

MINI-REVIEW

Loss of the Y chromosome in blood cells and its influence on men health

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Abstract

The Y chromosome is unique to males. As men age, some of their somatic cells lose the Y chromosome during mitosis, creating two distinct cell populations. This phenomenon is known as somatic mosaicism of the Y (mLOY). While mLOY is primarily associated with aging, other factors, such as smoking, heavy drinking, air pollution, and exposure to toxic substances, can exacerbate it. Recent studies have associated mLOY with an increased risk of age-related disorders and reduced life expectancy. This mini-review aims to determine the association between mLOY and diseases in men. A literature search identified 40 articles addressing this issue in men from various populations. This review found an association between mLOY and Alzheimer's disease, Parkinson's disease, cardiovascular events, several cancers, hypercholesterolemia, hypertension, diabetes, asthma, lung diseases, kidney disease, rheumatoid arthritis, and an increased susceptibility to respiratory infections, including SARS-CoV-2. Additionally, mLOY was associated with an elevated risk of mortality from various diseases, such as cardiovascular events and chronic kidney disease. The mechanism by which increased mLOY levels in blood cells lead to higher morbidity or mortality is unclear. However, the leading hypothesis suggests that immune dysfunction caused by the dysregulation of several genes on both sex chromosomes and autosomes plays a role. Nevertheless, mLOY-associated risks likely depend on multiple factors, particularly lifestyle. Identifying potential causes of increased mLOY levels is important for developing preventive measures. However, it is unclear to what extent lifestyle changes can impede, delay, or reverse mLOY. Additionally, the clinical usefulness of measuring mLOY has yet to be determined, and its incorporation into routine risk prediction requires validation. Therefore, longitudinal studies are necessary to establish standardized thresholds, as well as the prognostic value and clinical significance of mLOY. These studies must also determine whether detecting mLOY can help identify age-related disorders in men at an early stage.

Keywords

Men; Y chromosome; Y chromosome somatic mosaicism; mLOY; mLOY-associated disease

1. Introduction

The karyotype of a chromosomally normal male is 46,XY. The Y chromosome is unique to males. It contains approximately 62.46 megabases and 106 protein-coding genes, which are primarily involved in testicular development and spermatogenesis. However, the reported number of genes varies depending on annotation methods and isoforms [1]. Major genes on the Y chromosome are shown in Fig. 1. As men age, some of their somatic cells randomly lose the Y chromosome during mitosis. This event generates two genetically distinct cell populations: one with normal Y chromosome and one lacking the Y chromosome (Fig. 2). This phenomenon commonly occurs

in seemingly healthy individuals and is known as somatic mosaicism of the Y chromosome (mLOY) [2]. Although mLOY can occur in any tissue, it is more easily detected in blood cells using DNA-based methods. One such method is the multiplex quantitative fluorescence polymerase chain reaction, which estimates the ratio of Y-chromosome to X-chromosome signals [3]. Another method is single-nucleotide polymorphism (SNP)-array-based analysis of the mean log-R ratios of SNPs in the male-specific region of the Y chromosome (mLRR-Y). An mLRR-Y estimate close to zero indicates a normal Y-chromosome state, whereas increasingly negative values indicate a greater proportion of cells with Y-chromosome loss [4]. Additionally, some RNA-based methods can be used to

