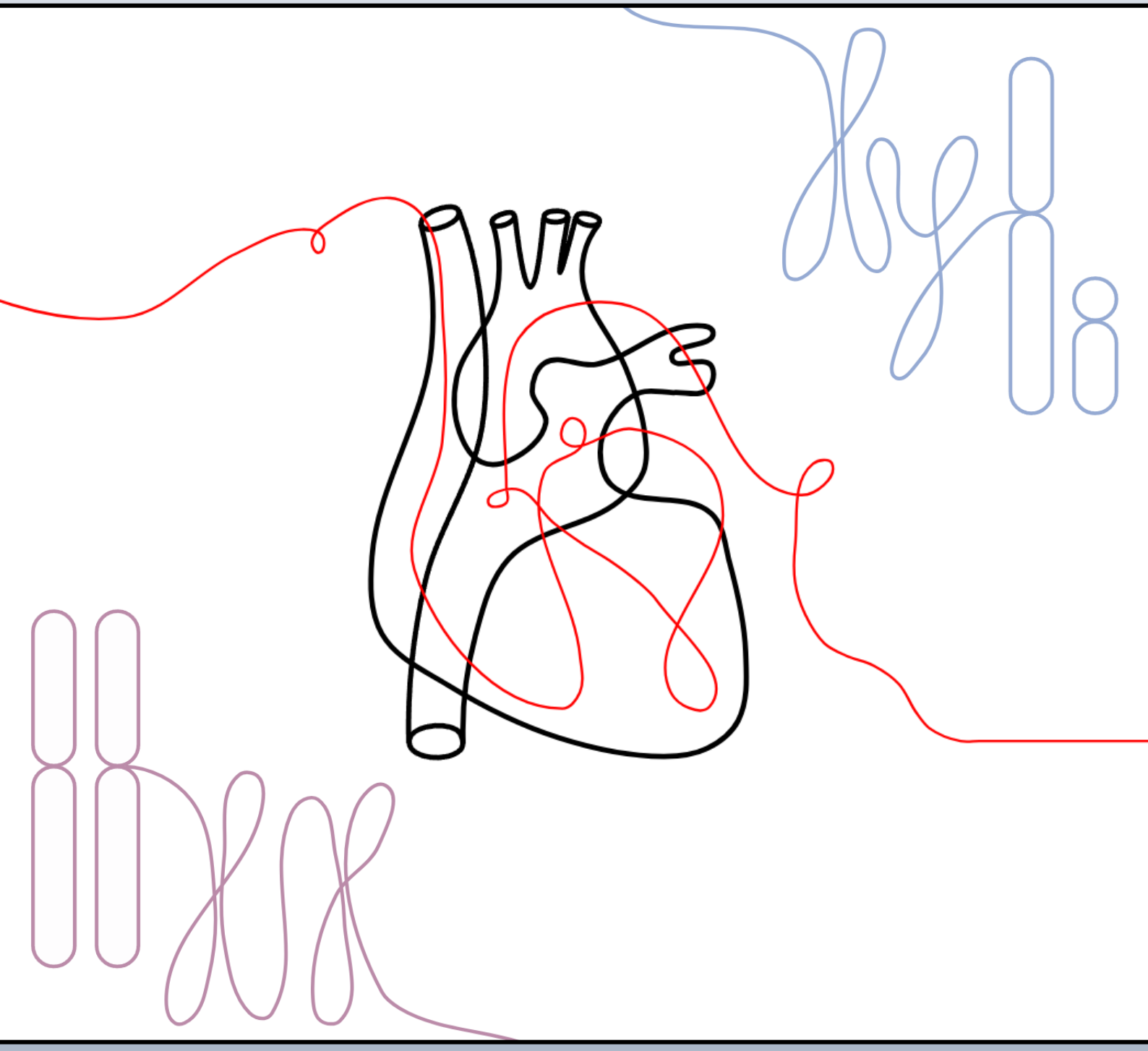
The Impact of Sex Chromosomes on Cardiovascular Disease: A Systematic Review



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Content

Plain language summary

Cardiovascular (heart and blood vessel) diseases are the leading cause of death for both men and women around the world. While many studies look at how hormones affect cardiovascular health, we know less about sex chromosomes. Sex chromosomes are parts of our inherited traits that determine if a person is male or female. Females have two X sex chromosomes, one from their mother and one from their father. Males have one X chromosome from their mother and one Y sex chromosome from their father. This review looks at how changes and variations in sex chromosomes can affect the risk of cardiovascular disease in men and women.

We searched a medical database for studies about sex chromosomes and cardiovascular diseases. We collected important information from each study and sorted them by different types of sex chromosome changes.

We found 29 studies that looked at how sex chromosomes relate to cardiovascular disease. There were no links between losing an X chromosome in females and disease. Changes in how the X chromosome works may be linked to a higher risk of cardiovascular disease. Losing the Y chromosome in males can harm cardiovascular health and lead to serious problems. Some studies linked specific variations of the Y chromosome to cardiovascular disease, while others did not.

Our review suggests that some changes in sex chromosomes are connected to a higher risk of cardiovascular disease. However, we still need to understand better how these sex chromosomes influence cardiovascular health and how to improve the way we check for disease risk in men and women.

Abstract

Background: Cardiovascular disease (CVD) remains the leading cause of death worldwide for both men and women. While most research on CVD sex differences focuses on sex hormones, the role of sex chromosomes is less understood. This systematic review examines how sex chromosome abnormalities and variations—loss of chromosome X (LOX) and Y (LOY), X chromosome inactivation (XCI) skewing and escape, and X and Y chromosome variations—affect CVD risk and outcomes.

Methods: A systematic search was conducted in PubMed on September 4, 2024, using Medical Subject Heading (MeSH) terms related to CVDs and sex chromosomes, excluding congenital sex chromosome disorders. After removing duplicates, records were screened for relevance based on predefined criteria, focusing on clinical and population-based studies. Data extraction included study characteristics, population details, sex chromosome abnormalities, and key findings. Records were categorized by type of chromosomal abnormality: LOX, XCI skewing, X chromosome variations, LOY, and Y chromosome variations.

Results: 29 studies were included, examining the role of sex chromosomes in CVD. There was only one study on LOX and CVD, which found no significant association between the two. Three studies on XCI skewing identified connections to thrombosis in essential thrombocythemia patients and atherosclerotic CVD risk in the general population. Additionally, XCI skewing in atherosclerotic patients was linked to plaque hemorrhage and peripheral artery events. One study on X chromosome variation linked maternal family history to hypertension. Seven studies indicated that LOY negatively affects cardiovascular outcomes and all-cause mortality. Seventeen studies investigated Y chromosome haplogroups (e.g. P, K, R, YAP, I); some identified associations with CVD risk, while others found no significant links.

Conclusion: Sex chromosome abnormalities and variations—particularly XCI skewing, LOY, and Y chromosome haplogroups—are associated with CVD. However, the causal relationships remain unclear, highlighting the need for further research to elucidate underlying mechanisms and enhance CVD risk assessment.

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide for men and women (1). Extensive research has focused on sex differences in CVD typically attributed to hormonal factors (2). However, the role of sex chromosomes in CVD remains underexplored (2). Emerging evidence indicates that sex chromosomes significantly influence disease development and overall health throughout life (2). This review aims to explore the impact of sex chromosome abnormalities and variations on CVD. We review acquired abnormalities and variations in sex chromosomes, including loss of chromosome X (LOX), skewing and escape of X chromosome inactivation (XCI), loss of chromosome Y (LOY), and X and Y chromosome variations. Notably, studies on LOX, XCI skewing, and escape focus on females, while LOY and Y chromosome variations are examined in males. X chromosome variations are relevant to both sexes.

LOX refers to the general loss of an X chromosome in a cell. In contrast, mosaic LOX (mLOX) occurs when some cells in an individual lose one X chromosome while others retain both, creating a mosaic of genotypes within one individual (**Figure 1A**) (3). mLOX is more prevalent than losses in autosomes and mainly affects the inactivated X chromosome (3). Additionally, mLOX is associated with an increased risk of leukemia, underscoring its health implications (4).

XCI equalizes gene dosage between sexes, as females have two X chromosomes (one maternal and one paternal), while males have one (maternal) (5). In females, one X chromosome is randomly inactivated, forming a transcriptionally inactive chromosome (Xi); this irreversible process is clonally transmitted to daughter cells (3). Skewing occurs when one X chromosome is preferentially inactivated, leading to a deviation from the expected random XCI (**Figure 1B**) (6). An estimated 1.5%-23% of females exhibit skewed XCI, which may influence the occurrence and severity of CVD. XCI escape refers to genes on the Xi that evade inactivation, with approximately 15%-30% of Xi genes remaining expressed (**Figure 1C**) (6). These "X escape genes" vary among individuals and cell types and can contribute to differences in gene expression between sexes, potentially influencing pathogenesis (2,6). In this review, we do not address the impact of specific escape genes on CVD.

LOY refers to the absence of the Y chromosome in male cells (**Figure 1D**). Mosaic LOY (mLOY) is particularly prevalent in elderly men, representing the most common chromosomal alteration in their leukocytes (7). mLOY is associated with shorter life expectancy, increased mortality, and various disorders, including cancer (8).

Variations in the X and Y chromosomes may influence CVD risk, but they are often overlooked in genome-wide association studies (GWAS), which typically focus on single nucleotide polymorphisms (SNPs). Haplogroups refer to large groups of haplotypes that share a common ancestor identified by specific genetic mutations (9,10). These mutations can provide insights into population history. In contrast, haplotypes consist of smaller sets of DNA variations that are inherited together. This review focuses on Y chromosome haplogroups to explore how variations contribute to CVD risk. Studying Y chromosome haplogroups is relevant as they may uncover male-specific genetic factors and population differences in CVD.

Despite established associations between acquired sex chromosome abnormalities and various diseases, their specific relationship with CVD remains fragmented and not widely acknowledged. This systematic review synthesizes current knowledge on LOX, XCI skewing and escape, LOY, and X and Y variations in CVD to clarify sex differences in CVD characteristics and risks.

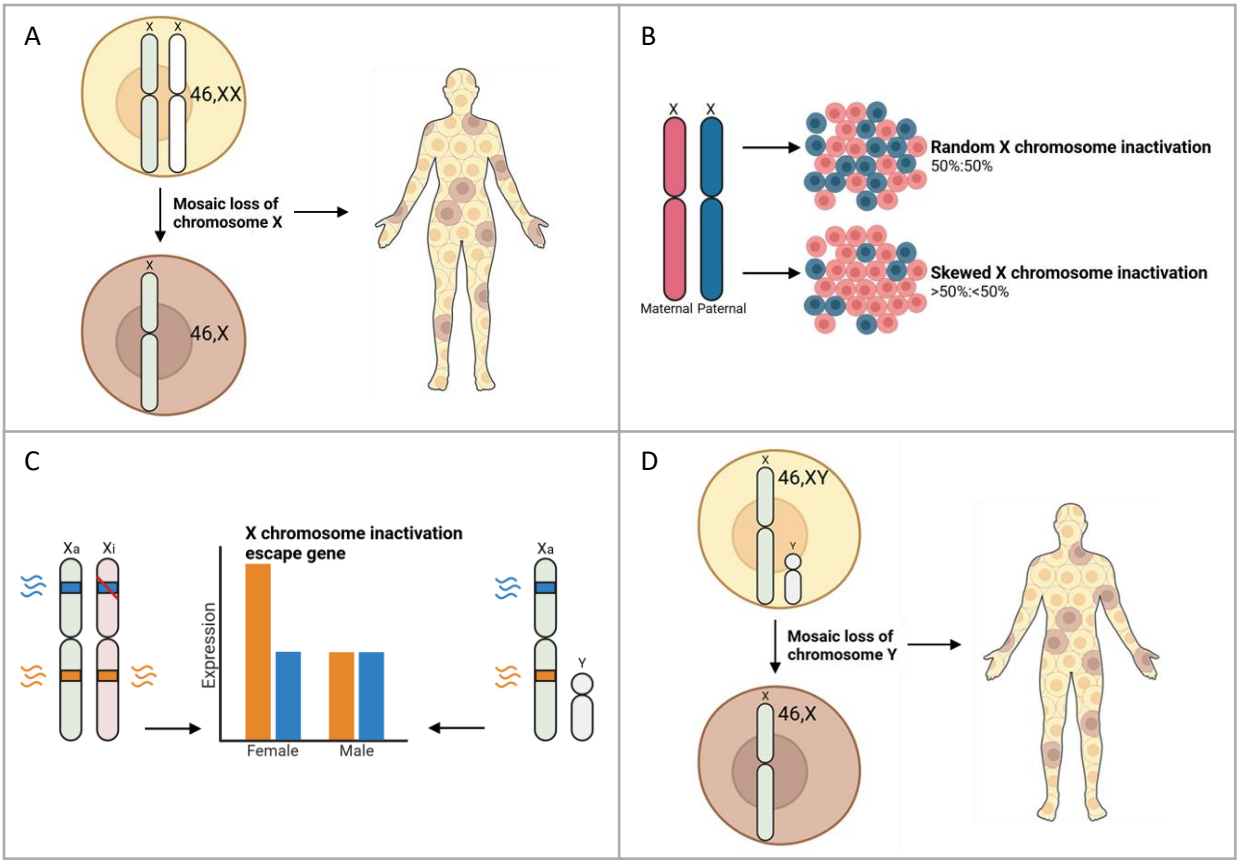

Figure 1. Schematic overview of sex chromosome abnormalities: A) mosaic loss of chromosome X; B) X chromosome inactivation skewing; C) X chromosome inactivation escape; D) mosaic loss of chromosome Y. (made with BioRender)

