

## Chromosome Y loss and drivers of clonal hematopoiesis in myelodysplastic syndrome

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doi:10.3324/haematol.2020.266601

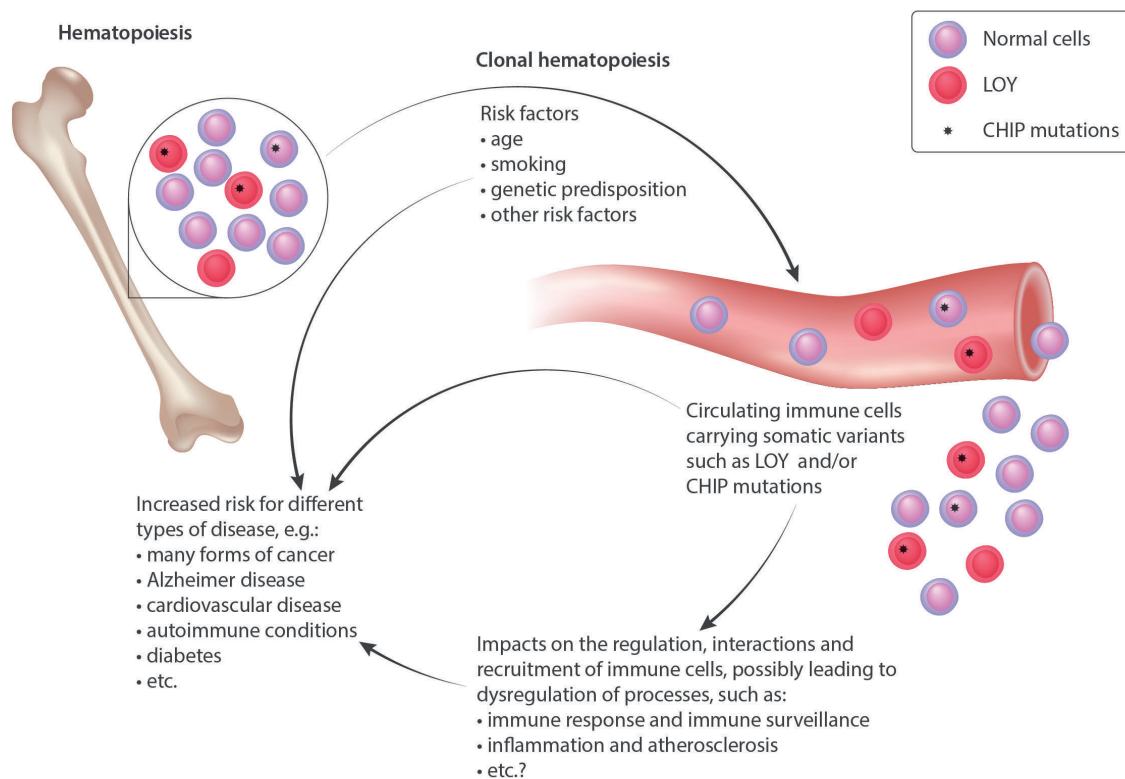
In the current issue of *Haematologica*, Ouseph *et al.*<sup>1</sup> present new results on the relation between somatic Y chromosome loss and hematologic malignancies. Mosaic loss of chromosome Y (LOY) refers to chromosome Y aneuploidy acquired during life and it is the most common somatic mutation in human blood cells.<sup>2,4</sup> Affected men carry cells without the entire Y chromosome in a mosaic fashion due to its loss from progenitor cells during the lifetime. Thus, in a single cell LOY is a binary event causing the absence of almost 2% of the male haploid nuclear genome and when measured in bulk blood samples, it is present as a continuous mosaicism affecting a fraction of cells. In normally aging populations, LOY is detectable in at least 10% of peripheral blood cells in about 5%, 20%, 40% and 60% of men around 50, 60, 70 and 90 years of age, respectively.<sup>4,12</sup> Furthermore, longitudinal results from subjects without known hematologic malignancy suggest that the frequency of blood cells without the Y chromosome typically increases over time.<sup>11</sup> However, profound variation in longitudinal patterns can be observed between individuals, with some subjects recovering from LOY over time.<sup>11</sup> Interestingly, longitudinal data presented by Ouseph *et al.* suggest a general increase in the frequency of LOY within subjects developing myelodysplastic syndrome (MDS).