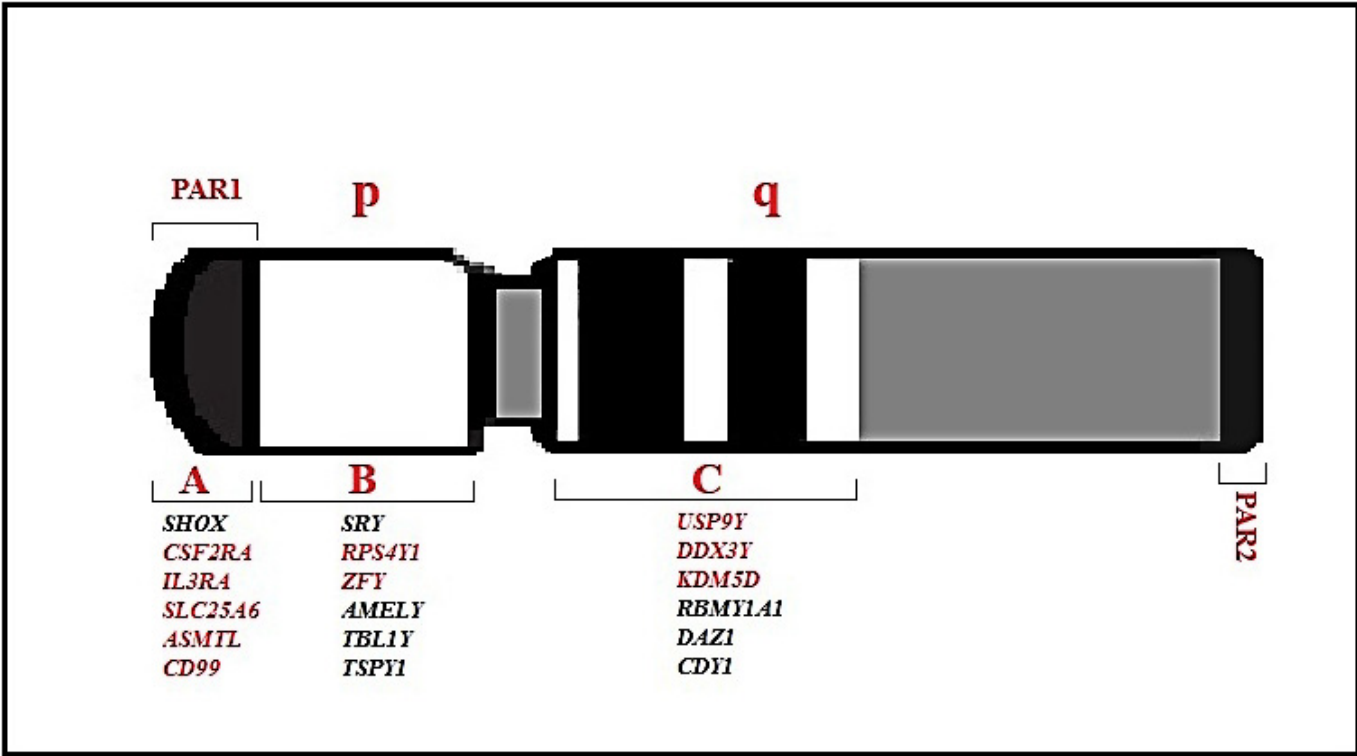


FIGURE 1. Representation of the human Y chromosome showing some genes. A: Genes located in pseudoautosomal region 1 (PAR1). B: Genes located on Yp11.2. C: Genes mapping to Yq11.22-11.23. The genes highlighted in red are dysregulated in males with mLOY.

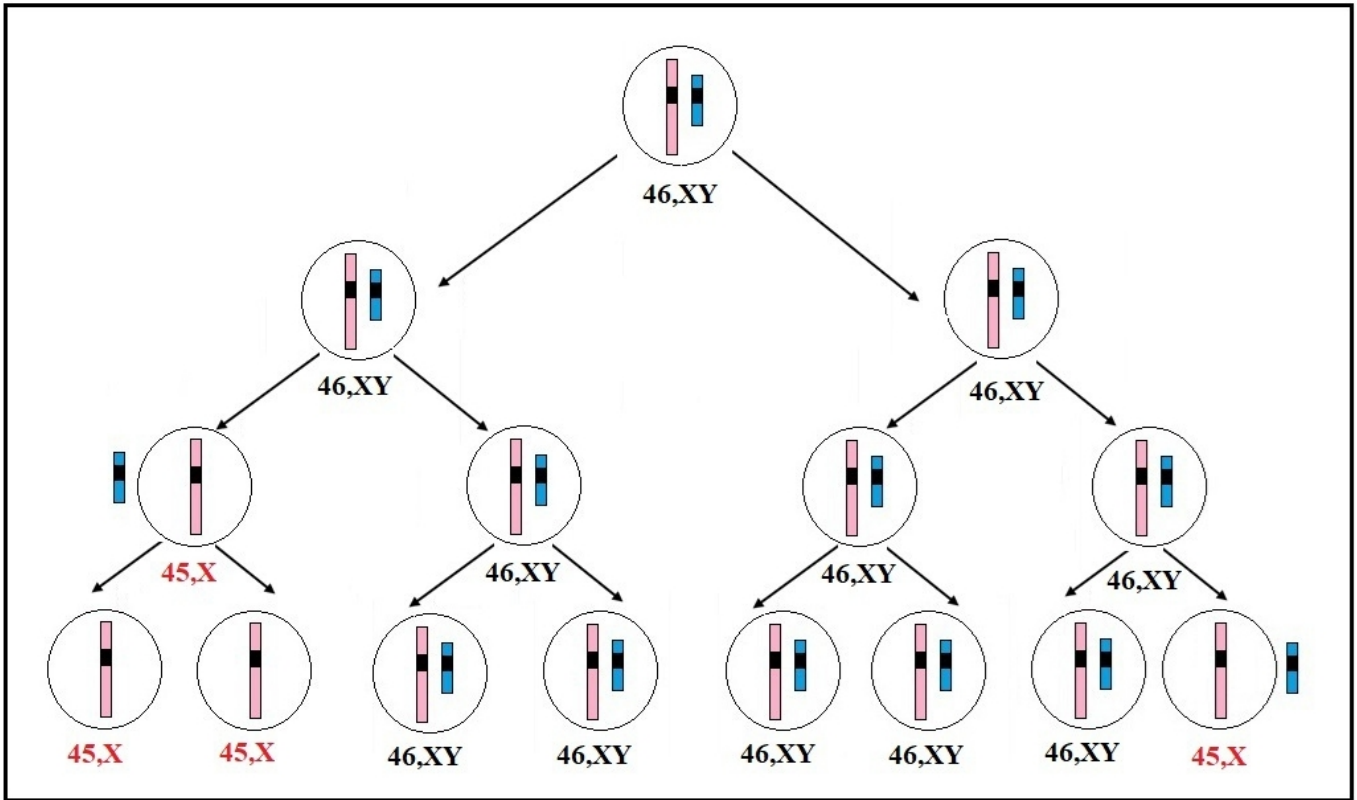


FIGURE 2. Schematic illustration of the process leading to mLOY, which may result from the loss of the Y chromosome in various tissues over a lifetime. This leads to the presence of both normal cells and monosomic X cells in an individual (45,X/46,XY).

estimate mLOY. However, the sensitivity and specificity of these methods may vary among approaches [5].