Methods

Data base search and study selection

To assess the role of sex chromosomes in CVD, a systematic search was performed in PubMed on September 4, 2024. The following Medical Subject Heading (MeSH) terms were used: 'Cardiovascular Diseases', 'Sex Chromosomes', 'Y Chromosome', 'X Chromosome', 'Chromosomes, Human, Y' and 'Chromosomes, Human, X' and variations thereof were used (**Supplementary Methods**). Additionally, the MeSH term 'Sex Chromosome Disorders of Sex Development' was used in combination with the Boolean operator "NOT" to exclude records dealing with congenital disorders where sexual development is atypical due to abnormal sex chromosome constitutions. The search was limited to English-language records.

Subsequently, duplicates were removed and titles and abstracts of all records were screened for relevance by one researcher (P.J.G.), using the online tool Rayyan. Records were considered irrelevant if they: 1) were no original research article (e.g. reviews, comments, letters, editorials, conference abstracts); 2) had no link with the role of sex chromosomes or CVD or the association between the two; 3) focused on inherited diseases/abnormalities or a single gene/gene mutation.

A further selection was made based on study type; experimental (animal/cell) studies were excluded, and only clinical/population studies were included. To obtain additional relevant records, we screened bibliographies of included records, performed a citation search and subjected obtained records to the aforementioned criteria. After that, the selection was refined after reviewing the full texts and applying the same inclusion and exclusion criteria. In cases of doubt or disagreements, consensus was reached through discussion between two researchers (P.J.G. and A.S.). Finally, the records were classified into groups based on their focus: 1) LOX; 2) XCI skewing; 3) XCI escape; 4) X chromosome variation; 5) LOY; 6) Y chromosome variation.

Data extraction

Data were extracted by one researcher (P.J.G.). From each article, we extracted bibliographical information (e.g. title, year of publication, journal, authors, DOI).

Next, we extracted the study population characteristics (e.g. age, ethnicity, health or disease status, and sample size by sex). Additionally, the source of the population, whether from biobanks, hospitals, or population cohorts, was extracted.

Lastly, we extracted information on methodology related to the sex chromosomal abnormalities, including LOX, XCI skewing, XCI escape, X chromosome variation, LOY, and Y chromosome variation. For each abnormality, we documented its definition, detection techniques, and control usage in the study. Additionally, we collected data on follow-up time (if applicable) and the main findings regarding the association between sex chromosomes and CVD.

Results

Data base search and study selection

The initial PubMed search resulted in 1,447 records, with no duplicates. After screening titles and abstracts, we included 30 records (**Figure 2**). In addition to the initial search, three relevant studies were identified through the citation search, leading to the identification of 33 population studies (**Figure 2**). A total of 33 studies were assessed for eligibility based on the full text. Of these, four studies were excluded. Consequently, 29 relevant population studies were included in this systematic review (**Figure 2**).

These studies were categorized into groups based on their focus: one focused on LOX, three studies focused on XCI skewing, one on X chromosome variation, seven studies on LOY, and 17 studies focused on Y chromosome variation (**Figure 2**). Extraction tables summarizing these studies are provided in the supplementary information (**Supplementary Results Tables S1-S5**).

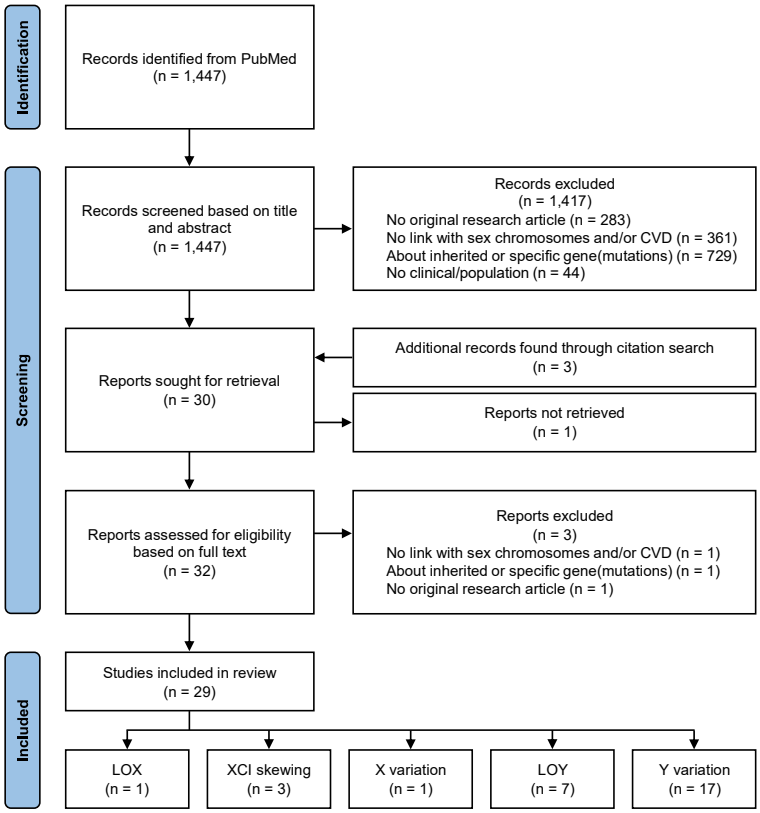

Figure 2. PRISMA flow diagram.
CVD = cardiovascular disease; LOX = loss of chromosome X; XCI = X chromosome inactivation; LOY = loss of chromosome Y

Sex chromosomes and cardiovascular disease

The X chromosome and cardiovascular disease

We selected five studies on the X chromosome and CVD. One study focuses on LOX (5), while three studies examine XCI skewing (11–13). Additionally, there is one study investigating X chromosome variation (14).

Loss of chromosome X

LOX has been linked to several oncological conditions, but its influence on CVD is less clear. Only one study fit our inclusion criteria (5).

Methodology

Liu et al. (2024) used blood samples to identify mLOX in females by analyzing leukocytes through SNP arrays. mLOX was detected using the Mosaic Chromosomal Alterations (MoChA) pipeline, which quantifies mLOX by analyzing the imbalance of the B allele frequency (BAF) and Log R Ratio (LRR) on the X chromosome. BAF measures the relative intensity of the B allele to indicate chromosomal abnormalities, while LRR reflects the total intensity of both alleles to assess chromosomal imbalance. Subsequently, the cell fraction of mLOX in leukocytes was calculated, reflecting the proportion of cells affected by mLOX (5).

Associations with cardiovascular disease

The study analyzed data from female participants across eight biobanks, which included both patient and general population biobanks. It revealed that approximately 12% of participants exhibited detectable mLOX, with a median fraction of affected leukocytes around 2%. A meta-analysis found no significant association between mLOX and a wide range of circulatory diseases. Although mLOX was associated with hematological abnormalities—such as increased leukemia risk and changes in blood cell counts, including higher lymphocyte and lower neutrophil counts—no statistically significant connection to CVD was identified (5).

X chromosome inactivation skewing

Three studies examined the link between XCI skewing and CVD, focusing on vascular complications in essential thrombocythemia (ET) (11), atherosclerotic cardiovascular disease (ASCVD) risk in the general population (13), and the risk of peripheral artery events after carotid endarterectomy (CEA) in advanced atherosclerotic plaques (12).

Methodology

XCI skewing was measured in peripheral blood in all three studies (11–13). Additionally, Buono et al. (2023) also examined skewing in atherosclerotic lesions from carotid arteries (12).

All three studies employed the Human Androgen Receptor Assay (HUMARA) to measure XCI skewing, a well-established PCR-based method that amplifies a polymorphic region of the androgen receptor gene on the X chromosome (11–13). The ratio of expressed alleles in the amplified DNA reveals the proportion of cells with either active X chromosome, enabling determination of the degree of skewing.

However, the studies applied different criteria for defining and categorizing XCI skewing. Shih et al. (2002) classified XCI patterns (XCIP) by analyzing granulocytes and T cells (11). “Clonal XCIP” is an example of XCI skewing, where the skewing is pronounced enough to categorize the cell population as clonal. Clonal XCIP was defined as having over 50% clonal granulocytes and a Relative Gene Expression (RG) value below 0.33, indicating that one X chromosome is predominantly inactivated across a significant portion of cells. Additionally, a T Cell Allele Ratio (RT) of 1.0, where T cells express only one

allele, further supported clonal expansion. “Polyclonal XCIP” included cases with less than 50% clonal granulocytes and RG values above 0.33, reflecting a more balanced X chromosome expression and a heterogeneous cell population (11).

Roberts et al. (2022) defined XCI skewing as over 75% inactivation of one X chromosome and extreme skewing as over 91% (13). They categorized XCI skew based on the distribution of absolute values from normalized XCI percentage data: values within 1 SD from the mean were classified as random XCI, between 1 and 2 SDs as skewed XCI, and over 2 SDs as extreme skewing (13).

Buono et al. categorized XCI skewing in atherosclerotic plaques using both dichotomous and binned approaches. The dichotomous variable for skewed plaques was determined using the Ordered Quantile Normalization technique, with a cut-off set at greater than 63.9% inactivation of one X chromosome. The binned categories were defined as follows: less than 60% (non-skewed), 60-70% (lowly skewed), 70-80% (moderately skewed), and over 80% (highly skewed) (12).

Associations with cardiovascular disease

In the first study, Shih et al. examined female ET patients at Chang Gung Memorial Hospital, China. They found that 68% exhibited clonal XCIPs, while 19% had polyclonal patterns. Clonal XCIPs were associated with a higher risk of thrombosis and correlated with increasing age, but did not significantly affect hemorrhage occurrence, platelet counts or other hematological features (11).

In the second study, Roberts et al. examined the relationship between XCI skewing and ASCVD risk using data from the TwinsUK cohort, which included female monozygotic twins, dizygotic twins, and singletons. Among the females for whom the ASCVD risk score was determined, 68% had random XCI, 25% had skewed XCI, and 7% had extreme skewed XCI. XCI skewing significantly associated with an increased ASCVD risk score, estimating 10-year CVD risk based on traditional cardiovascular risk factors. To rule out age confounding, the researchers analyzed age-matched monozygotic and dizygotic twin pairs discordant for XCI skew status, confirming the link between higher XCI skew and elevated ASCVD risk. They also found that XCI skew remained stable over a 15-17 year follow-up. Additionally, XCI skewing correlated with increased monocyte abundance, independent of other biological aging markers, highlighting the role of monocytes/macrophages in CVD inflammation (13).