Since a paper published in 1963,<sup>13</sup> mosaic Y chromosome loss has been recognized as a frequent event in cells of the hematopoietic system and in blood cells of aging men and it was long viewed as a neutral event. In contrast to that old paradigm, recent epidemiological results suggest the opposite, showing that men with LOY in blood have an increased risk of all-cause mortality.<sup>5,14</sup> For example, in a cohort of old men we described that men with LOY in at least 35% of peripheral blood cells at study entry survived on average only half as long as controls during the follow-up period.<sup>5</sup> During the last years, LOY in blood has been linked with an increased risk of a continuously growing list of diseases, such as various forms of hematologic and non-hematologic cancer,<sup>1,5,7,15-18</sup> Alzheimer disease,<sup>6</sup> autoimmune conditions,<sup>19,20</sup> cardiovascular diseases,<sup>14,21</sup> schizophrenia,<sup>22</sup> diabetes<sup>14</sup> and age-related macular degeneration.<sup>10</sup> Although LOY is more common in the elderly, it is detectable in younger subjects<sup>4,9</sup> and associations with outcomes such as testicular germ cell tumors<sup>17</sup> and age-related macular degeneration<sup>10</sup> have been reported also in younger men. Of note, epidemiological and clinical data suggest that, on average, men with COVID-19 have more severe symptoms and higher rates of death than women with this disease. However, the impact of LOY in males vulnerable to the Sars-Cov-2 virus and other infectious diseases is largely unknown. As further discussed by Ouseph *et al.*,<sup>1</sup> the role of LOY in hematologic

malignancies has been elusive. However, in their study they showed that LOY in at least 75% of metaphases in bone marrow samples from a cohort of clinically defined patients was associated with incident as well as prospective diagnoses of myelodysplastic syndrome (MDS). Furthermore, they also describe new results showing that patients with  $\geq 75\%$  LOY had a high prevalence of somatic mutations in genes linked with myeloid neoplasia (especially MDS) and clonal hematopoiesis of indeterminate potential (CHIP). The authors suggest that a high level of LOY ( $\geq 75\%$ ) is associated with an MDS-type mutation signature, representing a disease-associated clonal proliferation, and conclude that high-proportion LOY is likely to be a true MDS-associated cytogenetic aberration rather than an incidental finding due to aging. Their study provides molecular proof supporting the current praxis of the majority of diagnostics laboratories when it comes to the interpretation of LOY in patients with a suspicion/diagnosis of MDS. In particular, when LOY is observed in low number of metaphases ( $< 80\%$ ) it is considered more an aging-related phenomenon, not important for the clinical management, while when present in a high number of metaphases it is included in the prognostic algorithm.

In addition to age itself, a number of intrinsic and external risk factors influence individual risk of being a carrier of blood cells without chromosome Y. Genetic susceptibility to LOY has been reported in several recent genome-wide association studies.<sup>4,7,8,23</sup> In the largest to date, variants in 156 genetic loci preferentially found near genes involved in cell-cycle regulation, cell proliferation and genome instability were identified.<sup>4</sup> The nature of the risk loci suggests that LOY might primarily be an effect of chromosome mis-segregation during mitosis. Given the genetic component in individual propensity to be affected with LOY during lifetime, it is interesting that men of African ancestry display, on average, a lower frequency of LOY compared with men of European ancestry.<sup>14</sup> Other reported risk factors for LOY in blood include smoking,<sup>7,8,10,14,24</sup> obesity<sup>14</sup> and exposure to environmental risk factors such as air pollution<sup>25</sup> and polycyclic aromatic hydrocarbons.<sup>26</sup> For example, we showed that current smokers have an up to 4-fold increased risk of being affected compared with never smokers, with the increase being dose-dependent, and that smoking cessation is associated with recovery from LOY.<sup>24</sup> The transient effect from smoking has been replicated<sup>7</sup> and causality established by Mendelian randomization.<sup>8</sup>

Still largely unresolved questions include how LOY in blood might be associated with risk of disease in other organs. As illustrated in Figure 1, LOY in the immune cells of blood might represent a new and understudied disease mechanism driven by the accumulation of different types



