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Review

Mosaic Loss of Chromosome Y (LOY): From Genomic Instability to Disease and Single-Cell Detection

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Abstract

Mosaic loss of chromosome Y (LOY) is the acquired absence of the Y chromosome in a fraction of cells, is most readily observed in the haematopoietic compartment, and represents the most common form of clonal mosaicism in older men. Once dismissed as a benign correlate of aging, LOY is now recognized as a clinically meaningful biomarker associated with reduced survival and an expanding range of age-related disorders, including multiple solid and haematological cancers, cardiovascular disease, Alzheimer's disease, and type 2 diabetes mellitus. Large-scale genome-wide analyses have shown that susceptibility to LOY is highly heritable and associated with genes involved in cell cycle regulation, the DNA damage response, and apoptosis, supporting a model in which detectable LOY in blood reflects broader genomic instability across tissues. In parallel, functional studies in genetically engineered mice have demonstrated that haematopoietic LOY can contribute causally to pathologic processes such as cardiac fibrosis, indicating that loss of dosage-sensitive Y-linked genes in immune cells may exert direct effects rather than merely serving as a passive marker. Progress in this field has been constrained by detection methods that are laborious, costly, or insufficiently sensitive at low mutant cell fractions. This constraint is now easing on two fronts. Haplotype- and coverage-based callers can detect LOY from whole-genome and exome sequencing data generated for other purposes, extending measurement to ancestrally diverse cohorts and tumour genomes, while newer single-cell droplet-based approaches permit accurate quantification of LOY and its female counterpart, mosaic loss of chromosome X (LOX), at single-cell resolution. Here, we summarize the biology, genetic architecture, disease associations, and proposed mechanisms of LOY and discuss how improved detection may help clarify its causal contribution to human aging and disease.

Keywords: mosaic loss of chromosome Y (LOY); Y chromosome; sex chromosome aberrations; clonal hematopoiesis; mosaicism; aging; genomic instability; cardiovascular diseases

1. Introduction

The Y chromosome occupies a unique position in human genetics. Apart from its master role in male sex determination, much of its sequence is heterochromatic and repetitive, and it has been regarded as a largely inert genetic wasteland for decades [1]. However, this view has recently been overturned. The clearest demonstration of the Y chromosome's continuing biological relevance is the mosaic loss of the Y chromosome (LOY), which is the acquired, age-related absence of the Y chromosome from a variable proportion of an individual's somatic cells. Because it is most easily assayed in circulating leukocytes, LOY is now recognized as the most common form of clonal mosaicism and one of the most frequent acquired genetic changes in aging men [2,3,4]. Although a sex-dependent change in chromosome counts with age was noted as early as the 1960s [5], LOY was dismissed for many years as a benign feature of aging. Population-scale studies have shown that detectable LOY in the blood is associated with shortened survival and an unexpectedly broad spectrum of age-related diseases [6,7]. The relevance of the Y chromosome to disease is not limited to acquired changes; constitutional Y-chromosomal lesions, including microdeletions of the azoospermia factor (AZF) regions and supernumerary X of Klinefelter syndrome, are well-established causes of spermatogenic failure and male infertility [8,9]. LOY is conceptually distinct from these, being an acquired, post-zygotic, and mosaic event that accumulates with age rather than a germline or constitutional abnormality (Figs. 1,2). This review synthesises the current understanding of the biology, genetic architecture, clinical associations, and mechanistic basis of LOY and discusses how recent advances in single-cell detection can resolve outstanding questions regarding its causal role.

Several substantial reviews have recently synthesised parts of this rapidly growing field, including broad surveys of the effects of LOY on male health [10], its emerging role in cancer biology [11], and its molecular mechanisms and systems-level modelling [12,13,14]. The present review is intended to complement, rather than duplicate, these accounts. Two emphases distinguish it. First, it integrates the recent extension of LOY detection to single-cell resolution and its application to the female counterpart, LOX explicitly within the marker-versus-driver framework that