In the third study, Buono et al. investigated the relationship between XCI skewing in advanced atherosclerotic plaques and CVD using data from the Athero-Express biobank. Analysis of plaques and blood samples from female patients undergoing CEA showed XCI skewing in 49% of the plaques and 67% of the blood samples. Traditional cardiovascular risk factors were not linked to plaque skewing. However, plaques with XCI skewing were significantly associated with plaque hemorrhage and had a strong correlation with peripheral artery events over a 3-year follow-up. In contrast, skewed plaques did not correlate with major adverse cardiovascular events (MACE) (12).

The three studies illustrate that XCI skewing influences CVD risk in females, with varying prevalence across different tissues and contexts. Shih et al. found clonal XCI skewing in 68% of female ET patients, associated with a higher risk of thrombosis, but notably, it showed no effects on blood characteristics such as platelet counts (11). In contrast, Roberts et al. found that XCI skewing in 36% of females was linked to increased ASCVD risk but also to higher monocyte counts, suggesting a role in inflammation (13). Buono et al. observed XCI skewing in 49% of atherosclerotic plaques and 67% of blood samples from females post-CEA, associated with plaque hemorrhage and peripheral artery events (12). Despite differing skew definitions and CVD contexts, all studies highlight a substantial prevalence of XCI skewing, underscoring its role in cardiovascular health for females.

X chromosome variation

One study by Ciccarelli et al. (2017) examined the influence of maternal and paternal familiarity on hypertension, highlighting the potential implications of X chromosome variability on hypertensive phenotypes (14).

Methodology

DNA was extracted from blood samples of 1,200 participants and genotyped using a SNP array to identify variants associated with hypertension. Associations with hypertension were then assessed across additive, dominant, and recessive genetic models (14).

Associations with cardiovascular disease

The study analyzed data from the Campania Salute Network at Federico II University Hospital in Naples, Italy, involving both hypertensive and normotensive individuals. Results showed that 75% of hypertensive patients had a family history, versus 26% of normotensives, with family history increasing risk by 2.91 times. Maternal history had a stronger association with hypertension than paternal history. Additionally, specific X chromosome regions were linked to hypertension in males with maternal history, suggesting a role for X-linked variants in maternal transmission (14).

The Y chromosome and cardiovascular disease

We have selected a total of 24 studies focusing on the role of the Y chromosome in CVD. This includes 7 studies examining the role of LOY in CVD (15–21) and 17 studies exploring various Y chromosome variations (22,23,32–38,24–31).

Loss of chromosome Y

We included seven studies about the relationship between LOY and various cardiovascular outcomes, including atherosclerosis (17), abdominal aortic aneurysm (AAA) (18), aortic valve stenosis (19), ischemic stroke (21), and heart failure (20). Additionally, some studies addressed CVD in general and mortality (15,16,20).

Methodology

In all studies, LOY was measured in peripheral blood samples (15–21), with some also examining non-blood tissues like atherosclerotic plaques (17) and AAA tissue (18). Measuring techniques included SNP arrays (15–17,21), digital PCR (19,20), and fluorescence in situ hybridization (FISH) (18).

The most common method, SNP genotyping, used arrays like Affymetrix UK BiLEVE (15), UK Biobank Axiom (15), and Illumina Infinium (21) to detect LOY by analyzing the median log R ratio (mLRR) of Y-chromosomal SNPs. Digital PCR, used in two studies, determined the Y/X ratio using a TaqMan-based approach targeting the homologous AMELX and AMELY genes (19,20). FISH was used in one study to quantify LOY by calculating the percentage of cells with Y chromosome loss in T-lymphocytes and AAA tissue (18).

LOY was defined as either a continuous percentage of cell count, a dichotomous variable with a cut-off, or both across studies. Two studies quantified LOY continuously as a percentage of total cell count (2, 4). In six studies, LOY was dichotomized, applying a cut-off to determine if Y chromosome loss occurred in a significant proportion of cells (15–17,19–21).

Different cell proportion cut-offs were used in the dichotomous analyses to define the presence of LOY (**Table 1**). Several studies set a cut-off of mLRR < -0.15 for LOY in peripheral blood, corresponding to approximately 10% LOY cell proportion (16,21). One study applied a stricter threshold of mLRR < -0.40,

indicating around 24% LOY cell proportion (16). Another study established a cut-off of mLRR < -0.075 based on blood mLRR distribution (17). For atherosclerotic plaques, a cut-off of mLRR < -0.129 was used (17). In two studies, LOY cut-offs were determined using the Youden index from receiver operating characteristic (ROC) analyses, identifying >17% LOY cell proportion as optimal (19,20). Some cut-offs were based on previous studies (15,16,21), while others were newly adapted based on the findings within the research (17,19,20).

Study	Tissue	LOY mLRR cut-off	LOY cell proportion cut-off	Based on
Haitjema et al. (2017)	Blood	< -0.075	NA	mLRR distribution
Haitjema et al. (2017)	Plaque	< -0.129	NA	mLRR distribution
Loftfield et al. (2018)	Blood	< -0.15	>10%	Previous research
Loftfield et al. (2018)	Blood	< -0.40	NA	Previous research
Mas-Peiro et al. (2023)	Blood	NA	>17%	Youden index from ROC analyses
Dorvall et al. (2023)	Blood	< -0.15	>24%	Previous research
Weyrich et al. (2024)	Blood	NA	>17%	Youden index from ROC analyses

Table 1. Dichotomous LOY cell proportion cut-offs.
LOY = loss of chromosome Y; mLRR = median log R ratio; NA = not available; ROC = receiver operating characteristic

Associations with cardiovascular disease

Haitjema et al. (2017) investigated LOY in blood and excised atherosclerotic plaques of males undergoing CEA due to severe atherosclerosis to assess its relationship with plaque characteristics and cardiovascular outcomes. Among patients in the Athero-Express Biobank, 16.7% exhibited LOY in blood, while only 3% showed LOY in atherosclerotic plaques. Although LOY in blood appeared to be associated with larger plaque size, this correlation did not hold after multiple testing correction. Notably, LOY in blood was independently linked to an increased risk of MACE during a three-year follow-up, suggesting a role in CVD progression independent of age and other risk factors. Importantly, no significant associations were found between LOY in blood and inflammatory plaque phenotypes or systemic inflammatory markers, indicating that LOY's impact may occur through non-inflammatory mechanisms (17).

Loftfield et al. (2018) investigated mLOY in blood within a large general population cohort from the UK Biobank. They found that mLOY increased exponentially with age and was strongly associated with smoking. Notably, males of African descent exhibited lower rates of mLOY (0.4%) compared to European males (1.8%). Additionally, mLOY was linked to diabetes and CVDs, as well as an increased risk of all-cause mortality (mLRR < -0.40) (16).

Tang et al. (2019) studied male patients with AAA from the China Medical University aneurysm Biobank and aneurysm blood Biobank. They measured LOY in peripheral T lymphocytes and AAA tissue, investigating its association with age and AAA development. Results indicated that LOY cell proportion was significantly higher in peripheral T lymphocytes of the AAA group (9.11%) compared to healthy controls (5.56%) and the matched control group of aortic occlusive disease patients (6.42%). LOY was also significantly elevated in AAA tissue and positively correlated with age. These findings suggest that LOY is a systemic phenomenon in both blood and affected tissue, potentially playing a role in AAA progression (18).

In another study, Lin et al. (2020) investigated mLOY in blood in a general male population cohort from the UK Biobank to assess its relationship with blood cell counts. Among the participants, 19.3% exhibited mLOY, which was associated with variations in blood cell counts independent of age and

smoking. Specifically, mLOY correlated with a decrease in erythrocytes and increases in platelets and leukocytes, particularly neutrophils and monocytes (15).

Mas-Peiro et al. (2023) examined the correlation between mLOY in blood and survival rates following transcatheter aortic valve replacement (TAVR) in males with advanced aortic stenosis. Among the males who successfully underwent TAVR, 29.6% exhibited mLOY in >17% of their cell count. The study found that three-year all-cause mortality increased with mLOY, identifying it as a significant independent predictor of mortality during follow-up. Additionally, single-cell RNA sequencing of circulating monocytic blood cells from seven patients revealed a pro-fibrotic gene profile in monocytes lacking the Y chromosome, suggesting that cardiac fibrosis may significantly contribute to the negative impact of mLOY on survival after TAVR (19).

Dorvall et al. (2023) investigated the association between mLOY in blood and functional outcomes following ischemic stroke in two male patient cohorts: the Sahlgrenska Academy Study on Ischemic Stroke Phase 2 and the Lund Stroke Register. Functional status was assessed three months post-stroke using the Modified Rankin Scale (mRS). The results indicated that males with mLOY had a higher risk of poor functional outcomes, including dependency or death, especially among those who did not receive recanalization therapy. In this group, the association remained significant after adjusting for age, stroke severity, and diabetes (21).

Weyrich et al. (2024) explored the relationship between mLOY in blood and all-cause mortality and cardiovascular outcomes in chronic kidney disease patients from two cohorts: CARE for HOMe with stable chronic kidney disease patients and the 4D study with hemodialysis patients. mLOY in >17% of cells was associated with higher mortality and heart failure risk, though not with atherosclerotic events. Patients with elevated mLOY also exhibited reduced ejection fraction and an increased E/E' ratio, suggesting poorer cardiac function within five years. Enhanced expression of C-C chemokine receptor type 2 (CCR2) in monocytes and higher plasma C-C motif ligand 2 (CCL2) levels were observed, potentially contributing to the increased risk of heart failure (20).

The studies collectively indicate that LOY is linked to higher cardiovascular risk and worse outcomes, regardless of the cutoffs used (15–21). The findings generally agree that LOY prevalence rises with age and is influenced by environmental factors like smoking (16,18). Furthermore, LOY's effects are observed both systemically in blood and locally in affected tissues, including aneurysms and, to a lesser extent, atherosclerotic plaques (17,18). However, the studies diverge on the specific CVDs investigated and the mechanisms at play: for instance, Haitjema et al. found no inflammatory association with LOY in atherosclerosis patients (17), while Weyrich et al. identified inflammatory markers like CCR2 and CCL2 as contributors to heart failure risk in kidney disease patients (20).

The prevalence of LOY varied among the different populations and tissues (**Table 2**). In the general population, Loftfield et al. reported LOY in 1.8% of European males and 0.4% of males of African descent within a large UK Biobank cohort (16). In another general population study, Lin et al. found LOY in 19.3% of participants, with 20% in white individuals and 5.8% in Black individuals (15). Tang et al. reported that LOY was more prevalent among cardiovascular patients, observing rates of 9.11% in males with abdominal aortic aneurysms (AAA) compared to 5.56% in healthy controls (18). Among ischemic stroke patients, 15.6% exhibited LOY (21), while 11.1% of individuals with chronic kidney disease displayed LOY (20). Additionally, 29.6% of patients who underwent TAVR showed LOY (19). In patients with advanced atherosclerosis, 16.7% had LOY in their blood, whereas only 3% of atherosclerotic plaques exhibited LOY (17). Overall, these findings suggest that LOY is more prevalent in individuals with CVDs compared to the general population, as reported by Loftfield et al. (16).

Variations in LOY prevalence may arise from cut-off values, the specific tissues measured, ethnicity, age, disease type and severity, and environmental influences like smoking.

Study	Population	Tissue	LOY prevalence
Haitjema et al. (2017)	Atherosclerosis patients undergoing CEA	Blood	16.7%
		Plaque	3%
Loftfield et al. (2018)	General population - African ancestry	Blood	0.4%
	General population - European ancestry	Blood	1.8%
Tang et al. (2019)	AAA patients	Blood T lymphocytes	9.11%
	Healthy controls	Blood T lymphocytes	5.56%
Lin et al. (2020)	General population	Blood	19.3%
	General population - Black	Blood	5.8%
	General population - white	Blood	20%
Mas-Peiro et al. (2023)	Advanced aortic valve stenosis patients undergoing TAVR	Blood	29.6%
Dorvall et al. (2023)	Ischemic stroke patients	Blood	15.6%
Weyrich et al. (2024)	Stable chronic kidney disease patients	Blood	11.1%

Table 2. LOY prevalence in different populations and tissues.
LOY = loss of chromosome Y; CEA = carotid endarterectomy; AAA = abdominal aortic aneurysm; TAVR = transcatheter aortic valve replacement

Y chromosome variation

Seventeen studies examined the role of Y chromosome variation in CVD. While several identified associations between specific haplogroups—such as P, K, R, YAP (also known as DE), and I—and CVD (22,23,26,27,29–31,35,36,38), others reported no significant link between Y chromosome haplogroups and CVD (24,25,28,32–34,37). One study focused on a specific Y chromosome haplotype and its association with CVD (26).

