

# Clonal Hematopoiesis Shapes Alzheimer's Disease Trajectory

Evidence for cognitive resilience and reduced neurodegeneration in the DELCODE cohort

Nicoleta Carmen Cosma<sup>1,2</sup>, Klara Kopp<sup>4</sup>, Patricia Silva<sup>4</sup>, Raphael Habesreiter<sup>4</sup>, Hannah Andrea Leptin<sup>4</sup>, DELCODE-Study Group, Oliver Peters<sup>1,3</sup>, Julian Hellmann-Regen<sup>1,3</sup>, Frederik Damm<sup>4</sup>

1 Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt Universität zu Berlin, Department of Psychiatry and Neurosciences, Berlin, Germany  
2 Berlin Institute of Health at Charité - Universitätsmedizin Berlin, BIH Biomedical Innovation Academy, BIH Charité Clinician Scientist Program, Berlin, Germany  
3 German Center for Neurodegenerative Diseases (DZNE) within the Helmholtz Association, Berlin, Germany  
4 Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt Universität zu Berlin, Department of Hematology, Oncology, and Cancer Immunology, Berlin, Germany

## Background and Objectives

Clonal hematopoiesis of indeterminate potential (CHIP) is characterized by the acquisition of somatic mutations in hematopoietic stem cells that confer clonal expansion in otherwise healthy individuals and are associated with myeloid malignancies (1). Unexpectedly, CHIP has been associated with a reduced risk of Alzheimer's disease (AD) (2,3). However, the mechanisms underlying this apparent protective effect remain largely unknown, as the influence of CHIP on longitudinal cognitive trajectories and neurodegenerative progression has not been systematically investigated in a deeply phenotyped prospective cohort. Here, we examined the prevalence, molecular landscape, clinical relevance, and biomarker correlates of CHIP in AD within the prospective German Center for Neurodegenerative Diseases (DZNE) Longitudinal Cognitive Impairment and Dementia (DELCODE) cohort (4). DELCODE is enriched for individuals with subjective cognitive decline (SCD) recruited from memory clinics, representing a population at increased risk of preclinical AD, and provides comprehensive biomarker and longitudinal cognitive data with up to 8 years of follow-up.

