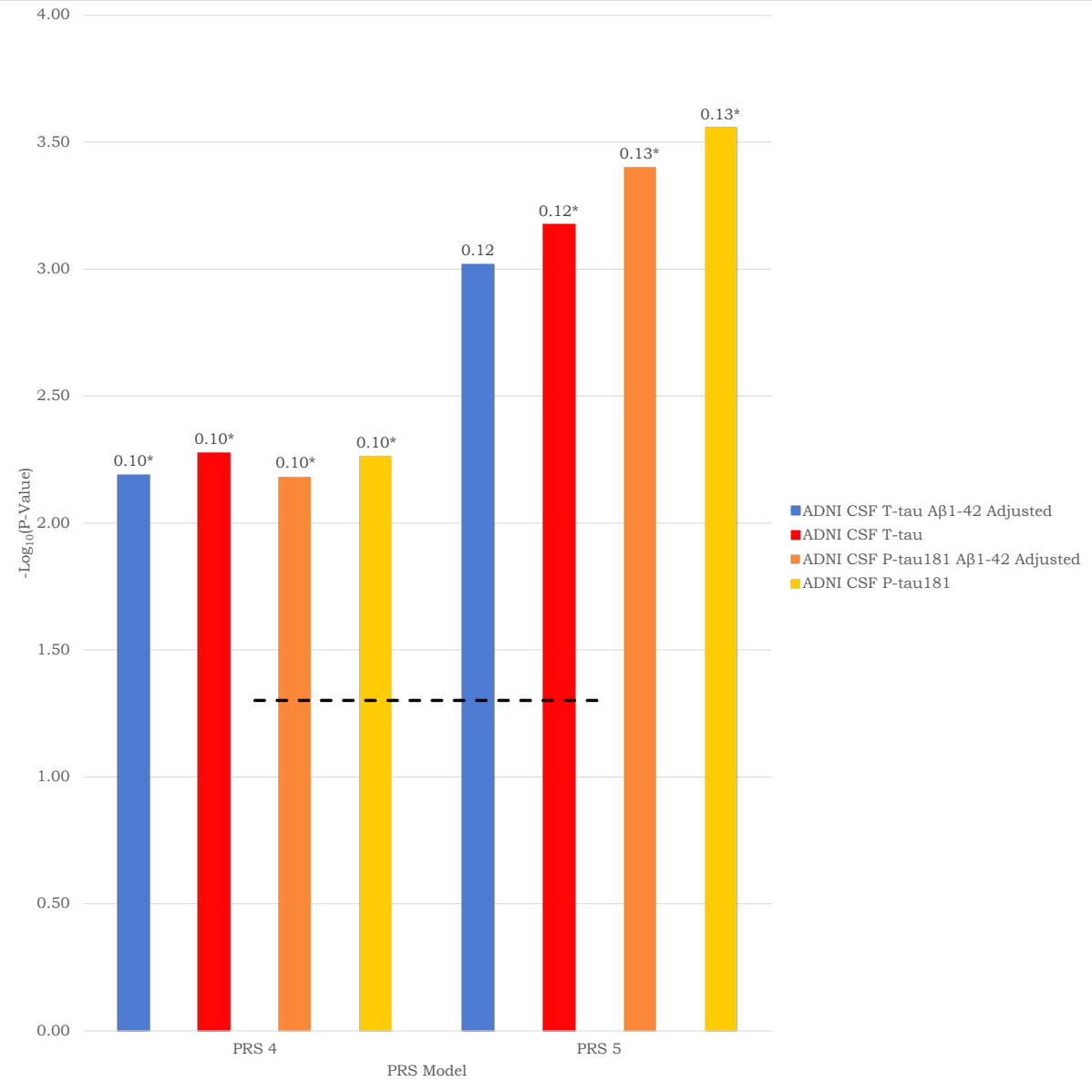
Oskar Hansson: oskar.hansson@med.lu.se

Niklas Mattsson-Carlgren: niklas.mattsson-carlgren@med.lu.se

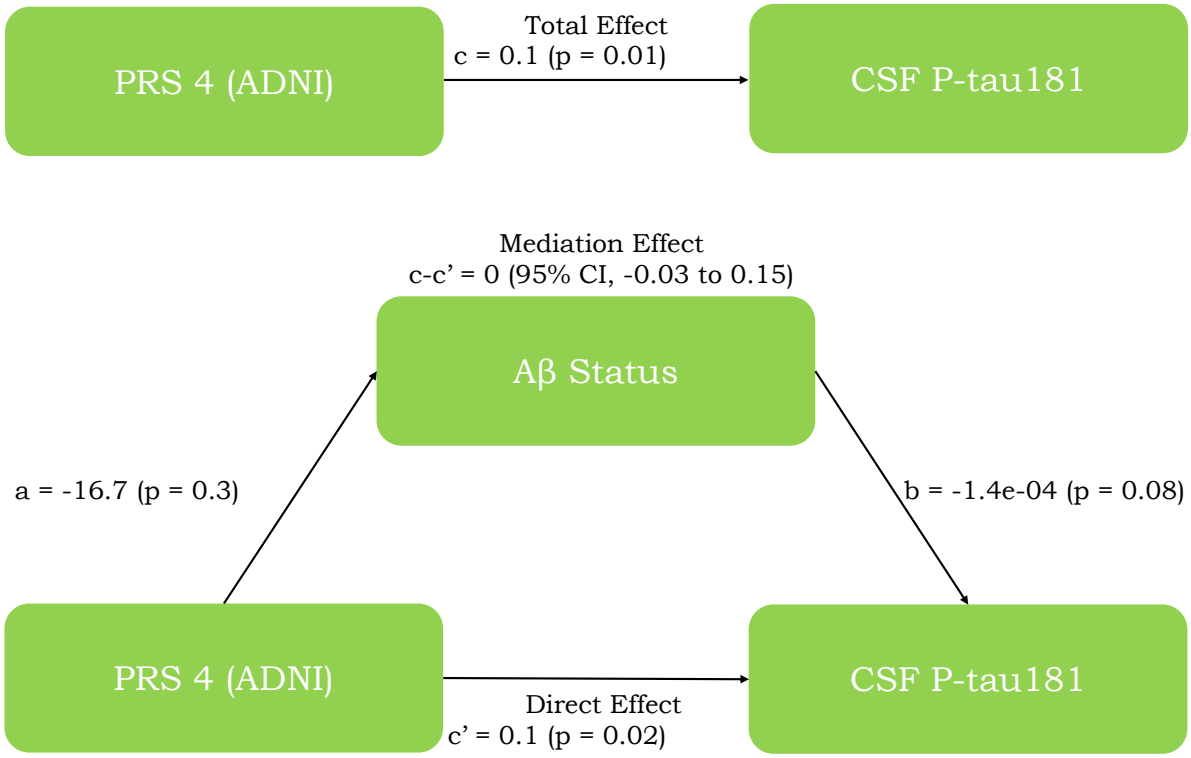


eFigure 1. Comparative results for associations between Polygenic Risk Scores (PRS) and CSF Aβ1-42 in BioFINDER (BF) and ADNI. The x-axis represents the 7 different PRS models at different p-value thresholds based on the GWAS summary statistics (PRS1 ≤ 0.05, PRS2 ≤ 5e-3, PRS3 ≤ 5e-4, PRS4 ≤ 5e-5, PRS5 ≤ 5e-6, PRS6 ≤ 5e-7, PRS7 ≤ 5e-8). The models were adjusted for age, gender, education, baseline MMSE, *APOE* ε2 and ε4 count, and the top 10 principal components (PC) from the principal component

