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# A Comprehensive Review on the Telomeric Repeat Sequence in Different Organisms

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**Abstract:** Telomeres protect the terminal ends of eukaryotic chromosomes, making them essential for genome stability, cellular senescence, and species evolution. These structures consist of tandem repeats of nucleotides, referred to as telomeric repeat sequences. The enzyme telomerase, along with various telomere-binding proteins, manages the synthesis of these repeat sequences. Telomerase functions by adding telomeric repeats to the ends of chromosomes, counteracting the shortening that occurs during DNA replication. In most somatic cells, telomerase activity is generally low or absent, leading to gradual telomere loss and, eventually, cellular senescence. Although the ancestral telomeric repeat sequence is often proposed to be TTAGGG, studies have shown that convergent evolution has produced similar telomeric motifs in various evolutionary lineages. This is evidenced by variations in telomeric repeat sequences among organisms, which may include single or double nucleotide substitutions, deletions, and even exceptionally large telomeric repeats in certain species. Investigating these telomeric repeat sequences across a wide range of organisms and identifying the evolutionary changes within each phylum offer valuable insights into telomeric sequences and the telomerases responsible for their synthesis. Such research not only deepens our understanding of telomere biology across different organisms but also holds potential for addressing age-related challenges and cancer, paving the way for innovative solutions to some of the most critical issues in contemporary medicine.

**Keywords:** evolution, invertebrates, nucleotides, repeats, telomere

## 1. Introduction

The ends of eukaryotic chromosomes have specialized structures known as telomeres, which play a crucial role in various biological processes [1]. It has a variety of highly repetitive non-coding DNA sequences that shield the DNA's genetic information [2]. Two issues with eukaryotic chromosomes are resolved by telomeres: during cell replication, they conserve the coding nucleotides since traditional DNA polymerases cannot replicate the ends of linear chromosomes, and they conceal the chromosomal ends by preventing telomeric-binding proteins, terminal non-coding DNA sequences, and detection by DNA repair machinery, thereby hindering the initiation of pathological fusions or DNA damage response [3]. Telomeric sequences are produced by an enzyme called telomerase. Telomerase consists of two subunits: telomerase RNA (TER) and telomerase reverse transcriptase (TERT) [4]. Telomerase RNA serves as a template for the synthesis of telomeric DNA, and telomerase reverse transcriptase produces complementary DNA bases. Telomerase activity is highly abundant during the fetal stage and then becomes less abundant later in life. Due to the absence of telomerase, telomeric sequences are not produced further and they gradually get removed with each cell division. When they are removed completely, it leads to the death of the cell which is known as cell senescence. The shortening of telomeres is closely related to the aging process [5]. The examination of telomeric repeat sequences across diverse organisms yields profound insights into the intricate mechanisms governing genomic stability, cellular senescence, and species divergence [6]. These entities ensure integrity and are involved in age-related illnesses and cellular aging processes. By studying the patterns of repeat sequences across a range of organisms, scientists gain valuable insights into how these important genetic elements have evolved. Additionally, analyzing the similarities and differences in repeat sequences provides us with an understanding of how different species are interconnected through evolution. Through analyses based on sequences, we can better understand the evolutionary histories and divergences within various groups of organisms. This comprehensive review focuses on elaborating the repeat sequences found in organisms.

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## 2. Telomere Homeostasis

Telomere degradation can be mitigated by telomerase activity and alternative lengthening of telomeres, which includes recombination processes [7]. An RNA-dependent DNA polymerase complex known as telomerase helps to maintain telomere length. Telomerase consists of human telomerase reverse transcriptase (hTERT) and human telomerase RNA (hTR). Normal somatic cells fail to produce hTERT protein, while absence of TER in vitro not only produce telomerase negative cells but are likely to be effective in ribonucleoprotein complex functioning with hTERT introduction [8]. A 451-nucleotide long RNA component, known as hTR, facilitates assembly and localization of telomerase by serving as template for TTAGGG insertion to chromosomal ends [9]. A difference is observed when telomerase transports its template RNA for telomeric DNA

synthesis. The RNA component serves as a template for telomere replenishment due to its complementary sequence to human DNA [7]. The template region of telomeric repeat is crucial for alignment and elongation. Base-pairing is utilized to align a portion of template with primer 3' segment, and then elongation is used to replicate at 5' end. The length of template ensures that the telomeric repeat sequence is fully replicated, regardless of where synthesis starts within the template region.

