

Review Article

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Evidence for asymmetric DNA strand inheritance in vertebrate mitochondria

A classical experiment performed by Meselson and Stahl in 1958 confirmed the semiconservative mechanism of DNA replication in cellular organisms. According to this mechanism, following DNA replication and cell division, each daughter cell inherits chromosomes consisting of one parental strand (W or C) and one newly synthesized complementary strand (C' or W'). Since each DNA strand is replicated the same number of times during successive rounds of cell division, the W and C strands can be considered equivalent as a result of the coupling between cell division and semiconservative DNA replication. However, some non-cellular organisms, including single-stranded DNA and RNA viruses, do not conform to the concept of strand equivalence. A key feature of vertebrate mitochondrial genomes is a highly skewed nucleotide composition between the two complementary strands. This compositional asymmetry allows the strands to be separated by ultracentrifugation in an alkaline cesium chloride density gradient, yielding a heavy (H) strand enriched in guanine and thymine and a light (L) strand enriched in cytosine and adenine. Despite extensive research, the exact mechanism of human mitochondrial DNA replication and its relationship to nucleotide compositional bias remain unclear. In this review, we propose a conceptual model of asymmetric mitochondrial DNA strand inheritance to account for the strand-specific mutational asymmetry characteristic of vertebrate mtDNA.

Keywords: mitochondrial DNA, DNA strand equivalence, patterns of mutation, Chargaff's second parity rule, DNA replication.

Introduction

Mitochondrial DNA (mtDNA) in vertebrates consists of a compact circular molecule between 16–24 kb [1, 2]. In mammals, the mitochondrial genome is a circular DNA molecule of ~16.6 kb that carries 37 genes (13 protein-coding genes, 2 ribosomal RNAs and 22 transfer RNAs). The only major non-coding region, known as the control region or D-loop, contains key cis-acting elements essential for mtDNA transcription and replication, including the light-strand promoter (LSP) and heavy-strand promoter (HSP), which initiate transcription from the respective strands. Figure 1 presents a map of the human mitochondrial genome [3, 4].

The mitochondrial genome comprises two strands—the heavy (H) strand, enriched in guanine (G) and thymine (T), and the light (L) strand, enriched in cytosine (C) and adenine (A)—that exhibit marked differences in nucleotide composition. This compositional asymmetry contributes to distinct buoyant densities, enabling physical separation of the strands by alkaline CsCl density gradient centrifugation.

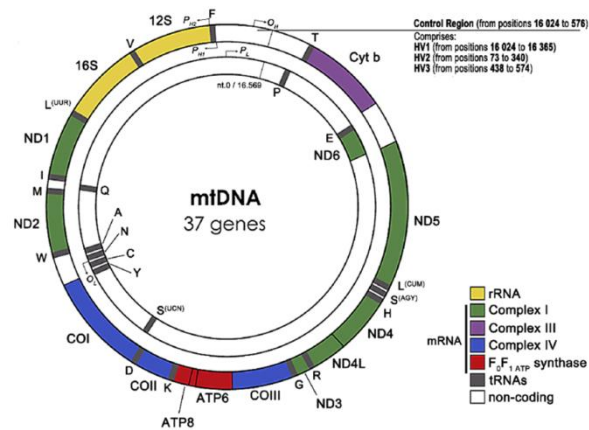


Figure 1. Structure of human mitochondrial DNA [5]

Table 1 quantifies these conserved patterns across vertebrates, illustrating how skew metrics (AT- and GC-skew) deviate from Chargaff's second parity rule and correlate with asymmetric replication dynamics. The pronounced H-strand skews—particularly negative AT- and GC-skews—facilitate strand displacement during replication and localize mutation hotspots near OriH [6, 7].

Table 1

Nucleotide composition and skews reveal conserved strand asymmetry in vertebrate mtDNA. H-strand G+T bias (vs. L-strand C+A enrichment) violates Chargaff's second parity rule across species. Skew metrics: AT-skew = $(A-T)/(A+T)$; GC-skew = $(G-C)/(G+C)$.

Adapted from; own compilation

Species	Strand	A (%)	C (%)	G (%)	T (%)	AT-skew	GC-skew
Human	H	30.98	12.21	13.24	43.57	-0.168	-0.041
	L	29.65	28.21	12.21	30.98	+0.022	+0.398
Mouse	H	31.49	11.90	13.31	43.30	-0.156	-0.112
	L	30.12	27.31	11.90	30.67	+0.009	+0.393
Chicken	H	29.81	13.45	14.20	42.54	-0.177	-0.032
	L	28.92	27.45	13.45	30.18	+0.021	+0.328

The pronounced H-strand skews (Table 1)—particularly negative AT-skew and GC-skew—facilitate strand displacement during replication, underpin physical separation via alkaline CsCl density gradient centrifugation, and localize mutation hotspots near OriH.

MtDNA is inherited strictly maternally: paternal mtDNA is diluted in the zygote and actively degrades after fertilisation [8, 9]. Two main mechanisms are thought to underlie the absence of paternal mtDNA in the offspring. First, the small amount of mtDNA carried by sperm is negligible compared with the large number of maternal copies present in the oocyte and zygote, which leads to simple dilution [5, 10]. Second, an active degradation process selectively eliminates sperm-derived mitochondria after fertilisation [11–13]. Research revealed that a mammalian oocyte contains about 100,000 copies of mtDNA, which are distributed to daughter cells as the fertilized egg begins to divide [14]. However, mtDNA replication does not commence until after implantation. During development, only a small fraction of maternal mtDNA is designated for the germ line, eventually giving rise to primordial germ cells that will produce future oocytes. Despite the high mutation rate of mtDNA in somatic tissues, several protective mechanisms in the germline prevent the maternal transmission of deleterious mtDNA mutations [15]: (1) only a limited amount of the maternal mtDNA is passed on to the next generation [16]; (2) purifying selection within the maternal germline reduces mtDNA mutations that alter protein amino acids [17]; (3) embryos actively eliminate cells with high levels of mtDNA mutations affecting transfer RNA (tRNA) genes [18]; and (4) women with significant mtDNA mutations in their reproductive cells often face fertility problems [19].

Evidences suggest that mitochondrial DNA represent a vestigial genome of the alpha-proteobacterial endosymbiont captured ~1.5-2 billion years ago during eukaryogenesis, retaining ~5 % of progenitor genes while outsourcing bioenergetics to nuclear genome [20]. Remarkably conserved across Metazoa (human-chicken 93 % identity), mtDNA exhibits clade-specific rearrangements reflecting reductive evolution [21].

Strand asymmetry traces to ancestral displacement replication, paralleling T-odd/ssDNA bacteriophages and supporting alpha-proteobacterial phage-endosymbiont hypothesis [22]. Maternal uniparental inheritance precludes mtDNA recombination, yielding a low nonsynonymous/synonymous substitution ratio ($dN/dS \approx 0.2$) that indicates strong purifying selection. Tissue-specific mtDNA copy number variation and heteroplasmy thresholds then determine bioenergetic capacity [5, 23].

To understand the origin and maintenance of chain asymmetry, it is necessary to consider the mechanisms of mtDNA replication. Key proteins are polymerase γ (POL γ), TWINKLE helicase, and mitochondrial RNA polymerase (POLRMT), which synthesises primers [24, 25]. RNase H1 removes RNA primers [26].

Factors involved in mammalian mitochondrial DNA replication

Mammalian mitochondrial DNA (mtDNA) replication uses a specialised set of proteins that is distinct from the nuclear replication machinery [27]. DNA polymerase γ (POL γ) plays a central role as the only polymerase that synthesises both the H and L strands [28]. POL γ forms a heterotrimer: the catalytic subunit POL γ A (~140 kDa, family A, related to T7 DNA polymerase) has 3'→5' exonuclease activity (error <1 per 10^6 nt), while the two accessory subunits POL γ B (~55 kDa, structurally similar to class IIa aminoacyl-tRNA synthetases) increase processivity and stability of binding to the template [29, 30].

