

## GENETICS

# Polygenic risk scores modify the association between amyloid and tau PET accumulation in patients with Alzheimer's disease

Carolina Valentim<sup>1</sup> | Jannis Denecke<sup>1</sup> | Simon Frerich<sup>1</sup> | Rainer Malik<sup>1</sup> |  
Nicolai Franzmeier<sup>1,2,3</sup> | Michael Ewers<sup>1,4</sup>

<sup>1</sup>Institute for Stroke and Dementia Research (ISD), LMU University Hospital, LMU Munich, Munich, Germany

<sup>2</sup>University of Gothenburg, The Sahlgrenska Academy, Institute of Neuroscience and Physiology, Psychiatry and Neurochemistry, Gothenburg, Sweden

<sup>3</sup>Munich Cluster for Systems Neurology (SyNergy), Munich, Bavaria, Germany

<sup>4</sup>German Center for Neurodegenerative Diseases (DZNE), Munich, Bavaria, Germany

**Correspondence**

Carolina Valentim, Institute for Stroke and Dementia Research (ISD), LMU University Hospital, LMU Munich, Munich, Germany.  
Email:  
[carolina.valentim@med.uni-muenchen.de](mailto:carolina.valentim@med.uni-muenchen.de)

**Abstract**

**Background:** Genome-wide association studies (GWAS) have identified a larger number of genetic variants that are associated with increased risk of AD dementia. The biological pathways that underlie the link between SNPs and the development of core AD pathologies remain however unclear. Here, we generated pathway-specific polygenic risk scores to test their modulating effect on the association between amyloid-beta ( $A\beta$ ) chronicity and tau deposition in patients with AD.

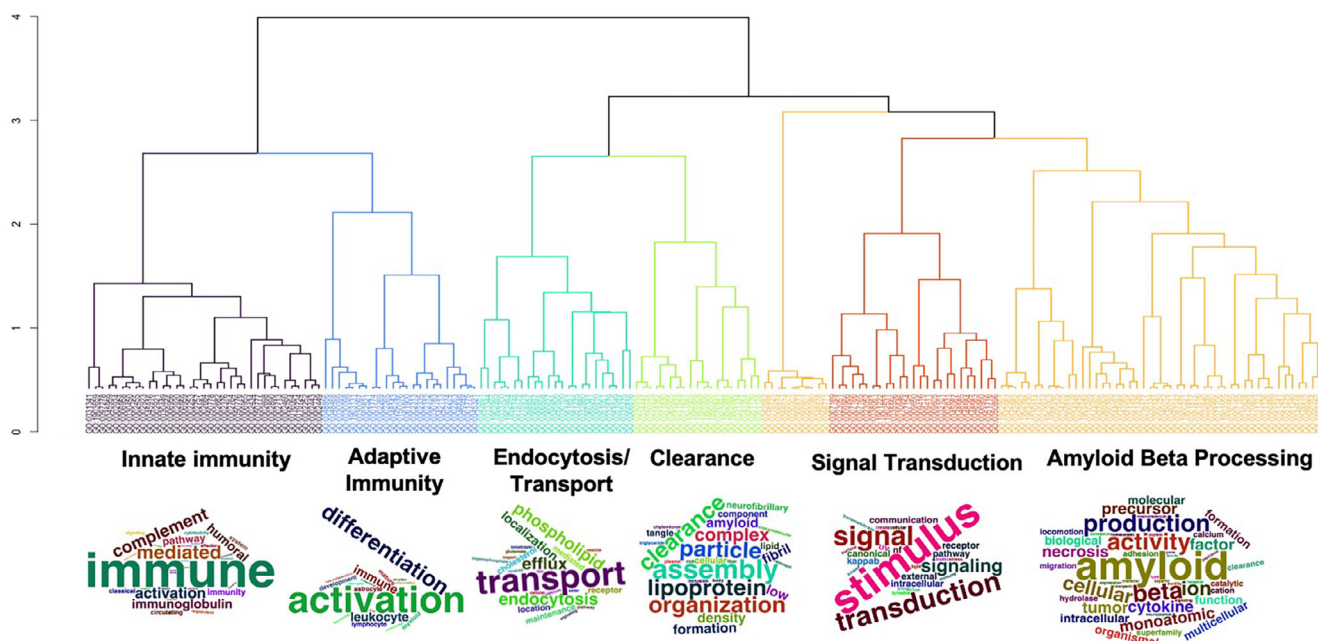
**Method:** We analysed 295 amyloid-PET-positive participants from ADNI (mean age  $76.5 \pm 7.6$ ; 165 CU, 85 MCI, 45 Dementia) with cross-sectional genetic, cognitive, and tau-PET (AV1451) and  $A\beta$ -PET (Florbetapir and Florbetaben) data. We identified in a meta-analysis of recent genome-wide association studies (GWAS) 388 independent SNPs associated with AD. We computed six pathway-specific PRS based on gene set enrichment analysis identifying the pathways implicating amyloid beta, immune activation, endocytosis/transport, clearance and signal transduction (Figure 1).  $A\beta$ -chronicity was estimated using the Sampled Iterative Local Approximation (SILA) technique (Betthausen et al., 2022), which infers the temporal trajectory and extent of amyloid accumulation by aligning PET-derived amyloid burden across longitudinal data points. Robust linear regression (Huber method) models assessed interactions between SILA-derived  $A\beta$ -chronicity and tau-PET uptake in Braak-stage ROIs (I, III-IV, and V-VI), controlling APOE- $\epsilon 4$  status, age, sex and education. Outliers were defined as three standard deviations from the mean.

