

Epigenetic age of female *BRCA1* mutation carriers appears not to be correlated with their chronological age

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The changes of epigenetic age of blood cells have previously been associated with increased cancer mortality. For instance, a study on 2 029 women from WHI cohort has shown that a one-year increase of blood epigenetic age is associated with a 5% risk of lung cancer mortality ($p = 0.031$) [1]. Also, a study on 1 863 older participants from ESTHER cohort reported that increased epigenetic age of blood cells is associated with an elevated risk of any cancer mortality (HR = 1.22 [95 % CI 1.03–1.45])[2].

We hypothesized that epigenetic age acceleration observed in blood cells may be associated with *BRCA1* epimutations and germline mutations, both of which have been shown to increase risk of breast cancer.

Our study included 93 blood samples from healthy participants: 43 women with *BRCA1* germline mutation and no epimutation, 29 women with *BRCA1* epimutation and confirmed negative for germline mutations in *BRCA1* gene and 21 controls with neither *BRCA1* mutation nor epimutation present.

DNA methylation profiling of DNA extracted from whole blood samples was performed using Infinium MethylationEPIC BeadChip (Illumina). Data analysis was conducted using R 4.2.2. (IDAT processing and BMIQ normalization – ChAMP). Epigenetic age was estimated using an online tool <https://dnamage.clockfoundation.org/> website and included calculation of five types of epigenetic clocks: Hannum [3], Horvath [4], skinBloodClock [5], PhenoAge [1] and GrimAge [6] (error – median absolute difference, years). Correlation between chronological and epigenetic age was assessed using linear regression. Epigenetic age acceleration was calculated using residuals from regressing epigenetic age on chronological age.

Every type of the epigenetic clock predicted epigenetic age that was coherent with chronological age for women with epimutation, as well as for women that did not carry neither epimutation or germline mutation. Moreover, women in those two groups, exhibited similar epigenetic age acceleration for all types of epigenetics clocks. However, in case of germline *BRCA1* mutation carriers neither of the epigenetic clocks, except of real-age-based GrimAge, was able to correctly predict chronological age.

In conclusion, our preliminary results indicate that *BRCA1* germline mutation carriers acquire genome-wide methylation changes that affect methylation levels at the loci used for calculation of the epigenetic age. The origins of this phenomenon are unknown and need further exploration. However, it is plausible that impaired *BRCA1* gene related DNA repair mechanisms contribute to this phenomenon.

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