TWINKLE helicase (hexameric complex, ~420 kDa; 5'→3' activity; homologous to T7 gp4) unwinds double-stranded DNA at the replication fork, while its limited priming capacity is supported by mitochondrial RNA polymerase (POLRMT), which synthesizes 25–75 nt RNA primers on single-stranded DNA templates. Mitochondrial single-stranded DNA-binding protein (mtSSB; tetrameric complex, ~60 kDa) prevents secondary structure formation, inhibits non-specific priming, and enhances the activities of both TWINKLE and POL γ [31–36]. Accessory polymerases (PrimPol, POL β , POL θ , POL ζ) focus on repair. TFAM (HMG box) packs mtDNA and initiates truncated transcripts for priming [27, 29, 36].

The D-loop in the control region is a docking station for nucleoids with an R-loop (7S DNA on the non-template strand), which ensures the organisation and separation of mtDNA [35, 37]. Depletion of MGME1 (ssDNA nuclease 5'→3'/3'→5') leads to the accumulation of 7S DNA, confirming its role in D-loop turnover and prevention of linear fragments. MtSSB coordinates replication, increasing the efficiency of POL γ [34, 37].

mtDNA replication modes

Three primary models of mtDNA replication have been proposed for vertebrates: the classical strand-displacement model (SDM), the ribonucleotide incorporation throughout the lagging strand model (RITOLS), and the strand-coupled model (Fig. 2). These models have been confirmed by electron microscopy, two-dimensional agarose gel electrophoresis (2D-AGE), atomic force microscopy, analysis of DNA-RNA hybrids of replication intermediates, and ChIPmtSSBin *vivo* [38–43].

Figure 2 illustrates the topological differences: SDM features prolonged ssDNA displacement, RITOLS provides transient RNA protection, and SCM shows coupled forks. Each contributes to strand asymmetry maintenance.

Strand displacement model (SDM)

The classic SDM model was formulated in the early 1970s based on electron microscopic analysis of circular mitochondrial molecules containing extended single-stranded regions corresponding to the displaced parental strand. In these works, molecules were observed where one daughter strand was double-stranded and the other was partially or completely single-stranded, leading to the introduction of the term “strand displacement” to describe this mechanism [43, 45, 46]. Within the SDM, replication begins in the control region, near the origin of replication of the heavy chain (OriH), from where a new H chain is continuously synthesised on the L chain template [46]. As the replication fork progresses, the parental H-strand is displaced and remains in a single-stranded state, forming characteristic replication intermediates with an increasing length of the single-stranded segment [38]. The origin of L-strand replication (OriL) lies roughly two-thirds of the way around the circular mtDNA genome from OriH [40].

L-strand synthesis is initiated by mitochondrial RNA polymerase, which synthesises primers that are then extended by DNA polymerase γ (Pol γ), resulting in the formation of a functional analogue of the lagging strand, but without the classic Okazaki fragments [44, 48]. This asynchrony, as well as the prolonged existence of the single-stranded displaced H-strand, distinguishes SDM from nuclear DNA replication and served as the basis for the concept of “asynchronous chain synthesis” in mitochondria [47].

Later work using atomic force microscopy and 2D-AGE showed that SDM well explains the observed replication intermediates in mouse liver mitochondria and that there are additional L-strand initiation sites besides the classic OriL [45, 49].

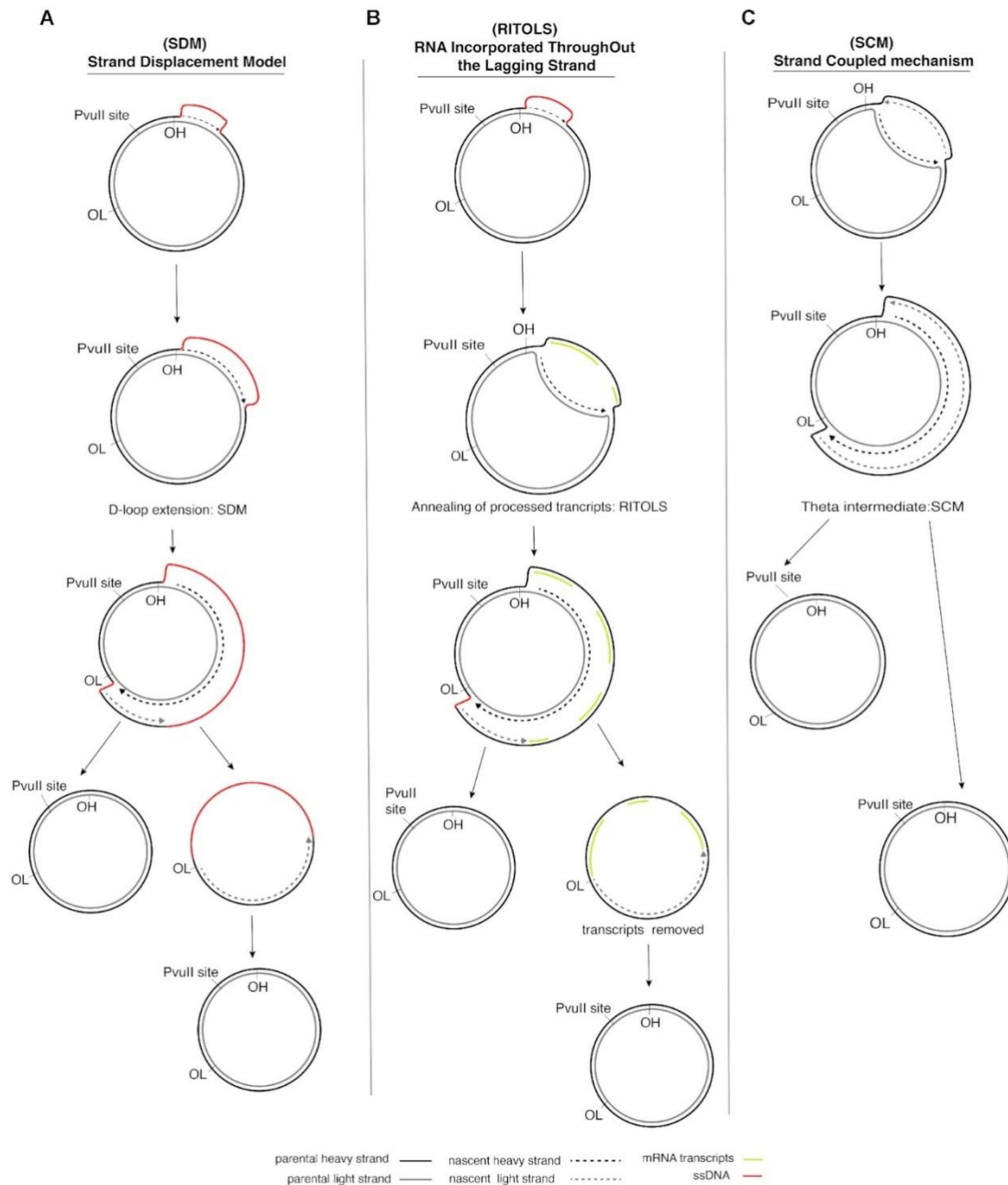


Figure 2. Schematics of the three main mtDNA replication models in vertebrates. (A) Strand-displacement model (SDM): leading-strand synthesis initiates at OriH, displacing the parental H strand (red) to form a D-loop until OriL activation and lagging-strand priming. (B) RITOLS model (RNA incorporation throughout the lagging strand): the displaced H strand is initially coated with RNA transcripts synthesized on the L strand (“bootlace” mechanism, yellow), later replaced by POL γ -synthesized DNA. (C) Strand-coupled model (SCM): bidirectional replication forks with coupled H/L-strand synthesis (Y-arc intermediates observed by 2D-AGE). Color code: black = parental strands; green = newly synthesized DNA; yellow = RNA [43, 44]