Methodology

The studies investigating Y chromosome haplogroups included DNA extraction, genotyping, and haplogroup classification. All studies extracted DNA from blood samples (22–31), with some also using tissue samples from CAD-relevant sites (including subcutaneous adipose tissue, visceral adipose tissue, aorta, coronary artery, tibial artery, atrial appendage tissue, and left ventricle tissue), atherosclerotic plaques or aneurysms (33,35). Genotyping techniques typically involved PCR-RFLP for HindIII polymorphism analysis and SNP genotyping arrays to detect other specific Y chromosome markers (26,27,29–31,33,35–38).

SNP genotyping and haplogroup classification were performed using software such as yHaplo, following phylogenetic frameworks from the Y Chromosome Consortium (YCC) (**Supplementary Figure S1**) and the International Society of Genetic Genealogy (ISOGG) (27–35,37). Some studies utilized advanced techniques like next-generation sequencing to investigate chromatin states and gene expression, employing resources such as ENCODE and GTEx (35). The primary haplogroups analyzed included E, G, I, J, and R, representing major Y chromosome lineages in European populations (29,34).

Associations with cardiovascular disease

Early studies examining Y chromosome variation have primarily focused on the HindIII polymorphism's impact on blood pressure (BP) and its implications for CVD risk (22–25,28). The HindIII(-) genotype corresponds to Y chromosome haplogroup P (10). Ellis et al. (2000) found that HindIII(+) was significantly associated with lower diastolic BP in white males but did not link it to systolic BP (14) (22). In contrast, Charchar et al. (2002) reported that HindIII(+) correlated with higher systolic and diastolic BP in Polish and Scottish males, indicating a potential association with elevated BP (23). Rodríguez et

al. (2005), analyzing a UK cohort, and Russo et al. (2006), studying populations from Italy, the UK, and Belgium, both found no significant associations between HindIII polymorphisms and BP (24,25). Similarly, Kostrzewa et al. (2013) reported no link between HindIII and BP in a Polish population (28). In summary, while Ellis et al. and Charchar et al. found contrasting associations with BP (22,23), other studies did not confirm these links (24,25,28). The prevalence of HindIII(+/-) varied across ethnic groups, indicating that HindIII's impact on BP might differ by geographic and ethnic factors.

Several later studies have linked Y chromosome haplogroups K, R, YAP, and I to CVD (26,27,29–31,35,36,38). Notably, the TBL1Y(A) USP9Y(A) haplotype in males of African descent is associated with better lipid profiles—lower triglycerides and higher HDL cholesterol—contributing to a reduced risk of coronary heart disease (CHD) (26).

A study of Greek Cypriot males found that carriers of the YAP haplogroup had approximately a 50% reduced risk of plaques in the femoral bifurcation. In contrast, haplogroup K and its sub-haplogroup R were linked to a 2.5-fold increased risk of atherosclerotic plaques in arterial bifurcations (31). Further investigation of haplogroup R in Spanish males under 55 years old with premature ST-Elevation Myocardial Infarction (STEMI) revealed an association with CVD. The study found that haplogroup R, particularly sub-haplogroup R1b, was more prevalent in these STEMI patients compared to controls (38). Additionally, a study comparing males with Chagas disease to controls assessed the R1b haplogroup and found a potential protective cardiovascular effect. Patients lacking the R1b haplogroup were nearly five times more likely to have a cardio-thorax index greater than 0.5% and 2.5 times more likely to show echocardiographic alterations, indicating that R1b may offer protection in Chagas cardiomyopathy (36).

Furthermore, haplogroup I has been associated with CVD, particularly coronary artery disease (CAD), in several studies (27,29,30,35). One study of British males found that carriers of haplogroup I faced approximately a 50% increased risk of CAD, independent of traditional cardiovascular and socioeconomic factors (27). Furthermore, research involving white European cohorts indicated that haplogroup I is linked to the downregulation of the UTY and PRKY genes, potentially contributing to the increased CAD risk observed in these individuals (29). In a Polish cohort, Bloomer et al. (2014) investigated potential explanations for the link between haplogroup I and CAD, concluding that sex steroids or early-life aggression are unlikely causes, suggesting other underlying mechanisms (30). A comprehensive analysis of males from the UK Biobank and STAGE study linked haplogroup I1 to an 11% increased CAD risk. The study identified I1-specific variants enriched in regulatory chromatin states, affecting gene regulation in atherosclerosis-related tissues. Additionally, haplogroup I1 was shown to influence key atherosclerosis pathways, including immune response, mitochondrial function, lipid metabolism, coagulation, and extracellular matrix remodeling (35).

While some studies suggest links between Y chromosome haplogroups and CVD, others report no associations (28,32–34,37). For instance, Kostrzewa et al. (2013) found that Y chromosome genetic variation likely does not influence cardiovascular risk in a Polish cohort (28). Another study indicated that Y haplogroups do not influence cardiometabolic risk or cardiovascular measures in childhood and adolescence (34). In a study by de Haan et al. (2016) on venous thrombosis (VT) in northwest European males, six major Y haplogroups—R1b, I, R1a, J, E, and G—were analyzed. Although haplogroup E showed a slight, non-significant trend towards increased recurrent VT risk, no haplogroups were associated with first or recurrent VT (32). Haitjema et al. (2017) found no association between Y chromosome haplogroups and vascular disease in Dutch males undergoing vascular surgery, primarily from haplogroups I and R. Histological analyses showed no significant differences in vessel wall or aneurysmal tissue characteristics, indicating these haplogroups do not affect atherosclerosis or aneurysm development (33). This contrasts with earlier studies linking haplogroup I to atherosclerosis

pathways and haplogroup R to increased plaque formation (31,35). Recent research by Timmers et al. (2022) using UK Biobank data confirmed that there are no significant associations between Y chromosome haplogroups and CVD risk, CAD, or all-cause mortality among white British males (37).

Together, these studies highlight the complex role of Y chromosome variation in CVD. Some identify specific haplogroups as potential risk factors, while others suggest these haplogroups do not consistently affect CVD across populations.

Discussion

From an initial search of 1,447 PubMed records and three records identified through citation search, only 29 relevant studies on the impact of sex chromosomes on CVD were included in this systematic review. These studies covered LOX in one study, XCI skewing in three studies, X chromosome variation in one study, LOY in seven studies, and Y chromosome variations in 17 studies.

Sex chromosomes and cardiovascular disease

Loss of chromosome X

No significant associations were found between mLOX and circulatory diseases based on a single study (5). While mLOX was linked to hematological issues such as increased leukemia risk and altered blood cell counts, no connection to CVD was identified. Although mLOX and mLOY show a moderate genome-wide correlation, their overlapping variants are few, suggesting distinct biological processes in their loss (5). Shared variants are associated with cancer susceptibility and blood cell traits, but mLOX effects are weaker than those of mLOY (5). mLOX-specific variants are associated with immune responses and genes linked to mitotic missegregation (5). Limitations include the exclusive focus on leukocyte mLOX and a study population primarily of European and Asian descent, which restricts generalizability. The fact that only one study has investigated the relationship between LOX and CVD, finding no significant association, suggests that either LOX may not play a role in CVD, or that insufficient research has been conducted to draw conclusions. Further research is needed to determine LOX's role in CVD across different tissues.

X chromosome inactivation skewing

Three out of 29 eligible studies indicate that XCI skewing is associated with CVD risk in females. Clonal XCIPs increased thrombosis risk in ET patients without impacting other hematological features (11). In the general population, higher XCI skewing correlated with elevated ASCVD risk and increased monocyte counts (13). Additionally, XCI skewing in atherosclerotic plaques was linked to plaque hemorrhage and peripheral artery events post-CEA, though not with MACE (12). These findings underscore the significance of XCI skewing for cardiovascular health in females.

However, several limitations must be acknowledged. Small sample sizes may limit the generalizability of the findings. For instance, Roberts et al. assessed ASCVD risk in only 14% of 1,575 individuals, with just 32% of those showing skewing (13). Shih et al. and Buono et al. focused on smaller, patient populations that may not represent broader demographics (11,12). These studies reported higher XCI skewing percentages than Roberts et al., potentially due to difference in XCI skewing definitions, or it may suggest that XCI skewing is more prevalent in groups with ET and advanced atherosclerosis. Additionally, the absence of healthy control tissues in Shih et al. and Buono et al. is a significant limitation for establishing associations with CVD (11,12).

The observational nature of these studies restricts the ability to establish causality between XCI skewing and CVD outcomes, limiting findings to correlations (11–13). This is evident in Buono et al.'s study, where skewing correlated with plaque hemorrhage and peripheral events but did not align with traditional cardiovascular risk factors, raising questions about the mechanisms linking XCI patterns to vascular pathology (12). Similarly, clonal XCIP has been associated with thrombosis without affecting platelet counts or other hematological features, suggesting that the link between skewing and thrombosis may involve other mechanisms (11).

Future research should explore how XCI skewing affects different types of CVD across various tissues. One hypothesis is that XCI skewing may influence symptoms in carriers of recessive X-linked disorders

(39). Additionally, translating the biological significance of XCI skewing into clinical applications is essential for improving risk assessment and treatment strategies.

X chromosome variation

One study examined the relationship between hypertension and X chromosome variability, finding that a family history of hypertension significantly increased risk, particularly through maternal lineage (14). Specific X chromosome regions were linked to hypertension in males with a maternal history, suggesting that X-linked variants play a key role in the maternal transmission of hypertensive phenotypes (14).

However, the small sample size for genetic evaluations limits statistical power. Additionally, focusing on only two X chromosome regions without examining specific hypertension-associated genes restricts understanding of underlying genetic mechanisms and may overlook other relevant variations (14).

Future research should explore X chromosome variations in other CVDs and their interactions with environmental factors. While the study of Ciccarelli et al. suggests a link between X chromosome regions and maternal hypertension, it lacks detailed insights into genetic variation patterns, underscoring the need for further investigation (14).

Loss of chromosome Y

Seven studies link LOY to increased CVD risks and adverse outcomes. In the general population, mLOY is associated with diabetes, CVDs, and all-cause mortality, along with reduced erythrocytes and increased platelets and leukocytes counts (15,16). In patients with atherosclerosis, LOY in blood correlates with a higher risk of MACE, but not with inflammation (17). Patients with AAA show a higher frequency of LOY in T lymphocytes compared to controls (18). In those with aortic stenosis post-TAVR, mLOY is linked to increased all-cause mortality and a pro-fibrotic gene profile (19). Furthermore, mLOY predicts worse outcomes in ischemic stroke, particularly without recanalization therapy. In chronic kidney disease patients mLOY is associated with higher mortality and heart failure risk, likely through inflammatory pathways (20). Collectively, these findings suggest that LOY worsens various CVDs.

A significant limitation of these studies is the small sample sizes, particularly in non-blood tissue research. For instance, the prevalence of LOY in atherosclerotic plaques is only 3%, much lower than in blood samples. This low occurrence limits the availability of plaques with LOY for assessing its role in plaque formation (17). Similarly, the limited sample size in the AAA study restricted insights into LOY's contribution to disease progression (18). While LOY is primarily studied in blood, comparable levels in AAA blood T lymphocytes and tissue suggest its potential relevance in other tissues (18).

Measurement methods for LOY varied across studies, with some using continuous cell counts and others applying different dichotomous cut-offs, complicating comparisons and contributing to variability in LOY prevalence rates. Additionally, missing data on pre-existing conditions and the absence of healthy tissue comparisons may further affect outcomes (18,21). The generalizability is limited, as many studies primarily involved individuals of European descent, with some not reporting ethnicity. Moreover, the observational nature of these studies hinders causal conclusions about whether LOY contributes to disease progression or results from underlying conditions. For example, LOY is strongly associated with increasing age, making it challenging to disentangle whether LOY directly contributes to CVD or if both are simply correlated with aging. This complicates the interpretation of LOY as an independent risk factor for CVD. Furthermore, the lack of mechanistic evidence linking LOY to CVD questions the robustness of this association.