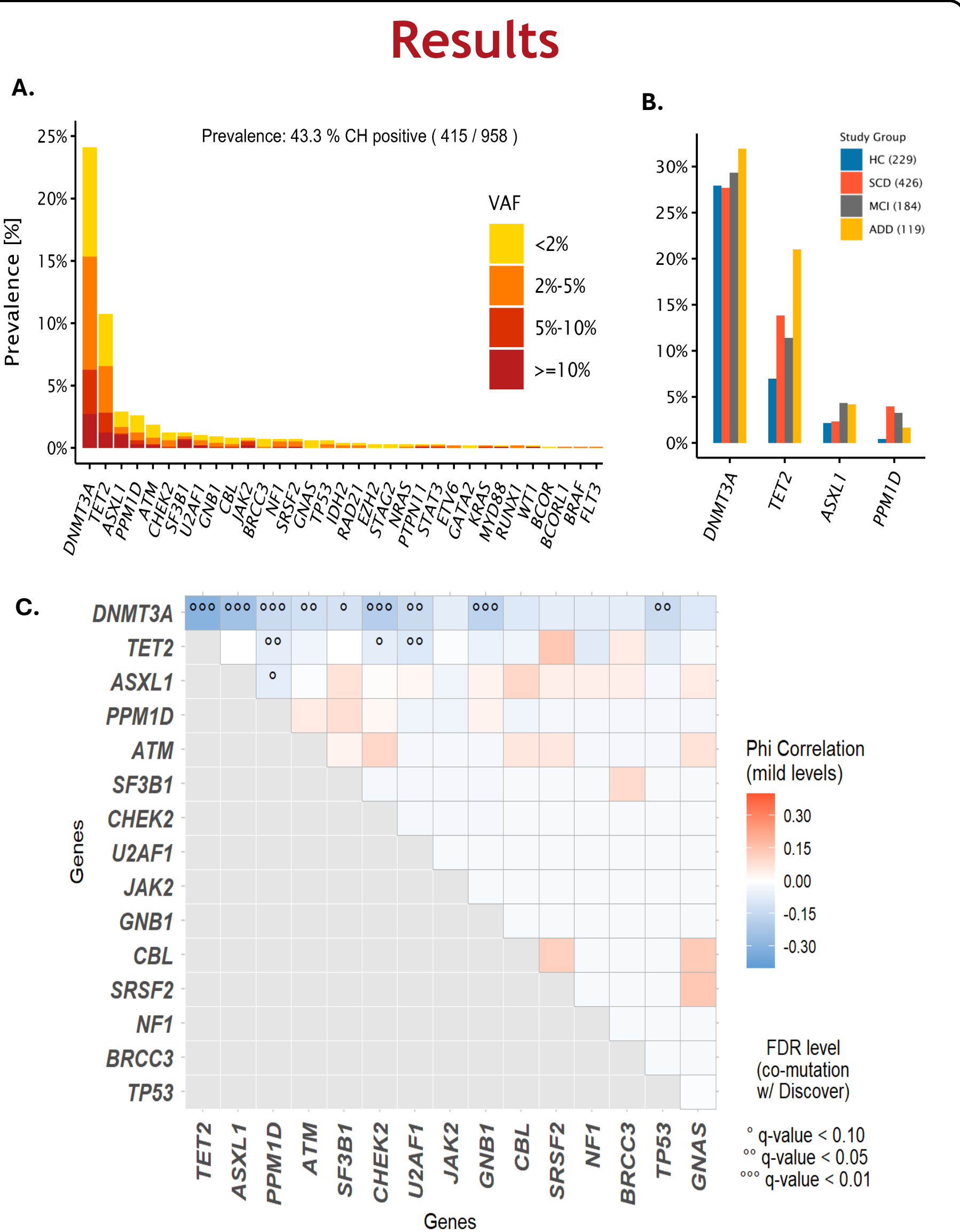
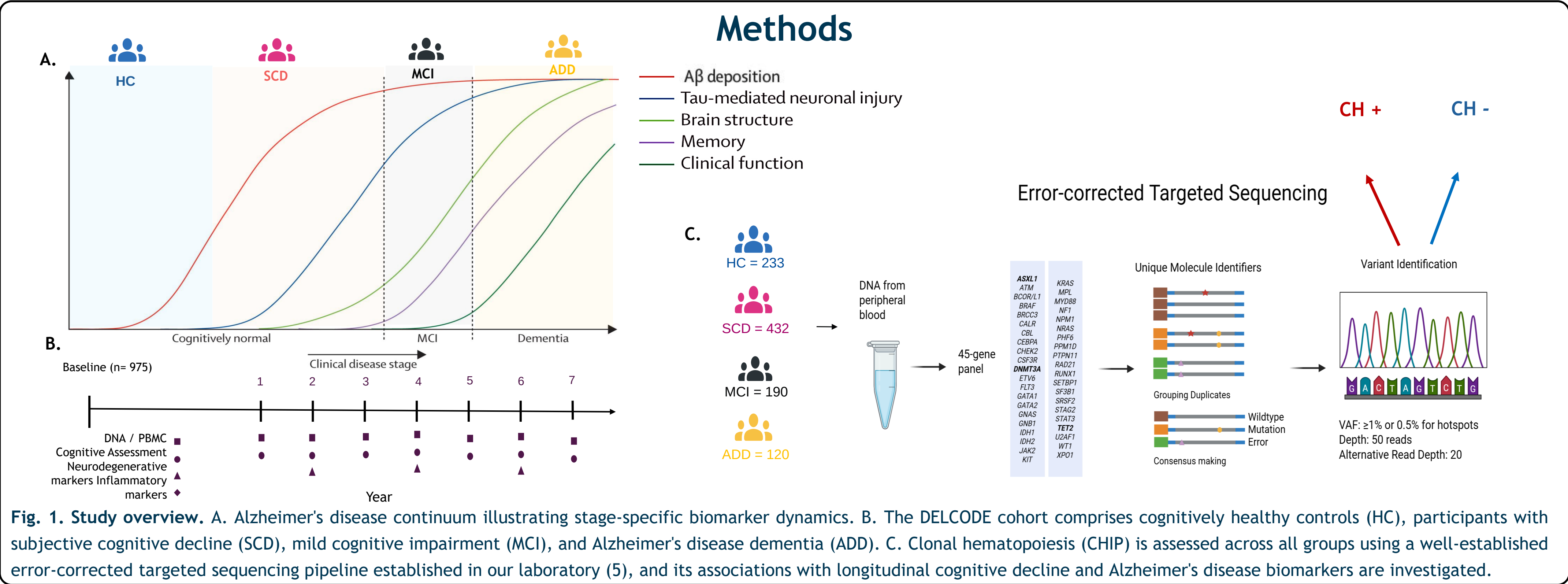


Fig. 2. A. Gene-specific prevalence of clonal hematopoiesis (CHIP)-associated somatic mutations in the DELCODE cohort. B. Gene-specific distribution of CHIP clone size across diagnostic groups. C. Co-occurrence matrix of CHIP mutations.