In summary, the defining features of SDM are: (1) strictly unidirectional, continuous H-strand synthesis initiating at OriH; (2) the displaced parental H-strand persisting as naked single-stranded DNA until OriL is reached approximately two-thirds around the genome; (3) L-strand synthesis commencing only after OriL is exposed, without Okazaki fragment formation; and (4) the prolonged single-stranded state of the parental H-strand as the principal source of its mutational vulnerability [38, 45, 46]. This model is best supported by electron microscopy and mtSSB occupancy data, and it provides the direct mechanistic basis for the replication-coupled mutational gradient that is the focus of the present work [39]. The key limitation of the pure SDM is its prediction of extended single-stranded intermediates that, in practice, appear partly RNA-coated in many experimental systems—a discrepancy addressed by the RITOLS model [40, 41].

The RITOLS model and the “bootlace” mechanism

With the development of methods that allow for the preservation of fragile replication intermediates and the analysis of DNA–RNA hybrids, it has been shown that many structures previously interpreted as extended single-stranded regions of the displaced H-strand actually contain long RNA tracts complementary to the L-strand [41, 46, 47]. These observations led to the formulation of the RNA Incorporated ThroughOut the Lagging Strand (RITOLS) model, according to which as the replication fork progresses, the displaced H-strand is temporarily covered by pre-synthesized transcripts that hybridize with the template and act as a temporary lagging strand [43, 47].

Metabolic labelling of isolated mitochondria with DNA and RNA precursors showed that RNA strands in these intermediates are not synthesised “on the fly” at the fork, but are preformed L-strand transcripts that are sequentially “threaded” (bootlaced) onto the displaced H-strand as the replication fork progresses [45, 47]. In the next stage, these RNA primers are gradually displaced and replaced by DNA synthesised by Pol γ , leading to the formation of a complete L-strand [41].

Thus, the RITOLS model largely retains the topology of SDM (initiation in the control region, the key role of OriH/OriL, and asynchronous strand synthesis), but radically reduces the lifetime of long single-stranded DNA segments by replacing them with stable DNA–RNA duplexes [43, 44, 50]. This is considered a potential adaptation necessary for maintaining mitochondrial genome integrity, given the relatively low replication rate of mtDNA compared to nuclear and bacterial DNA, and the high sensitivity of single-stranded DNA to breaks and deletions [44].

In summary, RITOLS shares with SDM its unidirectional initiation at OriH, its asynchronous activation of OriL, and its overall topology of leading-strand displacement. The critical distinction is mechanistic rather than topological: in RITOLS, the displaced parental H-strand is not naked ssDNA but is coated by preformed L-strand RNA transcripts via the “bootlace” threading mechanism, forming transient RNA–DNA duplexes that are subsequently matured into dsDNA by POL γ -mediated RNA replacement [41, 43]. This RNA coverage substantially shortens the window of H-strand single-stranded exposure compared to SDM, potentially reducing (but not eliminating) the mutational vulnerability of the H-strand [44]. Critically for the asymmetric inheritance model, both SDM and RITOLS produce the same net outcome: leading-strand (H-strand) synthesis is continuous and membrane-anchored, while lagging-strand (L-strand) synthesis is delayed and produces a diffusible daughter molecule [40, 43, 44]. The two models therefore differ in the degree, not the existence, of H-strand vulnerability, and both are fully compatible with the asymmetric strand inheritance model [50].

Synchronous (strand-coupled) replication

Along with SDM and RITOLS, analysis of replication intermediates using 2D-AGE revealed characteristic Y-shaped arcs (y-arcs) corresponding to double-stranded replication forks with synchronous synthesis of the leading and lagging strands [49]. Such structures are poorly consistent with the rigidly asymmetric model of pure chain displacement, as they suggest the existence of classical two-strand forks in significant portions of the mitochondrial genome [43].

However, mtSSBChIP-seq with a pronounced bias towards the displaced strand contradicts the uniform distribution of mtSSB expected in linked forks [51]. Y-loops likely reflect transient bidirectional progress or replication stress-induced structures rather than a dominant mechanism, as Kearns-type forms remain rare in vertebrates [64].

Refined models integrate elements of transient ligated replication before SDM dominance, reconciling 2D-AGE observations with single-stranded DNA persistence and asynchronous origin activation. Such a hybrid approach preserves the primacy of SDM while acknowledging the contribution of ligated forks in physiological variability [39].

In summary, the strand-coupled model (SCM) differs fundamentally from both SDM and RITOLS in its topology: it posits bidirectional replication forks in which H- and L-strand synthesis proceed simultaneously and in a coupled fashion, analogous to classical nuclear DNA replication [44]. The key evidence in its favour is the detection of Y-arc intermediates by 2D-AGE, consistent with double-stranded fork progression [49, 50].

However, SCM stands in direct conflict with several lines of evidence that support asynchronous displacement synthesis:

(1) mtSSBChIP-seq data show a strong bias of single-stranded DNA binding toward the displaced strand, incompatible with the uniform distribution expected at coupled forks [39, 51];

(2) the existence of a discrete OriL site and its delayed activation are mechanistically unnecessary under a fully coupled model [38, 40];

(3) the compositional asymmetry and mutation gradient from OriH to OriL are not readily explained by synchronous fork movement [50].

The current consensus therefore treats SCM not as an independent dominant mechanism but as a minor or context-specific mode—possibly reflecting replication stress, repair synthesis, or a transitional phase preceding SDM-type displacement [39]. Unlike SDM and RITOLS, SCM does not readily account for the persistent H-strand mutational bias that is the subject of the asymmetric inheritance model.

Consequences of replication asymmetry in mtDNA

The strand-specific mutational bias observed in vertebrate mtDNA arises from the interplay between replication dynamics, nucleotide compositional asymmetry, and limited DNA repair capacity. The heavy (H) strand, exhibiting G+T bias (~59 % G+T vs. 41 % in L-strand), remains predominantly single-stranded during leading-strand displacement synthesis from OriH (~6500 nucleotides before OriL activation), rendering it highly vulnerable to hydrolytic deamination of cytosine and adenine residues in DNA (C→U→T and A→Hx→G), polymerase slippage during POL γ processivity, and ROS-induced a basic sites/oxidized purine and pyrimidine bases [51].

L-strand priming at OriL initiates bidirectional lagging-strand synthesis, but the RITOLS “bootlace” mechanism provides only transient RNA coverage of nascent H-strand templates (~25–75 nt primers), leaving the displaced parental H-strand exposed [38]. Mitochondrial SSB (mtSSB) preferentially coats this ssDNA, yet protection proves incomplete compared to nuclear RPA dynamics (H-strand exposure: hours vs. nuclear replication ~minutes; replication cycle ~1 h [52]). Nucleoid architecture exacerbates asymmetry: TFAM compaction (~1 TFAM/10 bp) and selective membrane anchoring *via* H-strand-transcribed oxidative phosphorylation (OXPHOS) complexes (I, III, IV, V; ATP6/8) restrict H-strand-enriched nucleoids to high-replication niches near cristae, amplifying POL γ infidelity (error rate 1:10⁴ nt vs. nuclear 1:10⁸) and replication-associated mismatches [28].