Approximately 20% of men aged 40 to 70 have a significant loss of the Y chromosome, increasing to 43.6% in men aged 70. This makes mLOY the most common genetic alteration in humans [6]. It has been hypothesized that the Y chromosome is susceptible to loss during mitosis due to three characteristics: its small size, the lack of centromeric protein B (CENPB) [7], and its palindromic sequences [8]. These sequences may induce sister chromatid exchanges can potentially lead to the formation of dicentric chromosomes, which may cause errors in chromosomal segregation [9, 10], particularly in blood cells [6]. While most studies agree that aging is the primary cause of mLOY, other factors, such as smoking, heavy drinking, obesity, and genetic susceptibility, are known to influence its levels [11, 12]. Several environmental factors may also increase the frequency of mLOY, including the use of herbicides such as glyphosate [13] and organochlorine insecticides [14], air pollution [15, 16], polycyclic aromatic hydrocarbons [17], as well as local radiotherapy for cancer treatment [18]. Additionally, mLOY has been associated with ethnicity, as White men have been reported to have a higher risk profile than Asian and Black men [19, 20]. Genes associated with mLOY include the nicotinic receptor *CHRNA3* (rs1051730), *MAD1L1* (rs1801368), *NREP* (rs11559), *NPAT* (rs2070661), *PMF1* (rs1052053), *TCL1A* (rs2887399) [4]; *BCL2L1* (rs2376992), *QKI* (rs4709819), and *TSC22D2* (chr3:150284878) [21]. Moreover, *ACAT1*, *ATM*, *CENPN*, *HM13*, *NPAT*, *SENP7*, *SMPD2*, and *TNK1* show altered expression in individuals with increased mLOY levels. Some of these genes play a role in mitosis, which could explain their association with mLOY. Epigenetics may also be implicated [4]. A genome-wide study identified 61 genetic variants (61 genes) across all autosomes, except chromosomes 19, 20, and 22, that were associated with mLOY [22]. These findings suggest that genetics may also play a key role in the presence and/or ratio of mLOY. In the broader context of cellular aging, mLOY is a prominent, male-specific manifestation of age-related genomic instability and clonal hematopoiesis. Although distinct from telomere attrition, mLOY shares similar underlying drivers, including defective DNA damage repair and the accumulation of mitotic errors in aging hematopoietic stem cells [5, 23].

Since none of the Y chromosome's genes are essential for cell survival or life in general, mLOY is not considered a disease. However, recent studies have shown that mLOY, detected in blood cells, is strongly associated with an increased risk of age-related disorders, including Alzheimer's disease (AD), macular degeneration, cardiovascular disease, metabolic disease, certain types of cancer, poor health, and reduced life expectancy [12, 24–26]. This study aims to review the literature to determine the impact of mLOY in blood cells on diseases in older men.

2. Literature review

2.1 Search strategy

A review was conducted in March 2026 using the PubMed and Scopus databases to identify articles examining Y-chromosome loss in blood cells and its association with diseases, biochemical and metabolic traits, and mortality in men. The search covered the period from 2016 to 2026 because research on this topic is relatively recent. The review used the phrase “mosaicism loss of the Y chromosome in blood cells”, the term “mLOY”, and combinations of these with the Boolean operators “AND” and “OR,” as well as the phrase “diseases in (older) men”.

2.2 Eligibility criteria

Only studies published in English that analyzed Y-chromosome mosaicism in blood cells using molecular techniques and evaluated associations using odds ratios (OR) and hazard ratios (HR) were considered. Articles on congenital Y-chromosome mosaicism, which generally involve disorders of sexual differentiation, and articles describing loss of the Y chromosome associated with leukemic or oncological processes detected through karyotyping, whether from blood or bone marrow, were excluded.

2.3 Selection of studies

Fig. 3 shows the selection process for this review. After screening, 40 studies met the inclusion criteria.

3. Results

This review included 40 articles that investigated the relationship between mLOY and diseases, biochemical or metabolic traits, and mortality or survival. Table 1 (Ref. [19, 22, 27–42]) summarizes the findings from several populations.

3.1 Conditions associated with mLOY

Thus, mLOY has been associated with an increased risk of age-related macular degeneration [27] and neurological disorders, such as AD in European populations [28, 29], Parkinson's disease, as well as accelerated motor impairment and cognitive decline across patients of various ethnicities [30], and amyotrophic lateral sclerosis [31]. Furthermore, two prospective studies found that men with mLOY in blood cells were at a greater risk of being diagnosed with incident AD during nearly eight years of follow-up (HR = 6.80 (2.16–21.43); $p = 0.0011$) [28]. In the Netherlands, mLOY was associated with secondary major cardiovascular events in patients with severe atherosclerosis [32], while in the United Kingdom (UK), it was linked to hospitalization for atrial fibrillation [33]. Another study found a higher proportion of mLOY in men who had experienced a heart attack or stroke compared with the control group (3.4% vs. 1.6%, $p = 0.01$) [26]. A recent study confirmed an increased cardiovascular risk in men with mLOY, particularly the risks of valvular heart disease, aortic stenosis, and mitral regurgitation [34]. Similarly, mLOY increases the risk of hypercholesterolemia by 1.5-fold and the risk of hypertension by 1.34-fold [19]. In Japanese and North American populations, mLOY was associated with wild-