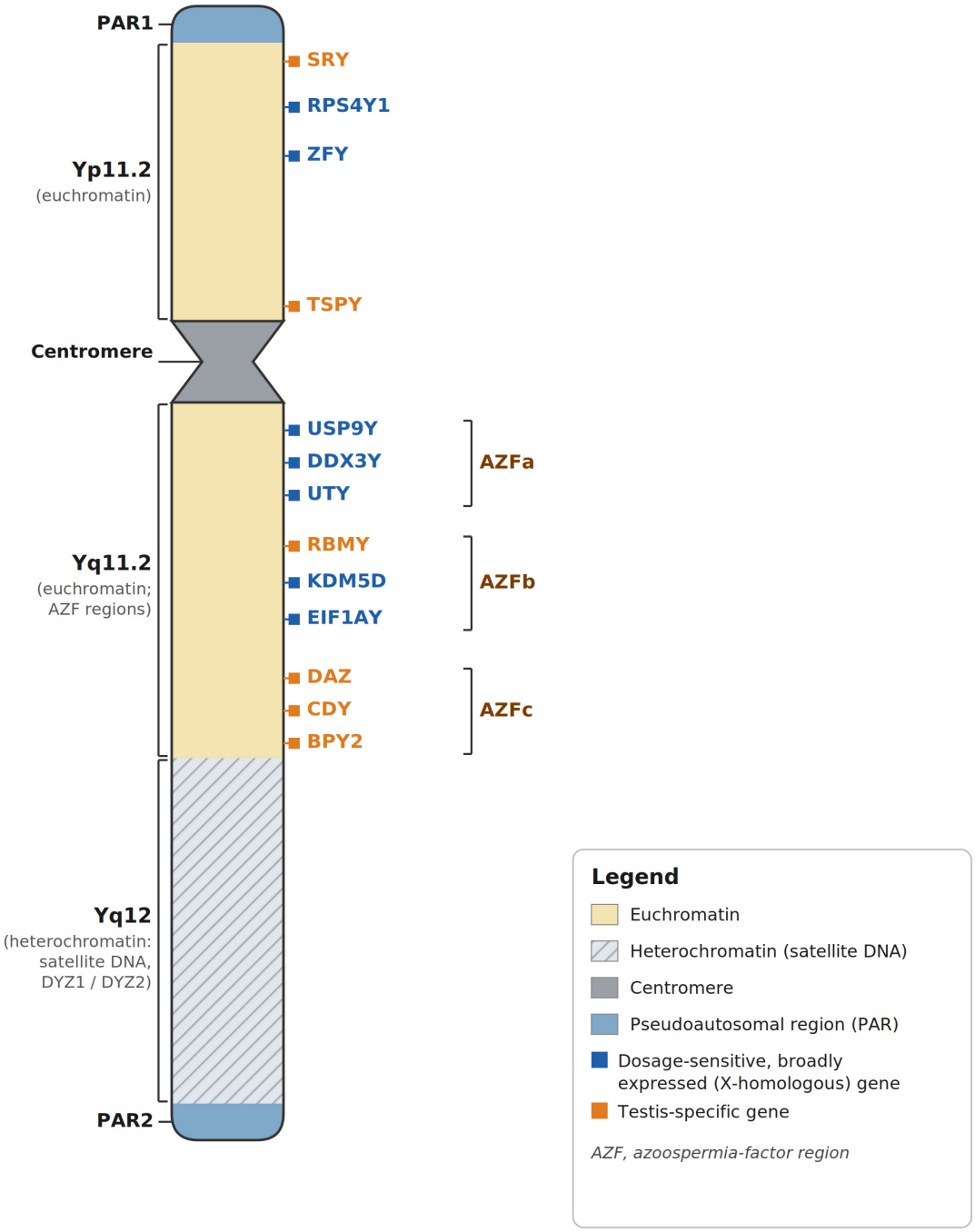

Fig. 1. Architecture and gene content of the human Y chromosome. Schematic ideogram of the Y chromosome showing the pseudoautosomal regions (PAR1 and PAR2; blue), euchromatic short arm (Yp), proximal long arm (Yq11) (cream), centromere (gray), and large distal heterochromatic block (Yq12; hatched) composed of satellite DNA repeats (DYZ1 and DYZ2). Representative genes of the male-specific region of the Y chromosome (MSY) are mapped to their approximate cytogenetic positions and coloured by functional class: dosage-sensitive, broadly expressed X-homologous genes (blue; for example, *RPS4Y1*, *ZFY*, *USP9Y*, *DDX3Y*, *UTY*, *KDM5D*, and *EIF1AY*), whose reduced dosage is the presumed basis for the somatic consequences of Y chromosome loss, and testis-specific genes (orange; for example, *SRY*, *TSPY*, *RBMY*, *DAZ*, *CDY*, and *BPY2*), required for sex determination and spermatogenesis. The three azoospermia factor (AZF) intervals on Yq11 (AZFa, AZFb, and AZFc) are indicated.

organises the field's central causal debate, rather than treating detection methods and disease mechanisms as separate topics. Second, it situates LOY within the Y chromosome's unusual repetitive, recombination-poor architecture and its singular evolutionary history, a structural perspective that falls outside the scope of these companion reviews but that plausibly bears on why this particular chromosome is so prone to somatic loss. Consistent with the concision of a fo-

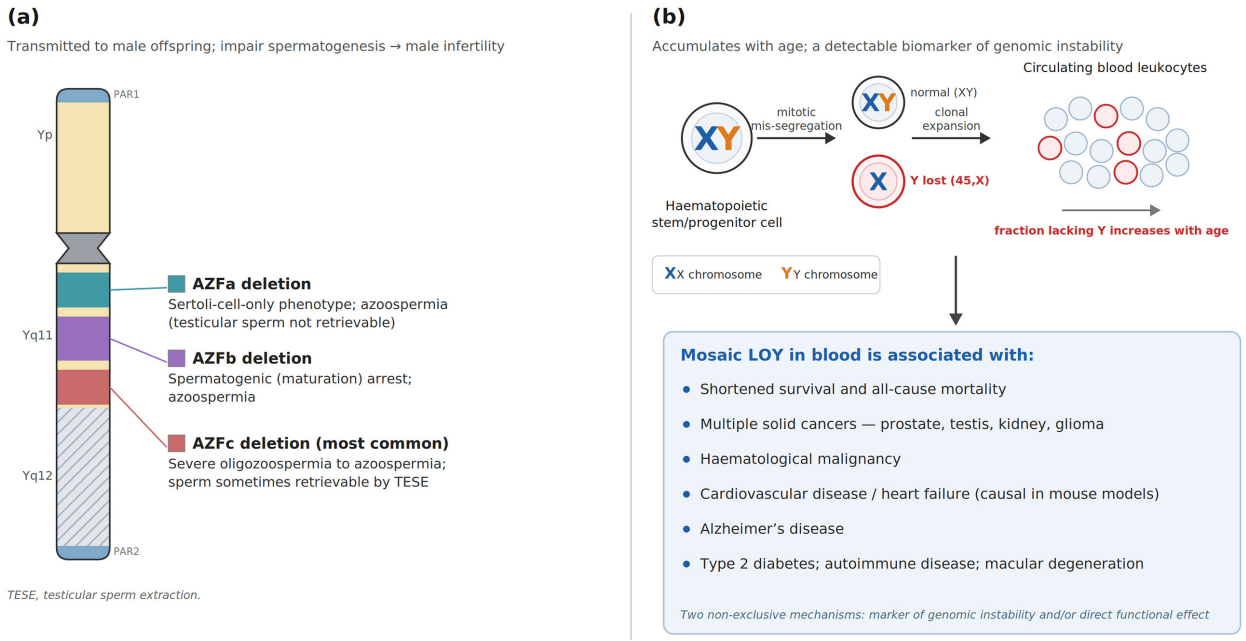

Fig. 2. Constitutional and acquired abnormalities of the human Y chromosome. (a) Constitutional Y-chromosome microdeletions of the AZFa, AZFb, or AZFc intervals on the long arm (Yq11) arise in the germline and remove genes required for spermatogenesis. AZFa and AZFb deletions cause complete azoospermia and are almost always de novo; AZFc deletions can occasionally be transmitted to male offspring via TESE and ICSI. AZFa deletions typically cause a Sertoli-cell-only phenotype with azoospermia and no retrievable testicular sperm; AZFb deletions cause spermatogenic (maturation) arrest with azoospermia; and AZFc deletions, the most frequent type, cause severe oligozoospermia to azoospermia, with sperm sometimes retrievable by testicular sperm extraction (TESE). (b) Acquired (somatic) mosaic loss of chromosome Y (LOY). Mitotic missegregation in a haematopoietic stem or progenitor cell yields a daughter cell that has lost the entire Y chromosome (45,X). Age-related clonal expansion of these cells produces a measurable mosaic fraction of Y-deficient leukocytes in the peripheral blood, which increases with age. LOY is the most common acquired clonal mosaicism in aging men and is associated with shortened survival and several age-related diseases. Two non-mutually exclusive mechanisms have been proposed: LOY may act as a marker of generalised genomic instability and/or exert direct functional effects through the loss of dosage-sensitive Y-linked genes.

cused synthesis, the discussion that follows is deliberately selective; readers seeking an exhaustive catalogue of the primary literature are referred to these companion reviews [10,11,12,13,14].