Mitochondrial base excision repair (BER) operates at reduced efficiency (~10–50 % nuclear rates) for key lesions (8-oxoG glycosylase OGG1, AP-endonuclease APE1), with TFAM-dependent “transcription-coupled scanning” exhibiting strand bias toward transcriptionally hyperactive H-strand regions (14/15 transcripts) [53]. Replication forks frequently stall at D-loop damage hotspots, favoring mutagenic translesion synthesis (PrimPol/TLS polymerases) over faithful repair or double-strand break resolution (absent canonical HR/NHEJ) [54].

OXPHOS coupling imposes additional selection: H-strand anchoring facilitates rapid copy-number restoration post-damage but selects deletion mutants with replication advantage in aging tissues (e.g., “common delete” Δ mtDNA4977 amplifies in neurons). Maternal inheritance bottlenecks (~100–1000 germline mtDNA copies) impose purifying selection, yet somatic clonal expansion evades this filter [54–58].

Mutational bias in vertebrate mtDNA

Replication of mitochondrial DNA in vertebrates causes a strong asymmetry of mutations: in the heavy (H) strand A>G and C>T substitutions are dominant type of mutation (about 70 % of all mutations), whereas complementary L-strand exhibits T>C and G>A substitutions and very few A>G and C>T mutations [19, 57]. This strand-specific mutation pattern is maintained across all vertebrate species from fish to mammals, resulting in the observed nucleotide compositional bias between G+T-rich H-strand and C+A-rich L-strand.

The mutation frequency varies along the genome: the maximum is observed at the replication origin (OriH)—up to 10 times higher than at OriL [1]. This is directly related to the fact that the H-strand remains in a single-stranded state longer during replication according to the SDM and RITOLS models [42, 47, 59, 60–63].

The nucleotide compositional bias of vertebrate’s mtDNA violates Chargaff’s second parity rule: in the H-strand, adenine exceeds thymine by 20–40 %, and guanine exceeds cytosine by 30–50 %. Such a violation is typical for vertebrate’s mtDNA and is absent in nuclear DNA [44].

In brain neurons, the asymmetry is even stronger: in the H-strand 85–90 % of somatic mutations consist of G>A substitutions which is 4–5 times more frequent than C>T [64]. This is characteristic of aging brain tissues—the putamen and the cortex. Main reasons: the H-strand remains longer in single-stranded form as compared to L-strand [65] and high levels of reactive oxygen species (ROS) in neurons cause guanine oxidation [66]; weak DNA repair in brain mitochondria [59]; neurons do not divide, as a result mutated mtDNA clonally expands [67].

In the brains of patients with Alzheimer’s disease, mutations in the control region (D-loop) suppress mtDNA replication [68]. Point mutations and large deletions in mtDNA are associated with increased inci-

dence of age-related diseases across human and animal models. mtDNA accumulates mutations at rates $\sim 10\text{--}100\times$ higher than nuclear DNA, primarily due to elevated replication frequency ($\sim 500\text{--}10000$ copies/cell/day), Poly infidelity and proximity to ROS-generating ETC complexes. Somatic mutation burden in the human prefrontal cortex increases $\sim 5\text{-fold}$ by age 80, dominated by transitions (purine $\leftrightarrow$ pyrimidine) with oxidative transversions ($G\rightarrow T/C\rightarrow A$) as hallmarks of 8-oxoG lesions [69, 70]. Critically, H- and L-strands exhibit asymmetric accumulation: young brains show C $\rightarrow$ T bias on H-strand mirroring L-strand composition (31 %G vs. 13 %C), shifting to $T_L\rightarrow C_L$ dominance with age [64, 71].

The conceptual framework of asymmetric DNA strand inheritance in vertebrate mitochondria, originally proposed by Matkarimov and Saparbaev [72], provides a mechanistic explanation for the observed strand-biased mutation patterns in mtDNA. According to this model, the majority of mtDNA progeny after multiple replication rounds derives predominantly from the heavy (H) strand. This bias arises from asymmetric strand replication, which is anchored to the inner mitochondrial membrane via the D-loop structure [56, 72].

mtDNA replication initiates in the D-loop region where the parental H-strand serves as the template for leading-strand synthesis at OriH. This unidirectional replication displaces the parental H-strand, exposing OriL $\sim 2/3$ genome length away to trigger lagging L-strand synthesis. The H-strand remains anchored to the inner mitochondrial membrane via D-loop interactions and OXPHOS complexes, undergoing continuous replication cycles. In contrast, the L-strand replicates once to generate a diffusible daughter molecule containing the parental L-strand paired with newly synthesized H-strand (Fig. 3).

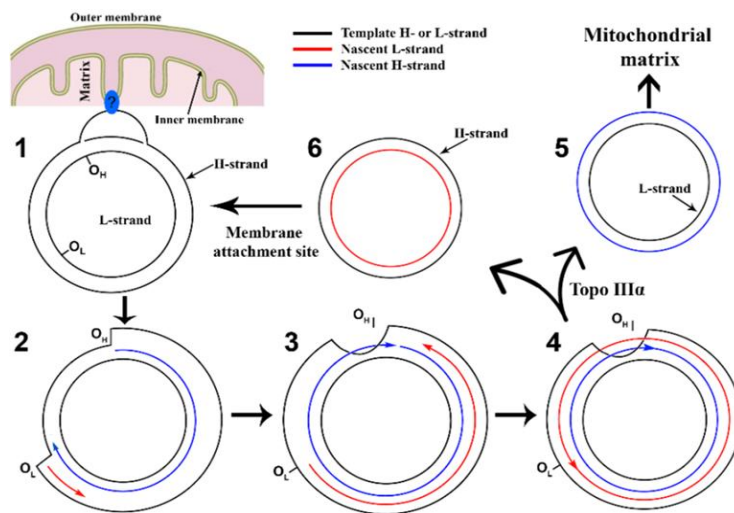


Figure 3. The model of asymmetrical mtDNA strand inheritance [71]

This asymmetric segregation occurs through SDM and RITOLS mechanisms [29, 73, 74] with certain features proposed by Matkarimov and Saparbaev [71]. Premature termination of leading H-strand synthesis creates a hemicatenane linking parental and daughter molecules [75] resolved by mitochondrial topoisomerase III α into two distinct mtDNA populations [76]. The resulting molecule containing the parental H-strand remains membrane-anchored for sustained replication, while the parental L-strand molecule diffuses freely through the matrix and is characterized by high transcriptional activity (L-strand is the transcribed strand for 12 out of 13 mitochondrial protein-coding genes) [77].

This model elegantly explains the characteristic mutational bias or asymmetry: “transitions of T $\rightarrow$ C/G $\rightarrow$ A predominate on the L-strand template, while C $\rightarrow$ T/A $\rightarrow$ G occur on the H-strand”, contradicting expected ROS-induced damage patterns but matching prolonged single-stranded H-strand exposure during asynchronous replication [72]. Preferential use of H-strand as a template for replication may explain long replication cycles (~ 2 hour/cycle), POL γ error rate ($1:10^4$ nt), and absence of 8-oxoG derived mutational signature in mtDNA from post-mitotic tissues.

This asymmetric replication strategy appears conserved across vertebrates, paralleling single-stranded bacteriophages (M13, ϕ X174) [45, 78] and suggesting shared evolutionary origins. The model predicts testable mutation gradients peaking at OriH and requires validation through single-molecule long-read sequencing, nucleoid anchoring disruption experiments and quantitative replication dynamics modeling. Understand-

ing this fundamental replication asymmetry illuminates mitochondrial contributions to aging, neurodegeneration, and cancer evolution.

