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Epidemiology / Risk and protective factors in MCI and dementia

Clonal Hematopoiesis of indeterminate potential and the risk of mild cognitive impairment or probable dementia in the Women's Health Initiative Memory Study

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Abstract

Background: Clonal Hematopoiesis of Indeterminate Potential (CHIP) occurs when hematopoietic stem cells in bone marrow undergo somatic mutations and yield genetically distinct leukocyte subpopulations with increased expression of inflammatory genes in innate immune cells. Genes commonly mutated in CHIP are associated with DNA methylation, inflammation, generation of reactive oxygen species, and DNA damage response. Factors associated with CHIP, including inflammation, cardiovascular disease (CVD), metabolic disorders, and stroke are risks for Alzheimer's disease and other dementias, however the association between CHIP and dementia is unknown. We examined the association between CHIP and the incidence of MCI or probable dementia over 22 years of follow-up in the Women's Health Initiative Memory Study (WHIMS). We also examined these associations by common driver mutations for CHIP.

Method: Women without a baseline (1993-1998) history of stroke, who participated in WHIMS and had baseline blood sample, were followed with annual cognitive assessments, adjudication of MCI or probable dementia, and provided self-report of dementia diagnoses for up to 22 years. CHIP was defined by whole genome sequencing through TOPMed. Proportional hazards models were used to examine survival to onset of cognitive impairment (mild cognitive impairment (MCI), probable dementia, or self-reported dementia).

Result: We classified 934 women into two groups, CHIP (11%) and no CHIP (89%). A total of 300 women developed cognitive impairment by Year 22. Survival analyses for time to cognitive impairment was adjusted for baseline age, education, 3MS score, hypertension, diabetes, and BMI. There was no difference in risk of cognitive impairment between the women with and without CHIP ($p = 0.63$). When CHIP was categorized by gene-specific driver mutations, survival free of impairment among women

with *DNMT3A* mutations was not different from those without CHIP. Risk for impairment was higher among women with *TET2* (HR 1.75, p=0.19). Overall results were not statistically significant, however power was limited by low numbers of women with CHIP (see Figure).

Conclusion: CHIP was not associated with cognitive outcomes overall but when stratified by the primary CHIP mutations (*DNMT3A* or *TET2*), different trends emerged. Future work in WHIMS will explore the cognitive performance over time by different CHIP mutations.

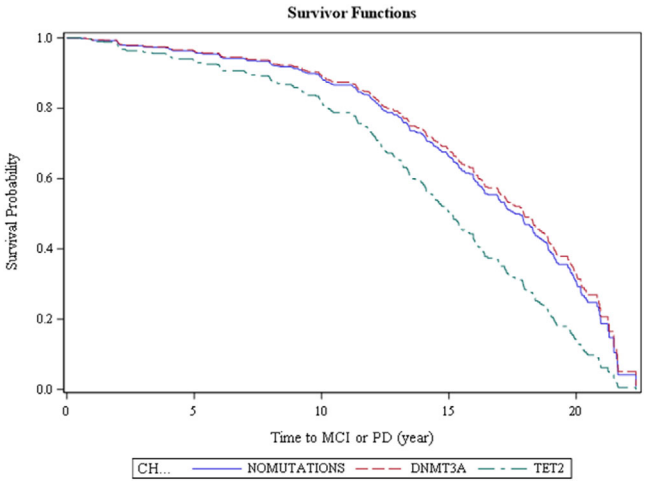

FIGURE 1