2. The Y Chromosome and the Consequences of Its Loss

The human Y chromosome spans approximately 57 Mb and comprises two pseudoautosomal regions (PAR1 and PAR2), which recombine with the X chromosome during male meiosis, and a large male-specific region (MSY) [15]. The MSY contains both euchromatic sequences and an extensive heterochromatic block on its long arm, composed of highly similar satellite repeats, and carries only approximately 40 protein-coding genes or gene families, far fewer than any autosome [15,16] (Fig. 1). Crucially, these genes fall into two broad functional categories. The first comprises MSY genes that are evolutionarily conserved with homologues on the X chromosome, are broadly expressed across tissues, and perform dosage-sensitive regulatory functions in chromatin modification, transcription, translation, and RNA processing; examples include the histone demethylase *KDM5D*, the related *UTY*, and the transcription and translation factors *ZFY*, *DDX3Y*, *EIF1AY*, and *RPS4Y1* [17]. The second category comprises testis-specific genes, such as *SRY*, *TSPY*, and *RBMY*, whose primary roles are in male gonadal development and spermatogenesis. The distinction matters because the loss of a chromosome carrying broadly expressed, dosage-sensitive regulators provides a plausible route by which LOY could perturb cellular homeostasis in non-gonadal tissues, whereas the loss of testis-specific genes is expected to be largely silent outside the germline [15].

3. Prevalence, Aging and Environmental Risk

Applying a sensitive computational approach to genotyping data from more than 200,000 men in the UK Biobank, one study estimated that approximately one in five men had detectable LOY, with a prevalence rising from approximately 2.5% at age 40 to approximately 44% by age 70 [3]. Single-cell measurements extend this trajectory

further into late life, with detectable LOY reported in approximately 40% of men in their seventies and more than half of men in their nineties, which is higher than array-based estimates at the same ages because single-cell assays are more sensitive to low-fraction mosaicism, not because the underlying populations differ [18]. Notably, sensitive single-cell assays detect a small fraction of Y-deficient cells in essentially all men, irrespective of age, suggesting that such cells arise throughout life but undergo clonal expansion only once selective constraints relax in later decades, a pattern that would be consistent with the classical evolutionary theory of aging, in which the intensity of natural selection against late-acting deleterious effects declines with age (the "selection shadow"), although this interpretation remains to be tested directly for LOY [19]. Beyond age, smoking is a well-replicated and potentially reversible risk factor; current smokers have 2.4- to 4.3-fold higher odds of LOY than non-smokers [20]. Susceptibility is also markedly heritable, with one analysis estimating that approximately one-third of the variance in LOY liability is attributable to common germline genetic variation distributed across all chromosomes in proportion to their size [3]. Reported prevalence depends on the population studied as well as on the assay. In the Trans-Omics for Precision Medicine (TOPMed) programme, whole-genome sequencing of more than 25,000 ancestrally diverse men detected LOY in 11.5% of participants, and age-adjusted frequencies were highest in the group of European genetic similarity, with odds ratios of approximately 0.69, 0.54 and 0.80 for men of African, East Asian and admixed American similarity, respectively. These differences persisted after adjustment for smoking and for the density of informative heterozygous markers, and were attenuated but not abolished after conditioning on protective alleles at *TCL1A* and *BCL2L1*, which are, for example, about twice as common in the African-similarity group as in the European one; the similarity groups are used here as a statistical device to control for population structure and are not equivalent to racial or ethnic categories [21].

4. Genetic Architecture and the Origin of Y-Deficient Clones

Genome-wide association analysis has transformed our understanding of why some men develop LOY. Building on earlier studies that identified the first susceptibility loci and implicated cell cycle genes [22], a landmark analysis resolved 156 independent autosomal susceptibility loci replicated across hundreds of thousands of men of European and Japanese ancestry [3]. These loci are strongly enriched for genes that govern chromosome segregation and the broader cell cycle, including components of the condensin complex, the kinetochore, and the mitotic spindle-assembly checkpoint, together with central regulators of the DNA damage response and apoptosis, such as *ATM*, *TP53*, *CHEK2*, *PARP1*, and members of the *BCL*-2 family. This genetic signature suggests a two-step model for the origin of Y-deficient clones: the chromosome is first lost through mis-segregation during mitosis, and the resulting aneuploid cell then expands clonally in a permissive environment, having escaped the surveillance mechanisms that would normally eliminate it. In this respect, LOY is best understood as one facet of age-related clonal haematopoiesis. Clonal haematopoiesis driven by somatic point mutations in genes such as *DNMT3A*, *TET2*, and *ASXL*1 is detectable in approximately 10% of people older than 65 years and carries substantially increased risks of haematological malignancy and cardiovascular disease and death [23,24]; mosaic chromosomal alterations, of which LOY is by far the most common in men, constitute the large-scale chromosomal counterpart of this same process [4]. Single-cell analysis has begun to illuminate why such clones gain a foothold: among the genes near LOY susceptibility loci, *TCL1A*, which encodes a co-activator of the *AKT* survival kinase and is recurrently overexpressed in lymphoid malignancies, is markedly upregulated specifically in B lymphocytes that have lost the Y chromosome, and its aberrant activation has been shown experimentally to promote stem- and progenitor-cell expansion, providing a mechanistic explanation for the growth advantage conferred by Y loss in this lineage [3,22,25,26]. Whether Y-deficient clones and point-mutation-driven clonal haematopoiesis coexist or compete has begun to be addressed directly. In TOPMed, the crude prevalence of clonal haematopoiesis of indeterminate potential (CHIP) was about twice as high in men with LOY as in men without it, but this reflects the shared age dependence of the two processes: after adjustment for age, ancestry and study, CHIP was associated with lower odds of LOY (odds ratio 0.78), an inverse relationship driven mainly by *DNMT3A*-mutant and multi-gene CHIP. Among men carrying both, LOY clones were larger when CHIP was present, whereas CHIP clones were smaller when LOY was present, a reciprocal pattern interpreted as competition in which expanding Y-deficient clones limit the growth of CHIP clones [21].

5. Marker or Driver? Two Complementary Mechanisms

A central question is whether LOY in blood is a passive readout of an underlying process or an active contributor to disease. Two non-mutually exclusive hypotheses have emerged [3,15]. The first holds that detectable LOY is a barometer of genomic instability, a readily measurable manifestation of error-prone cell division occurring in parallel in other tissues, sometimes described as a common soil shared with cancer and other age-related diseases. A particularly compelling line of support comes from women, who lack a Y chromosome altogether: a polygenic score built from LOY susceptibility variants is nonetheless associated with female-specific cancers and with a later age at natural menopause, neither of which can be explained by Y loss itself, implying that the shared variants act through

general mechanisms of genome maintenance and apoptosis. The *CHEK2* locus exemplifies this logic: loss of CHEK2 function increases LOY in men while delaying menopause and raising breast-cancer risk in women, effects attributable to altered apoptotic control. The second hypothesis proposes that loss of the Y chromosome exerts a direct functional effect, for example, by impairing the immune surveillance carried out by leukocytes [3,27]. Decisive support has come from experimental modelling: male mice reconstituted with Y-deficient bone marrow developed cardiac dysfunction and increased mortality relative to controls with an intact Y chromosome, establishing that haematopoietic LOY can be causal rather than merely correlative [28]. The two hypotheses are therefore best regarded as complementary rather than competing, and the molecular basis of the direct effects is considered next.

