The Disappearing Y Chromosome:

The Degeneration and Future of the Y Chromosome

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ABSTRACT

The Y chromosome, once believed to be stable and essential, now appears to be going through a process of deterioration and is prone to possible extinction. Its slow degeneration of genes has made it the center of debate in the fields of genetics and evolution. This review elaborates the processes of degeneration of the Y chromosome, the evolutionary aspects of the same, and the future of humankind. It compares the mechanisms of sex determination in various model organisms, i.e., Amami spiny rat, mole vole, *Drosophila miranda*, and chimpanzee. Researchers are consistently exploring new pathways and attempting to find answers to fundamental questions related to future developments and the mechanisms which would make it possible to reach there. Clinical implications of loss of the Y chromosome, along with its possible association with cancer and aging, is another vast area of research. This article presents a thorough background of the history, current state, and future of the Y chromosome.

KEYWORDS

Chromosomal evolution; gene degeneration; mosaic loss of Y; sex determination; SRY gene; Y chromosome

INTRODUCTION

The XX-XY mechanism of sex determination is widespread amongst mammals, including humans, as well as in insects such as *Drosophila melanogaster*. Males in such species have a heterogametic XY chromosomal composition, whereas females are homogametic with XX chromosomes. While the X chromosome is relatively large and harbors an enviable number of genes, the Y chromosome paints a depleted and diminished picture. Infamously termed a 'functional wasteland', it bears approximately ~55 functional genes today, and yet it remains essential for male gonadal differentiation and fertility.

Interestingly, during the fifth-sixth week of embryonic development, all individuals are potentially hermaphrodite. The SRY (Sex Determining Region of Y), located on the short arm of the Y chromosome, functions as the key testis-determining factor responsible for triggering male sexual development. Its expression in undifferentiated cells of the gonadal ridge leads to the formation of the primordial sex cords, which later develop into seminiferous tubules – among the first male-specific reproductive structures to appear [1]. These seminiferous tubules later become the primary area of spermatogenesis that highlights just how important the Y chromosome is in male fertility. However, the Y chromosome remains a riddle yet to be solved. It structural and evolutionary features have long puzzled geneticists and scientists. Unlike autosomes and the X chromosome, which undergo recombination during meiosis, the Y chromosome presents a unique anomaly, wherein it only undergoes recombination at only the

tips in regions known as Pseudo Autosomal Regions (PARs). Due to discrepancies of homologous recombination, the chromosome accumulates deleterious mutations, and undergoes progressive gene loss. This slow, yet harmful process is termed as Muller's Ratchet. This ongoing degeneration and limited gene content raises questions about its stability, relevance and the ultimate fate of the Y chromosome. Is the Y chromosome destined for inevitable degeneration, or has it reached a point of equilibrium? Investigating the mechanisms underlying Y chromosome degeneration, its evolutionary trajectory and the biological consequences of this process is essential for understanding the future of sex determination systems and male fertility.

THE Y CHROMOSOME: EVOLUTIONARY HISTORY AND STRUCTURAL FEATURES

The historical emergence of the sex chromosomes is believed to trace back to a pair of homologous autosomes, as proposed by Susumu Ohno [2]. Over time, these chromosomes acquired sex-determining functions and diverged significantly. One key factor in this divergence is recombination suppression. In the Y chromosome, recombination is now restricted to the terminal pseudoautosomal regions (PARs), while the remainder of the chromosome is largely non-recombining and has become highly differentiated from the X chromosome. According to Lahn and Page [3], the human X chromosome contains four distinct evolutionary strata on the human X chromosome, each representing gene blocks that ceased recombining with their Y-linked counterparts at different time points spanning roughly over 300 million years. This sequential suppression of recombination, driven by chromosomal inversions, resulted in the gradual degeneration of the Y chromosome
The evolution of the Y chromosome represents a sequential process, driven by chromosomal inversions that resulted in restricted recombination with the X chromosome (Figure 1).
Each inversion enlarged the non- recombining regions, effectively isolating the Y linked genes from genetic exchange to prevent the deleterious mutations. Over time, these regions formed evolutionary strata, visible today, as layers of divergence between the X and Y genes [3, 4]. Although inversion protected the sex- specific genes, they also began degeneration as mutation accumulation and inefficient repair continually eroded the Y linked gene content [5, 6]. Inversions represent the mechanism of Y chromosome differentiation as well as the trigger of its genetic decline over evolutionary timescales.