Alternative Hypotheses for Mutational Asymmetry

While the asymmetric strand inheritance model provides a compelling replication-centric framework, it is important to consider alternative and complementary hypotheses that have been proposed to explain strand-specific mutational bias in vertebrate mtDNA. A comprehensive evaluation of these alternatives provides a broader context for evaluating the asymmetric strand inheritance model and clarifies its scope and limitations [1].

An alternative explanation for H-strand mutational bias invokes transcriptional activity rather than replication dynamics. The L-strand serves as the template for the vast majority of mitochondrial transcripts (14 of 15 rRNA/mRNA genes in humans), making it the predominant transcribed strand, as a consequence during transcription H-strand remains in single-stranded form. Transcription-coupled damage repair (TCR), well established in nuclear genomes [79] (may also operate in mitochondria and remove lesions from the template strand. Consequently, strand asymmetry in repair efficiency could amplify mutational bias even in the absence of replication-driven strand exposure [80], although the extent of this phenomenon and its mechanistic basis remain incompletely understood.

Additionally, the passage of mitochondrial RNA polymerase (POLRMT) through damaged or structurally unusual DNA regions may interfere with replication fork progression, giving rise to transcription–replication conflicts that can influence strand-specific mutational patterns. Distinguishing replication-driven from transcription-driven asymmetry requires strand-specific quantification of lesion loads and repair intermediates in cells with selectively inhibited [81] transcription or replication [82].

Reactive oxygen species (ROS) generated by the electron transport chain (ETC) represent a major source of mtDNA damage, primarily generating 8-oxodeoxyguanosine (8-oxoG) and oxidized cytosines [83]. Some authors have proposed that the spatial proximity of the H-strand, via its membrane-anchoring interactions with OXPHOS complexes, leads to its preferential exposure to superoxide and hydrogen peroxide generated in complexes I and III [84]. This model predicts an excess of G→T transversions (the hallmark of 8-oxoG mispairing) on the H-strand, a prediction that has partial support in aging somatic tissues [85]. However, ROS-based models alone cannot fully account for the predominance of hydrolytic deamination products (C→T and A→G transitions) in the observed mutation spectrum, suggesting that oxidative damage and replication exposure act synergistically rather than as exclusive mechanisms [7].

Structural features of mtDNA, including the D-loop and protein-binding sites, may also contribute to local variation in mutagenesis [86]. The D-loop region, described above as a specialized nucleoprotein structure, contains a persistently unpaired DNA segment that may increase its susceptibility to chemical damage and mutagenesis [86]. Because this region remains locally unpaired on at least one strand, it represents a site of elevated local mutagenicity independent of active replication [72]. TFAM binding throughout the mitochondrial nucleoid creates regions of constrained topology that may modulate polymerase slippage rates and base-excision repair access [87]. Mutational hotspots in the control region are observed across vertebrate species and correlate with D-loop boundaries, suggesting that structural rather than purely kinetic factors can concentrate damage [88]. Integrating structural mapping of protein occupancy (via ChIP-seq or CUT&RUN adapted for mitochondria) with mutation frequency data along the genome would help distinguish structural from replication-kinetic contributions to asymmetry [1].

Taken together, these alternative mechanisms are not mutually exclusive with the asymmetric strand inheritance model [72]. Rather, the asymmetric inheritance hypothesis provides the primary replication-based scaffold that explains the genome-wide gradient of mutation frequency from OriH to OriL, while transcription-coupled processes, ROS proximity, and structural features of the D-loop are also likely to contribute to the formation of local and context-dependent mutation rates [50, 85]. Future experimental designs should aim to decompose these contributions quantitatively, for example through strand-specific single-molecule sequencing in cells with disrupted nucleoid anchoring or selective POLRMT inhibition.

Conclusion

In conclusion, this review has examined the structural features of mtDNA, its replication mechanisms, and patterns of somatic mutation accumulation. The proposed theory of asymmetric strand inheritance offers a heuristic explanation for observed strand-specific mutational biases that challenge conventional replication models coupled to segregation via cell division. According to this theory, the leading chain (H-chain) undergoes continued DNA replication possibly via anchoring of OriH in the D-loop region to membrane, while the

lagging chain (L-chain) undergoes only one replication cycle and then detaches from the inner mitochondrial membrane and diffuses to matrix. The asymmetric nature of replication creates prerequisites for the accumulation of different types of mutations on Watson (top) and Crick (bottom) strands. Understanding this asymmetric strand inheritance model is crucial for elucidating mitochondrial aging, the pathogenesis of mitochondrial diseases, and tissue-specific mutation patterns. Consequently, further investigation into these mechanisms holds promise for developing novel diagnostic and therapeutic strategies for mitochondrial disorders.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. CRediT: **Alikul A.B.** — conceptualization, investigation, writing — original draft; **Manapkyzy D.** — data curation, formal analysis, visualization, writing — review & editing; **Saparbaev M.K.** — supervision, validation, writing — review & editing; **Taipakova S.M.** — supervision, writing — review & editing.

Conflict of Interest

The authors declare no conflict of interest.

References

- 1 Gomes-dos-Santos, A., Vilas-Arrondo, N., Machado, A. M., Román-Palacios, C., & Rocha, E. P. C. (2023). Mitochondrial replication's role in vertebrate mtDNA strand asymmetry. *Open Biology*, 13(12), 230181. <https://doi.org/10.1098/rsob.230181>
- 2 Boore, J. L. (1999). Animal mitochondrial genomes. *Nucleic Acids Research*, 27(8), 1767–1780.
- 3 Kolesnikov, A. A., & Gerasimov, E. S. (2012). Diversity of mitochondrial genome organization. *Biochemistry (Moscow)*, 77(13), 1424–1435.
- 4 Lee, W. -J., Conroy, J., Howell, W. H., & Kocher, T. D. (1995). Structure and evolution of teleost mitochondrial control regions. *Journal of Molecular Evolution*, 41(1), 54–66.
- 5 Berk, A. J., & Clayton, D. A. (1974). Mechanism of mitochondrial DNA replication in mouse L-cells: asynchronous replication of strands, segregation of circular daughter molecules, aspects of topology and turnover of an initiation sequence. *Journal of Molecular Biology*, 86(4), 801–824.
- 6 Picard, M., Wallace, D. C., & Burrelle, Y. (2016). The rise of mitochondria in medicine. *Mitochondrion*, 30, 105–116. <https://doi.org/10.1016/j.mito.2016.07.003>
- 7 Gibson, A., Gowri-Shankar, V., Higgs, P. G., & Rattray, M. (2005). A comprehensive analysis of mammalian mitochondrial genome base composition and improved phylogenetic methods. *Molecular Biology and Evolution*, 22(2), 251–264.
- 8 Noack, K., Zardoya, R., & Meyer, A. (1996). The complete mitochondrial DNA sequence of the bichir (*Polypterus ornatipinnis*), a basal ray-finned fish: ancient establishment of the consensus vertebrate gene order. *Genetics*, 144(3), 1165–1180.
- 9 Clayton, D. A. (1982). Replication of animal mitochondrial DNA. *Cell*, 28(4), 693–705.
- 10 Gustafsson, C. M., Falkenberg, M., & Larsson, N. -G. (2016). Maintenance and expression of mammalian mitochondrial DNA. *Annual Review of Biochemistry*, 85, 133–160. <https://doi.org/10.1146/annurev-biochem-060815-014402>
- 11 Gyllenstein, U., Wharton, D., Josefsson, A., & Wilson, A. C. (1991). Paternal inheritance of mitochondrial DNA in mice. *Nature*, 352, 255–257.
- 12 Wolff, J. N., & Gemmell, N. J. (2008). Lost in the zygote: the dilution of paternal mtDNA upon fertilization. *Heredity*, 101, 429–434.
- 13 Nishimura, Y., Yoshinari, T., Naruse, K., et al. (2006). Active digestion of sperm mitochondrial DNA in single living sperm revealed by optical tweezers. *Proceedings of the National Academy of Sciences of the USA*, 103, 1382–1387.
- 14 DeLuca, S. Z., & O'Farrell, P. H. (2012). Barriers to male transmission of mitochondrial DNA in sperm development. *Developmental Cell*, 22, 660–668.