## 3. Evolutionary Perspective of Telomeric Repeat Sequence

According to studies, TTAGGG is the primordial telomeric repeat sequence of eukaryotes [10], but there are cases where similar telomere sequences have evolved independently in different lineages, indicating a notable level of homoplasy in the evolution of telomere motifs. Homoplasy describes the presence of similar traits or features in distinct species or lineages, not attributable to shared ancestry (homology) but rather arising from convergent evolution or alternative processes [11]. The repetition of particular telomere sequences is probably driven by selection pressures that prioritize precision in DNA-protein interactions specific to those sequences. The stability of telomere sequences over evolution is attributed to the necessity of maintaining the telomeric nucleoprotein structure for genome stability [12]. However, a vast number of species have developed telomeric repeat sequences that diverge from the ancestral repeat. Modification in the telomerase RNA component, single nucleotide mutations in telomeric repeats, and variations in the binding affinity of telomere-binding proteins contribute to the heterogeneity of telomeric repeat sequence among different organisms [10]. Telomerase, the enzyme responsible for the synthesis of telomere repeats, might evolve from a ribonucleoprotein which was involved in the addition of nucleotides to the ends of RNA molecules [13]. Over time, this ribonucleoprotein could have changed, developing reverse transcriptase activity as DNA emerged as the primary genetic material. Telomerase expression exhibits variations across tissues and is species-specific. In comparison with shorter-lived organisms where telomerase remains active with longer telomeres, longer-lived species such as humans tend to repress telomerase in most somatic tissues, leading to relatively short telomere lengths, usually less than 20 kb [14]. Telomere length benefits organisms by delaying "replicative senescence" in those with long telomeres, while organisms with shorter telomeres that limit cell replication are protected against cancer [15].

## 4. Mechanism of Telomerase Action

Telomerase consists of a template RNA and a reverse transcriptase subunit. Moreover, auxiliary proteins such as telomerase Cajal body protein 1, GAR1, non-histone protein 2, dyskerin, and nucleolar protein 10 are linked to it [16]. Telomerase catalyzes the reverse transcription of its RNA template into DNA, thereby elongating the telomeric repeat sequences at chromosome ends. This process involves the addition of nucleotide units onto the 3' end of the telomere overhang [17]. Before seeing the mechanism of telomerase action, there is a need to see the overview of DNA replication. During cell replication, the double helix DNA is unwound by an enzyme called helicase, and RNA primers are added by primase for the synthesis of both the leading and lagging strands. RNA primers are required by DNA polymerase enzyme to initiate the process of addition of nucleotides. The leading strand undergoes continuous synthesis (in the direction of unwinding of double helix DNA), while the lagging strand is synthesized discontinuously, resulting in the formation of Okazaki fragments. After synthesis, RNA primers are removed either by Ribonuclease H1 or by FEN1 (Flap endonuclease 1). DNA ligase then joins the gaps between Okazaki fragments by adding deoxyribonucleotides. Although the RNA primer is removed, a 3' overhang is still present at the very end of the lagging strand, which cannot be removed by FEN1 as it is a part of the genome. To resolve this issue, telomerase comes into action. Telomerase contains a template RNA (TER), which interacts with the 3' overhang of the parent DNA strand [18]. The reverse transcriptase subunit of telomerase synthesizes complementary DNA bases to the RNA template, thereby extending the length of the 3' overhang. The synthesized repeats are called telomeric repeats and they protect the ends of chromosomes. The extra non-coding strand can be removed by FEN1. Figure 1 describes the telomerase catalytic cycle.