6. Dosage-Sensitive Y-Linked Genes and Tissue-Specific Effects

The plausibility of a direct, cell-intrinsic contribution of Y loss rests on the molecular functions of the broadly expressed, X-homologous genes of the male-specific region, several of which act as general regulators of chromatin and gene expression rather than in male reproduction [15,17]. *KDM5D* and *UTY* encode histone demethylases that act on histone H3, at lysine 4 and lysine 27, respectively, mirroring their X-linked paralogues *KDM5C* and *KDM6A*; *DDX3Y* is an RNA helicase paralogous to *DDX3X* with roles in translation; and *ZFY*, *EIF1AY*, and *RPS4Y1* contribute to transcriptional and translational control [29,30,31]. Because these factors are dosage-sensitive and their X-linked counterparts do not fully compensate in every cellular context, the abrupt loss of the entire chromosome can shift the balance of chromatin modification and protein synthesis, thereby providing a mechanistic route by which Y loss perturbs cellular function outside the germline [15]. Consistent with this, single-cell transcriptomic profiling has shown that leukocytes lacking the Y chromosome display dysregulated expression of numerous autosomal genes, rather than a simple reduction in Y-linked transcripts alone [32]. The pseudoautosomal genes offer a more direct route still. Comparing men with and without LOY in two population cohorts, the transcripts most clearly reduced in blood were *TMSB4Y* and *RPS4Y1* from the male-specific region, together with the pseudoautosomal genes *SLC25A6*, *CSF2RA* and *CD99*, the last encoding a leukocyte surface protein involved in transendothelial migration and immune-cell interaction, whose abundance is correspondingly reduced on Y-deficient leukocytes. In the same men, at heterozygous pseudoautosomal sites the allele associated with higher *CD99* expression was preferentially retained, that is, it lay on the X-linked copy, raising the possibility that germline variation in *CD99* dosage influences which cells tolerate loss of the Y chromosome [21].

The functional consequences of this dysregulation are tissue- and lineage-specific. In the haematopoietic system, the Y chromosome shapes immune-cell transcriptomes [27], and Y-deficient leukocytes are proposed to mount weakened immune surveillance, a mechanism that could link LOY to both cancer and neurodegeneration. Direct support for an immune mechanism has come from solid tumours: cancers that have lost the Y chromosome or that have specifically downregulated *KDM5D* and *UTY* drive CD8+ T-cell dysfunction and exhaustion and follow a more aggressive clinical course, yet are correspondingly more sensitive to immune-checkpoint blockade, linking the loss of individual dosage-sensitive Y genes to both tumour immune evasion and a potential therapeutic vulnerability [33]. The most direct evidence at the tissue level comes from the heart: in mice, haematopoietic LOY drove profibrotic polarisation of cardiac macrophages and consequent cardiac fibrosis, reduced cardiac function, and increased mortality, and neutralisation of transforming growth factor-beta1 rescued the cardiac phenotype, pinpointing a specific effector pathway by which Y loss in immune cells damages a distant organ [28]. Taken together, these observations indicate that the effects of Y loss are channelled through the dosage of broadly expressed regulatory genes and then shaped by the transcriptional program of each cell type, so that the same genomic event may be silent in some lineages yet pathogenic in others [28].

7. Clinical Associations

The catalogue of conditions epidemiologically linked to LOY has expanded considerably, and several of these associations are quantitatively substantial (Table 1, Ref. [2,3,4,6,7,8,9,15,27,28,33,34,35,36,37,38,39,40]). In a cohort of elderly men, LOY in peripheral blood was associated with all-cause mortality (hazard ratio (HR) approximately 1.9) and most strikingly with non-haematological cancer mortality (HR approximately 3.6), corresponding to a median survival roughly 5.5 years shorter among men with LOY [6]. Beyond mortality and both haematological and non-haematological cancers [3,6], LOY susceptibility shows a systematic genetic overlap with the risk of prostate, testicular, and renal cancers and with glioma and breast cancer in women. LOY has additionally been associated with cardiovascular events [34], Alzheimer's disease [35], type 2 diabetes [38], autoimmune conditions, and age-related macular degeneration. The breadth of these associations and their male preponderance have reinforced interest in the Y chromosome as a determinant of men's health [1].

Several recent reports have extended and sharpened these associations. In pan-cancer analyses, LOY detected concurrently in tumour epithelium and in circulating $CD4^+$ and $CD8^+$ T cells independently predicted survival, with the poorest outcomes seen in men with LOY in both compartments, directly linking the acquired mosaicism discussed here to clinical prognosis rather than to genetic suscepti-

Table 1. Human diseases and conditions associated with changes of the Y chromosome.

Condition/disease	Y-chromosome change	Principal mechanism/key genes	Reference(s)
Germline (constitutional) changes present in all cells; heritable			
Male infertility (azoospermia/severe oligozoospermia)	AZFa, AZFb or AZFc microdeletion (Yq11)	Loss of spermatogenesis genes (*USP9Y*, *DDX3Y*, *RBMY*, *DAZ*)	[8,9,15]
Disorders of sex development (46,XX testicular DSD; 46,XY gonadal dysgenesis)	*SRY* translocation or loss-of-function	Aberrant or absent testis-determining factor *SRY*	[15]
Gonadoblastoma (in dysgenetic gonads)	GBY locus (*TSPY*) susceptibility	*TSPY* acting as a germ-cell proto-oncogene	[15]
Somatic (acquired) mosaic loss of chromosome Y (LOY) in blood accumulates with age			
Shortened survival; all-cause mortality	Mosaic LOY	Genomic instability; loss of dosage-sensitive Y genes	[2,6,7]
Haematological malignancy	Mosaic LOY/clonal mosaicism	Clonal expansion; cell-cycle dysregulation	[3,4,6]
Solid cancers (prostate, testis, kidney; glioma)	Mosaic LOY/LOY susceptibility	Shared "common-soil" genomic instability; tumour immune evasion, with concurrent T-cell LOY	[3,6,33,37]
Cardiovascular disease; heart failure	Mosaic LOY	Causal cardiac and pulmonary fibrosis in mouse models	[28,34,39,40]
Alzheimer's disease	Mosaic LOY	Impaired immune surveillance; genomic instability	[35]
Type 2 diabetes (with vascular complications)	Mosaic LOY/clonal mosaicism	Shared cell-cycle and apoptosis pathways; LOY detected in pancreatic β-cells	[3,36,38]
Autoimmune disease; immune dysregulation	Mosaic LOY	Altered immune-cell transcriptomes (Y as immune regulator)	[15,27]
Aberrant somatic activation of Y-linked genes (non-gonadal tissues)			
Parkinson's disease; Hirschsprung disease (reported associations)	Ectopic/aberrant expression of MSY genes (e.g., *SRY*)	*SRY* interference with SOX/RET regulatory networks	[15]

AZF, azoospermia factor; DSD, disorder of sex development; GBY, gonadoblastoma-on-the-Y locus; LOY, mosaic loss of chromosome Y; MSY, male-specific region of the Y chromosome. Gene symbols are italicised. The reference numbers correspond to the reference list in the main article. The analogous somatic event in females is the mosaic loss of the inactive X chromosome (LOX), which does not occur in males.

bility alone [37]. In type 2 diabetes, integrative analysis of germline Y haplogroups together with somatic LOY has shown that LOY increases diabetes risk particularly in men whose polygenic risk score is otherwise low, and LOY has been identified in pancreatic β-cells themselves, suggesting a direct, tissue-intrinsic contribution rather than a purely haematopoietic one [38]. The cardiovascular associations have likewise been extended beyond the general population: LOY predicts adverse cardiovascular events in patients with chronic kidney disease [39], and a large prospective cohort of older men has confirmed that LOY forecasts major cardiovascular events independently of conventional risk factors [40]. Taken together, these recent reports reinforce the view that LOY is not merely a static epidemiological correlate but a dynamic, tissue-relevant signal with growing clinical relevance across multiple organ systems.