- 15 Lee, W., et al. (2023). Molecular basis for maternal inheritance of human mitochondrial DNA. *Nature Genetics*, 55, 1632–1639.
- 16 Shoubridge, E. A., & Wai, T. (2007). Mitochondrial DNA and the mammalian oocyte. *Current Topics in Developmental Biology*, 77, 87–111. [https://doi.org/10.1016/S0070-2153\(06\)77004-1](https://doi.org/10.1016/S0070-2153(06)77004-1)
- 17 Larsson, N. G. (2010). Somatic mitochondrial DNA mutations in mammalian aging. *Annual Review of Biochemistry*, 79(1), 683–706.
- 18 Taylor, R. W., & Turnbull, D. M. (2005). Mitochondrial DNA mutations in human disease. *Nature Reviews Genetics*, 6(5), 389–402. <https://doi.org/10.1038/nrg1606>
- 19 Stewart, J. B., Freyer, C., Elson, J. L., & Larsson, N. G. (2008). Strong purifying selection in transmission of mammalian mitochondrial DNA. *PLoS Biology*, 6(1), e10. <https://doi.org/10.1371/journal.pbio.0060010>
- 20 Lima, A., et al. (2021). Cell competition acts as a purifying selection to eliminate cells with mitochondrial defects during early mouse development. *Nature Metabolism*, 3(8), 1091–1108.
- 21 Yang, L., et al. (2020). Mitochondrial DNA mutation exacerbates female reproductive aging via impairment of the NADH/NAD⁺ redox. *Aging Cell*, 19(9), e13206. <https://doi.org/10.1111/acer.13206>
- 22 Roger, A. J., Muñoz-Gómez, S. A., & Kamikawa, R. (2017). The origin and diversification of mitochondria. *Current Biology*, 27(21), R1177–R1192.
- 23 Ricchetti, M., Tekaia, F., & Dujon, B. (2004). Continued colonization of the human genome by mitochondrial DNA. *PLoS Biology*, 2(9), e273.
- 24 Park, C. B., & Larsson, N. G. (2011). Mitochondrial DNA mutations in disease and aging. *The Journal of Cell Biology*, 193(5), 809–818. <https://doi.org/10.1083/jcb.201010024>
- 25 Wallace, D. C., et al. (1988). Mitochondrial DNA mutation associated with Leber's hereditary optic neuropathy. *Science*, 242(4884), 1427–1430.
- 26 Xu, B., & Clayton, D. A. (1995). A persistent RNA–DNA hybrid is formed during transcription at a phylogenetically conserved mitochondrial DNA sequence. *Molecular and Cellular Biology*, 15, 580–589.
- 27 Fusté, J. M., et al. (2010). Mitochondrial RNA polymerase is needed for activation of the origin of light-strand DNA replication. *Molecular Cell*, 37, 67–78.
- 28 Cerritelli, S. M., et al. (2003). Failure to produce mitochondrial DNA results in embryonic lethality in Rnaseh1 null mice. *Molecular Cell*, 11, 807–815.
- 29 Falkenberg, M. (2018). Mitochondrial DNA replication in mammalian cells: overview of the pathway. *Essays in Biochemistry*, 62(3), 287–296. <https://doi.org/10.1042/EBC20170100>
- 30 Falkenberg, M., & Gustafsson, C. M. (2020). Mammalian mitochondrial DNA replication and mechanisms of deletion formation. *Critical Reviews in Biochemistry and Molecular Biology*, 55(6), 509–524. <https://doi.org/10.1080/10409238.2020.1818684>
- 31 Wanrooij, S., Fusté, J. M., & Farge, G., et al. (2008). Human mitochondrial RNA polymerase primes lagging-strand DNA synthesis in vitro. *Proceedings of the National Academy of Sciences of the USA*, 105(32), 11122–11127.
- 32 Park, J., Baruch-Torres, N., & Yin, Y. W. (2023). Structural and molecular basis for mitochondrial DNA replication and transcription in health and antiviral drug toxicity. *Molecules (Basel, Switzerland)*, 28(4), 1796. <https://doi.org/10.3390/molecules28041796>
- 33 Oláhová, M., et al. (2021). POLRMT mutations impair mitochondrial transcription causing neurological disease. *Nature Communications*, 12(1), 1135.
- 34 Jiang, M., et al. (2021). The mitochondrial single-stranded DNA binding protein is essential for initiation of mtDNA replication. *Science Advances*, 7(27), eabf8631.
- 35 Shi, Y., Posse, V., & Zhu, X., et al. (2016). Mitochondrial transcription termination factor 1 directs polar replication fork pausing. *Nucleic Acids Research*, 44(12), 5732–5742.
- 36 Akbari, M., Nilsen, H. L., & Montaldo, N. P. (2022). Dynamic features of human mitochondrial DNA maintenance and transcription. *Frontiers in Cell and Developmental Biology*, 10, 984245.
- 37 Wanrooij, S., & Falkenberg, M. (2010). The human mitochondrial replication fork in health and disease. *Biochimica et Biophysica Acta (BBA) — Bioenergetics*, 1797(8), 1378–1388.
- 38 Nicholls, T. J., et al. (2014). Linear mtDNA fragments and unusual mtDNA rearrangements associated with pathological deficiency of MGME1 exonuclease. *Human Molecular Genetics*, 23(23), 6147–6162.
- 39 Matic, S., et al. (2018). Mice lacking the mitochondrial exonuclease MGME1 accumulate mtDNA deletions without developing progeria. *Nature Communications*, 9(1), 1202.
- 40 Yasukawa, T., & Kang, D. (2018). An overview of mammalian mitochondrial DNA replication mechanisms. *Journal of Biochemistry*, 164(3), 183–193. <https://doi.org/10.1093/jb/mvy058>
- 41 MirallesFusté, J., et al. (2014). In vivo occupancy of mitochondrial single-stranded DNA binding protein supports the strand displacement mode of DNA replication. *PLoS Genetics*, 10(12), e1004832.
- 42 Pohjoismäki, J. L., et al. (2010). Mammalian mitochondrial DNA replication intermediates are essentially duplex but contain extensive tracts of RNA/DNA hybrid. *Journal of Molecular Biology*, 397(5), 1144–1155.
- 43 Reyes, A., Kazak, L., Wood, S. R., et al. (2013). Mitochondrial DNA replication proceeds via a “bootlace” mechanism involving the incorporation of processed transcripts. *Nucleic Acids Research*, 41(11), 5837–5850. <https://doi.org/10.1093/nar/gkt196>