**Result:** Significant interactions between  $A\beta$ -chronicity and pathway-PRS for amyloid beta and endocytosis/transport were observed, with higher genetic risk amplifying the association between longer amyloid exposure and tau accumulation in Braak-stage ROIs III-IV & V-VI ( $p < 0.03$ ). Effects remained significant after the removal of predefined outliers ( $p < 0.02$ ).

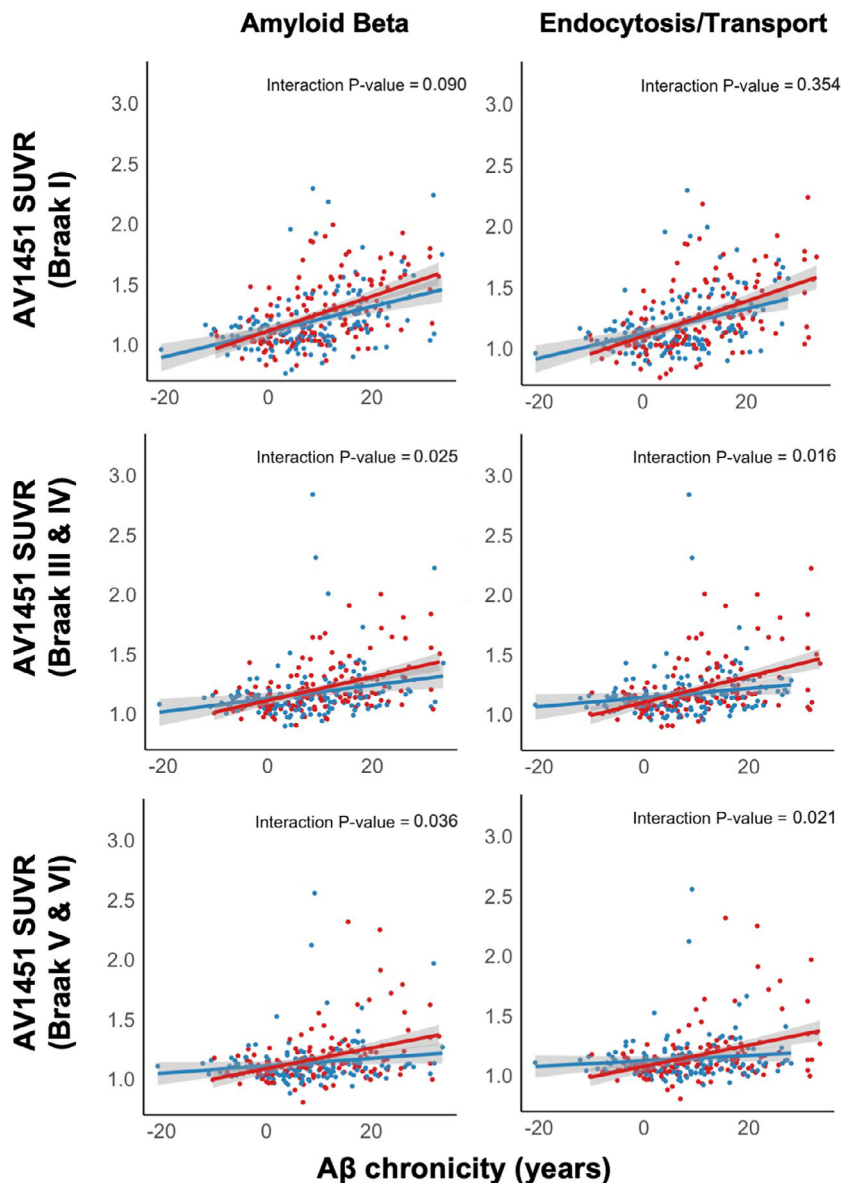
This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2025 The Alzheimer's Association. *Alzheimer's & Dementia* published by Wiley Periodicals LLC on behalf of Alzheimer's Association.

**Conclusion:** Our findings indicate that genetic variations, particularly within the amyloid-beta and endocytosis/transport pathways, strengthen the association between longer amyloid exposure and increased tau pathology. The significance of the amyloid-beta pathway suggests a direct genetic contribution to amyloid-driven tau accumulation, whereas the endocytosis/transport pathway findings support the hypothesis that amyloid-tau interactions at the synaptic level drive AD progression. These results align with prior evidence on mechanistic links between amyloid and tau pathology in AD.



**Figure 1.** Results from the hierarchical clustering, which grouped pathways into biologically relevant clusters based on gene-to-pathway mapping. Word clouds visualize the most frequent terms from the pathway descriptions within each cluster, using the method described by Tesi et al. (2021) and Lorenzini et al. (2024).



**Figure 2.** Interaction of both amyloid-beta and the endocytosis/transport pathway-PRSs and SILA-estimated Aβ chronicity across Braak regions. Scatter plots illustrate the relationship between Aβ chronicity (x-axis, estimated in years) and tau deposition (y-axis, AV1451 SUVR) in Braak regions I, III-IV, and V-VI. Data points are colored based on PRS median split (red: high PRS, blue: low PRS). Regression lines indicate the association between Aβ chronicity and tau deposition for each PRS group.