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POSTER

503. CLONAL HEMATOPOIESIS, AGING, AND INFLAMMATION

Clonal hematopoiesis is associated with the risk of Alzheimer's disease in the UK biobank apoe ε3/ε3 genotype cohort

Burcu Cevik[1,2], *Meram Saka*[3], *Atilla Elhan*[4], *Isinsu Kuzu*[2]

[1] Biotechnology Institute, Ankara University, Ankara, Türkiye
[2] Ankara University School of Medicine, Department of Pathology, Ankara, Türkiye
[3] Ankara University School of Medicine, Department of Psychiatry, Ankara, Türkiye
[4] Ankara University School of Medicine, Department of Biostatistics, Ankara, Türkiye

Abstract The presence of a mutation with a variant allele fraction (VAF) of at least 2% in a gene associated with myeloid malignancies in blood or bone marrow cells in individuals without morphological evidence of hematological cancers is termed Clonal Hematopoiesis of Indeterminate Potential (CHIP). CHIP has been associated with hematologic malignancies, cardiovascular disease, severe COVID-19, gout, and several solid tumors (PMID: 39196204). Previous studies examining the association between CHIP and Alzheimer's disease (AD), have been reported either no association or, interestingly, a potential protective effect of CHIP carrier status against AD (PMID: 37322115).

In this study, we investigated whether CHIP is a risk factor for AD using the UK Biobank (UKB) Whole Exome Sequencing (WES) data. Participants with hematologic malignancies, diseases of the circulatory system, and types of dementia other than AD, utilizing data from the cancer register, hospital diagnosis records, death register records, and self-reported records to prevent confounding effects were excluded from the UKB cohort. Individuals carrying the rs7412 or rs429358 APOE SNPs strongly associated with AD, were excluded. Only participants with APOE ε3/ε3 genotype and without genetic kinship to other participants in the cohort were included. Diagnosis of AD from the UKB, was identified through hospital records. The control group comprised age-and sex-matched individuals without AD, who met the same exclusion and inclusion criteria. As a result, we analyzed WES data from 521 participants (259 cases and 262 controls) with a mean age of 64.2 years. Most participants were self-reported White (93.3%); other ethnicities each comprised ≤3.5%. Variant calling on WES data was performed using NVIDIA Parabricks Mutectcaller (version 4.1.0) in tumor-only mode with default parameters within the UKB Research Analysis Platform. VCF files were annotated and filtered to include only variants in 74 genes known to be recurrent drivers in myeloid malignancies. In addition, variants with a gnomAD v4.1 allele frequency > 0.001 were excluded to filter out potential germline variants. Additional filtering was performed using quality metrics extracted from the VCF FORMAT fields to remove low-quality and potentially artifactual variants. From resulting variants, we selected those included in the published List of hematopoietic genes and variants queried (PMID: 28636844), World Health Organization (WHO) Classification (5th ed., vol. 11), or National Comprehensive Cancer Network (NCCN) Guidelines (v2.2025).

Of the 521 participants, 10.3% were identified as CHIP carriers, with the highest number of variants detected in the DNMT3A gene. Compared to controls, the AD group included a significantly higher proportion of CHIP carriers. In logistic regression analysis, CHIP was significantly associated with AD (OR: 1.83, 95% CI: 1.02–3.27, P=0.042); this association remained significant after adjusting for age, sex, smoking status, and BMI (Body Mass Index) (OR: 1.93, 95% CI: 1.06–3.49, P=0.031). However, when restricting the analysis to large clones (VAF >10%), the association was no longer significant (OR: 1.20, 95% CI: 0.54–2.67, P=0.663). As expected, CHIP presence was strongly associated with age ($P < 0.001$), while it was not associated with sex, smoking status, or BMI.

The association between CHIP and blood count parameters was also investigated, but no significant relationships were observed. In a small subgroup of the cohort with available proteomics data (N=63), levels of inflammatory markers were assessed. IL-6, IL-18, and TNF-α levels were found to be significantly higher in CHIP carriers compared to non-carriers ($p = 0.019$, $p = 0.006$, and $p = 0.029$, respectively).

In conclusion, our findings suggest that CHIP presence is associated with an increased risk of AD in individuals with the APOE ε3/ε3 genotype which is considered a neutral type for AD. As earlier studies are not all in accordance our results will add to the current evidence. The discrepancies between our findings and theirs may be attributable to differences in filtering based

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on sequencing metrics, as well as sequencing depth and population characteristics. Further studies with standardized CHIP detection methods are needed to clarify the mechanisms underlying relationship between CHIP and AD.
This research has been conducted using the UK Biobank Resource under Application Number 81793.

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