8. Detecting LOY: From Bulk Estimates to Single-Cell Resolution

Progress in this field has been shaped, and at times constrained, by the available detection methods, which differ in the resolution at which Y loss is scored, the lowest mutant cell fraction they can reliably detect, throughput, cost, and applicability to tissues other than blood (Table 2, Ref. [3,4,18,21,41]). Cytogenetic karyotyping resolves chromosome complements in single metaphase spreads but requires dividing cells and is low-throughput, biasing observations toward proliferating populations, whereas interphase fluorescence *in situ* hybridisation retains single-cell information but is limited by the manual scoring of a small number of nuclei [18]. Genotyping microarrays moved the field to a population scale: early estimates relied on the mean log R ratio across the male-specific region (mLRR-Y), a bulk summary vulnerable to technical noise that can even imply a biologically implausible gain of the chromo-

Table 2. Comparison of methods for detecting mosaic loss of chromosome Y.

Method	Resolution	Sensitivity (lowest reliable fraction)	Throughput	Main limitation	Reference(s)
Karyotyping	Single cell	Low; rare events missed	Low	Requires dividing cells; culture bias	[18]
Interphase FISH	Single cell	Moderate	Low-moderate	Manual scoring; limited rare-event sensitivity	[18]
Genotyping array (mLRR-Y)	Bulk	Low; noisy at low fractions	High	Technical noise; implausible estimates	[3,18]
Genotyping array (allele-specific)	Bulk	Improved in large cohorts	High	No single-cell information	[3,4]
Droplet digital PCR (bulk)	Bulk	10% mutant fraction	Moderate-high	Unreliable below 10%	[18]
Whole-genome sequencing (read depth only)	Bulk	Depth-dependent; large clones only	Low-moderate	Coverage alone misses small clones	[18]
Whole-genome sequencing, haplotype-based (PAR1 allelic imbalance)	Bulk	Cell fractions to about 5%; one third of calls below 10%	Moderate	Requires WGS; depends on heterozygous marker density in PAR1	[21]
Copy-number callers on sequencing data (e.g., Control-FREEC, FACETS)	Bulk	Segment-level; large clones	Low-moderate	Built for tumour CNV calling; on exomes usually needs a matched normal	[41]
Exome or genome coverage, matched-exon normalisation (MosCoverY)	Bulk	About 12% at the statistical threshold	High; reuses existing data	Kit-specific exon matching; threshold derived from a cohort	[41]
Single-cell droplet (SinChro)	Single cell	Low fractions in all individuals	High	Newer; validation across tissues needed	[18]

Resolution indicates whether the Y loss is scored across a cell population (bulk) or in individual cells. The reference numbers correspond to the reference list of the main article. mLRR-Y, mean log R ratio of the Y chromosome; PAR1, first pseudoautosomal region; CNV, copy-number variant; WGS, whole-genome sequencing; FISH, fluorescence *in situ* hybridisation.

some, whereas later methods that model allele-specific intensities in the pseudoautosomal region substantially improved sensitivity in very large cohorts [3,4,18]. Droplet digital PCR offers a rapid, quantitative readout of the Y-to-autosome ratio; however, as a bulk assay, it loses reliability once Y-deficient cells fall below approximately one in ten. Whole-genome sequencing can map the loss directly, although a readout based on chromosome Y read depth alone resolves only comparatively large clones [18].

Two developments have since turned sequencing data into a practical substrate for LOY calling at population scale, and they differ in whether they exploit haplotype information or read depth. The first applies haplotype-based callers, originally written for mosaic chromosomal alterations on genotyping arrays, to whole genomes. Because a male cell carries one copy of the first pseudoautosomal region (PAR1) on the X chromosome and one on the Y, loss of the Y produces an allelic imbalance at heterozygous PAR1 markers that is visible in allele-specific read depth. Applied to more than 25,000 men from TOPMed sequenced at approximately 38-fold coverage, this approach detected LOY in 11.5% of participants, with a median mutant cell fraction of 13.4% and one third of calls below 10%; in the 2450 men who also had genotyping array data, it identified over five times as many carriers and recovered every event the array had called, with the gain concentrated among small clones [21]. The decisive variable is marker density rather than sequencing depth as such: whole-genome sequencing yielded a median of 1022 informative heterozygous markers in PAR1 per man, against a median of 93 on the Affymetrix 6.0 array and approximately 321 reported for the array used in the UK Biobank. Chromosome Y read depth alone tracked LOY status only for clones above roughly 10% of cells and could not reproduce the haplotype-based calls, which identifies allelic information, rather than coverage, as the source of sensitivity at low cell fractions [21].

The second development runs in the opposite direction and recovers LOY from coverage alone, which makes exome data usable, a substantial practical gain given how much more abundant exomes are than genomes in existing biobank and clinical collections. General-purpose copy-number callers can be applied to sequencing data, but they were built for tumour analysis and, on exomes, generally require a matched normal sample that single-sample cohorts do not provide [41]. Coverage-based calling on chromo-

some Y is also intrinsically awkward, because exome capture kits target few of its exons, GC content biases coverage, and much of the chromosome is either ampliconic or nearly identical to sequences on the X chromosome. MosCoverY addresses these problems by restricting the analysis to the exons of the 13 single-copy X-degenerate genes of the male-specific region and normalising each such exon to 100 autosomal exons matched on GC content and length; the median across exons yields a per-individual estimate of normalised chromosome Y coverage, which is rescaled so that the population median corresponds to the expected haploid value, dichotomised at the first quartile minus 1.5 times the interquartile range, and converted linearly into a cell fraction [41]. In 212,062 UK Biobank men this identified LOY in 5.6%, with cell fractions correlating above 0.8 with both array-based estimates and agreeing more closely with whole-genome copy-number calls than either array method did; the expected associations with age, smoking, all-cause mortality and germline susceptibility loci were reproduced, in most comparisons with somewhat larger effect estimates than the array-based traits. Estimates remained highly correlated with the originals when reads were downsampled, although agreement degraded as the retained fraction fell, and the approach transferred to tumour exomes from The Cancer Genome Atlas, in which the frequency of LOY ranged from 2% in papillary thyroid carcinoma to 89% in papillary renal carcinoma [41]. Its limitations follow from its design: the exon-matching step must be repeated for every capture kit; the binary threshold is derived from the distribution across a cohort, so a single sample can be scored only against an external threshold obtained with the same kit; and the rescaling step may inflate the estimated cell fraction, which was on average higher than the array-based estimates [41]. Neither sequencing strategy resolves individual cells; what they change is the cost of asking the question, since both recover LOY retrospectively from data generated for other purposes, and both extend measurement to cohorts and tissues that array-based studies have not covered.

