LETTER to the EDITOR

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Unraveling the Genetic Associations with Epigenetic Age Acceleration in Childhood Cancer Survivors: Insights from GWAS Studies

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Dear Editor

Epigenetic age acceleration (EAA) has gained attention in childhood cancer survivors, particularly regarding its genetic basis [1]. Research from St. Jude Children's Research Hospital has identified significant links between genetic variants and EAA in this population [2]. Variants in the SELP gene and the HLA region, associated with age-related diseases—especially since SELP is upregulated in Alzheimer's—were highlighted. Using a Genome-Wide Association Study (GWAS), researchers analyzed over 8 million genetic variants among childhood cancer survivors and compared them with community controls showing different levels of biological aging. EAA, which reflects the disparity between biological age based on DNA methylation and chronological age, indicated that certain genetic variants are strongly associated with increased EAA in survivors. This accelerated biological aging is concerning due to its correlation with a higher risk of chronic health issues later in life [3, 4].

We analyzed the associations between genetic variants and epigenetic age acceleration in childhood cancer survivors utilizing data from recent genetic studies. This research involved genetic data from large, publicly available biobanks and consortia, such as the Children's Oncology Group and the Genomics of Drug Sensitivity in Cancer project, alongside databases like dbGaP (Database of Genotypes and Phenotypes), EMBL-EBI (European Molecular Biology Laboratory - European Bioinformatics Institute), GEO (Gene Expression Omnibus), GTEx (Genotype-Tissue Expression project), SNPedia, ClinVar, CANCER-GENOME-ATLAS (TCGA), and EGA (European Genome-phenome Archive). Standardized assessments were conducted to evaluate the epigenetic age of childhood cancer survivors. Genome-wide genotype data were generated using Illumina SNP chips, with rigorous quality control to eliminate samples and variants with low call rates, Hardy-Weinberg equilibrium violations, or substantial missing data. SNPs associated with epigenetic age acceleration were identified through GWAS meta-analysis and confirmed in independent cohorts, with a significance threshold of $p < 5 \times 10^{-8}$ for genome-wide significance. Relevant search keywords included childhood cancer survivor's genetics, epigenetic age, GWAS epigenetic acceleration, SNPs age association, genetic predisposition epigenetic age, age acceleration factors in cancer survivors, Illumina SNP chips, GWAS meta-analysis epigenetic age, and genome-wide significance in epigenetic studies.

A pivotal study published in Genome Medicine by Dong et al. (2022) conducted GWAS to discover novel genetic loci associated with EAA in a sample of 2,640 individuals of European ancestry. Using advanced genotyping technology, the researchers assessed epigenetic status and aging traits. This study emphasizes the unique epigenetic changes and their potential long-term health implications for childhood cancer survivors. Although full summary statistics are not yet available, the findings enhance our understanding of the complex interplay between genetic factors and epigenetic modifications in this vulnerable group, potentially leading to targeted interventions to address age-related health risks [3].

The data highlight genetic variants related to EAA in childhood cancer survivors, where biological age, measured by epigenetic markers, surpasses chronological age, affecting long-term health outcomes. Two variants associated with EAA in this population were reported. The first variant, rs28366133-C, shows a significant P-value of 4×10^{-11}, indicating a strong association with increased EAA as measured by the Hannum clock. While the odds ratio (OR) is not reported, the beta value suggests a 0.78 unit increase in epigenetic age with the risk allele. The confidence interval (CI) ranges from 0.54 to 1.02, hinting at a potential protective effect of the allele, as the beta indicates a relative increase in biological age linked to adverse health effects. Similarly, the second variant, rs732314-C, has a significant P-value of 3 x 10^-11, indicating a 0.57 unit increase in epigenetic age per the Horvath clock, with a CI of [0.39-0.75] suggesting a robust association. Both variants map to genes involved in critical biological processes, with MICA-AS1 and SELP potentially influencing immunological and inflammatory responses relevant to cancer and its treatment. These genetic variants may enhance our understanding of epigenetic mechanisms in aging, particularly for childhood cancer survivors facing unique metabolic and physiological challenges.

Overall, these findings highlight the significance of genetic research in understanding epigenetic aging and its implications for health management in childhood cancer survivors. Genetic testing could identify those at higher risk for accelerated aging, guiding early interventions.

The proteins produced by the identified genes may also be targets for future therapies. Further studies are needed to explore the mechanisms behind these associations, their influence on health outcomes, and whether interventions could alleviate the effects of accelerated aging in this population.

Author Contribution Statement

Concept and design: Maryam Yazdanparast; Data analysis and interpretation: Rezvan Nezameslami. Manuscript drafting: Maryam Yazdanparast. Critical review and statistical analysis: Alireza Nezameslami, Hossein Neamatzadeh. Administrative support: Bahareh Mehdikhani. All authors approved the final manuscript.

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Declarations

Ethics approval and consent to participate: This article does not involve any studies with human participants or animals conducted by the authors; therefore, consent to participate is not applicable.

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