## 5. Telomere Dynamics

Research has shown an association between telomere attrition and aging, supporting Alexey Olovnikov's theory from 1973 that shortening of telomere inhibits cell replication [19, 20]. Aging is usually accompanied by telomere loss and recent evolutionary studies have overlooked how the environment and life history affect telomere dynamics in various organisms [21]. Although the basis of telomeres is constant, telomere length and dynamics pattern differ among the species. For example, the relationship between telomere length and DNA methylation is generally weak in humans [22]. Another research reveals negative correlation between telomere loss and early DNA methylation changes in wild zebra finches [23], which may be influenced by environmental factors and age. Each species has a different relationship between telomere length and mortality risk. Nevertheless, determining the age accurately is deeply limited to individuals' differences in telomere length. In common lizards, this variation is observed between populations and ecotypes [24]. A study revealed laboratory organisms such as mice and yeast have longer telomeres than their counterparts [25]. This suggests that telomere may be influenced by confinement. A meta-analysis revealed telomere length and age of 98 vertebrate species have modest negative association especially greater in birds [26]. In comparison to ectotherms [27], endotherms like birds have a stronger correlation between telomere length and mortality risk [28]. A strong correlation was observed in captive zebra finches among telomere length and lifespan patterns [29], while vice versa was observed in wild Soay sheep [30]. Studies suggest that telomere loss may be an accurate indicator of longevity than telomere length. Research showed that organisms exhibit low rates of reproduction and delayed development typically reduced telomere degradation [31]. Furthermore, telomere length can be affected by prenatal circumstances in species such as Atlantic salmon and Seychelles warblers where environmental variables have an influence on telomere dynamics [32]. Telomere lengthening in warbler adult species was identified with rapid early growth which may not influence longevity [33]. In organisms like *Caenorhabditis elegans* and *Drosophila melanogaster,* genome instability can result from cells evading that stop cell division when telomeres become uncapped. In order to preserve telomere length, these cells may activate telomerase or other strategies which may lead to malignant tumor formation. Association between telomere dynamics and cancer suggests senescent cells in tissues may encourage precancerous cells to become malignant [34]. In certain plants, studying

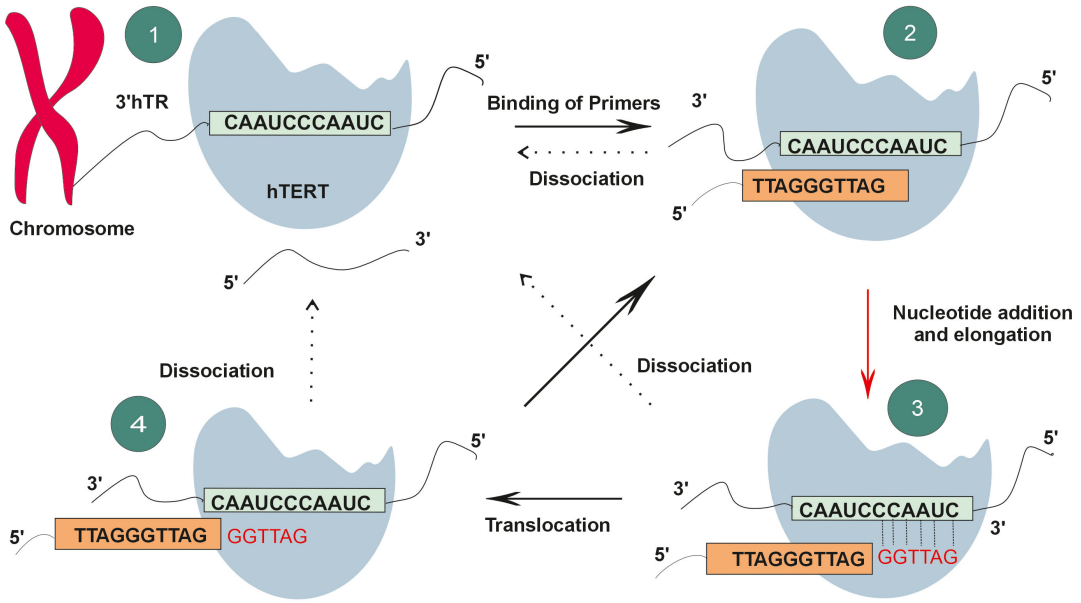


**Figure 1. The telomerase catalytic cycle. The RNA template (TER) and protein component (TERT) that make up telomerase get attached to the 3' end of telomeric DNA. Telomerase lengthens the telomere by incorporating nucleotide repeats into the DNA. The enzyme translocates to align its RNA template with the new DNA end for further extension after elongation. The telomeric repeat synthesis ends when the process is repeated and telomerase dissociates**

*Arabidopsis thaliana* in lunar regolith simulant explores how plants handle oxidative stress in space-like conditions. This simulant mimics lunar soil and introduces stressors to generate reactive oxygen species (ROS). These ROS can accelerate telomere shortening, impacting cell division and longevity. By growing Arabidopsis in this environment and assessing oxidative stress and telomere dynamics, researchers aim to understand plant resilience in extra-terrestrial conditions, which is crucial for future space exploration and potential agricultural practices [35]. Telomere and subtelomeres play crucial roles in early chromosome interactions during meiosis, influencing the formation of homologous chromosome pairs and segregation of genetic component. Their dynamics affect recombination and chromosome stability, which are essential for accurate meiosis. Understanding these interactions can provide insights into genetic variation and inheritance with implication for plant breeding. By leveraging telomere and subtelomere behavior, breeders enhance crop yields and resistance to diseases [36]. These studies highlight the intricacy of telomere dynamics and the need for comprehensive, long-term research to comprehend the connection between development, reproduction, and environmental variables.