Structurally, the Y chromosome is significantly smaller than the X chromosome, containing approximately 45 protein-coding genes in contrast to the X chromosome's ~1,000. It is enriched with repetitive DNA sequences and heterochromatin, rendering large portions of it genetically inert. Although most mammals share the XX-XY sex determination system, the gene content and structural organization of the Y chromosome differ considerably among species.
The male-specific region of the Y chromosome (MSY) is composed of:

1. **PARs (Pseudo-Autosomal Regions):** These regions recombine with the X chromosome and vary among species.
2. **X-Transposed Region:** Unique to humans, this region originated from the X chromosome about 3-4 million years ago.
3. **X-Degenerated Region:** It harbours ancestral genes common to the X chromosome, many of which are responsible for essential housekeeping functions.

4. **Ampliconic Regions:** Characterized by repetitive sequences and multi-copy gene families, these regions are often organized within palindromic structures and are primarily associated with functions related to male fertility. [4].

Comparative studies reveal that the chimpanzee Y chromosome, despite a recent divergence from humans (~6 million years ago), shows significant gene loss and more extensive palindromic structures. This highlights the dynamic and lineage-specific evolution of chromosome.

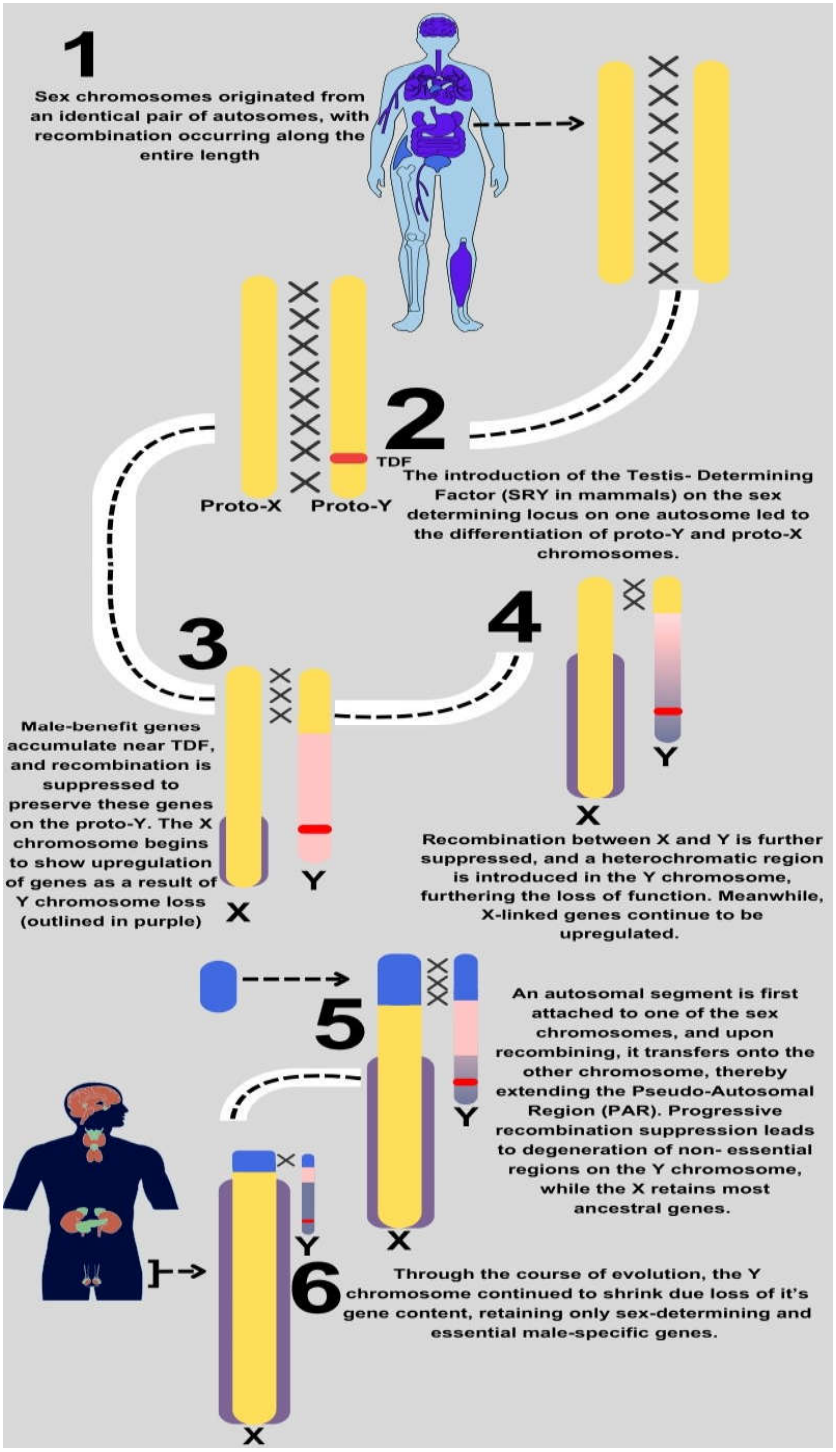

Figure 1: Evolution of the human Y chromosome. A representation showing the progressive degeneration of the Y chromosome during evolution, highlighting structural changes and gene losses.

MECHANISMS OF Y CHROMOSOME DEGENERATION

Three primary factors contribute to Y chromosome degeneration:

- **Lack of Recombination:** Without recombination (except at PARs), deleterious mutations accumulate over generations, a process described by Muller's Ratchet [4, 5]. Once mutation-free chromosomes are lost due to genetic drift, they cannot be regenerated, leading to progressive degeneration.
- **Inefficient DNA Repair Mechanisms:** The Y chromosome lacks robust repair systems. Gene conversion within palindromic sequences serves as a partial repair strategy by using one palindrome arm as a template to correct mutations in the other [4, 7]. However, this repair is restricted to palindromic regions, leaving other genes vulnerable to irreversible decay.