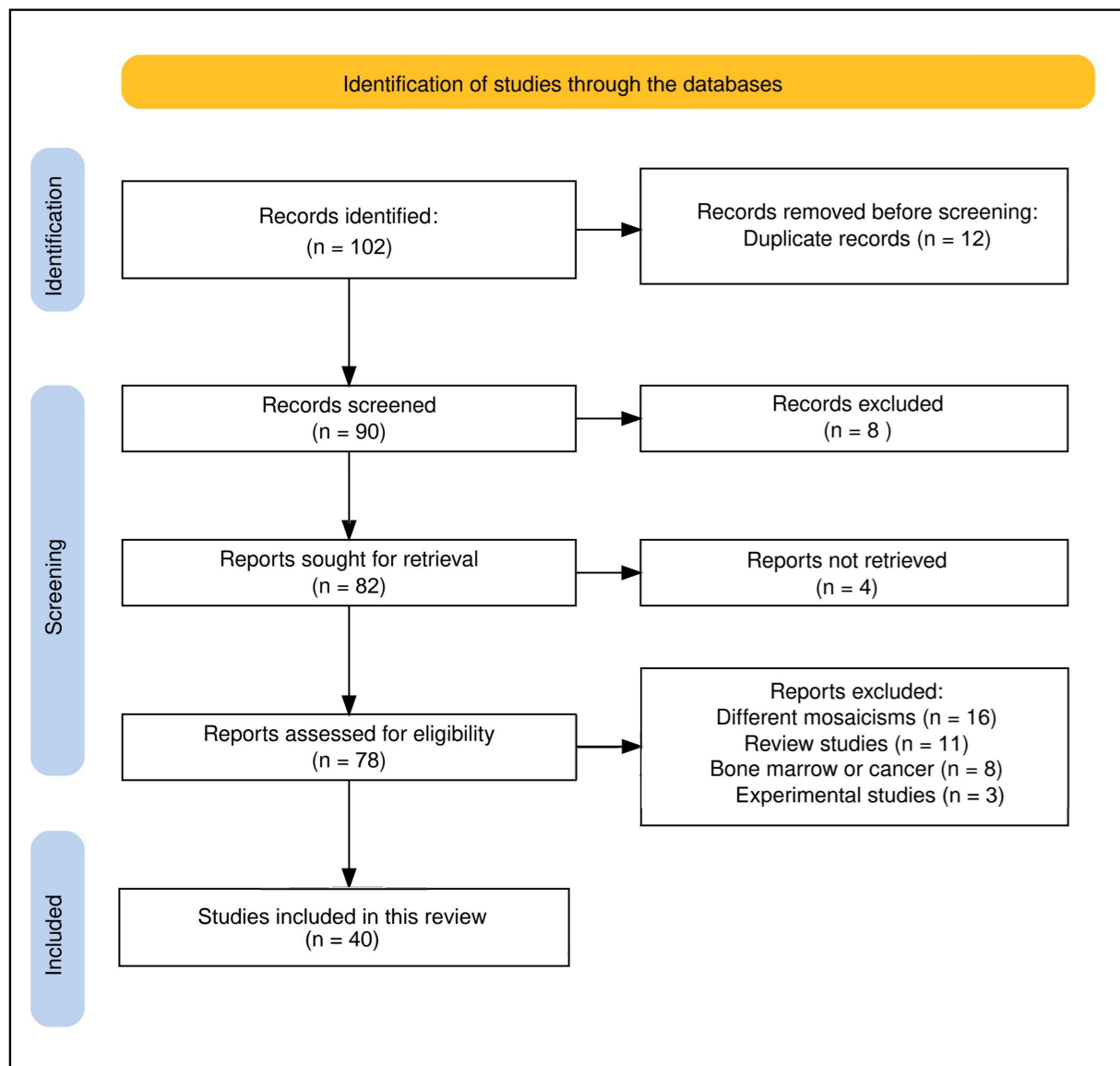


FIGURE 3. Flowchart of the studies selected for this review. The “Records Excluded” item ($n = 8$) refers to articles identified from the databases used that showed no relevance to mLOY.

type transthyretin cardiac amyloidosis (WTCA), and an allele fraction threshold of $\geq 21.6\%$ was linked to a 2.8-fold increased risk of all-cause mortality in these patients [35]. In East Asian populations, mLOY was associated with type 2 diabetes [22], and with asthma in European populations [36].

On the other hand, mLOY was significantly associated with colorectal and prostate cancer, as lower Y/X ratios were detected compared with controls: 0.88 ± 0.15 for colorectal cancer ($p < 0.0001$) and 0.94 ± 0.06 for prostate cancer ($p = 0.0001$) in Macedonian men [3]. In the UK, mLOY was linked to solid tumors, particularly lung cancer, especially among smokers [36, 37]. Moreover, it was associated with leukemia and abnormalities in blood parameters in healthy men, including decreased red blood cell count and mean corpuscular hemoglobin, increased mean corpuscular volume, white blood cell, and platelet counts in men from various ethnic groups [21]. Additionally, mLOY was associated with a higher risk of developing lung diseases, including chronic obstructive pulmonary disease (COPD) [36, 38], idiopathic

pulmonary fibrosis (IPF) [36], and impaired spirometry [38] across various populations. Smokers with expanded mLOY were at a higher risk for COPD and IPF (HR = 3.38 (3.07–3.72); HR = 1.72 (1.31–2.26), respectively) [36]. Similarly, mLOY was linked to chronic kidney disease (CKD) and acute kidney injury (AKI). The latter association was stronger in men with stage 5 CKD and mLOY levels higher than 60% in the UK [39]. Furthermore, mLOY has been associated with suicidal behavior [40] and late-onset rheumatoid arthritis [41] in Japanese individuals, as well as with an increased susceptibility to respiratory infections [42], including SARS-CoV-2 (OR = 1.40, $p < 0.05$) [43] and greater severity of COVID-19 [44]. High levels of mLOY have also been associated with familial testicular germ cell tumors, but not with sporadic tumors, in a USA population [45], and with relapses in patients with giant cell arteritis (HR = 17.4, $p = 0.003$) [46].