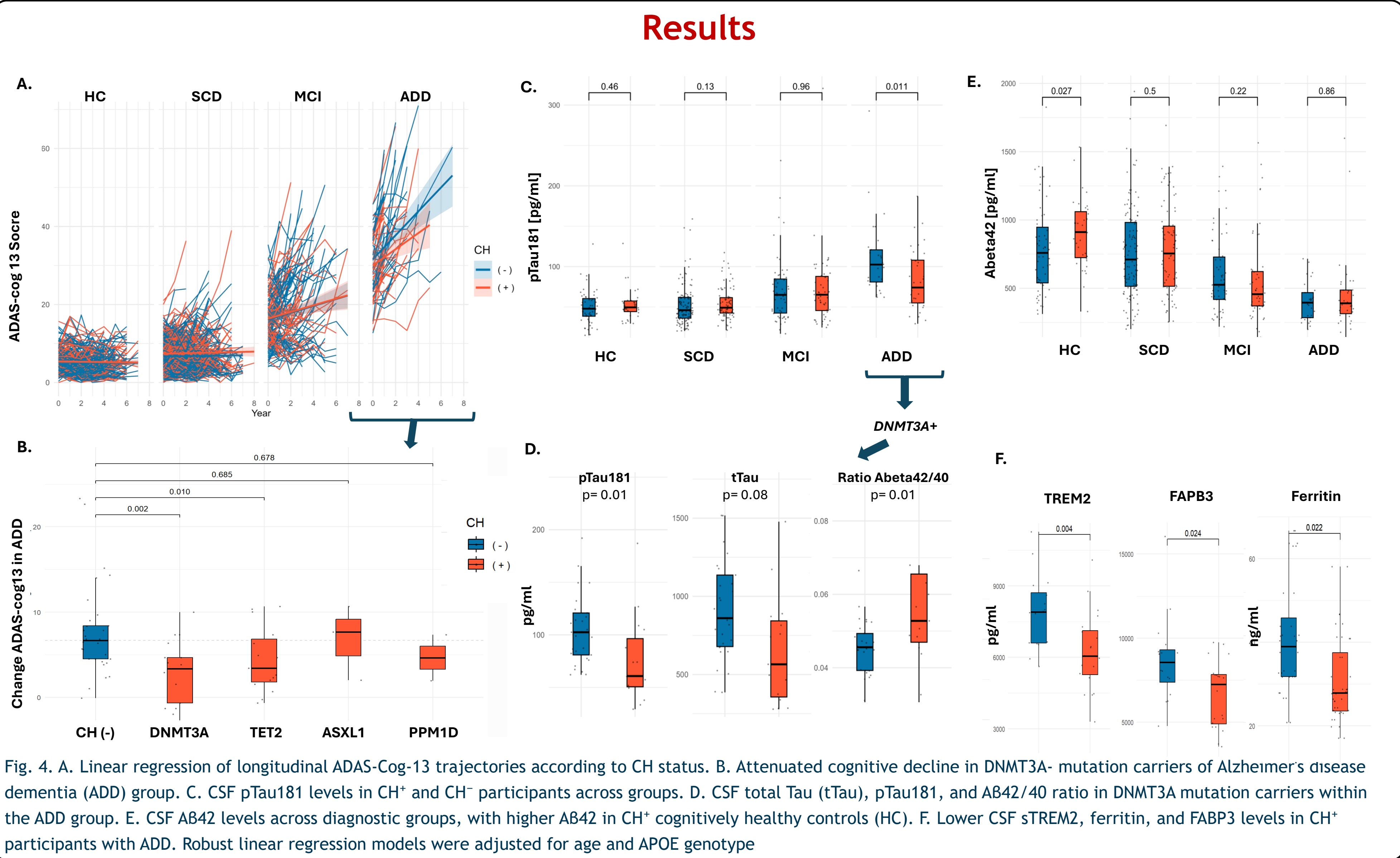


Fig. 4. A. Linear regression of longitudinal ADAS-Cog-13 trajectories according to CH status. B. Attenuated cognitive decline in DNMT3A- mutation carriers of Alzheimer's disease dementia (ADD) group. C. CSF pTau181 levels in CH+ and CH- participants across groups. D. CSF total Tau (tTau), pTau181, and Aβ42/40 ratio in DNMT3A mutation carriers within the ADD group. E. CSF Aβ42 levels across diagnostic groups, with higher Aβ42 in CH+ cognitively healthy controls (HC). F. Lower CSF sTREM2, ferritin, and FAPB3 levels in CH+ participants with ADD. Robust linear regression models were adjusted for age and APOE genotype

## Conclusions

Clonal hematopoiesis (CH), particularly DNMT3A mutations, is associated with attenuated cognitive decline and reduced AD-related neurodegeneration. Gene-specific and clonal burden-dependent effects, together with lower CSF markers of microglial activation and tau pathology in CH+ individuals, support immune modulation as a potential mechanism underlying cognitive resilience. These findings identify CH as a novel modifier of AD progression, linking somatic hematopoietic mutations to neurodegeneration and highlighting the innate immune system as a promising target for biomarker development and future immunomodulatory therapies.

## References

1. Jaiswal S. et al. Blood. 2020;136(14):1606-14.
2. Bouzid H. et al. Nat Med. 2023 Jul;29(7):1662-1670.
3. Matatall KA et al. Cell Stem Cell. 2025 Jun
4. Jessen F. et al. Alzheimers Res Ther. 2018;10(1):15.
5. Arends CM, et. Al. Blood. 2023; 141 (7): 787-799.

Contact:  
Nicoleta Carmen Cosma  
nicoleta-carmen.cosma@charite.de