- **Mutation Accumulation:** Deleterious mutations, including frameshift and nonsense mutations, persist and accumulate over time. Research in *Drosophila miranda* reveals the ongoing degeneration of a newly formed neo-Y chromosome, providing evidence that Y chromosome decay is primarily driven by the accumulation of mutations rather than by adaptive processes. [8].

The Y chromosome undergoes a slow and progressive degeneration, driven by these mechanisms. The suppression of recombination prevents the Y from removing harmful mutations, allowing them to accumulate through generations. Furthermore, inefficient DNA repair aggravates this vulnerability, by only allowing limited regions in the palindromic sequences to undergo gene- conversion corrections, leaving most of the chromosome exposed to damage. Hence, these deleterious mutations continue to accumulate without any mechanism to eliminate them. Together, these factors create a cycle where the Y chromosome is unable to repair or recombine and this accelerates genetic decay.

Although intrachromosomal gene conversion within palindromic regions can partially slow degeneration, its limited reach means that the architectural stability of the Y chromosome continues to deteriorate over evolutionary timescales. This persistent decline highlights the intricate and fragile path of Y chromosome evolution.

COMPARATIVE GENOMICS ACROSS SPECIES

Comparative genomic studies across insects, fishes, primates, rodents, and marsupials reveal diverse sex determination mechanisms. In certain species, including the Amami spiny rat and the Transcaucasian mole vole, evolutionary processes have resulted in the complete elimination of the Y chromosome; nevertheless, sex determination continues via autosomal or X-linked genes (Figure 2). In contrast, the human Y chromosome has remained relatively unchanged throughout the last 25 million years, suggesting a plateau in gene loss. Understanding the sex determination mechanisms in other species offers valuable insights into possible evolutionary trajectories for humans.