Some studies have found no association between elevated mLOY levels and certain diseases. For example, the risk of lung cancer was not confirmed in Chinese individuals (OR =

TABLE 1. Studies conducted in men in which mLOY showed a significant association with specific conditions.

Population	Disease/Condition	Sample size	Mean or range age	Analysis method	*OR (95% CI)	p-value	Reference
Retrospective studies							
Multiethnic	Hypercholesterolemia	206,353	37–73	mLRR-Y	1.51 (1.47–1.55)	<0.0001	[19]
Multiethnic	Hypertension	206,353	37–73	mLRR-Y	1.34 (1.31–1.38)	<0.0001	[19]
Multiethnic	Diabetes	206,353	37–73	mLRR-Y	1.12 (1.07–1.71)	<0.0001	[19]
East Asian	Diabetes	122,683	~60	mLRR-Y	1.15 (1.07–1.21)	<0.0001	[22]
Europeans	Age-related macular degeneration	12,504	~75	mLRR-Y	1.33 (1.21–1.47)	<0.0001	[27]
Europeans	Alzheimer disease	3218	>70	mLRR-Y	2.80 (1.19–6.61)	<0.02	[28]
Spaniards	Alzheimer disease	2697	75.5	mLRR-Y	2.74 (1.29–6.16)	0.01	[29]
Japanese and USA	WTCA	236	NR	AMELY/ AMELX ratio	3.44 (1.98–6.11)	<0.001	[35]
USA	COPD	5097	40–85	mLRR-Y	1.84 (1.10–3.07)	<0.05	[38]
USA	Impaired spirometry	5097	40–85	mLRR-Y	2.87 (1.09–7.56)	<0.05	[38]
Multiethnic	CKD	216,608	40–70	mLRR-Y	1.23 (1.03–1.46)	<0.022	[39]
Multiethnic	AKI	216,608	40–70	mLRR-Y	6.41 (2.59–15.89)	<0.001	[39]
Japanese	Suicidal behavior	286	~46	AMELY/ AMELX ratio	3.50 (1.21–10.10)	0.021	[40]
Japanese	Rheumatoid arthritis	95,336	51–73	mLRR-Y	1.43 (1.10–1.86)	0.007	[41]
Cohort studies							
East Asian	Diabetes	122,683	~60	mLRR-Y	1.22 (1.04–1.44)	0.014	[22]
East Asian	Dyslipidemia	122,683	~60	mLRR-Y	1.19 (1.07–1.33)	0.0018	[22]
East Asian	COPD	122,683	~60	mLRR-Y	1.30 (1.00–1.67)	0.05	[22]
Europeans	COPD	181,472	57.1	mLRR-Y	1.22 (1.11–1.35)	<0.001	[22]
Europeans	Asthma	181,472	57.1	mLRR-Y	1.19 (1.04–1.36)	<0.01	[22]
Multiethnic	Parkinson disease	222,598	58.7	mLRR-Y	1.16 (1.01–1.34)	0.04	[30]
Multiethnic	Amyotrophic lateral sclerosis	158,953	57	mLRR-Y	1.62 (1.06–2.48)	0.026	[31]
Netherlands	Major cardiovascular events	366	62–79	mLRR-Y	2.28 (1.11–4.67)	0.02	[32]
Multiethnic	Atrial fibrillation	190,613	40–69	mLRR-Y	1.06 (1.03–1.11)	0.0011	[33]
Multiethnic	Valvular heart disease	90,123	~65	mLRR-Y	1.31 (1.04–1.65)	0.022	[34]
Multiethnic	Aortic stenosis	90,123	~65	mLRR-Y	1.47 (1.00–2.15)	0.049	[34]
Multiethnic	Mitral regurgitation	90,123	~65	mLRR-Y	1.69 (1.12–2.55)	0.013	[34]
Multiethnic	COPD	260,639	~55	mLRR-Y	1.20 (1.13–1.28)	<0.001	[36]
Multiethnic	Asthma	260,639	~55	mLRR-Y	1.17 (1.04–1.31)	<0.01	[36]
Multiethnic	IPF	260,639	~55	mLRR-Y	1.34 (1.16–1.56)	<0.001	[36]
Multiethnic	Lung cancer	260,639	~55	mLRR-Y	1.34 (1.21–1.48)	<0.001	[36]
Multiethnic	Solid tumor	207,603	40–69	mLRR-Y	1.36 (1.09–1.71)	0.007	[37]
Multiethnic	Lung cancer	207,603	40–69	mLRR-Y	2.25 (1.36–3.71)	0.002	[37]
Multiethnic	Respiratory infections	358,551	~57	mLRR-Y	1.09 (1.03–1.16)	0.005	[42]

*Adjusted ORs were taken when possible. AKI: Acute kidney injury; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; IPF: Idiopathic pulmonary fibrosis; mLRR-Y: Median of the log R ratio of the Y chromosome based on SNP arrays; NR: Not reported; WTCA: Wild-type transthyretin cardiac amyloidosis; OR: Odds ratio; CI: Confidence interval. In cohort studies, hazard ratios (HR) are reported.