One hypothesis for the occurrence of LOY suggests that chromosomal segregation errors during mitosis cause aneuploidy (7). Kinetochores form on centromeric chromatin, where centromere protein C

(CENP-C) binds to centromere protein A (CENP-A). The lack of centromere protein B (CENP-B) on the Y chromosome may hinder CENP-A recruitment and kinetochore binding. In vitro studies indicate that Y chromosome segregation errors lead to micronuclei that fragment in subsequent cell cycles.

The mechanisms linking LOY to CVD are not well understood. Some studies indicate that LOY in blood cells often co-occurs with clonal hematopoiesis of indeterminate potential (CHIP) (19). Mas-Peiro et al. found that specific CHIP driver mutations are associated with poor outcomes after TAVR, similar to LOY; however, CHIP does not affect LOY-related mortality (19). Another theory suggests that LOY may contribute to fibrosis, with macrophages from Y chromosome-deficient hematopoietic stem cells infiltrating the heart after injury or replacing aging cardiac macrophages (7). These LOY macrophages may activate profibrotic pathways, leading to increased cardiac fibroblast proliferation and extracellular matrix production, ultimately impairing cardiac function.

Future research should clarify LOY's impact on cardiovascular outcomes, particularly regarding the influence of risk factors like smoking and age on the LOY-CVD relationship. Additionally, studies must explore how LOY in blood, aortic aneurysms, and atherosclerotic plaques affects CVD progression, potentially establishing LOY as a biomarker for cardiovascular risk assessment.

Y chromosome variation

The relationship between Y chromosome haplogroups and CVD is complex and contradictory. Haplogroups K, R, YAP, and I are associated with varying CVD risks (26,27,29–31,35,36,38), with haplogroup K and sub-haplogroup R linked to an increased risk of atherosclerotic plaques, while YAP may reduce this risk (31). Sub-haplogroup R1b is prevalent in premature STEMI patients and may heighten the risk of Chagas disease-related cardiomyopathy (36,38). Haplogroup I is associated with CAD (29,35). Conversely, some studies report no significant associations between Y haplogroups and CVD, including general cardiovascular risk, VT, atherosclerotic or aneurysmal characteristics, CAD, and all-cause mortality (28,32–34,37).

The 17 studies on Y chromosome haplogroups and CVD have limitations, including small sample sizes for rare haplogroups and limited ethnic diversity, which affect generalizability (22–26,32,38). However, two UK Biobank studies had relatively large sample sizes; Eales et al. (2019) linked haplogroup I1 to CAD risk but found no associations with other common haplogroups, while Timmers et al. found no significant link between Y chromosome haplogroups and CVD risk, CAD, or all-cause mortality (35,37). Many studies used broad haplogroup classifications, potentially overlooking subgroup-specific effects (32,33,36). Additionally, indirect measures of phenotypes, such as aggression and steroid levels, may not accurately reflect CVD risk (30), and conflicting results hinder consensus. Future research should prioritize larger, more diverse cohorts and explore rarer haplogroups, as well as the biological mechanisms linking them to CVD risk.

Strengths and Limitations

This systematic review provides valuable insights but has limitations. A major strength is its broad search strategy, which aimed to capture a wide range of CVD types. However, limitations include the screening process, conducted by a single researcher, which may have introduced bias. The exclusion of inherited conditions such as Turner and Klinefelter syndromes narrowed the scope and may have missed important insights. Additionally, the review focused on general sex chromosomal variations like haplogroups, without addressing specific single genes or polymorphisms. Studies on XCI escape were also excluded for focusing on specific escape genes. The lack of experimental studies limited the exploration of mechanisms linking sex chromosome abnormalities to CVD. Finally, the diversity and small number of included studies prevented statistical analysis, making the findings largely hypothesis-

generating. Overall, the review highlights the need for more comprehensive research to fully understand how sex chromosomes influence CVD.

Future Research

Further investigation into the impact of sex chromosomes on CVD is warranted, as current studies are limited and primarily establish associations without demonstrating causality. Synthesizing current hypotheses on the mechanisms of sex chromosome abnormalities in CVD, incorporating experimental studies, is essential to strengthen the robustness of the associations and establish causality. Testing these hypotheses in future research could lead to advancements in our understanding of their contribution to CVD. Additionally, research should focus on the clinical implications of sex chromosome abnormalities and variations to enhance CVD risk assessment.

Future efforts should include a comprehensive review of genetic variations on the X and Y chromosomes, including XCI escape genes, which were excluded from this review. This includes examining X-wide association studies (XWAS) and GWAS to identify potential sex chromosome variations that influence CVD.

LOY and XCI skewing emerge as the sex chromosome abnormalities most consistently associated with CVD. In contrast, while certain Y chromosome haplogroups have been linked to CVD, their associations are less consistent, despite being the focus of most studies. Future research should prioritize investigations into LOY and XCI skewing in relation to CVD. Additionally, variations in the X and Y chromosomes warrant more in-depth studies to clarify their potential roles in CVD risk.

Conclusion

This systematic review highlights the significant associations between acquired sex chromosome abnormalities and variations—particularly XCI skewing, LOY, and Y chromosome haplogroups—and CVD risk. XCI skewing correlates with thrombosis in ET, increased ASCVD risk, and adverse events in atherosclerosis. LOY is consistently linked with CVD, all-cause mortality, and other adverse outcomes. Specific Y haplogroups, such as K and R, show associations with heightened atherosclerosis risk, while others, like YAP, appear protective. However, some studies found no significant associations between Y haplogroups and CVD, underscoring the variability in findings. Despite these correlations, causality remains unclear, highlighting the need for research into underlying mechanisms and clinical implications to improve CVD assessment and management.

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Supplementary Information

Supplementary Methods

Search

("Cardiovascular Diseases" [MeSH]
OR "Cardiovascular Disease" OR "CVD" OR "Heart Disease" OR "Vascular Disease")
AND
("Sex Chromosomes" [MesH] OR "Y Chromosome" [MeSH] OR "X Chromosome" [MeSH] OR
"Chromosomes, Human, Y" [MeSH] OR "Chromosomes, Human, X" [MeSH]
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Article language: English

Examples of topics that led to exclusion

Macular degeneration, COVID-19, cancer, immune diseases, infertility, muscular dystrophy, Barth syndrome, Fabry disease, Turner syndrome, Klinefelter syndrome, or studies on prenatal screening methods.

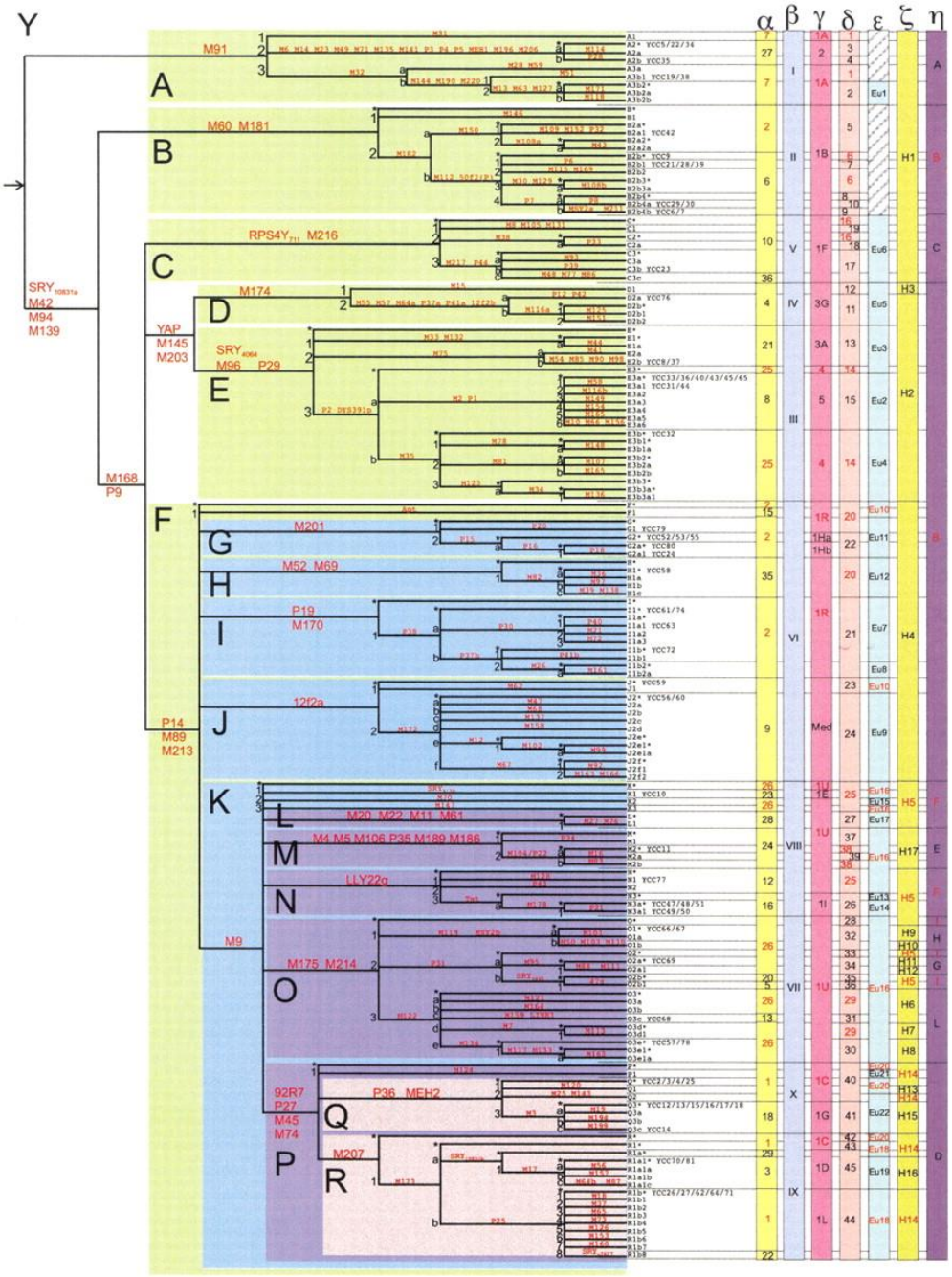

Figure S1. Haplogroup tree of the human Y chromosome (NRY) showing 153 haplogroups and their relationships with previous nomenclatures. (Figure obtained from Hammer et al. (2002) (10)) *Major clades are labeled with capital letters, and haplogroup names along with Y Chromosome Consortium (YCC) sample numbers are indicated at the tips. Internal nodes are marked with an asterisk (*), while mutation names are provided along the branches, which are not scaled to represent mutation frequency or age. Red haplogroup names indicate multiple positions in the phylogeny, and cross-hatching in the "Semino" nomenclature highlights unnamed lineages. Prior nomenclatures are attributed to the following publications: (α) Jobling and Tyler-Smith (2000) and Kaladjieva et al. (2001); (β) Underhill et al. (2000); (γ) Hammer et al. (2001); (δ) Karafet et al. (2001); (ε) Semino et al. (2000); (ζ) Su et al. (1999); and (η) Capelli et al. (2001).*

Supplementary Results

Table S1. Overview of the included studies on loss of chromosome X (LOX).

Title	Year	First author	CVD	Age in years	Ethnicity	Population health/ disease/ risk	N subjects	N male	N female	Population source	Method LOX measurements	Tissue	Binary/ continuous LOX	Control	Follow -up time	Important findings
Genetic drivers and cellular selection of female mosaic X chromosome loss.	2024	Liu A	Circulatory system diseases	44-65 (range of biobank means)	European and Asian ancestries	General population and patients	883,574	0 0%	883,574 100%	8 Biobanks (European: FinnGen, EBB, UKBB, BCAC, MVP, MGB, PLCO; East Asian: BBJ)	- Leukocyte DNA - SNP arrays - MoChA, GRCh38 reference - Signal metrics: BAF, LRR - mLOX detection: BAF imbalance - mLOX cell fraction	Peripheral leukocytes from blood	Continuous: proportion of cells affected by mLOX	NA	NA	- 12% of females had mLOX in 2% of leukocytes. - mLOX was linked to leukemia. - mLOX was associated with higher lymphocyte counts ($P=9.3\times10^{-126}$) and lower neutrophil counts ($P=3.3\times10^{-62}$). - No associations between mLOX and circulatory system diseases.