- 44 Yasukawa, T., et al. (2006). Replication of vertebrate mitochondrial DNA entails transient ribonucleotide incorporation throughout the lagging strand. *The EMBO Journal*, 25(22), 5358–5371. <https://doi.org/10.1038/sj.emboj.7601392>
- 45 Hsieh, C. L. (2019). Novel lines of evidence for the asymmetric strand displacement model of mitochondrial DNA replication. *Molecular and Cellular Biology*, 39(2), e00406-18. <https://doi.org/10.1128/MCB.00406-18>
- 46 Kosar, M., Piccini, D., Foiani, M., & Giannattasio, M. (2021). A rapid method to visualize human mitochondrial DNA replication through rotary shadowing and transmission electron microscopy. *Nucleic Acids Research*, 49(21), e121. <https://doi.org/10.1093/nar/gkab770>
- 47 Brown, T. A., et al. (2005). Replication of mitochondrial DNA occurs by strand displacement with alternative light-strand origins, not via a strand-coupled mechanism. *Genes & Development*, 19(20), 2466–2476.
- 48 McKinney, E. A., & Oliveira, M. T. (2013). Replicating animal mitochondrial DNA. *Genetics and Molecular Biology*, 36, 308–315.
- 49 Wanrooij, S., et al. (2008). Human mitochondrial RNA polymerase primes lagging-strand DNA synthesis in vitro. *Proceedings of the National Academy of Sciences of the USA*, 105(32), 11122–11127. <https://doi.org/10.1073/pnas.0805399105>
- 50 Holt, I. J., Lorimer, H. E., & Jacobs, H. T. (2000). Coupled leading- and lagging-strand synthesis of mammalian mitochondrial DNA. *Cell*, 100(5), 515–524.
- 51 Taanman, J. -W. (1999). The mitochondrial genome: structure, transcription, translation and replication. *Biochimica et Biophysica Acta (BBA) — Bioenergetics*, 1410(2), 103–123.
- 52 Xia, X. (2019). Is there a mutation gradient along vertebrate mitochondrial genome mediated by genome replication? *Mitochondrion*, 46, 30–40. <https://doi.org/10.1016/j.mito.2018.06.004>
- 53 Berk, A. J., & Clayton, D. A. (1974). Mechanism of mitochondrial DNA replication in mouse L-cells: asynchronous replication of strands, segregation of circular daughter molecules, aspects of topology and turnover of an initiation sequence. *Journal of Molecular Biology*, 86(4), 801–824.
- 54 Alexeyev, M., Shokolenko, I., Wilson, G., & LeDoux, S. (2013). The maintenance of mitochondrial DNA integrity — critical analysis and update. *Cold Spring Harbor Perspectives in Biology*, 5(5), a012641.
- 55 Sies, H., et al. (2022). Defining roles of specific reactive oxygen species (ROS) in cell biology and physiology. *Nature Reviews Molecular Cell Biology*, 23(7), 499–515. <https://doi.org/10.1038/s41580-022-00456-z>
- 56 Stewart, J. B., & Larsson, N. G. (2014). Keeping mtDNA in shape between generations. *PLoS Genetics*, 10(10), e1004670.
- 57 Ross, J. M., et al. (2013). Germline mitochondrial DNA mutations aggravate ageing and can impair brain development. *Nature*, 501(7467), 412–415.
- 58 Burger, G., Gray, M. W., & Lang, B. F. (2003). Mitochondrial genomes: anything goes. *Trends in Genetics*, 19, 709–716. <https://doi.org/10.1016/j.tig.2003.10.012>
- 59 Sanchez-Contreras, M., et al. (2023). The multi-tissue landscape of somatic mtDNA mutations indicates tissue-specific accumulation and removal in aging. *eLife*, 12, e83395. <https://doi.org/10.7554/eLife.83395>
- 60 Pohjoismäki, J. L., Forslund, J. M., Goffart, S., et al. (2018). Known unknowns of mammalian mitochondrial DNA maintenance. *BioEssays*, 40(9), 1800102.
- 61 Kirschner, R. H., Wolstenholme, D. R., & Gross, N. J. (1968). Replicating molecules of circular mitochondrial DNA. *Proceedings of the National Academy of Sciences of the USA*, 60(4), 1466–1472.
- 62 Ciesielski, L., Oliveira, M. T., & Kaguni, L. S. (2016). Animal mitochondrial DNA replication. *The Enzymes*, 39, 255–292.
- 63 Holt, I. J., & Jacobs, H. T. (2014). Unique features of DNA replication in mitochondria: a functional and evolutionary perspective. *BioEssays*, 36(11), 1024–1031.
- 64 Kennedy, S. R., Salk, J. J., Schmitt, M. W., & Loeb, L. A. (2013). Ultra-sensitive sequencing reveals an age-related increase in somatic mitochondrial mutations that are inconsistent with oxidative damage. *PLoS Genetics*, 9(9), e1003794. <https://doi.org/10.1371/journal.pgen.1003794>
- 65 Albrecht-Buehler, G. (2006). Asymptotically increasing compliance of genomes with Chargaff's second parity rules through inversions and inverted transpositions. *Proceedings of the National Academy of Sciences of the USA*, 103(47), 17828–17833. <https://doi.org/10.1073/pnas.0605553103>
- 66 MirallesFusté, J., et al. (2014). In vivo occupancy of mitochondrial single-stranded DNA binding protein supports the strand displacement mode of DNA replication. *PLoS Genetics*, 10(12), e1004832. <https://doi.org/10.1371/journal.pgen.1004832>
- 67 Williams, S. L., Mash, D. C., Züchner, S., & Moraes, C. T. (2013). Somatic mtDNA mutation spectra in the aging human putamen. *PLoS Genetics*, 9(12), e1003990. <https://doi.org/10.1371/journal.pgen.1003990>
- 68 Coskun, P. E., Beal, M. F., & Wallace, D. C. (2004). Alzheimer's brains harbor somatic mtDNA control-region mutations that suppress mitochondrial transcription and replication. *Proceedings of the National Academy of Sciences of the USA*, 101(29), 10726–10731. <https://doi.org/10.1073/pnas.0403649101>
- 69 Filograna, R., et al. (2021). Mitochondrial DNA copy number in human disease: the more the better? *FEBS Letters*, 595(8), 976–1002.
- 70 Ju, Y. S., et al. (2014). Origins and functional consequences of somatic mitochondrial DNA mutations in human cancer. *eLife*, 3, e02935.
- 71 Matkarimov, B. T., & Saparbaev, M. K. (2020). DNA repair and mutagenesis in vertebrate mitochondria: evidence for asymmetric DNA strand inheritance. In *Mechanisms of Genome Protection and Repair*, 77–10.