0.96, $p = 0.29$) [47] and in a multiethnic group (OR = 1.02, $p > 0.1$) [20]. In contrast, mLOY was associated with a lower risk of lung cancer in nonsmokers (OR = 0.80, $p = 0.004$) [47], as well as a reduced risk of developing hyperlipidemia (OR = 0.49, $p = 0.012$), hypertension (OR = 0.42, $p = 0.002$), and diabetes (OR = 0.43, $p = 0.004$) in patients with WTTCA [35]. A study of Mexican mestizo individuals found no difference in the mLOY ratio between patients with IPF and controls (0.95 ± 0.09 vs. 0.93 ± 0.10 , respectively ($p = 0.28$)) [48]. Likewise, the presence of mLOY was similar between patients with schizophrenia and controls from China ($p = 0.534$). However, age of onset (OR = 1.06, $p = 0.013$) and duration of the disease (OR = 1.06, $p = 0.017$) were associated with mLOY [49].

Other studies suggest that mLOY is associated with potential health benefits. Thus, high mLOY levels have been linked to a reduced risk of retinal disease (OR = 0.65, $p < 0.0001$) and certain metabolic conditions, including type 2 diabetes (OR = 0.80, $p < 0.0001$), obesity (OR = 0.87, $p < 0.0001$), gout (OR = 0.87, $p < 0.0001$), and hypertension (OR = 0.91, $p < 0.0001$) in the UK population [50]. Additionally, while mLOY was associated with an increased risk of late-onset rheumatoid arthritis, it was associated with a lower risk of early-onset rheumatoid arthritis (OR = 0.66, $p = 0.0034$) among Japanese individuals [41]. It is noteworthy that while mLOY was associated with elevated mortality in men aged 56 to 80 years, it was associated with higher survival in men over 100 years of age (HR = 0.50, $p = 0.044$) [51].

Across cohorts, mLOY demonstrates a sharp, non-linear, age-dependent trajectory, with its frequency and cell-fraction representation increasing rapidly after the age of 70. Although there is no clear reason why some studies detected significant associations while others did not, these differences could be explained by the intrinsic characteristics of the analyzed populations, including race, genetic background, age, sample size, diagnostic criteria, lifestyle factors, as well as the methods and cutoff values used to define mLOY. Additionally, confounding variables, such as smoking, alcohol consumption, and obesity, may have influenced the analysis.

3.2 Mortality risk increased in patients with mLOY

On the other hand, mLOY has been associated with an increased risk of mortality in several disorders, including cancer (HR = 1.48, $p = 0.01$) [26], CKD (HR = 2.58, $p = 0.005$) [52], WTTCA (OR = 2.79, $p < 0.02$) [35], IPF (HR = 1.01, $p = 0.009$) [53], among patients who underwent a coronary angiography (HR = 1.41, $p = 0.009$) [54], and following ischemic stroke (OR = 2.5, $p < 0.001$) [2]. Additionally, mLOY has been linked to an increased risk of mortality after a transcatheter aortic valve replacement at the three-year follow-up (HR = 2.01, $p = 0.001$) [55]; in patients with chronic heart failure (HR = 1.57, $p = 0.034$) [56]; and in subjects with ST-segment elevation myocardial infarction at 1- (HR = 2.45, $p = 0.018$), 2- (HR = 2.11, $p = 0.024$), and 3-year follow-up (HR = 1.88, $p = 0.043$) [57], as well as in men aged 56 to 80 years (HR = 2.03, $p = 0.027$) [51].

However, it should be noted that all these findings of increased morbidity and mortality are based on observational

studies, which, by their nature, do not establish causation. Therefore, these associations should be interpreted as indicators of increased risk, rather than as proof of causality, and their significance may also vary according to population characteristics, methodological approaches, and residual confounding factors.

3.3 How mLOY increases pathogenicity

The mechanism by which increased levels of mLOY in blood cells may contribute to an elevated risk of morbidity or mortality in men remains unclear. However, leading hypotheses suggest that impaired immune function may be involved, potentially through dysregulation of multiple genes on both sex chromosomes and autosomes [58]. In this context, studies have shown that loss of the Y chromosome (LOY) influences the differentiation and functional trajectories of hematopoietic and immune cells [59]. In the myeloid lineage, for instance, monocyte counts increase, and these cells may shift toward a pro-fibrotic phenotype, which may contribute to low-grade inflammation. There is also biased activation of natural killer (NK) cells and defective differentiation of immature and naïve B cells into memory B cells [59]. Additionally, T lineage cells with LOY differentiate into T regulatory cells. These changes may result in impaired immune surveillance and promote chronic inflammation [60, 61]. The loss of Y-linked genes, particularly *KDM5D* and *UTY*, might be an early driver of these changes in the immune response [62]. The loss of *CD99*, which encodes a T-cell surface protein, may also contribute to this impairment [58]. Collectively, these cellular alterations indicate that systemic immune dysfunction and aberrant inflammatory signaling, rather than isolated gene dosage deficits alone, act as central drivers connecting mLOY in blood to multi-organ pathology.