**Figure 1.** During lifetime, acquired mutations, such as point mutations, structural variants and aneuploidies, in hematopoietic progenitors give rise to accumulation of immune cells carrying somatic variants associated with clonal hematopoiesis. Harboring genetically altered leukocytes is associated with disease vulnerability and could be linked with dysregulation of normal immune cell functions. Known risk factors for common diseases and clonal hematopoiesis are largely overlapping and their relative contributions to disease risks need further evaluation.

of somatic variants (including LOY, CHIP and other types of somatic alterations) in immune cells. In addition to being associated with clonal hematopoiesis in aging individuals, it has been hypothesized that such somatic variants in leukocytes could have a negative impact on normal immune cell functions. For instance, LOY has been found to be associated with a substantial impact on genome-wide transcriptional regulation<sup>27-30</sup> while we reported that patients diagnosed with prostate cancer and Alzheimer disease were primarily affected with LOY in different types of leukocytes.<sup>29</sup> Our studies of gene expression in immune cells from blood (i.e., different types of leukocytes and single cells with LOY collected *in vivo*) identified LOY-associated dysregulation of nearly 500 autosomal genes.<sup>29</sup> The nature of the affected genes support the hypothesis that LOY could contribute to disease vulnerability by altering normal immune cell biology. However, it is still not known how the expression of hundreds of autosomal genes is dysregulated in cells after losing the Y chromosome. That said, the Y chromosome is not a ‘genetic wasteland’ and encodes proteins involved in processes such as transcription, translation and chromatin modifications,<sup>29</sup> processes that would be affected in cells without chromosome Y.

A direct physiological effect could help to elucidate how LOY in blood is associated with an increased risk of disease in tissues of the entire body. However, it should be emphasized that the risk factors for many of the dis-

eases associated with LOY show a substantial overlap with the known risk factors for LOY and clonal hematopoiesis, such as age, smoking and genetic susceptibility (Figure 1). Clearly, such covariance is challenging when trying to make causal inferences and deduction of links with potential disease mechanisms. For example, many of the identified LOY-associated risk loci are also linked with cancer susceptibility and other types of disease, such as type 2 diabetes, as well as age at menopause in women.<sup>4</sup> Hence, associations between LOY and disease are in part explained by a ‘common soil’ of genetic predisposition to genomic instability,<sup>4</sup> independently associated with an increased risk of LOY in the blood and disease development in various tissues. Remarkably, Ouseph *et al.*<sup>1</sup> report a high prevalence of somatic variants in genes linked with myeloid neoplasia and CHIP in samples from MDS patients with high levels of LOY. Further studies are needed to understand the co-occurrence and implications of different types of somatic variants in immune cells associated with clonal hematopoiesis in normally aging populations. In conclusion, the increased risk of disease in men with LOY and other somatic variants in immune cells can likely be explained by several non-exclusive disease mechanisms. Hence, a reduced capability of altered immune cells to combat disease processes (driven by somatic variants and clonal hematopoiesis) would be operating in parallel with more traditional risk factors (Figure 1).

Finally, it has been known for centuries that, throughout the world, men live a shorter time than women<sup>31</sup> but until recently, the biological mechanisms behind this sex difference were poorly understood. Regardless of the underlying disease mechanism(s) discussed here, LOY is a male-specific somatic aneuploidy that can help to explain part of this bias in longevity. Interestingly, a recent study demonstrated that across 229 different species, the heterogametic sex has on average a shorter lifespan than the homogametic sex.<sup>32</sup> For example, females tend to live longer in mammals and males tend to live longer in birds, as predicted by the “unguarded X hypothesis”. Accordingly, a reduced sex chromosome in the heterogametic sex (e.g., chromosome Y in mammals and chromosome W in birds) might explain part of the differences in lifespan due to exposure of recessive deleterious mutations in the heterogametic sex.<sup>32</sup> Future studies could shed light on the relative contribution of effects associated with LOY and the unguarded X hypothesis to the observed differences in disease incidence and mortality between men and women in human populations.

### Disclosures

LAF is cofounder and shareholder in Cray Innovation AB.

### Contributions

PB and LAF wrote the manuscript.

### Acknowledgments

This work was supported by the European Research Council ERC (#679744), the Swedish Research Council (#2017-03762) and Kjell och Märta Beijers Stiftelse to LAF.

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