Table S2. Overview of the included studies on X chromosome inactivation (XCI) skewing.

Title	Year	First author	CVD	Age in years	Ethnicity	Population health/ disease/ risk	N subjects	N male	N female	Population source	Method skew measurements	Tissue	Binary/continuous skew	Control	Follow-up time	Important findings
Predictive values of X-chromosome inactivation patterns and clinicohematologic parameters for vascular complications in female patients with essential thrombocythemia.	2002	Shih LY	ET	57 (median) 15-92 (range)	Chinese/Han ethnic group 1 Filipino	ET patients	89	0 0%	89 100%	Hematology Division, Chang Gung Memorial Hospital, China	HUMARA-PCR assay	Granulocytes and T cells were from heparinized bone marrow/blood	Binary: - Clonal XCIP: GC >50%, RG <0.33, RT = 1.0 - Polyclonal XCIP: GC <50%, RT >0.33 - Ambiguous XCIP: GC <50%, RT <0.33	NA	13-156 months (range), 45 months (median)	- Clonal (68.4%) and Polyclonal (19.0%). - Clonal XCIP associated with 6.9x higher thrombsis risk (95% CI 0.78-60.66). - No association between XCIP and hemorrhage. - Older age linked to clonal XCIP. - No correlation between XCIP and platelet count or hematologic traits. - Excessive skewing is more common in granulocytes, especially in older healthy women.
Age acquired skewed X chromosome inactivation is associated with adverse health outcomes in humans.	2022	Roberts AL	ASCVD	61 (median) 19-99) (range)	NA (UK study)	General population	1,575 (423 mono-twins; 257 dizygotic twins; 215 singletons)	0 0%	1,575 100%	TwinsUK population cohort	HUMARA-PCR assay	Blood	Binary: - Random XCI: <75% XCI (<1 SD from distribution mean) - Skewed XCI: ≥75% XCI (1–2 SDs from mean) - Extreme Skewing: ≥91% XCI (>2 SDs from mean)	3 groups: mono-, dizygotic twins, singletons	10 years	- XCI-skew is linked to increased ASCVD risk, cross-sectionally and in XCI-skew discordant twin pairs. - XCI-skew predicts cancer incidence over 10-year follow-up - XCI-skew reflects hematopoietic stem cell changes; may serve as a unique chronic disease biomarker - XCI-skew not associated with other aging markers; stable over 15-17 years - Higher XCI-skew associated with increased monocyte abundance
X chromosome inactivation skewing is common in advanced carotid atherosclerotic lesions in females and predicts secondary peripheral artery events.	2023	Buono MF	Atherosclerosis	66 (mean)	NA (Dutch study)	post-CEA atherosclerosis patients	Plaque: 154 Blood: 55	0 0%	Plaque: 154 Blood: 55 100%	Athero-Express biobank	HUMARA-PCR assay	Atherosclerotic plaques, blood	Dichotomous: >63.9% XCI (Ordered Quantile Normalization) Binned: - Non-skewed: <60% XCI - Low: 60-70% XCI - Moderate: 70-80% XCI - High: >80% XCI	NA	3 years	- XCI skewing in 49.4% of carotid plaques and 67% of blood samples. - XCI skewing predicts peripheral artery events within 3 years post-CEA (HR 1.46, P=0.007). - Skewed plaques linked to higher plaque hemorrhage risk (OR 1.44, P=0.02). - XCI skewing unrelated to traditional CVD risk factors or MACE.

Table S3. Overview of the included studies on X chromosome variation.

Title	Year	First author	CVD	Age in years	Ethnicity	Population health/ disease/ risk	N subjects	N male	N female	Population source	Method X measurements	Tissue	Control	Follow-up time	Important findings
The possible role of chromosome X variability in hypertensive familiarity.	2017	Ciccarelli M	Hypertension (CVD risk factor)	Hypertensive: 52.44 (mean) Normotensive: 45 (mean)	NA (Italian study)	Hypertensives Normotensives	18,856 (12,504 hypertensives, 6,352 normotensives)	10,352 55% (6,868 hypertensives, 3,484 normotensives)	8504 45% (5636 hypertensives, 2868 normotensives)	CSN database of Campania Salute Network of Hypertension center of the Federico II University Hospital of Naples, Italy	- DNA extracted from blood. - Genotyping: 320K Infinium II Assay using HumanHap 317K duo BeadChip SNP array. - SNP dataset expanded through imputation. - Additive, dominant, and recessive genetic models for hypertension.	Blood	Normotensives	NA	- 75% of hypertensive cases had familial history of hypertension (OR 3.77), compared to 26% in normotensives (OR 0.94). - Familiarity increases hypertension risk (OR 2.91; 95% CI 2.67–3.17; P<0.001). - Maternal familiarity in 37% of hypertensives (OR 3.01; 95% CI 2.66–3.41; P<0.001) - Paternal familiarity in 21% (OR 2.31; 95% CI 2.01–2.68; P<0.001). - Double familiarity in 17% (OR 3.45; 95% CI 2.87–4.01; P<0.001). - Genome-wide analysis identified SNPs linked to maternal familiarity for hypertension. - Maternal familiarity influences hypertension more in men than women.

Table S4. Overview of the included studies on loss of chromosome Y (LOY).

Title	Year	First author	CVD	Age in years	Ethnicity	Population health/ disease/ risk	N subjects	N male	N female	Population source	Method LOY measurements	Tissue	Binary/ continuous LOY	Control	Follow-up time	Important findings
Loss of Y Chromosome in Blood Is Associated With Major Cardiovascular Events During Follow-Up in Men After Carotid Endarterectomy.	2017	Haitjema S	Atherosclerosis	LOY: 75 No LOY: 69	NA (Dutch study)	Atherosclerosis patients undergoing CEA	366	366 100%	0 0%	Athero-Express biobank, AAA-Express biobank	- Genome-wide SNP genotyping: mLRRY from MSY probes. - Peak of mLRRY histogram identified using kernel density estimation (R). - Noise distribution mirrored to determine cut-off for LOY based on kernel density peak.	Atherosclerotic plaques Blood	Binary: Blood: mLRRY < -0.075 Plaque: mLLRY< -0.129	Loss of chromosome 21, 2 cohorts	3 years	- LOY in blood independently associated with higher MACE. - LOY in 16.7% of blood samples and 3% of plaques. - LOY association with plaque size not significant after multiple testing correction. - No link between LOY and systemic/local inflammatory markers.
Predictors of mosaic chromosome Y loss and associations with mortality in the UK Biobank.	2018	Loftfield E	CVD	57 (mean) 58 (median) 37-73 (range)	94.6% white, 0.5% mixed, 2.6% Asian, 1.5% Black, 0.8% other	General population	223,338 (LOY: 3,789)	223,338 100%	0 0%	UK Biobank	- Genotyping SNP array: mLRR of Y	Blood	Binary: mLRR< -0.15 (cellular proportion 10%) mLRR< -0.40 (24%) (based on previous studies)	NA	5-10 years	- mLOY increases exponentially with age (P<4.9×10^-324) (significant rise after age 50) and is strongly associated with current smoking (P=7.8×10^-184). - mLOY prevalence: 0.4% in African ancestry vs. 1.8% in European ancestry. - Associations observed with diabetes (P=0.003), CVD (P=0.01), BMI, and self-reported health. - Higher mLOY (mLRR < -0.40) linked to increased all-cause mortality (HR=1.35, 95% CI=1.08–1.70; P=0.009).
Y chromosome loss is associated with age-related male patients with abdominal aortic aneurysms.	2019	Tang D	AAA	AAA: 64.53; AOD: 61.25; HC: 63.55 (mean)	NA (Chinese study)	AAA patients	140 (AAA: 37; AOD: 12; HC: 91)	140 100%	0 0%	CMUaB, CMUabB	- FISH: LOY rate expressed as % of the total number of nuclei counted.	AAA tissue specimen, Peripheral blood T lymphocytes	Continuous: % of the total number of nuclei counted	AOD, HC	NA	- mLOY in T lymphocytes higher in AAA group (9.11%) than HC (5.56%; P<0.001) and AOD (6.42%; P=0.029). mLOY in AAA tissue and blood positively correlated with age. - LOY associated with lower SRY expression and free testosterone levels.

															- Suggests systemic LOY involvement in AAA progression.
Mosaic chromosome Y loss is associated with alterations in blood cell counts in UK Biobank men.	2020	Lin SH	Blood cell count	no LOY: 55.2; LOY: 61.9 (mean)	no LOY: 155,443 white, 922 mixed, 4,932 Asian, 2,914 Black, 1,648 other; LOY: 38,790 white, 97 mixed, 436 Asian, 181 Black, 138 other	General population	206,353 (LOY: 39,809)	206,353 100%	0 0%	UK Biobank	- Genotyping SNP array: MSY SNPs on Affymetrix UK BiLEVE or UK Biobank Axiom arrays	Blood	Binary: NA (based on Thompson et al.), Continuous: mLRR	NA	NA	- mLOY in blood cells is linked to changes in blood cell counts, independent of age and smoking. - mLOY in 19.3% of participants. - Reduced erythrocyte count (-0.009 × 10^{12} cells/L, p=2.75×10^{-5}). - Increased thrombocyte count (5.523 × 10^{9} cells/L, p=2.32×10^{-60}). - Increased leukocyte count (0.218 × 10^{9} cells/L, p=9.22×10^{-95}), particularly in neutrophils (0.174 × 10^{9} cells/L, p=1.24×10^{-99}) and monocytes (0.021 × 10^{9} cells/L, p=6.93×10^{-57}). - Lymphocyte count changes were less consistent, showing variations based on smoking status and age.
Mosaic loss of Y chromosome in monocytes is associated with lower survival after transcatheter aortic valve replacement.	2023	Mas-Peiro S	Aortic valve stenosis	81.7 (median) (no LOY: 81; LOY: 83)	NA (German study)	Advanced aortic valve stenosis patients undergoing TAVR	362	362 100%	0 0%	University Hospital of the Goethe University, Frankfurt, Germany	- LOY quantified using PCR in blood samples. - Relative X/Y chromosomes via TaqMan method targeting AMELX/AMELY genes. - Percentage of LOY cells, from AMELY/AMELX ratio. - ScRNAseq performed on circulating peripheral monocytic blood cells in 7 patients.	Blood	Binary: >17% (Youden-index based on the AUC from ROC analyses)	NA	3 years	- mLOY in 29.6% of men post-TAVR. - mLOY identified as an independent predictor of mortality (HR 2.2; 1.4–3.4) post-TAVR. - mLOY associated with increased 3-year all-cause mortality. - Pro-fibrotic gene signature in mLOY monocytes linked to enhanced TGFβ signaling and cardiac fibrosis. scRNA-seq of monocytes revealed pro-fibrotic activity in mLOY cells.
Mosaic Loss of Chromosome Y Is Associated With Functional Outcome After Ischemic Stroke.	2023	Dorvall M	Ischemic stroke	SAHLSIS2: 71 LSR: 74 (median)	NA (Swedish study)	Ischemic stroke patients	1323 (SAHLSIS2: 588; LSR: 735; 987 non-recanalization therapy)	1323 100% (SAHLSIS2: 588; LSR: 735)	0 0%	SAHLSIS2, LSR	- DNA from peripheral blood collected at index stroke - Genotyping SNP array: Illumina	Blood	Binary: mLRR < -0.15 (based on Loftfield et al. distribution mLLR-Y)	External validation cohort	3 months	- Higher risk of poor functional outcomes (dependency or death) assessed via mRS at 3 months. - mLOY-poor outcomes in

											Infinium microarray					men without recanalization therapy independent of age, stroke severity, and diabetes. - 15.6% of cohort with mLOY.
Loss of Y Chromosome and Cardiovascular Events in Chronic Kidney Disease.	2024	Weyrich M	All-cause mortality, CVD, heart failure (cardiovascular events)	64 (mean)	Mainly white (German study)	Stable chronic kidney disease patients (stage G2-4) (CARE for HOMe) Hemodialysis patients with type 2 diabetes (4D study)	CARE for HOMe: 622 4D: 1,255	CARE for HOMe: 279 4D: 544	CARE for HOMe: 287 4D: 578 (not used for analyses)	The CARE for HOMe study, 4D study	- LOY quantified using PCR in blood samples. - Relative X/Y chromosomes via TaqMan method targeting AMELX/AMELY genes. - Percentage of LOY cells, from AMELY/AMELX ratio.	Blood	Binary: >17% (Youden-index based on the AUC from ROC analyses), Continuous: linear	2 cohorts	CARE for HOMe: 5.3 years (mean) 4D: 2.7 years (mean)	- LOY increases with age, steep rise after 60 years. - LOY observed in 11.1% of individuals. - mLOY linked to higher mortality and heart failure risk, but not atherosclerotic events. - mLOY associated with worsening cardiac function: reduced ejection fraction, increased E/E' ratio. - Higher plasma levels of CCL2 and enhanced CCR2 expression in monocytes linked to increased heart failure risk. - mLOY predicts heart failure outcomes in CKD.