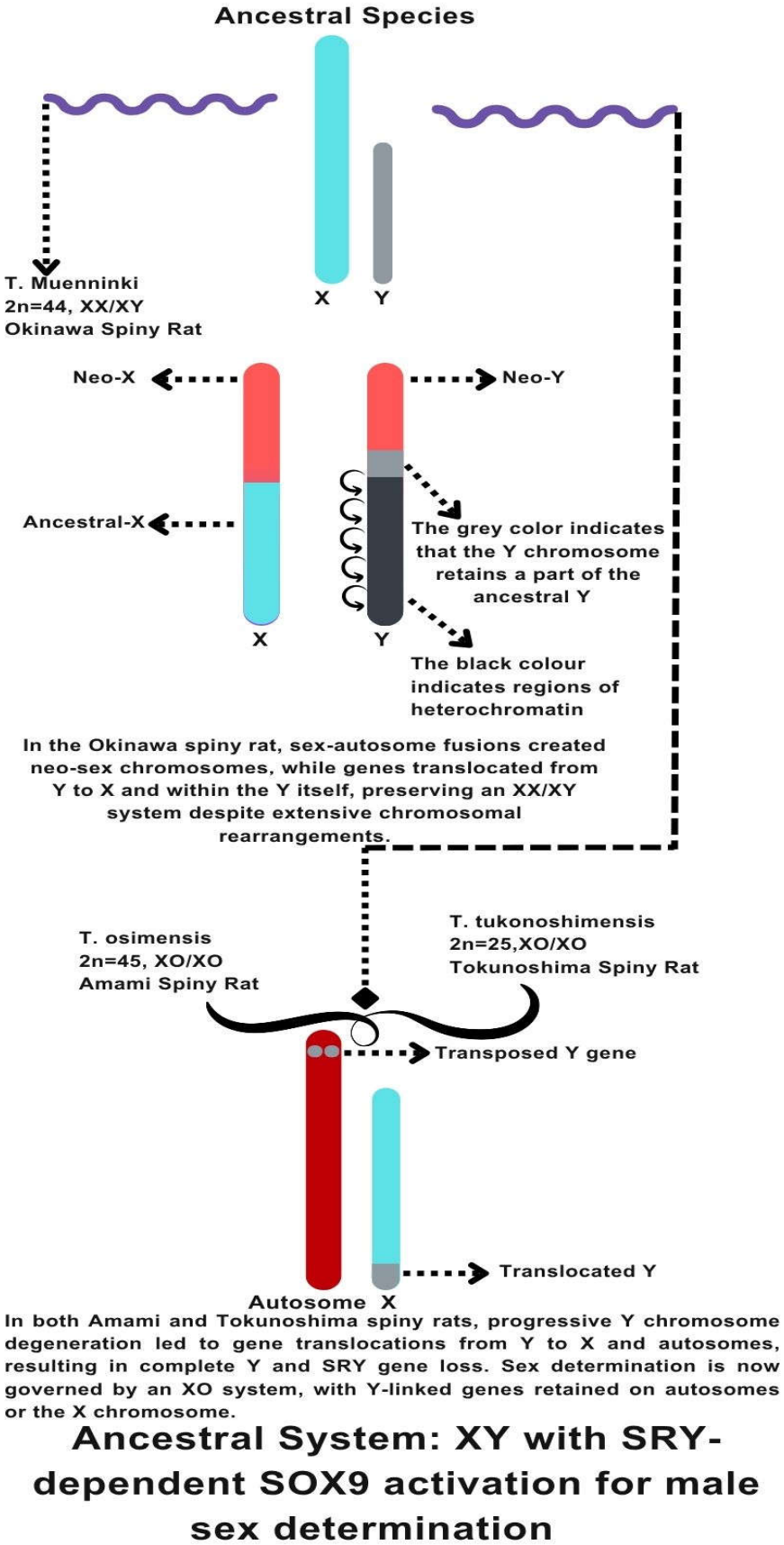

Figure 2 : Phylogenetic origin of different sex-determining mechanisms in *Tokudaia* species. The phylogenetic tree illustrates the divergence of *Tokudaia* species and the evolution of their sex determination systems

Amami Spiny Rat

The Amami spiny rat, native to Japan's Amami-Oshima Islands, entirely lacks a Y chromosome and instead exhibits an XO sex determination system [9]. In these rats, the SRY gene is missing, and the SOX9 gene is activated by an enhancer element called Enh- 13, which is responsible for the initiation of testis differentiation (Figure 3). This raises the question of whether humans might have similar enhancer-based mechanisms capable of bypassing the need for the Y chromosome. Supporting this idea, an enhancer that regulates SOX9, has been found in mice and conserved in humans [10]. In the Amami spiny rat, these enhancers are located on an autosome, suggesting that autosomal mechanisms could be involved in sex determination, even without a Y chromosome.