A further advance closes the remaining gap in resolution by moving from bulk DNA to single cells: the SinChro assay partitions permeabilised leukocytes into thousands of droplets and interrogates each cell with many primer-probe sets distributed across chromosome Y and a reference autosome, the design of which depends on dedicated multiplex primer-design tools [42], converting the presence or absence of the Y chromosome in each cell into a separable fluorescent signal [18]. Because each droplet is scored independently, the method accurately quantifies the low mutant cell fractions that are inaccessible to bulk approaches while remaining rapid and inexpensive, and a matched configuration extends the same principle to the loss of the X chromosome [18]. As with any newly described method, these figures come from the assay's originating laboratory, and independent replication across cohorts, together with a clearer picture of its cost and throughput relative to established microarray and droplet-digital PCR workflows, will be needed before its performance can be considered generalisable. Computational approaches that improve sensitivity from existing array data, such as allele-specific intensity pipelines, remain a complementary and more widely validated option in the interim. Such single-cell assays are well placed to standardise LOY and LOX measurements across studies and to extend them to tissues beyond blood.

9. Loss of the X Chromosome: the Female Counterpart

An analogous phenomenon occurs in women, in which the inactive X chromosome is lost in a fraction of cells (loss of X chromosome [LOX]). Using a configuration of the single-cell droplet assay adapted to the X chromosome, an age-dependent accumulation of LOX was demonstrated in female blood, although the proportion of affected cells was consistently lower than that of LOY in men [18]. No LOX was detected in men, consistent with the expectation that the loss of the only X chromosome in a male cell, leaving it with a Y but no X chromosome, is incompatible with survival. The parallel between LOX and LOY underscores that age-related sex chromosome mosaicism is a general feature of somatic aging in both sexes.

10. Repetitive Architecture and Evolutionary Singularity of the Y Chromosome

The behaviour of the Y chromosome in somatic aging is best understood against its highly unusual architecture. The male-specific region is not uniform but a mosaic of sequence classes, comprising X-degenerate remnants of the ancestral autosome pair, X-transposed segments nearly identical to the X chromosome, and large ampliconic regions built from near-identical repeat units, all interspersed with heterochromatin [43]. A striking feature of the ampliconic class is a set of eight massive palindromes whose arms are kept almost perfectly identical by frequent intrachromosomal gene conversion, which helps preserve the testis-expressed gene families they contain [43]. Because these repetitive and heterochromatic regions long resisted assembly, more than half of the chromosome was absent from the human reference until the first complete telomere-to-telomere reconstruction resolved them, adding more than 30 Mb of previously missing sequence and revealing the full ampliconic structure of the *TSPY*, *DAZ*, and *RBMY* families together with the satellite arrays of the heterochromatic Yq12 block; much of this content derives from transposable elements and other repeats that propagate by reverse transcription [16], and dedicated computational tools are increasingly required to analyse such regions [44]. These features are a direct consequence of suppressed recombination across the male-specific region: lacking a homologous partner along most of its length, the Y chromosome cannot efficiently purge deleterious changes and has degenerated

over evolutionary time, retaining only about 40 protein-coding genes [15]. This architecture also has clinical consequences, because the same highly similar amplicons and palindromes provide substrates for non-allelic homologous recombination that generates recurrent AZF microdeletions underlying spermatogenic failure [15]; by the same logic, the intrinsic fragility of this repeat-rich, recombination-poor chromosome may predispose it to whole-chromosome mis-segregation that produces LOY. Finally, the Y chromosome is an evolutionary outlier: unlike the autosomes of present-day non-African populations, which retain a small component of Neanderthal ancestry, it carries essentially none, the archaic Y lineage having been replaced in modern humans much as archaic mitochondrial DNA was [45,46].

11. Conclusions and Future Perspectives

Mosaic loss of the Y chromosome has moved from a curiosity of cytogenetics to an informative and accessible window on somatic aging in men. The convergence of its genetic determinants on cell cycle and DNA repair pathways supports its interpretation as a biomarker of genomic instability. Functional studies have also shown that it can directly drive pathology. These two views are complementary rather than mutually exclusive.

Several limitations nonetheless temper current conclusions and define priorities ahead. Most population-scale evidence derives from the haematopoietic compartment because blood is readily sampled. The prevalence and consequences of sex-chromosome mosaicism in solid tissues remain largely uncharted [3,18]. Large association studies have, in addition, been conducted predominantly in men of European and, to a lesser extent, Japanese ancestry, leaving the transferability of effect estimates to other populations uncertain [3]. Sequencing-based calling has begun to narrow this gap, because it can be applied to the ancestrally diverse cohorts for which genotyping arrays were never optimised, and the first such survey has already shown that LOY frequency and its germline determinants differ between populations [21]; non-European men nonetheless remain heavily under-represented. Finally, the strongest causal evidence rests on engineered mouse models, whose correspondence to human pathophysiology requires confirmation in people [28]. Addressing these gaps will require standardised single-cell measurement of both LOY and LOX extended beyond blood, prospective cohorts that link clonal trajectories to incident disease, and functional studies that isolate the effects of individual dosage-sensitive Y-linked genes. Equally important is the translational question of whether LOY can be made clinically actionable. It could serve as a biomarker that refines risk stratification, or as a candidate predictor of response to immune-checkpoint blockade in Y-negative tumours [33], or as a modifiable trait whose trajectory might be altered by interventions such as smoking cessation [20]. Sensitive, scalable assays that quantify sex-chromosome mosaicism now provide the measurement foundation to answer these questions and to clarify the contribution of LOY and LOX to human aging and disease.

In my assessment, the most consequential near-term step is not further epidemiological confirmation of the associations catalogued here, most of which are now well replicated, but a shift toward tissue- and cell-type-resolved causal experiments capable of assigning specific phenotypes to specific dosage-sensitive genes. I would also argue that LOY's clinical utility will ultimately be judged less by its statistical association with disease, which is already well established, than by whether it can be shown, prospectively, to change a management decision; for instance, whether it can usefully refine surveillance intensity in a man with an intermediate cancer-risk score or flag a candidate for earlier cardiovascular risk-factor modification. Until such prospective decision-relevant studies exist, I regard LOY as a genuinely promising but not yet clinically actionable biomarker and consider this translational gap, rather than any remaining uncertainty about its epidemiology, as the field's central open problem.