Table S5. Overview of the included studies on Y chromosome variation.

Title	Year	First author	CVD	Age in years	Ethnicity	Population health/ disease/ risk	N subjects	N male	N female	Population source	Method Y measurements	Tissue	Binary/ continuous Y	Control	Follow-up time	Important findings
Association of the human Y chromosome with high blood pressure in the general population.	2000	Ellis JA	BP	A/HindIII(+): 54.8 B/HindIII(-): 54.7 (mean)	White	General population (parental generation)	409	409 100%	0 0%	VFHS	- DNA extraction from blood. - PCR-RFLP to detect Y chromosome variation using a 285-bp alphoid satellite sequence. - HindIII enzyme to digest amplified DNA. - Gel electrophoresis; A genotype produces 3 bands (285, 250, 35 bp), B genotype shows 1 band (285 bp).	Blood	Binarized HindIII status of the Y chromosome	NA	NA	- A Genotype (HindIII(+)): Found in 31.3% of men. - HindIII site more common in lowest diastolic BP decile (43.2%) vs highest (15.9%, P=0.007). - No significant difference in systolic BP between deciles (P=0.66). - Men with HindIII site had lower diastolic BP (P=0.03)
The Y chromosome effect on blood pressure in two European populations.	2002	Charchar FJ	BP	Polish: 53.9 Scottish: 44.9 (mean)	White European populations (Poland, Scotland)	General population	917 (Polish: 155 Scottish: 762)	917 100%	0 0%	The Silesian Hypertension Study, MIDSPAN family study	- Genotyping: PCR-RFLP. - DNA 50 ng per participant. - HindIII biallelic near the centromere. - Gel electrophoresis: HindIII(−) (290 bp) and HindIII(+) (290, 250, 40 bp).	Blood	Binarized HindIII status of the Y chromosome	2 cohorts	NA	- HindIII(−): 67% in Polish men, 72% in Scottish men. - HindIII(+) genotype linked to significantly higher systolic and diastolic BP in both Polish and Scottish studies. - BP Difference: 5.27 mm Hg (systolic, P=0.0014) and 2.6 mm Hg (diastolic, P=0.0045) in Poland; 3.14 mm Hg (systolic, P=0.0005) and 1.44 mm Hg (diastolic, P=0.0084) in Scotland. - HindIII(+)/TT SF1 combination associated with higher odds of elevated BP (OR = 3.92, P=0.023).
Non-recombining chromosome Y haplogroups and centromeric HindIII RFLP in relation to blood pressure in 2,743 middle-aged Caucasian men from the UK.	2005	RodrÃ-guez S	BP	51–62 (range)	UK-Caucasian (UK study)	General population	2,743	2,743 100%	0 0%	NPHSII cohort	- 5 SNPs and 2 microsatellites (DYS390, DYS392). - PCR for Y-microsatellites and HindIII, ARMS-PCR for SNPs. - SNPs analyzed: M9 (G/C), M170 (A/C), M173 (A/C), M223 (C/T). - HindIII polymorphism: Detected by RFLP (285 bp uncut, 250 + 35 bp	Blood	Binarized HindIII status of the Y chromosome	NA	NA	- No significant link between loci analyzed and BP, including the HindIII marker. - No significant difference in SBP or DBP between HindIII(−) and HindIII(+) genotypes. - Haplogroup Y(xI,R): 3.5 mmHg higher SBP compared to other haplogroups (P=0.057, adjusted for age/BMI). - Haplogroup I-M223:

											cut). - Quality control: Negative/positive controls, independent genotyping verification.					higher SBP (4.7 mmHg, P=0.040, adjusted for age/BMI). - Findings not statistically significant after Bonferroni correction (α=0.005).
HindIII(+/-) polymorphism of the Y chromosome, blood pressure, and serum lipids: no evidence of association in three white populations.	2006	Russo P	BP	49.3 (UK: 49.3; Belgum: 46.5; Italy: 50.0)	White European populations (UK, Belgium, Italy)	General population	1,983 (UK: 422 Belgium: 313 Italy: 1,248)	1,983 100%	0 0%	IMMIDIET project (IP), WHSS, OPHS	- Genotyping: PCR-RFLP. - Polymorphisms: HindIII (+/−) and −344C/T of CYP11B2. - HindIII genotyping per Charchar et al.; CYP11B2 per Russo et al.	Blood	Binarized HindIII status of the Y chromosome	3 cohorts (3 countries)	NA	- HindIII(+) in Italians (63%) vs British (31%) and Belgians (28%) (P < .0001). - HindIII(+/−) site not linked to hypertension, BP, or serum lipids in any population or the full sample. - No interaction between HindIII(+/−) and CYP11B2 (-344C/T) variant on BP. - No significant differences in total cholesterol, LDL, HDL, or triglycerides between HindIII(+) and HindIII(-) carriers after adjustment for confounding factors.
Genetic variants of Y chromosome are associated with a protective lipid profile in black men.	2008	Russo P	CVD risk	White: 50.3 Black:52 South Asian:49.3 (mean) 40-59 (range)	Black, white, South Asian (from the UK and whites from Italy)	General population (Black, white, South Asian)	880 (UK: 579 (white:182; black:174; south asian:223); Italy 301 whites)	880 100%	0 0%	Wandsworth Heart and Stroke Study, OPHS	- Analyzed 4 MSY polymorphisms: HindIII(±), rs768983 (TBL1Y), rs3212292 (USP9Y), and rs9341273 (UTY). - DNA samples genotyped using PCR-RFLP for HindIII(±) and SNPs in TBL1Y, USP9Y, and UTY genes. - Conducted haplotype analysis combining frequent alleles in Blacks (TBL1YA and USP9YA) and compared with other allelic combinations.	Blood	Binarized haplogroup status of the Y chromosome	Independant cohort from Italy	NA	- TBL1YA USP9YA haplotype: Found only in black individuals, most frequent allelic combination (AA: 125). - Lower triglycerides (P=0.025); higher HDL-cholesterol (P=0.005) compared to other haplotypes. - Suggests a favorable lipoprotein pattern contributing to reduced CHD susceptibility in black populations.
Inheritance of coronary artery disease in men: an analysis of the role of the Y chromosome.	2012	Charchar FJ	CAD	Cases: 60.6 Controls: 45.5	White European ancestry (British)	CAD patients and controls	3,233	3,233 100%	0 0%	BHF-FHS, WOSCOPS, Cardiogenics Study	- DNA extraction from peripheral leukocytes. - SNP selection: 11 biallelic SNPs (M9, M35, M45, M89, M170, M173, M201, M207, M269, M304, SRY10831) for genotyping, covering over 95% of UK MSY	Blood	Binarized haplogroup status of the Y chromosome	3 cohorts, Controls without CAD	NA	- 9 haplogroups, with R1b1b2 and I accounting for ~90% of Y variants in British men. - Carriers of haplogroup I had a 50% higher age-adjusted risk of CAD compared to other lineages. (BHF-FHS: OR 1.75 (95% CI 1.20–2.54,

											lineages. - Haplogroup assignment: Each Y assigned to one of 13 major European haplogroups based on the hierarchical configuration of the SNPs. - Genotyping: TaqMan assays on ABI PRISM 7900HT Sequence Detection System (Applied Biosystems).					p=0.004); WOSCOPS: OR 1.45 (95% CI 1.08–1.95, p=0.012); Joint Analysis: OR 1.56 (95% CI 1.24–1.97, p=0.0002)) - The association between haplogroup I and CAD risk was independent of traditional cardiovascular and socioeconomic factors. - 19 molecular pathways with strong differential expression between haplogroup I carriers and others, linked to inflammation and immunity relevant to atherosclerosis.
Male-specific region of the Y chromosome and cardiovascular risk: phylogenetic analysis and gene expression studies.	2013	Bloomer LD	CVD risk	YMCA1: 19.3 YMCA2: 18.9 (Young men in secondary school >17); GRAPHIC sons: 25.7	White European	General population	1,988 (YMCA1: 1,068; YMCA2: 509; GRAPHIC sons: 363)	1,988 100%	0 0%	YMCA1, YMCA2, GRAPHIC	- DNA from peripheral leukocytes. - Genotyping: 11 Y chromosome SNPs to classify into 13 common European haplogroups. - Genetic association analysis - Phylogenetic tree reconstruction: Based on 11 bi-allelic polymorphisms (M9, M35, M45, M89, M170, M173, M201, M207, M269, M304, SRY10831). - Gene expression analysis: Performed on all ubiquitous single-copy genes of MSY using quantitative real-time PCR.	Blood	Binarized haplogroup status of the Y chromosome	Multiple cohorts	NA	- 75% to 93% of Y chromosome variation attributed to I, R1a, and R1b1b2 lineages. - No traditional cardiovascular risk factors linked to haplogroup I in meta-analysis. - Haplogroup I associated with downregulation of UTY and PRKY genes in macrophages, not conventional risk factors. - R1a most common in Polish populations; R1b1b2 predominant in British men. - Haplogroup I: Second most common haplogroup across all cohorts, previously linked to increased CAD risk.
Genetic polymorphism of human Y chromosome and risk factors for cardiovascular diseases: a study in WOBASZ cohort.	2013	Kostrzewa G	CVD risk	20-74 (range)	Caucasian (Polish study)	General population	2,652	2,652 100%	0 0%	WOBASZ Cohort	- Haplogroup typing: Based on a phylogenetic tree from YCC. - Identified haplogroups: R1a1-M17, R1*(xR1a1-M17), J2-M172, N3-Tat, I-M170, E3b-M35. - Additional typing: M74 and M89 markers.	Blood	Binarized haplogroup status of the Y chromosome	NA	NA	- Y Chromosome Variation: Y chromosome genetic variation (HindIII, YAP, main haplogroups) unlikely to play a major role in cardiovascular risk in Poles. - Reason for Unlikeliness: 1) Associations did not withstand Bonferroni correction (n=7).