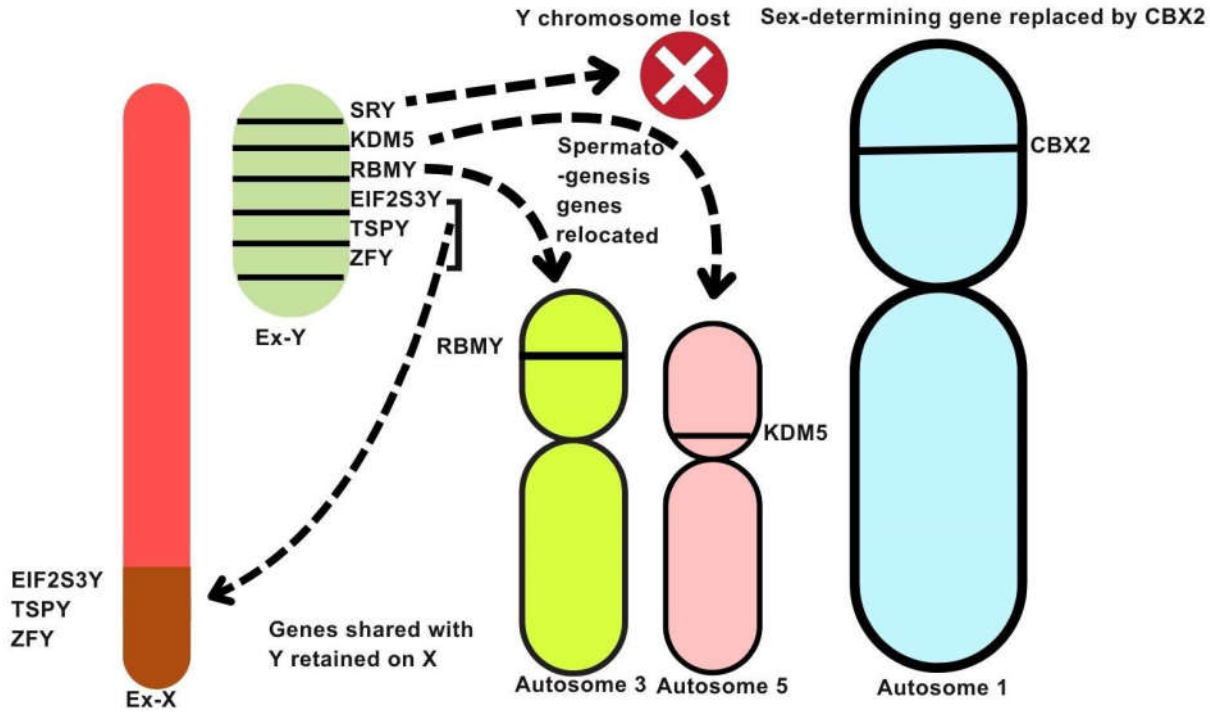

Figure 3: Loss of the Y chromosome in the Amami spiny rat (*Tokudaia osimensis*). Essential sex-determining genes have been translocated to autosomes (autosomes 3 and 5). Some genes (EIF2S3Y, TSPY, ZFY) were found to have been translocated from the Ex-Y to the Ex-X chromosome. The CBX2 gene, a novel sex-determining gene, has been acquired by autosome 1, replacing the function of the SRY gene.

Transcaucasian Mole Vole

Species of the *Ellobius* genus, including *Ellobius lutescens* and *Ellobius talpinus*, exhibit a unique sex determination system that functions entirely independently of the Y chromosome or the SRY gene. Both males and females have a 17, XO chromosomal composition. Before the Y chromosome was completely lost, essential Y-linked genes like *Eif2s3y* and *Zfy*, which are crucial for spermatogenesis, were translocated to autosomes [11]. Male differentiation in these species likely occurs through alternative autosomal regulatory elements or epigenetic modifications.

In contrast to *Ellobius*, humans have retained critical Y-linked genes under strong negative

selection, maintaining their integrity for millions of years [12]. This shows that in *Ellobius*, only essential Y genes were preserved, allowing the Y chromosome to be entirely lost without affecting male reproductive capacity.