Abbreviations

AZF, azoospermia factor; CHIP, clonal haematopoiesis of indeterminate potential; CNV, copy-number variant; FISH, fluorescence *in situ* hybridisation; HR, hazard ratio; LOX, loss of chromosome X; LOY, mosaic loss of chromosome Y; mLRR-Y, mean log R ratio of the Y chromosome; MSY, male-specific region of the Y chromosome; PAR1 and PAR2, first and second pseudoautosomal regions; TOPMed, Trans-Omics for Precision Medicine; WGS, whole-genome sequencing.

Author Contributions

RK designed the research study, performed the research, collected and analyzed the data, interpreted the results, and wrote the manuscript. RK contributed to editorial changes in the manuscript. RK read and approved the final manuscript. RK has participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The author declares no conflicts of interest.

References

[1] Maan AA, Eales J, Akbarov A, Rowland J, Xu X, Jobling MA, et al. The Y chromosome: a blueprint for men's health? European Journal of Human Genetics : EJHG. 2017; 25: 1181–1188. https://doi.org/10.1038/ejhg.2017.128

[2] Forsberg LA, Gisselsson D, Dumanski JP. Mosaicism in health and disease - clones picking up speed. Nature Reviews. Genetics. 2017; 18: 128–142. https://doi.org/10.1038/nrg.2016.145

[3] Thompson DJ, Genovese G, Halvardson J, Ulirsch JC, Wright DJ, Terao C, et al. Genetic predisposition to mosaic Y chromosome loss in blood. Nature. 2019; 575: 652–657. https://doi.org/10.1038/s41586-019-1765-3

[4] Loh PR, Genovese G, Handsaker RE, Finucane HK, Reshef YA, Palamara PF, et al. Insights into clonal haematopoiesis from 8,342 mosaic chromosomal alterations. Nature. 2018; 559: 350–355. https://doi.org/10.1038/s41586-018-0321-x

[5] JACOBS PA, BRUNTON M, COURT BROWN WM, DOLL R, GOLDSTEIN H. Change of human chromosome count distribution with age: evidence for a sex differences. Nature. 1963; 197: 1080–1081. https://doi.org/10.1038/1971080a0

[6] Forsberg LA, Rasi C, Malmqvist N, Davies H, Pasupulati S, Pakalapati G, et al. Mosaic loss of chromosome Y in peripheral blood is associated with shorter survival and higher risk of cancer. Nature Genetics. 2014; 46: 624–628. https://doi.org/10.1038/ng.2966

[7] Forsberg LA, Halvardson J, Rychlicka-Buniowska E, Danielsson M, Moghadam BT, Mattisson J, et al. Mosaic loss of chromosome Y in leukocytes matters. Nature Genetics. 2019; 51: 4–7. https://doi.org/10.1038/s41588-018-0267-9

[8] Agarwal A, Baskaran S, Parekh N, Cho CL, Henkel R, Vij S, et al. Male infertility. Lancet (London, England). 2021; 397: 319–333. https://doi.org/10.1016/S0140-6736(20)32667-2

[9] Tournaye H, Krausz C, Oates RD. Novel concepts in the aetiology of male reproductive impairment. The Lancet. Diabetes & Endocrinology. 2017; 5: 544–553. https://doi.org/10.1016/S2213-8587(16)30040-7

[10] Bruhn-Olszewska B, Markljung E, Rychlicka-Buniowska E, Sarkisyan D, Filipowicz N, Dumanski JP. The effects of loss of Y chromosome on male health. Nature Reviews. Genetics. 2025; 26: 320–335. https://doi.org/10.1038/s41576-024-00805-y

[11] Abdel-Hafiz HA, Hoelzen L, Theodorescu D. Beyond sex determination: the Y chromosome in male cancers. Nature Reviews. Cancer. 2026; 26: 586–603. https://doi.org/10.1038/s41568-026-00935-x

[12] Guo X, Dai X, Zhou T, Wang H, Ni J, Xue J, et al. Mosaic loss of human Y chromosome: what, how and why. Human Genetics. 2020; 139: 421–446. https://doi.org/10.1007/s00439-020-02114-w

[13] Guo X, Dai X. A complex systems approach to mosaic loss of the Y chromosome. GeroScience. 2025; 47: 631–651. https://doi.org/10.1007/s11357-024-01468-7

[14] Fukami M, Miyado M. Mosaic loss of the Y chromosome and men's health. Reproductive Medicine and Biology. 2022; 21: e12445. https://doi.org/10.1002/rmb2.12445

[15] Lau YFC. Y chromosome in health and diseases. Cell & Bioscience. 2020; 10: 97. https://doi.org/10.1186/s13578-020-00452-w

[16] Rhie A, Nurk S, Cechova M, Hoyt SJ, Taylor DJ, Altemose N, et al. The complete sequence of a human Y chromosome. Nature. 2023; 621: 344–354. https://doi.org/10.1038/s41586-023-06457-y

[17] Bellott DW, Hughes JF, Skaletsky H, Brown LG, Pyntikova T, Cho TJ, et al. Mammalian Y chromosomes retain widely expressed dosage-sensitive regulators. Nature. 2014; 508: 494–499. https://doi.org/10.1038/nature13206

[18] Tsuchiya J, Maki Y, Ayano M, Kikuchi T, Watanabe Y, Ohtake K, et al. A Novel Method for Acquired Sex Chromosome Mosaicism. Advanced Biology. 2024; 8: e2300512. https://doi.org/10.1002/adbi.202300512

[19] Hamilton WD. The moulding of senescence by natural selection. Journal of Theoretical Biology. 1966; 12: 12–45. https://doi.org/10.1016/0022-5193(66)90184-6

[20] Dumanski JP, Rasi C, Lönn M, Davies H, Ingelsson M, Giedraitis V, et al. Mutagenesis. Smoking is associated with mosaic loss of chromosome Y. Science (New York, N.Y.). 2015; 347: 81–83. https://doi.org/10.1126/science.1262092

[21] Jakubek YA, Ma X, Stilp AM, Yu F, Bacon J, Wong JW, et al. Genomic and phenotypic correlates of mosaic loss of chromosome Y in blood. American Journal of Human Genetics. 2025; 112: 276–290. https://doi.org/10.1016/j.ajhg.2024.12.014

[22] Wright DJ, Day FR, Kerrison ND, Zink F, Cardona A, Sulem P, et al. Genetic variants associated with mosaic Y chromosome loss highlight cell cycle genes and overlap with cancer susceptibility. Nature Genetics. 2017; 49: 674–679. https://doi.org/10.1038/ng.3821

[23] Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, Mar BG, et al. Age-related clonal hematopoiesis associated with adverse outcomes. The New England Journal of Medicine. 2014; 371: 2488–2498. https://doi.org/10.1056/NEJMoa1408617

