

Clonal Hematopoiesis of Indeterminate Potential Is Preferentially Associated with Inflammatory Pathology in Alzheimer's Disease

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Clonal hematopoiesis is selectively associated with inflammatory, but not amyloid- or tau-related, Alzheimer’s disease pathological components. Distinct CHIP mutations show different associations with specific inflammatory profiles, highlighting mutation-specific heterogeneity in AD pathogenesis.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
Clonal hematopoiesis of indeterminate potential (CHIP) has been implicated in Alzheimer's disease (AD). AD includes multiple pathological processes: beta-amyloid and tau pathology, inflammation, and neuronal injury. Whether CHIP and specific CHIP mutations are differentially associated with distinct AD pathological components remains unclear.	Exposures: CHIP overall and mutation-specific subtypes (DNMT3A, TET2, ASXL1, JAK2). Outcomes: five AD-related pathological principal components representing distinct neuropathological profiles. CHIP instruments: GWAS of European ancestry, N = 628,388 [1], P < 5e-8 and LD r2 < 0.001 within 10,000 kb. AD pathological PCs: EMIF-AD and ADNI multicenter cohorts [2]. Primary estimator: IVW; sensitivity analyses assessed pleiotropy and heterogeneity.	CHIP and specific mutation subtypes showed selective associations with inflammation-related AD pathological components. Specifically, CHIP with JAK2 mutation were primarily associated with the neuronal injury-inflammation (PC3) in AD (β=-0.167, P=0.004). In contrast, DNMT3A mutation was mainly associated with the non-AD inflammation (PC4) (β=-0.254, P=0.002).	Our findings indicate that CHIP is selectively associated with inflammatory, but not other, Alzheimer’s disease pathological components, with mutation-specific heterogeneity.	1. Kessler, M.D., et al., Common and rare variant associations with clonal haematopoiesis phenotypes. Nature, 2022. 612(7939): p. 301-309. 2. Neumann, A., et al., Multivariate GWAS of Alzheimer's disease CSF biomarker profiles implies GRIN2D in synaptic functioning. Genome Med, 2023. 15(1): p. 79. CONTACT  Xingzhi Guo, MD, PhD Department of Geriatric Neurology Shaanxi Provincial People's Hospital No. 256, Youyi West Road Xi'an 710068, China Tel. +86 2985251331 guo.heinz@spph-sx.ac.cn ALZHEIMER'S ASSOCIATION AAIC 26