Drosophila miranda

Drosophila miranda offers a unique model for observing Y chromosome degeneration as it occurs in real time. This species has a neo-Y chromosome that originated approximately one million years ago and still retains most of its original genes [8]. However, signs of degeneration are evident, including frameshift and nonsense mutations affecting approximately one-third of its genes, rapid protein evolution, and increasing heterochromatinization, indicating transcriptional inactivation. Comparative analysis with the neo-X chromosome, which shares its evolutionary origin, confirms this ongoing degeneration. Notably, mutation accumulation rather than adaptive processes drive the downregulation of gene expression on the neo-Y appears random, suggesting degeneration. The absence of recombination in the neo-Y chromosome hinders effective purifying selection, thereby promoting its gradual degeneration.

Chimpanzee

Chimpanzees (*Pan troglodytes*), believed to have diverged from humans around six million years ago, exhibit a Y chromosome that is remarkably different from that of humans. While humans possess ampliconic, X-transposed, X-degenerate, and palindromic regions, chimpanzees have almost double the palindromic sequence content (~10.4 Mb) [12]. Despite this, the chimpanzee Y chromosome has experienced greater gene loss and structural rearrangements. Multiple gene families that are expressed in the testes and exist in multiple copies in humans have either undergone pseudogenization or have been entirely lost in chimpanzees.This rapid divergence in a short evolutionary timeframe emphasizes the lineage-specific evolution of Y chromosomes among primates.

Humans

SOX9 is a transcriptional factor that plays a crucial role in testis differentiation. It is activated by SRY, and is responsible for initiating and maintaining the testis formation by promoting the development of sertoli cells. It suppresses ovarian pathways, thereby ensuring that the embryo develops as a male. Croft et al. [13] discovered an enhancer, namely the eSR-A, which plays a critical role in male development. It is located approximately 500 kb upstream of SOX9. A disruption in eSR-A's activity proves to be detrimental because its deletion leads to an XY sex reversal, wherein SOX9 is not activated and a genetically male individual develops as a female. On the other hand, ectopic expression of SOX9 in XX individuals can result in testis development.
This highlights the pivotal role of eSR-A in maintaining male differentiation. In mice, the corresponding element, Enh13, is regulated by both SRY and SF1. In humans, activation of the eSR-A enhancer is mediated by SF1 and SOX9, while SRY does not contribute to its regulation [13], indicating an evolutionary divergence in enhancer activation mechanisms.

SOMATIC MOSAICISM OF Y CHROMOSOME LOSS

Mosaic loss of the Y chromosome (LOY) is characterized by the absence of the Y chromosome in certain somatic cells within a male individual, leading to a karyotypically mosaic cell population [14]. Loss of the Y chromosome (LOY) has been closely linked to

various life-threatening diseases such as cardiovascular disease [15] and neurodegenerative disorders, with Alzheimer's disease being the most common [16]. It has been detected in over 40% of men aged 70 years and above [14]. However, most studies are focused on middle-aged and elderly men, making it challenging to determine when LOY initiates and how early-life factors may contribute to disease risk [16].

The distinctive structural features of the Y chromosome may render it particularly susceptible to mosaic loss (LOY). Palindromic sequences within the Y chromosome can form isodicentric chromosomes, which have two centromeres and are structurally unstable during mitosis, often leading to chromosome breakage. Additionally, while CENP-A is the primary centromeric histone variant essential for chromosome segregation, the Y chromosome lacks CENP-B, a stabilizing protein found in other chromosomes. This absence leaves the Y chromosome particularly vulnerable to segregation defects if CENP-A fails [17].

Longitudinal studies by Forsberg et al. [14] provided direct evidence of clonal expansion of Y-chromosome lacking hematopoietic cells over time. In a group of elderly men sampled over 6–14 years, the proportion of leukocytes with LOY increased significantly, reaching levels as high as 87%.
Notably, all five men in this cohort were later diagnosed with cancer, indicating a possible link between LOY and cancer development. Clonal expansion may therefore contribute to the high frequency of LOY in aging men and potentially promote cancer by eliminating Y-linked tumor suppressor functions.
Interestingly, LOY is not exclusive to humans. Recent research has identified age-related mosaic loss of the Y chromosome in rats, suggesting that LOY may be a conserved aging-associated phenomenon across mammals [18]. This discovery positions rodents as valuable models for further investigation into the mechanisms and health implications of LOY.

