

LETTER OPEN



NORMAL HEMATOPOIESIS

Loss of Y and clonal hematopoiesis in blood—two sides of the same coin?

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TO THE EDITOR:

Studies in recent years have revealed that increasing age is associated with the accumulation of post-zygotic genetic aberrations in different cell lineages even in the absence of active malignancy. Clonal hematopoiesis of indeterminate potential (CHIP) is defined as the detection of somatic mutations in genes commonly associated with myeloid neoplasms in the peripheral blood of individuals with no sign of hematological malignancy. The process of CHIP derives from ageing hematopoietic stem cells that have accumulated mutations, rendering proliferative advantage compared with their peers, resulting in clonal expansion [1, 2]. CHIP is an age-related phenomenon, regularly observed in healthy older individuals at frequencies up to 10% at age 70 years. CHIP has been associated with increased risk of hematological malignancies as well as cardiovascular diseases [1–3].

In parallel, peripheral leukocytes often show mosaic loss of chromosome Y (LOY) in ageing men [4], detectable in more than 40% of the men above the age of 70 years, in the UK Biobank [5]. Mosaic LOY manifests as a fraction of an individual's leukocytes lacking the Y chromosome. In longitudinal studies, LOY typically increases in frequency over time, comparably to the process of clonal hematopoiesis [6]. Remarkably, recent single-cell analyses of leukocytes from men diagnosed with Alzheimer's disease (median age 80 years) identified leukocytes with LOY in every studied subject [7]. This has established LOY as the most common post-zygotic mutation in the hematopoietic lineages of aging men. Risk factors for LOY in leukocytes include age, smoking, and germline genetic predisposition [5, 8, 9]. Leukocytes with LOY in peripheral blood are associated with increased risk for all-cause mortality [4, 9], hematological and non-hematological cancers [4, 10, 11] and other age-related disorders such as Alzheimer's disease, diabetes, and cardiovascular events [9, 12, 13].

Hence, carriers of leukocytes with post-zygotic mutations—including LOY and CHIP—display an increased risk for diseases both inside and outside of the hematopoietic system. The

mechanisms behind these associations, however, remain to be established, as does the relative contribution of these abnormalities to disease etiology [14]. Recent studies suggest that LOY in leukocytes could confer direct physiological effects through LOY-associated transcriptional effects affecting global gene expression, and acting as a biomarker of genomic instability in somatic tissue [5, 7]. Considering the similarities in age-related prevalence and disease risks conferred by LOY and CHIP, it is of considerable interest to determine whether the two phenomena co-exist or might occur in a mutually exclusive manner [15]. Of note, a recent study revealed a co-occurrence of LOY and CHIP in bone-marrow cells derived from patients referred for clinical bone-marrow evaluation [11].

To investigate whether LOY and CHIP may co-exist in peripheral blood of healthy individuals, we investigated the co-occurrence of LOY and CHIP in monocytes derived from 24 healthy men. Details on the studied cohort is provided in Supplementary Table 1. The men had no evidence of hematological disease, and the LOY-status in each sample had previously been established by SNP-array analyses of FACS isolated monocytes [7]. We sequenced monocyte-derived DNA collected from men with high or undetectable levels of LOY, using a TruSight sequencing panel targeting 54 genes often mutated in myeloid neoplasms (Supplementary Table 2). Two samples (one with LOY and one without) were excluded from final analysis after standard QC filtering of the sequencing data. The level of LOY mosaicism and CHIP mutations detected in the 22 age-matched samples are illustrated in Fig. 1 (e.g. 12 samples with LOY; median age = 83, range = 65–94 and 10 without evidence of LOY; median age = 83, range = 68–94). Pathogenic CHIP variants were detected in the following genes: *TET2* ($n = 5$), *DNMT3A* ($n = 4$), *SF3B1* ($n = 2$), *ASXL1* ($n = 1$), *TP53* ($n = 1$), with a median variant allele frequency (VAF) of 20.74% (range 4.3–55.4%). The gene panel also detected a set of CHIP variants classified as variants of uncertain significance, which consisted of: *BCOR* ($n = 5$), *ZRSR2* ($n = 3$), *BCORL1* ($n = 1$), *FBXW7* ($n = 1$), *FLT3* ($n = 1$), *GATA2* ($n = 1$),

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AUTHOR CONTRIBUTIONS

VJ, JM, PL, LC, JPD, PB, and LAF conceived the study; LC, JPD, PB, and LAF obtained the funding; TP, HD, ER-B, and MD performed the experiments; VJ, JM, JH, TP, MD, JPD, PB, and LAF analyzed the data; HD, ER-B, JPD, and LAF contributed to sample collection; VJ, JM, PB, and LAF wrote the first draft of the paper; all authors contributed to the final version of the paper.

COMPETING INTERESTS

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ADDITIONAL INFORMATION

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