Regarding the link between cancer and mLOY, it has been postulated that disturbances in the differentiation of immune cells with LOY may alter the monocyte/macrophage composition and lead to inflammatory or immunoregulatory responses involved in tumor initiation. However, it should be noted that, although mLOY in blood cells and LOY in malignant cells are similar, they should be considered distinct biological events: mLOY in blood cells usually originates from hematopoietic stem cells and expands clonally in older men, whereas tumor-cell LOY occurs within a malignant lineage [63]. In this context, the tumor microenvironment (TME) is an important link between LOY and cancer progression. In tumors associated with LOY, the TME is characterized by reduced antigen presentation. Research suggests that LOY may alter the TME by causing the dysfunction or exhaustion of CD8⁺ T cells within it [62]. These findings imply that early LOY may provide an adaptive advantage to tumor cells to evade immunity. Therefore, LOY may enhance the fitness of tumor cells and modify the immunological landscape in which these cells evolve [62]. In addition to CD8⁺ T cell dysfunction, tumors with LOY exhibit increased expression of immune checkpoint and co-inhibitory genes, such as *CTLA4*, *PDCD1*, *TIGIT*, *LAG3*, *CD27*, *IL2RA*, *HAVCR2*, *CD40*, *CD274*, and *PDCD1LG2* [64]. Thus, tumors with LOY possess an immunosuppressive tumor microenvironment that could suppress cytotoxic T-cell

responses and facilitate immune evasion [62]. Concurrently, LOY-positive immune cells may exhibit reduced antitumor function, further reducing immune-mediated elimination of malignant clones. Therefore, tumor cells with LOY and blood cells with mLOY may converge on a common phenotype of reduced antitumor immune surveillance [64]. While both mLOY in blood cells and tumor-cell LOY could influence cancer-related gene expression and immune function, the evidence supporting causality is stronger for the latter [62, 64].

The link between mLOY in blood cells and lung cancer may also be due to changes in immune surveillance, as mLOY has been associated with altered differentiation of myeloid cells. This may lead to elevated levels of neutrophils and monocytes, which can induce chronic inflammation and contribute to lung carcinogenesis [59]. Furthermore, alterations in T cells with mLOY may impair the ability to eliminate pre-malignant cells [64]. However, it remains to be determined whether LOY is a true driver or passenger event in cancer processes [5].

These processes of immune dysfunction, disturbances in leukocyte differentiation, and activation of inflammatory responses are primarily mediated by gene dysregulation. Some Y-chromosome genes that undergo dysregulation in males with mLOY include *CSF2RA*, *SLC25A6*, *CD99*, and *RPS4Y1* [21, 58], as well as *ZFY*, *USP9Y*, *DDX3Y*, *KDM5D*, and *EIF1AY* [58]. Other examples involve X-chromosome-linked genes such as *XIST*, a non-coding RNA essential for X-chromosome inactivation that is not typically expressed in males. There may also be an upregulation of genes that escape inactivation. These include *ZRSR2*, *DDX3X*, *KDM6A*, and *KDM5C*, which are associated with cancer [59]. Additional genes mapping to the pseudoautosomal regions (PARs) of the X and Y chromosomes include *VAMP7*, *GTPBP6*, *PPP2R3B*, *ASMTL*, *P2RY8*, *AKAP17A*, *DHRX*, *PLCXD1*, *IL3RA*, and *SPRY3* [58]. Regarding autosomal genes, a study revealed altered expression of 489 genes in leukocytes with mLOY, some of which are involved in immune functions and other biological processes, especially *MYCL1*, *LOC200772*, *CLEC4F*, *MERTK*, *IL1R2*, *TMEM176B*, *LYPD2*, *ZNF703*, *CTSL1*, *CDKN1C*, *CD3D*, *TMTCL1*, *LAG3*, *RNASE2*, *MTIE*, *ABCC3*, *CYP4F3*, and *CFD* [58]. Furthermore, mLOY has been linked to the dysregulation of 172 autosomal genes, 10 PAR genes, and three X-linked genes in microglia. Among these, there are genes involved in central nervous system development, neurodegeneration, and cancer-promoting processes, including roles in axon guidance (*ROBO1*, *DOCK1*, and *PTPRM*), immune cell and glioma migration (*ROBO1* and *SLIT2*), splicing regulation (*RBFox2*), phagocytosis (*DOCK1* and *CD163*), neuron-glia interaction (*ST6GALNAC3*), cell division and polarization (*PARD3B*), cell adhesion (*DSCAM*), and lipoprotein metabolism (*APOE*, *APOC1*, and *ABCA1*) [65]. PAR-dysregulated genes in microglia include *GTPBP6*, *LINC00685*, *CSF2RA*, *SLC25A6*, *IL3RA*, *P2RY8*, *AKAP17A*, *DHRX*, and *CD99* [65]. Autosomal genes that are dysregulated in both blood cells and microglia comprise *TMEM176B*, *S100Z*, *TMEM71*, *CD226*, *B2M*, *SCMH1*, *LITAF*, and *IL15*, which are involved in immune and inflammatory processes [58, 65]. Furthermore, mLOY may contribute to epigenetic changes, since altered methylation has been documented in 7105 granulocyte genes in men