ALTERNATIVE PATHWAYS OF SEX DETERMINATION

Across various taxa, a wide diversity of sex determination systems has evolved, although the SRY dependent XY system remains the most well studied in mammals. However, given the gradual but persistent degradation of the Y chromosome, it is crucial to explore potential alternative mechanisms that may emerge in the future. Comparative genomics provides valuable insights by allowing us to study species that share common evolutionary ancestry with humans but display differing sex determination systems.
For example, rodents and humans diverged approximately 75 million years ago, but comparative genomic studies reveal that much of their genomic structure remains conserved [19]. This genetic similarity emphasizes the role of rodent models in studying mammalian sex determination pathways and their possible evolutionary future. The elimination of both the Y chromosome and the SRY gene is exemplified by rodents like the mole vole (genus *Ellobius*), illustrating the outcomes of such loss. In these species, male differentiation continues despite this absence. Studies suggest that before the Y chromosome was completely lost, essential genes involved in spermatogenesis were translocated to autosomes, thereby compensating for the absence of the Y chromosome. [11]. Additionally, *Ellobius* species have unique meiotic adaptations that allow for the formation of univalent sex chromosomes while preserving fertility [20]. Although the specific molecular drivers of these adaptations are still unclear, they show that sex determination can continue through different genetic pathways.
Beyond mammals, teleost fishes, particularly those in the *Medaka* genus (*Oryzias*), show examples of rapid and flexible sex determination evolution. Even among closely related

species, *Medaka* display significant differences in their sex chromosomes despite having an XX-XY system. For example, *Oryzias marmoratus* and *Oryzias profundicola* use sex chromosomes homologous to linkage group 10 in *Oryzias latipes*, whereas *Oryzias celebensis* and *Oryzias matanensis* rely on linkage group 24. These differences arise from independent sex chromosome turnovers driven by diverse sex-determining genes [21].

In some *Medaka* species, the sex-determining gene *Sox3* has replaced the *Dmy* gene found in *Oryzias latipes*. Notably, the mammalian SRY gene itself is derived from *Sox3*, highlighting how sex- determining functions can evolve from transcription factors across species. This rapid evolutionary turnover in fish emphasizes that sex determination is not a fixed process but is susceptible to change under selective pressures.

While the Y chromosome remains essential for male development in humans today, these comparative examples suggest it may not be irreplaceable in the long-term evolutionary future. Observations across taxa show that autosomal genes or alternative regulatory mechanisms can emerge to take over sex-determining functions if required.

THE EVOLUTIONARY TRAJECTORY OF THE Y CHROMOSOME

The estimated timeline for the Y chromosome's extinction differs across various theoretical models. Initial linear models, extrapolating from historical gene loss rates, predict that the Y chromosome may vanish entirely within ~14 million years [6]. However, alternative models argue that the degeneration rate slows over time due to the reduced number of target genes and the strong purifying selection acting on essential genes, implying that the Y chromosome may persist indefinitely. Given the complexity of evolutionary processes, precise predictions remain challenging, as multiple mechanisms interact in ways that are yet not fully understood. As Graves [6] noted, the human Y chromosome appears unlikely to have reached a stable evolutionary state, rendering its long-term fate uncertain.

Comparative genomic studies offer critical insights into the Y chromosome's future. Evidence from Rhesus macaque and human Y chromosome comparisons suggests that degeneration has slowed, with gene loss appearing to plateau over the past 25 million years [22]. This stabilization may be influenced by several factors, though they remain incompletely studied.

One key stabilizing factor is the presence of palindromic sequences on the Y chromosome, which facilitate intrachromosomal gene conversion. This process acts as an internal repair mechanism by correcting deleterious mutations through sequence copying between palindrome arms [7]. However, this repair is limited to palindromic regions, leaving other genes vulnerable to decay.

Another important factor is the retention of dosage-sensitive genes, which regulate gene dosage across tissues. Loss of these genes would lead to harmful imbalances, subjecting them to strong purifying selection and promoting their preservation.