																2) No single haplogroup identified as harboring risk variants. - Statistical Associations: 3 significant associations at alpha=0.05: - Haplogroup I-M170: Mean HDL (53.8 mmol/l, SD=17.4, N=449) higher than others (51.7 mmol/l, SD=15.2, N=2195, P=0.02). - Haplogroup F(xI-M170, J2-M172, K-M9): Mean LDL (3.6 mmol/l, SD=1.1, N=54) higher than others (3.3 mmol/l, SD=0.95, N=2538, P=0.03). - Haplogroup N3-Tat: Mean BMI (25.8, SD=3.9, N=86) lower than others (26.6, SD=4.3, N=2559, P=0.04). - Bonferroni Correction: None of these associations remained significant after correction. - HindIII Distribution: 73% HindIII(-); 27% HindIII(+).
Coronary artery disease predisposing haplogroup I of the Y chromosome, aggression and sex steroids--genetic association analysis.	2014	Bloomer LD	CAD	19 (mean)	White European ancestry (Polish study)	General population	1,454 (YMCA1: 1,157; YMCA2: 597)	1,454 100%	0 0%	YMCA1, YMCA2	- Phylogenetic reconstruction: Reconstructed Y chromosome phylogenetic tree, classifying each Y chromosome into one of 13 common European lineages. - DNA extraction from peripheral leukocytes. - Genotyping: TaqMan assays on an ABI PRISM 7900HT Sequence Detection System (Applied Biosystems). - Polymorphisms analyzed: 11 bi-allelic MSY polymorphisms (M9, M35, M45, M89, M170, M173, M201, M207, M269, M304, and SRY10831). - Haplogroup	Blood	Binarized haplogroup status of the Y chromosome	NA	NA	- Approximately 17% of men inherited haplogroup I. - No overall association found between haplogroup I and sex-related phenotypes in young white men. - Haplogroup R1a was most common among Polish men (54% in YMCA1, 58% in YMCA2). - The frequency of haplogroup I (approximately 17%) aligns with previously reported estimates (17.3%). - No significant differences in sex steroids were observed between haplogroup I carriers and other MSY lineages after adjustments for age, BMI,

											classification: Genotypes used to classify Y chromosomes into 13 major European haplogroups, allowing classification of >95% of European Y chromosomes.					total cholesterol, and HDL-cholesterol.
Evidence for contribution of the y chromosome in atherosclerotic plaque occurrence in men.	2014	Voskarides K	Atherosclerosis, CVD	No plaque: 51.69 Plaque: 62.29 (mean) (40+ cohort)	NA (Greek Cypriot study)	General population	373 (no plaque:75; plaque:298)	373 100%	0 0%	Cyrus Study	- Genotyping: Analyzed six male-specific Y chromosome markers representing major haplogroups (YAP, G, I, J, K, R). - Phylogenetic tree analysis via PCR or PCR-RFLP. - Biallelic markers: Analyzed genetic biallelic markers for 5 phylogenetic clades: YAP, I (M258), K (M9), G (M201), J (M304). - Sub-haplogroup analysis: R (M207) of K (M9).	Blood	Binarized haplogroup status of the Y chromosome	NA	NA	- Haplogroups J and K: Account for 67% of Y-chromosome variance in Greek Cypriot men. - Haplogroup K: 2.5x higher age-adjusted risk for atherosclerotic plaque (OR 2.51, 95% CI 1.18-5.33, p=0.017). - YAP haplogroup: 50% reduced risk of femoral bifurcation plaque (OR 0.46, 95% CI 0.27-0.77, p<0.001). - Haplogroup K (M9) and sub-haplogroup R (M207): Associated with increased risk for plaques in carotid and femoral bifurcations. - Haplogroup I: Low frequency (2.2-2.4%) compared to British populations (14.5-17%).
Male-specific risk of first and recurrent venous thrombosis: a phylogenetic analysis of the Y chromosome.	2016	de Haan HG	VT	Patients: 53.1 Controls: 48.2 (mean)	Northwestern European origin (Dutch study)	VT patients (and controls)	3,742 (VT: 1,729; Controls: 2,013)	3,742 100%	0 0%	MEGA study	- Haplogroups according to the phylogenetic tree	Blood or buccal swap	Binarized haplogroup status of the Y chromosome	Controls without VT	5 years (mean)	- Men have a higher risk of first and recurrent VT. - Haplogroup I is not linked to VT risk. Potential increased risk of recurrent VT for haplogroup E carriers (OR 1.49, 95% CI 0.96–2.30). - Y Haplogroups Identified: 13 Y haplogroups observed in 3,742 men; 6 haplogroups (R1b, I, R1a, J, E, G) account for >98% of Y lineages. - Most Common: R1b (59%) and I (25%) - No clear predisposing effect of Y haplogroups on VT risk; unlikely to explain sex differences in VT risk.

Genetic variation within the Y chromosome is not associated with histological characteristics of the atherosclerotic carotid artery or aneurysmal wall.	2017	Haitjema S	Atherosclerosis, AAA	AE: 69 AAA: 68.4 (mean)	Dutch origin	Patients undergoing CEA, Patients undergoing open aneurysm repair	1,610 (AE: 1,217; AAA: 393)	1,610 100%	0 0%	Athero-Express biobank, Aneurysm-Express biobank	- Blood or tissue samples for DNA extraction. - Genotyping: Conducted by LGC Genomics using 11 MSY SNPs and additional BeadChip probes. - Discrepancy resolution: ExomeChip haplogroup retained, resulting in 1,217 genotyped individuals. - Lineage grouping: Lineages classified into haplogroups E, F, G, H, I, J, N, Q, R, and T for analysis.	Blood, atherosclerotic plaque, aneurysmal tissue	Binarized haplogroup status of the Y chromosome	2 cohorts	NA	- No association between haplogroups and diseased vessel walls. - Similar haplogroup distribution compared to the general population. - Majority of men carried haplogroups I (AE: 28%, AAA: 24%) and R (AE: 59%, AAA: 61%). - No association between Y haplogroups and histological characteristics of carotid artery plaques or aneurysm tissue. - No significant differences in macrophage, mast cell, neutrophil, and smooth muscle cell content or vessel density across haplogroups. - Plaque: No differences in calcification, collagen, fat content, or intraplaque hemorrhage between haplogroups. - Aneurysm Wall: No differences in aneurysm wall characteristics between Y chromosomal haplogroups.
Associations of Y chromosomal haplogroups with cardiometabolic risk factors and subclinical vascular measures in males during childhood and adolescence.	2018	O'Keeffe LM	Cardiometabolic risk	0-18 (range)	South West England	General child-adolescent population	9,912	9,912 100%	0 0%	ALSPAC	- Haplogroup categorization: Grouped into categories R, I, E, J, G, and combined other haplogroups (T, Q, H, L, C, N, O) based on phylogenetic relatedness. - Genotyping: e Illumina HumanHap550 SNP genotyping platform at the Wellcome Trust Sanger Institute and LabCorp, with support from 23andMe. - Quality control: PLINK software (v1.07). Data mapping: Y chromosomal genotypes (816 SNPs) mapped to the Y	Cord blood, whole blood, mouthwash samples	Binarized haplogroup status of the Y chromosome	NA	18 years	- Common Y chromosomal haplogroups show no association with cardiometabolic risk factors from birth to age 18. - No association found between haplogroups and cardiovascular structure and function at age 18. - Common Y haplogroups are not linked to cardiometabolic risk in males during childhood and adolescence.

											chromosome phylogenetic tree using Y-Fitter (v0.2) software based on the model by Karafet et al. - Haplogroup determination: Assigned respective Y haplogroups based on the mapping results.					
Human Y Chromosome Exerts Pleiotropic Effects on Susceptibility to Atherosclerosis.	2019	Eales JM	CAD, Atherosclerosis	56.7 (mean)	NA (haplogroup I1 most common in Northern Europe) (UK study)	General population (CAD: 11,234; CAD-free: 117,899)	129,133 (CAD: 11,234; CAD-free: 117,899)	129,133 100%	0 0%	UK Biobank, STAGE study	- Genotyping: Utilized UK BiLEVE and UK Biobank Axiom SNP arrays yHaplo8 software for haplogroup assignment, using reference phylogenetic tree structure with haplogroup-defining SNPs - Focused on common haplogroups (>1%): E, G, I1, I2, J, R1a, R1b. - Next-Generation - DNA Sequencing: Focused on haplogroup I1. - ENCODE analysis: Examined ChIP-seq data. - High-Coverage Sequencing: Conducted for MSY with variant calling and pathway analysis of gene expression data from GTEx.	8 atherosclerosis/ CAD-relevant tissues (subcutaneous adipose tissue, visceral adipose tissue, aorta, coronary artery, tibial artery, atrial appendage tissue, left ventricle tissue, whole blood)	Binarized haplogroup status of the Y chromosome	CAD-free controls, STAGE study replication cohort	NA	- Haplogroup I1: Associated with 11% increased risk of CAD (OR 1.11; 95% CI 1.04–1.18; $P=6.8\times10^{-4}$). - Regulatory chromatin: I1 variants enriched for promoter/enhancer states in atherosclerosis-relevant tissues. - Pathway changes: Linked to immunity, oxidative phosphorylation, mitochondrial respiration, lipid metabolism, coagulation, and extracellular matrix remodeling. - UTY expression in blood associated with haplogroup I1. - Pro-atherosclerotic transcriptome reprogramming, partly via UTY.
Preliminary study between Y chromosome haplogroups and chagasic cardiomyopathy manifestations in patients with Chagas disease.	2020	Lassen O	Cardiomyopathy, Cardiovascular characteristics	Chagas: 61 Non-chagas: 56 (mean)	NA (Argentina study)	Chagas disease, non-Chagas controls	300 (Chagas: 150 non-Chagas: 150)	300 100%	0 0%	Hypertension Department of the Córdoba Hospital in the city of Córdoba, Argentina	- Microsatellite analysis - DNA extraction from blood. - PCR amplification - Capillary electrophoresis - Data analysis: Analyzed data with specialized software to define Y chromosome haplogroups; used a Haplogroup Predictor for final haplotype classification.	Blood	Binarized haplogroup status of the Y chromosome	Non-Chagas men	NA	- R1b haplogroup: Potential protective cardiovascular effect. - R1b (43%), G2a (9%), E1b1b (9%). - Chagas patients without R1b had 5x higher risk of cardio-thorax index >0.5% (OR 5.1, 95% CI 3.31-8.17). - EcoCG alterations: Non-R1b men had 2.5x higher likelihood of EcoCG changes (OR 2.50, 95% CI 0.16-3.94).

																- R1b carriers showed fewer heart issues on thoracic XR and TTE.
Limited Effect of Y Chromosome Variation on Coronary Artery Disease and Mortality in UK Biobank-Brief Report.	2022	Timmers PRHJ	CAD, CVD risk factors, all-cause mortality	40-69 (range)	White british ancestry (British study)	General population	152,186	152,186 100%	Mothers as a negative control	UK Biobank	- 13,569 reference SNPs from yhaplo; 232 SNPs genotyped on UK Biobank arrays, with 39 low call rate (<95%) and 27 monomorphic SNPs removed, leaving 166 SNPs for haplogroup inference. - yhaplo reported 89 haplogroups directly; an additional 38 defined by combining derived groups to enhance statistical power for rarer haplogroups. - Haplogroup nomenclature: Named using up to 5 characters from the ISOGG, followed by defining SNP names (e.g., J1a2b-L817).	Blood	Binarized haplogroup status of the Y chromosome	Kin-cohort analysis (father disease acts as replication and mother disease acts as negative control)	NA	- Little evidence for any effect of MSY haplogroup on cardiovascular risk in participants. Parental models support findings. - No significant associations between Y haplogroups and CAD, its risk factors, or all-cause mortality in UK biobank. - R-P311 in British (47.8%), O-M122 in Chinese (55.0%), and E-M180 in African-heritage individuals (77.8%).
Chromosome Y Haplogroup R Was Associated with the Risk of Premature Myocardial Infarction with ST-Elevation: Data from the CholeSTEMI Registry.	2023	Lorca R	Premature STEMI (before the age of 55)	47.11 (mean age at STEMI)	European ancestry (from Asturias, Northern Spain)	Patients with premature STEMI (and controls, age <55)	322 (patients: 122; controls: 200)	122 100%	0 0%	CholeSTEMI, RENASTUR	- Genotyping of 8 Y SNPs defining common European haplogroups. - Real-time PCR with Taqman assays on ABI7500 equipment - Allele frequencies for Europeans from the Ensembl database.	Blood	Binarized haplogroup status of the Y chromosome	Control cohort	NA	- Haplogroup R higher in STEMI patients compared to controls. - Most Common Sub-haplogroups: R1 (M173) and R1B. - Haplogroup R linked to increased risk of premature STEMI (OR = 1.65, 95% CI = 1.02–2.69, p = 0.04).