## 6. Diseases Incidence due to Telomeres Dysfunction

Telomere dysfunction leads to telomere-mediated diseases. When the telomeric DNA repeat tracts become too short to sustain, a functional shelterin complex, malfunction arises [37]. As a result, short and dysfunctional telomeres trigger a DNA damage response similar to DNA double-strand breaks. This response activates checkpoints leading to cellular senescence or apoptosis, sometimes occurring simultaneously. A study conducted on telomerase null mice showed that telomere length is the primary determinant rather than telomerase loss. While the absence of telomerase does not cause immediate clinical effects in the first generation, late-generation mice with telomerase deficiency develop short telomeres, which results in degenerative organ failure and stem cell failure [38]. Another aspect linked to telomere-mediated diseases is mutations in the genes encoding the essential telomerase components, which include the two subunits of telomerase – TERT and TER [39]. Also, a gene called Dyskeratosis Congenita 1 (DC1), which is involved in the encoding of Dyskerin, may lead to problems if it is subjected to mutation. Dyskerin is a protein component of telomerase that binds to its RNA template and assists the reverse transcriptase enzyme in the elongation of telomeres [40]. Mutation in the gene encoding this protein leads to a syndrome called Dyskeratosis Congenita (DC). It was the first disorder to be linked to telomerase mutations and short telomeres. This syndrome mainly affects the bone marrow, skin, and gut. Affected individuals have shorter telomeres than normal individuals, and some are also found to have liver cirrhosis and skin cancer. Different types of DC include X-linked recessive DC, autosomal dominant DC, and autosomal recessive DC [41]. Idiopathic pulmonary fibrosis (IPF) is a chronic disease that is found to be associated with telomeric shortening. This association was proved in a study conducted on three types of individuals namely normal individuals, persons with sporadic IPF, and individuals with known telomerase mutations. It was found that IPF-affected individuals have shorter telomere length than normal individuals. Short telomere length is linked to difficulties with beta-cell insulin production, which have been linked to an increased risk of diabetes in people with IPF [42]. Patients are diagnosed with IPF mainly after their respiratory symptoms worsen, and their average lifespan is approximately 3 years. Mutations in hTERT and hTR genes are significant risk factors, accounting for 8–15% of familial cases and 1–3% of sporadic cases of IPF [43]. Figure 2 explains the comparison between different stages of telomere lengthening. Like short telomeres, the presence of longer telomeres than average also contributes to many diseases. Cells with longer telomeres exhibit