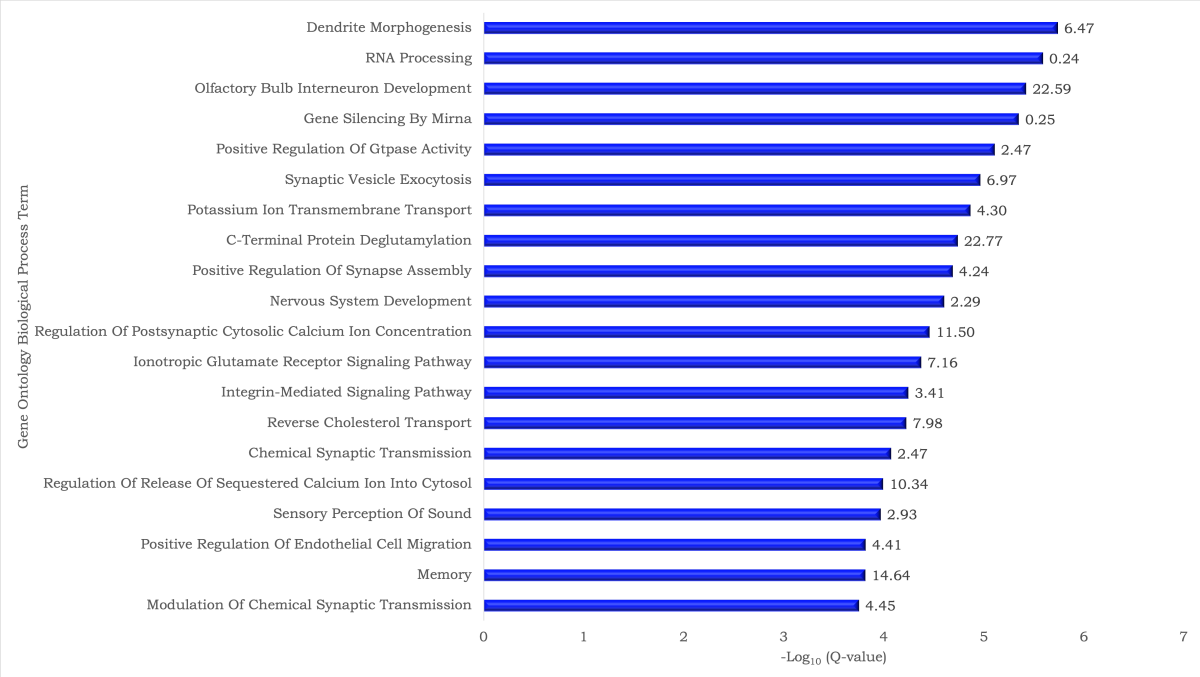
analysis (PCA) on the entire set of genotype data. The y-axis shows the negative log of the p-value for the significance of associations between PRS models with different tau measures. The values on the top of each bar show the association's effect size (beta-coefficient). The horizontal dotted line shows the p-value threshold of 0.05. *These PRSs were significant after Bonferroni-correction at p-value < 0.05.