with mLOY. These genes include *FLII*, *RUNX1*, *RARA*, *CANX*, *CEBPB*, *MYADM*, *OGG1*, *NFE2*, *DFFB*, *TNFRSF1A*, *CLEC16A*, and *TRADD*; some of them are involved in leukocyte differentiation and oncogenesis [66]. Furthermore, kidney cells with mLOY exhibit significant changes in the expression of hundreds of genes and are more likely to harbor additional large chromosomal gains, resulting in genome instability and impaired kidney function [67]. Additionally, mLOY has been linked to altered levels of serum biomarkers, including lipids, testosterone, sugars, proteins, vitamins, and minerals [68, 69], which can affect overall health. Along these lines, the expression levels of eleven plasma proteins involved in immune and inflammatory processes were significantly higher in mLOY patients with cardiovascular conditions, such as hypertension, heart failure, atrial fibrillation, and aortic aneurysms. These proteins were categorized into four groups: profibrotic mediators (*WFDC2*, *GDF15*, *MSLN*, and *TFF2*); general inflammatory markers (*PLAUR* and *CXCL17*); monocyte-specific activation markers (*CD300E* and *LILRA5*); and immune modulators or immunosuppressive proteins (*LAMP3*, *TNFRSF10B*, and *CEACAM5*). This is reflected by the transcriptional upregulation of numerous genes that encode the proteins upregulated in mLOY circulating mononuclear cells [70]. Thus, changes in gene expression can disrupt homeostasis, leading to a pathological state and potentially increasing the risk of chronic disorders.

4. Limitations

This mini-review provides an overview of the relationship between mLOY in blood cells and diseases affecting men. However, this analysis has some limitations. First, while studies on mLOY and its association with diseases in older men have been conducted for some time, this review is limited to studies published from 2016 onward. Thus, some important studies may have been omitted, which could limit the identification of additional associations. Nevertheless, this approach focuses on the most recent and relevant data. Second, the included studies show significant heterogeneity in terms of ancestry, sample size, participants' age, analysis methods, and cutoff values used to define mLOY. Differences in DNA integrity, sample processing, genotyping platforms with varying sensitivity and specificity, normalization strategies, and potential technical biases could have also influenced the detection and quantification of mLOY. Additionally, discrepancies in diagnostic criteria and variable outcome definitions may exist. All these factors, along with statistical approaches, could have contributed to key variations in the results, making direct comparisons among cohorts difficult. Third, the analyses were primarily based on blood cells because blood is a reliable and accessible tissue for studying mLOY. However, the presence or extent of mLOY in blood does not necessarily indicate its presence or extent in other tissues, because mutations, clonal selection, and expansion can vary across hematopoietic lineages and occur independently in different tissues and organs, such as the brain, kidney, bladder, heart, and buccal mucosa, and may vary with age [66]. Lastly, the studies included in this review are observational; therefore, their findings demonstrate associations rather than causality.

5. Conclusions and perspectives

The widespread presence of mLOY in aging men, along with its consistent association with several age-related diseases, suggests that it may be involved in the development of these diseases. However, it is unclear whether mLOY directly causes these disorders. The risks associated with mLOY likely depend on several factors, particularly genetic background and lifestyle. Therefore, identifying the factors that contribute to increased mLOY levels could be crucial for developing preventive measures. Nevertheless, the extent to which lifestyle modifications can prevent, delay, or reverse mLOY expansion remains to be determined. While mLOY is primarily associated with aging, environmental factors such as smoking, exposure to chemicals, a poor diet, and a sedentary lifestyle can potentially contribute to its expansion. Thus, adopting healthy habits and avoiding exposure to toxic agents may help reduce factors associated with accelerated increases in mLOY. Furthermore, determining the mLOY ratio could be useful for predicting age-related diseases in men. In fact, a predictive method based on a polygenic risk score has been developed to identify men at increased risk for mLOY in leukocytes [71]. This method could help identify individuals who may benefit from closer monitoring of age-related diseases. Nevertheless, the clinical usefulness of measuring mLOY remains to be determined, and its incorporation into routine risk prediction requires validation. Therefore, large-scale prospective longitudinal studies utilizing single-cell RNA sequencing, spatial transcriptomics, and multi-tissue matched sampling (comparing blood against tissue biopsies) are needed to unravel causal pathways, establish standardized thresholds, clarify the prognostic and clinical significance of mLOY, and determine whether its detection can be used to support the early prevention and detection of age-related disorders in men.

ABBREVIATIONS

AD, Alzheimer's disease; AKI, Acute kidney injury; CKD, Chronic kidney disease; COPD, Chronic obstructive pulmonary disease; HR, Hazard ratios; IPF, Idiopathic pulmonary fibrosis; LOY, Loss of the Y chromosome; mLOY, Somatic mosaicism of the Y chromosome; mLRR-Y, Mean log-R ratios of SNPs in the male-specific region of the Y chromosome; OR, Odds ratios; PAR, Pseudoautosomal region; SNP, Single nucleotide polymorphism; WTCA, Wild-type transthyretin cardiac amyloidosis; UK, United Kingdom.

AVAILABILITY OF DATA AND MATERIALS

Not applicable, because no database was generated in this study.

AUTHOR CONTRIBUTIONS

JPME—designed the research and drafted the manuscript. VJPC, DEMS, and JACG—conducted the literature search.

AKDHA and JJVS—revised the manuscript and made intellectual contributions. All authors analyzed the data and approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Verónica Judith Picos-Cárdenas, Alberto Kousuke De la Herrán-Arita, Dionicio Enrique Martínez-Saldaña, José Alfredo Contreras-Gutiérrez, José Johanatan Valdez-Sandoval, Juan Pablo Meza-Espinoza. Loss of the Y chromosome in blood cells and its influence on men health. *Journal of Men's Health*. 2026; 22(10): 29-38. doi: 10.22514/jomh.2026.082.