[24] Genovese G, Kähler AK, Handsaker RE, Lindberg J, Rose SA, Bakhoum SF, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. The New England Journal of Medicine. 2014; 371: 2477–2487. https://doi.org/10.1056/NEJMoa1409405

[25] Zhou W, Machiela MJ, Freedman ND, Rothman N, Malats N, Dagnall C, et al. Mosaic loss of chromosome Y is associated with common variation near TCL1A. Nature Genetics. 2016; 48: 563–568. https://doi.org/10.1038/ng.3545

[26] Weinstock JS, Gopakumar J, Burugula BB, Uddin MM, Jahn N, Belk JA, et al. Aberrant activation of TCL1A promotes stem cell expansion in clonal haematopoiesis. Nature. 2023; 616: 755–763. https://doi.org/10.1038/s41586-023-05806-1

[27] Case LK, Wall EH, Dragon JA, Saligrama N, Krementsov DN, Moussawi M, et al. The Y chromosome as a regulatory element shaping immune cell transcriptomes and susceptibility to autoimmune disease. Genome Research. 2013; 23: 1474–1485. https://doi.org/10.1101/gr.156703.113

[28] Sano S, Horitani K, Ogawa H, Halvardson J, Chavkin NW, Wang Y, et al. Hematopoietic loss of Y chromosome leads to cardiac fibrosis and heart failure mortality. Science (New York, N.Y.). 2022; 377: 292–297. https://doi.org/10.1126/science.abn3100

[29] Iwase S, Lan F, Bayliss P, de la Torre-Ubieta L, Huarte M, Qi HH, et al. The X-linked mental retardation gene SMCX/JARID1C defines a family of histone H3 lysine 4 demethylases. Cell. 2007; 128: 1077–1088. https://doi.org/10.1016/j.cell.2007.02.017

[30] Vogt PH, Rauschendorf MA, Zimmer J, Drummer C, Behr R. AZFa Y gene, DDX3Y, evolved novel testis transcript variants in primates with proximal 3'UTR polyadenylation for germ cell specific translation. Scientific Reports. 2022; 12: 8954. https://doi.org/10.1038/s41598-022-12474-0

[31] Vogt PH, Zimmer J, Bender U, Strowitzki T. AZFa candidate gene *UTY* and its X homologue *UTX* are expressed in human germ cells. Reproduction & Fertility. 2021; 2: 151–160. https://doi.org/10.1530/RAF-20-0049

[32] Dumanski JP, Halvardson J, Davies H, Rychlicka-Buniowska E, Mattisson J, Moghadam BT, et al. Immune cells lacking Y chromosome show dysregulation of autosomal gene expression.

Cellular and Molecular Life Sciences : CMLS. 2021; 78: 4019–4033. https://doi.org/10.1007/s00018-021-03822-w

[33] Abdel-Hafiz HA, Schafer JM, Chen X, Xiao T, Gauntner TD, Li Z, et al. Y chromosome loss in cancer drives growth by evasion of adaptive immunity. Nature. 2023; 619: 624–631. https://doi.org/10.1038/s41586-023-06234-x

[34] Haitjema S, Kofink D, van Setten J, van der Laan SW, Schoneveld AH, Eales J, et al. Loss of Y Chromosome in Blood Is Associated With Major Cardiovascular Events During Follow-Up in Men After Carotid Endarterectomy. Circulation. Cardiovascular Genetics. 2017; 10: e001544. https://doi.org/10.1161/CIRCGENETICS.116.001544

[35] Dumanski JP, Lambert JC, Rasi C, Giedraitis V, Davies H, Grenier-Boley B, et al. Mosaic Loss of Chromosome Y in Blood Is Associated with Alzheimer Disease. American Journal of Human Genetics. 2016; 98: 1208–1219. https://doi.org/10.1016/j.ajhg.2016.05.014

[36] Bonnefond A, Skrobek B, Lobbens S, Eury E, Thuillier D, Cauchi S, et al. Association between large detectable clonal mosaicism and type 2 diabetes with vascular complications. Nature Genetics. 2013; 45: 1040–1043. https://doi.org/10.1038/ng.2700

[37] Chen X, Shen Y, Choi S, Abdel-Hafiz HA, Basu M, Hoelzen L, et al. Concurrent loss of the Y chromosome in cancer and T cells impacts outcome. Nature. 2025; 642: 1041–1050. https://doi.org/10.1038/s41586-025-09071-2

[38] Sato G, Yamamoto Y, Sonehara K, Saiki R, Ojima T, Kanai M, et al. Genetic regulation across germline and somatic variation on the Y chromosome contributes to type 2 diabetes. Nature Medicine. 2026; 32: 894–905. https://doi.org/10.1038/s41591-026-04213-z

[39] Weyrich M, Cremer S, Gerster M, Sarakpi T, Rasper T, Zewinger S, et al. Loss of Y Chromosome and Cardiovascular Events in Chronic Kidney Disease. Circulation. 2024; 150: 746–757. https://doi.org/10.1161/CIRCULATIONAHA.124.069139

[40] Hussain SM, Bjurling J, Yu C, Tonkin AM, Reid CM, Tran C, et al. Loss of Y Chromosome and Major Cardiovascular Events in a Prospective Study of Older Men. Journal of the American College of Cardiology. 2026; 87: 36–45. https://doi.org/10.1016/j.jacc.2025.10.069

[41] Timonina V, Marchal A, Abel L, Cobat A, Fellay J. MosCoverY: A method to estimate mosaic loss of Y chromosome from sequencing coverage data. American Journal of Human Genetics. 2025; 112: 2509–2519. https://doi.org/10.1016/j.ajhg.2025.08.016

[42] Kalendar R. Comprehensive web-based platform for advanced PCR design, genotyping, synthetic biology, molecular diagnostics, and sequence analysis. Molecular Therapy. Nucleic Acids. 2025; 36: 102716. https://doi.org/10.1016/j.omtn.2025.102716

[43] Skaletsky H, Kuroda-Kawaguchi T, Minx PJ, Cordum HS, Hillier L, Brown LG, et al. The male-specific region of the human Y chromosome is a mosaic of discrete sequence classes. Nature. 2003; 423: 825–837. https://doi.org/10.1038/nature01722

[44] Kalendar R, Kairov U. Genome-Wide Tool for Sensitive de novo Identification and Visualisation of Interspersed and Tandem Repeats. Bioinformatics and Biology Insights. 2024; 18: 11779322241306391. https://doi.org/10.1177/11779322241306391

[45] Petr M, Hajdinjak M, Fu Q, Essel E, Rougier H, Crevecoeur I, et al. The evolutionary history of Neanderthal and Denisovan Y chromosomes. Science (New York, N.Y.). 2020; 369: 1653–1656. https://doi.org/10.1126/science.abb6460

[46] Mendez FL, Poznik GD, Castellano S, Bustamante CD. The Divergence of Neandertal and Modern Human Y Chromosomes. American Journal of Human Genetics. 2016; 98: 728–734. https://doi.org/10.1016/j.ajhg.2016.02.023