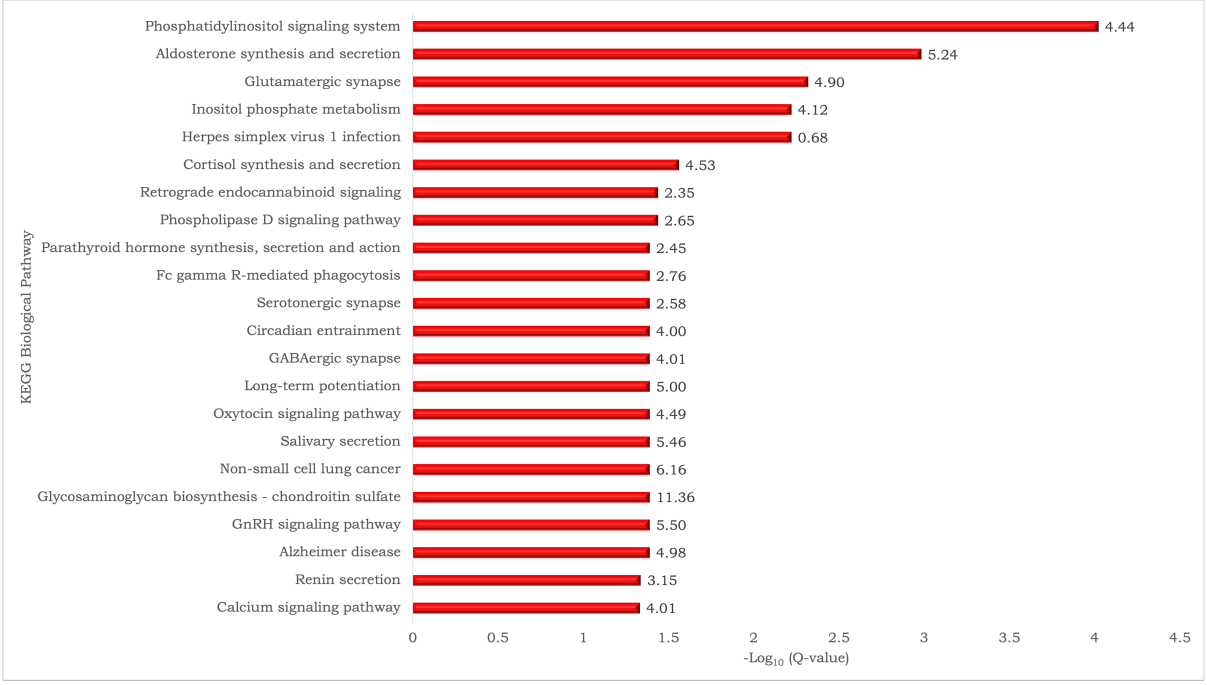
eFigure 2. Associations between significant Polygenic Risk Scores (PRS) and tau measures adjusted for CSF Aβ1-42 in ADNI. The x-axis shows the different PRS models (this analysis only included models that were significantly associated with tau measures when not adjusted for CSF Aβ1-42). The models were adjusted for age, gender, education, baseline MMSE (not for the intercept), *APOE* ε2 and ε4 count, and the top 10 principal components (PC) from the principal component analysis (PCA) on the entire set of genotype data, as well as CSF Aβ1-42). The y-axis shows the negative log of the p-value for the significance of associations between PRS models with different tau measures. The values on the top of each bar indicate the association's effect size (beta-coefficient). The horizontal dotted line shows the p-value threshold of 0.05. *These PRSs were significant after adjusted for CSF Aβ1-42 and Bonferroni-correction at p-value < 0.05.



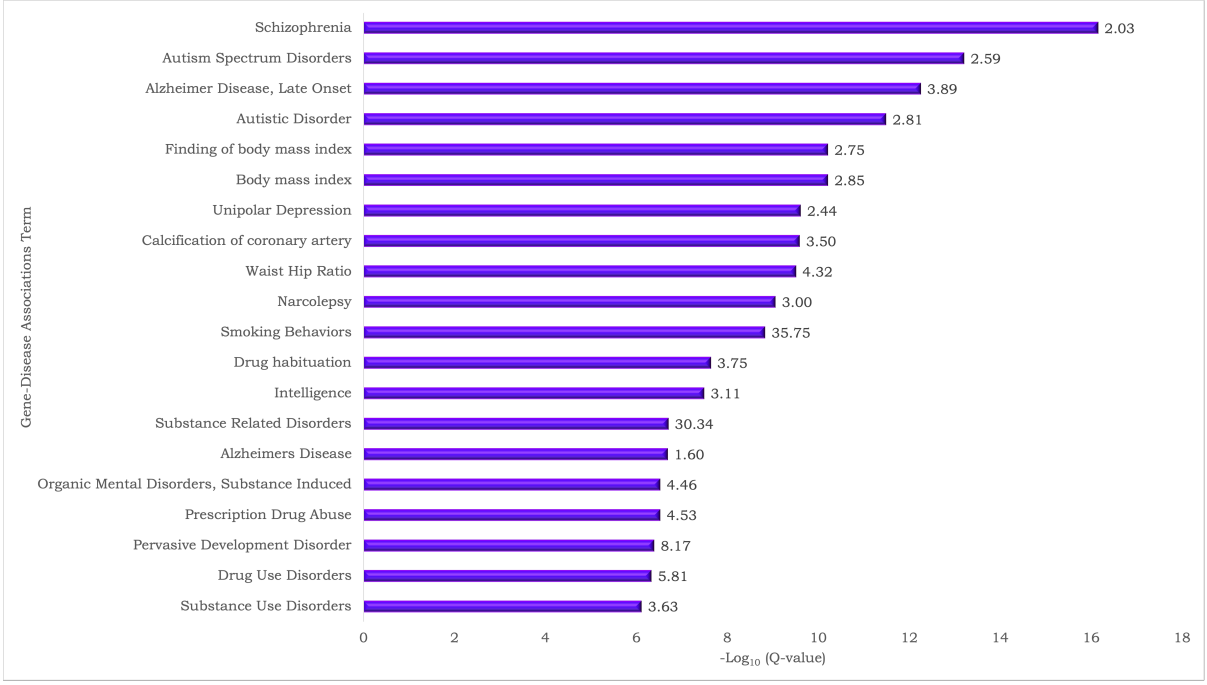
eFigure 3: Mediation analysis between PRS, Aβ status and CSF P-tau181. Mediation analysis with PRS4 as a predictor of CSF P-tau181, mediated by Aβ status. The figure includes the following standardized regression coefficients: a, the effect of PRS on Aβ; b, the effect of Aβ on CSF P-tau181 level; c, the direct association between PRS and CSF P-tau181 level; c', the association between PRS and CSF P-tau181 level when adjusting for Aβ; and c-c', the mediated effect on CSF P-tau181 level.