Despite these stabilizing forces, the potential disappearance of the Y chromosome cannot be ruled out. Comparative genomics across species highlights alternative sex determination systems that could potentially replace the Y chromosome. For example:

- Mole voles and the Amami spiny rat have lost their Y chromosomes entirely, yet sex determination persists through autosomal regulatory elements [9, 11].
- *Drosophila miranda* provides a rare opportunity to observe real-time Y chromosome degeneration. Its recently formed neo-Y chromosome already shows frameshift and nonsense mutations, offering valuable insights into the early stages of degeneration [8].

These comparative studies pose a significant evolutionary question: if the Y chromosome were to vanish in humans, what would take its place? Possible compensatory mechanisms involve the translocation of the SRY gene or other sex-determining genes to autosomes, as observed in the Amami spiny rat, or the evolution of entirely novel sex determination systems, as documented in several other species. In conclusion, while stabilizing mechanisms may significantly slow the Y chromosome's degeneration, its long-term fate remains uncertain, suspended between potential extinction and evolutionary rescue.

CLINICAL AND RESEARCH IMPLICATIONS

The degradation of the Y chromosome has important effects on both clinical and research areas, beyond reproductive biology, particularly in fields such as neurodegeneration, oncology, and genomic stability. Exploring Y chromosome loss offers valuable insights into the genetic factors of male-specific health risks and disease susceptibility.

Mosaic loss of the Y chromosome (LOY) has recently been linked to neurodegenerative conditions, particularly in Alzheimer's disease. Dumanski et al. [16] further linked LOY to higher risks of Alzheimer's disease, cancer, and type 2 diabetes. LOY-driven aberrant clonal expansions (ACEs) in blood cells can cause chromosomal instability, altered gene dosage, and compromised immune regulation. The absence of the Y chromosome in leukocytes hinders immunosurveillance, which is essential for clearing neurotoxic proteins in the brain. Additionally, LOY in blood cells also serves as a biomarker of genomic instability in other tissues, suggesting that aging men may have a greater risk of neurodegenerative diseases.

LOY is also significantly linked to cancer biology research. Forsberg et al. [14] found that men exhibiting high levels of LOY in peripheral blood cells faced a significantly higher risk of developing non-hematological cancers. Two key hypothesis explain this connection:

1. The presence of LOY weakens immune surveillance, thereby lowering the efficiency with which the body detects and eradicates cancer cells.
2. The parallel aneuploidy hypothesis suggests that LOY in blood reflects genomic instability across multiple tissues, increasing cancer susceptibility systemically.

The recurrent loss of the Y chromosome in diverse cancer cell types reinforces the potential of LOY as a predictive biomarker for cancer susceptibility.

In addition to its links with neurodegeneration and cancer, LOY serves as a biomarker of biological aging. Forsberg et al. [14] found that over 40% of men aged 70 and above exhibit detectable levels of LOY and Gutierrez-Hurtado et al. [17] emphasized its connection to age-related cellular decline. LOY is thus not only an indicator of genomic instability but also a harbinger of functional deterioration and disease susceptibility.

Collectively, these findings suggest that routine LOY screening could be a valuable tool in predictive and preventive medicine, enabling the early identification of men at higher risk for Alzheimer's disease, cancer and other age-associated conditions. Large-scale screening could also enhance the accuracy of population-level risk assessments.

Future research should explore compensatory mechanisms that may offset the detrimental effects of Y chromosome loss. For example, species like *Ellobius* demonstrate the successful translocation of essential Y-linked genes to autosomes, preserving male viability despite complete Y chromosome loss.

The study of Y chromosome degradation offers profound insights into male health, disease

vulnerability, and the adaptability of genetic systems. Model organisms such as the mole vole, Amami spiny rat, and *Drosophila miranda* illustrate the remarkable evolutionary resilience and ability of life to develop alternative pathways to sustain itself even after its genetic components degenerate.

CONCLUSION

Once thought to be a decaying genetic relic, the Y chromosome has shown resilience through mechanisms like gene conversion and the retention of critical genes. Comparative studies reveal its adaptability and the flexibility of sex determination systems, challenging assumptions about its extinction and highlighting nature's capacity for evolutionary innovation.

COMPETING INTERESTS

The author(s) declare(s) that they have no competing interests.

AUTHORS' CONTRIBUTIONS

Vaishali Bhatnagar conducted the literature review, and drafted the manuscript under guidance and supervision of Dr. Shruti Banswal.

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