- 72 Fonseca, M. M., Harris, D. J., & Posada, D. (2014). The inversion of the control region in three mitogenomes provides further evidence for an asymmetric model of vertebrate mtDNA replication. *PLoS ONE*, 9(9), e106654. <https://doi.org/10.1371/journal.pone.0106654>
- 73 Holt, I. J., & Reyes, A. (2012). Human mitochondrial DNA replication. *Cold Spring Harbor Perspectives in Biology*, 4(12), a012971. <https://doi.org/10.1101/cshperspect.a012971>
- 74 Pohjoismäki, J. L. O., Forslund, J. M. E., Goffart, S., Torregrosa-Muñumer, R., & Wanrooij, S. (2018). Known unknowns of mammalian mitochondrial DNA maintenance. *BioEssays*, 40(9), 1800102. <https://doi.org/10.1002/bies.201800102>
- 75 Laurie, B., Katritch, V., Sogo, J., Koller, T., Dubochet, J., & Stasiak, A. (1998). Geometry and physics of catenanes applied to the study of DNA replication. *Biophysical Journal*, 74, 2815–2822. [https://doi.org/10.1016/S0006-3495\(98\)77988-3](https://doi.org/10.1016/S0006-3495(98)77988-3)
- 76 Nicholls, T. J., Nadalutti, C. A., Motori, E., Sommerville, E. W., Gorman, G. S., Basu, S., ... Gustafsson, C. M. (2018). Topoisomerase 3a is required for decatenation and segregation of human mtDNA. *Molecular Cell*, 69(1), 9–23. <https://doi.org/10.1016/j.molcel.2017.11.033>
- 77 Lynch, A. S., & Wang, J. C. (1993). Anchoring of DNA to the bacterial cytoplasmic membrane through cotranscriptional synthesis of polypeptides encoding membrane proteins or proteins for export: a mechanism of plasmid hypernegative supercoiling in mutants deficient in DNA topoisomerase I. *Journal of Bacteriology*, 175, 1645–1655.
- 78 Shutt, T. E., & Gray, M. W. (2006). Bacteriophage origins of mitochondrial replication and transcription proteins. *Trends in Genetics*, 22(2), 90–95. <https://doi.org/10.1016/j.tig.2005.11.007>
- 79 Hanawalt, P. C., & Spivak, G. (2008). Transcription-coupled DNA repair: two decades of progress and surprises. *Nature Reviews Molecular Cell Biology*, 9(12), 958–970. <https://doi.org/10.1038/nrm2549>
- 80 Touchon, M., Arneodo, A., d'Aubenton-Carafa, Y., & Thermes, C. (2004). Transcription-coupled and splicing-coupled strand asymmetries in eukaryotic genomes. *Nucleic Acids Research*, 32(17), 4969–4978. <https://doi.org/10.1093/nar/gkh823>
- 81 Shi, Y., Posse, V., Zhu, X., Hyvärinen, A. K., Jacobs, H. T., Falkenberg, M., & Gustafsson, C. M. (2016). Mitochondrial transcription termination factor 1 directs polar replication fork pausing. *Nucleic Acids Research*, 44(12), 5732–5742. <https://doi.org/10.1093/nar/gkw302>
- 82 Cluett, T. J., Akman, G., Reyes, A., Kazak, L., Mitchell, A., Wood, S. R., et al. (2018). Transcript availability dictates the balance between strand-asynchronous and strand-coupled mitochondrial DNA replication. *Nucleic Acids Research*, 46(20), 10771–10781. <https://doi.org/10.1093/nar/gky852>
- 83 Cadet, J., Douki, T., & Ravanat, J. L. (2010). Oxidatively generated base damage to cellular DNA. *Free Radical Biology and Medicine*, 49(1), 9–21. <https://doi.org/10.1016/j.freeradbiomed.2010.03.025>
- 84 Balaban, R. S., Nemoto, S., & Finkel, T. (2005). Mitochondria, oxidants, and aging. *Cell*, 120(4), 483–495.
- 85 Degtyareva, N. P., Saini, N., Sterling, J. F., Placentra, V. C., Klimczak, L. J., Gordenin, D. A., & Doetsch, P. W. (2019). Mutational signatures of redox stress in yeast single-strand DNA and of aging in human mitochondrial DNA share a common feature. *PLoS Biology*, 17(5), e3000263. <https://doi.org/10.1371/journal.pbio.3000263>
- 86 Saccone, C., Attimonelli, M., & Sbisà, E. (1987). Structural elements highly preserved during the evolution of the D-loop-containing region in vertebrate mitochondrial DNA. *Journal of Molecular Evolution*, 26(3), 205–211 DOI: 10.1007/BF02099853
- 87 Brown, G. G., Gadaleta, G., Pepe, G., Saccone, C., & Sbisà, E. (1986). Structural conservation and variation in the D-loop-containing region of vertebrate mitochondrial DNA. *Journal of Molecular Biology*, 192(3), 503–511. [https://doi.org/10.1016/0022-2836\(86\)90272-X](https://doi.org/10.1016/0022-2836(86)90272-X)
- 88 Ji, X., Guo, W., Gu, X., Guo, S., Zhou, K., Su, L., et al. (2022). Mutational profiling of mtDNA control region reveals tumor-specific evolutionary selection involved in mitochondrial dysfunction. *eBioMedicine*, 80, 104058. <https://doi.org/10.1016/j.ebiom.2022.104058>

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Омыртқалылар митохондриясындағы ДНҚ тізбектерінің асимметриялық тұқым қуалауының дәлелдері

1958 жылы Мезельсон мен Сталь жүргізген классикалық эксперимент жасушалық организмдердегі ДНҚ репликациясының жартылай консервативті механизмін дәлелдеді. Бұл механизмге сәйкес, жасуша бөлінгеннен кейін әрбір еншілес жасуша бір ата-аналық тізбектен (W немесе C) және бір жаңадан синтезделген комплементарлы тізбектен (C' немесе W') тұратын хромосоманы иеленеді. Әрбір ДНҚ тізбегі жасуша әр бөлінген сайын бірдей үлгіде репликацияланатындықтан, W және C тізбектері жартылай консервативті репликация мен жасушалық бөліну нәтижесінде эквивалентті деп есептеледі. Алайда, кейбір жасушалық емес организмдер, мысалы, бір тізбекті ДНҚ немесе РНҚ вирустары, эквиваленттілік принципін сақтамайды. Сонымен қатар омыртқалылардың митохондриялық геномындағы екі тізбектің нуклеотидтік құрамының айқын теңсіздігі ерекше назар аударуға тұрарлық. Бұл теңсіздік сілтілі цезий хлориді градиентіндегі ультрацентрифугалау кезінде митохондриялық ДНҚ-ның екі тізбегінің — G+T-ге бай ауыр (H) және C+A-ға бай жеңіл (L) тізбектерге бөлінуімен көрініс табады. Адам митохондрияларындағы ДНҚ репликациясы ұзақ жылдар

бойы зерттеліп келе жатқанына қарамастан, репликация механизмі мен тізбектердің нуклеотидтік құрамындағы теңсіздіктің арасындағы ықтимал байланыс әлі де толық анықталмаған және ғылыми пікірталас тақырыбы болып отыр. Осыған байланысты бұл мақалада омыртқалылардың митохондриялық ДНҚ-сында байқалатын мутациялық паттерннің күшті ығысуын қарапайым эвристикалық жолмен түсіндіре алатын ДНҚ тізбектерінің асимметриялық тұқымқуалауы немесе олардың эквивалентті еместігі туралы ықтимал үлгісі ұсынылған.

Кілт сөздер: митохондриялық ДНҚ, ДНҚ тізбектерінің эквиваленттілігі, мутация заңдылықтары, Чаргаффың екінші ережесі, репликация.

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Доказательства асимметричного наследования цепей ДНК в митохондриях позвоночных

Классический эксперимент, предложенный в 1958 году Мезельсоном и Сталем, подтвердил полуконсервативный механизм репликации ДНК в клеточных организмах, согласно которому после деления клеток каждая дочерняя клетка наследует хромосому, состоящую из одной родительской цепи (W или C) и одной новосинтезированной комплементарной цепи (C' или W'). Поскольку каждая цепь ДНК реплицируется одинаковое количество раз после каждого деления клетки, можно предположить, что цепи W и C эквивалентны как результат сочетания деления клетки и полуконсервативного механизма репликации ДНК. Однако некоторые неклеточные организмы, такие как оцДНК- и РНК-вирусы, игнорируют принцип эквивалентности цепей. Также стоит отметить интересную особенность митохондриального генома позвоночных с необычным дисбалансом нуклеотидного состава на двух нитях митохондриальной ДНК, что приводит к разделению на тяжелую (H) G+T-богатую и легкую (L) C+A-богатую нити ДНК при ультрацентрифугировании в щелочном градиенте хлористого цезия. Несмотря на многолетние исследования репликации ДНК в митохондриях человека, механизм этой репликации и возможная связь с дисбалансом нуклеотидного состава остаются предметом дискуссий. В связи с этим в данной статье мы предлагаем возможную модель асимметричного наследования нитей ДНК или неэквивалентности нитей ДНК, которая предоставляет простое эвристическое объяснение сильно смещенного паттерна мутаций в мтДНК позвоночных.

Ключевые слова: митохондриальная ДНК, эквивалентность цепей ДНК, закономерности мутаций, второе правило Чаргаффа, репликация.

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