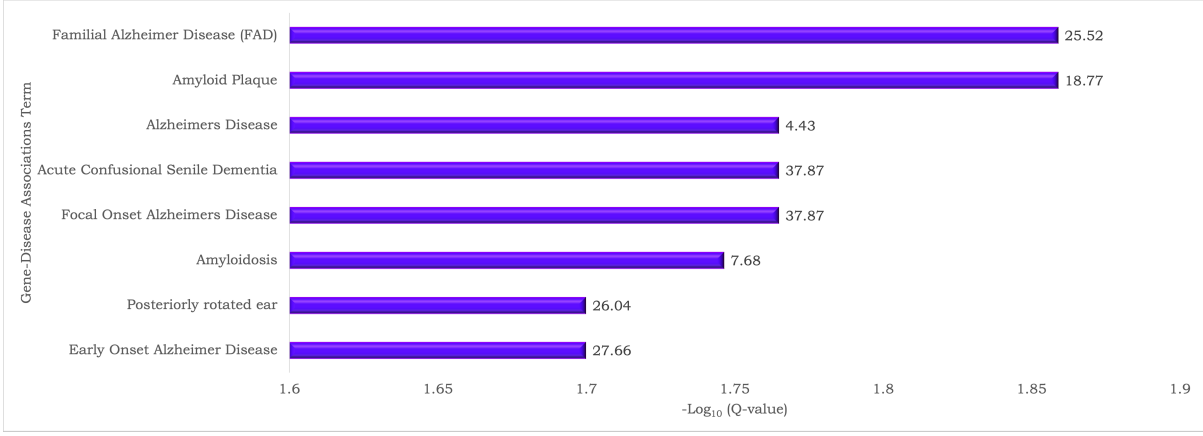
eFigure 4: Functional Enrichment analysis for the genes carrying the variants used for calculating PRS2. Genes enriched for Gene Ontology (GO) Biological Process (BP) terms: The x-axis represents the significance of enrichment (Negative log of corrected p-value) for the gene set involved in each category term. The y-axis shows the respective category terms. The Enrichment factor for each enriched term is marked corresponding to each bar.



eFigure 5: Functional Enrichment analysis for the genes carrying the variants used for calculating PRS2. Genes enriched for KEGG pathway terms: The x-axis represents the significance of enrichment (Negative log of corrected p-value) for the gene set involved in each category term. The y-axis shows the respective category terms. The Enrichment factor for each enriched term is marked corresponding to each bar.



eFigure 6: Functional Enrichment analysis for the genes carrying the variants used for calculating PRS2. Genes enriched for the gene-disease association: The x-axis represents the significance of enrichment (Negative log of corrected p-value) for the gene set involved in each category term. The y-axis shows the respective category terms. The Enrichment factor for each enriched term is marked corresponding to each bar.



eFigure 7: Functional Enrichment analysis for the genes carrying the variants used for calculating the Aβ-dependent PRS (PRS2-R-Incl-19).

Genes enriched for the gene-disease association. The x-axis represents the significance of enrichment (Negative log of corrected p-value) for gene set involved in category term. The y-axis shows the category terms. The Enrichment factor for each enriched term is marked corresponding to each bar.