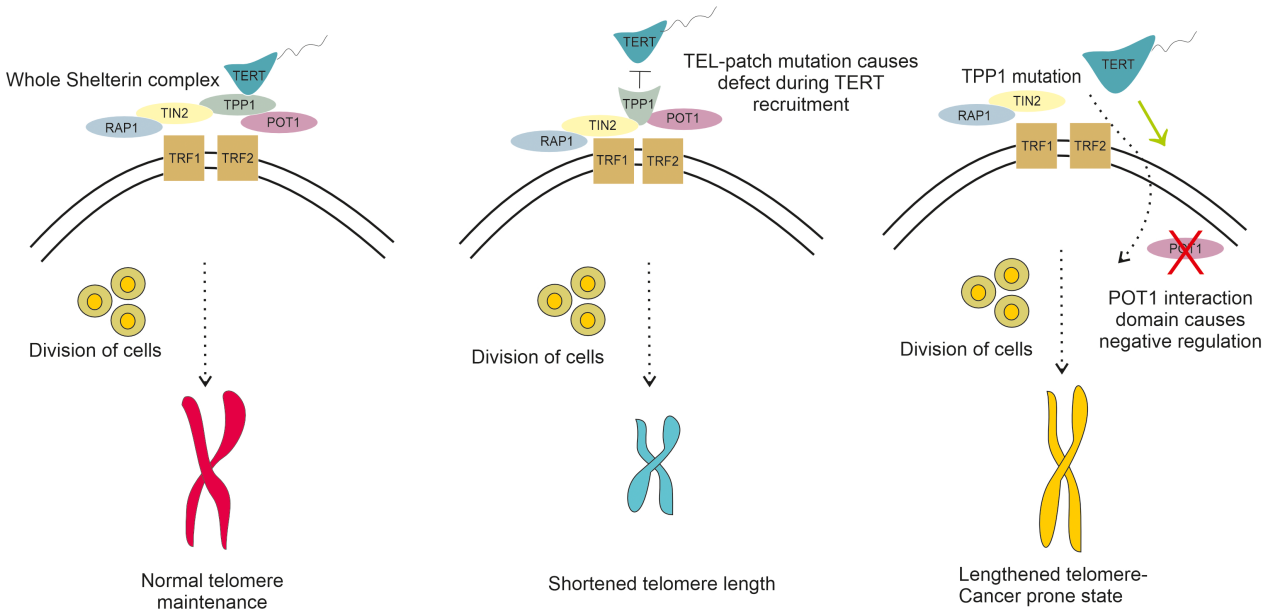


**Figure 2. Comparison between various states of telomere lengthening. Telomerase and the shelterin complex maintain the telomeres at normal length. Short telomere syndrome is caused by mutations in the TPP1 protein, which affects telomerase recruitment and shorten telomeres. Mutations in the POT1-interacting domain of TPP1 lead to excessive telomere extension in cancer-prone states, which permits unchecked cell proliferation leading to cancer.**

greater replicative potential, which results in immortalization of them [44]. Cells with normal telomeres undergoing telomere attrition are subjected to ATM and ATR signaling, which initiates DNA damage response and causes the natural cell death. This acts as a check for tumorigenesis. With the absence of these signals, chromosomes either get fused end-to-end or other kinds of genome instabilities occur. Mostly, people with a longer-than-average length of telomeres are associated with various types of cancers like melanoma, B cell lymphoma, and chronic lymphocytic leukemia [16]. It was found that a mutation in the shelterin component POT1 is associated with the occurrence of melanoma [45].

## 7. Telomeric Repeat Sequence in Varied Organisms

### 7.1. Vertebrates

For comprehensive and up-to-date information on telomeric repeat sequences across various organisms, specialized databases such as Telomerase Database (https://telomerase.asu.edu/sequences-telomere) [46] and TeloBase (http://cfb.ceitec.muni.cz/telobase/) (still in progress) are available. Earlier research revealed that the most common telomeric repeat sequence in vertebrate especially is "TTAGGG". Moreover, a recent finding reported two novel telomeric repeats such as CACAGA and TCTCTGCGCCTGCGCCGGCGCGGCGCGCC in human chromosomes [47]. The 'TTAGGG' telomeric repeat sequence is highly conserved across vertebrates. The 'TTAGGG' sequence serves as the binding site for telomerase. The human telomere system with a six-protein complex called shelterin, consisting of Telomeric repeat binding factor 1(TRF1), Telomeric repeat binding factor 2(TRF2), RAP1(the human ortholog of the yeast Repressor/Activator Protein 1), TRF1-Interacting Nuclear protein 2(TIN2), TPP1, and Protection of telomeres 1(POT1), is being associated with telomeric repeat sequence. Shelterin plays a crucial role in preventing DNA damage responses at chromosome ends and regulates telomerase activity [48]. The primary telomeric-binding proteins in human cells are TRF1 and TRF2, both acting as negative regulators of telomere length. TRF1 recognizes telomeric DNA through teloboxes and requires dimerization for stable binding. TRF2, binding to the TTAGGG repeat, serves as a stabilizer of the G string, preventing telomeric fusions. The overexpression of a dominant negative TRF2 mutant can lead to premature senescence and activation of the apoptotic cascade through protein kinase ATM and p53, suggesting its critical role in telomeric length regulation and terminal protection [49]. POT1 interacts with telomeric repeats in a single-stranded form. TIN2 serves as an adapter protein by binding to both TRF1 and the TPP1-POT1 complex, inducing conformational changes in TRF1 and stabilizing the telomeric structure. As a result of these modifications, TIN2 acts as a hindrance to telomerase access to telomeres, thereby functioning as an inhibitor of the telomerase enzyme [4]. Rap1 is bound to TRF2; however, it lacks a protective role. The study of the telomeric sequence has also been carried out on fish species using Fluorescence in situ hybridization (FISH), making interpretations about the relation between telomere length and age of the organisms. It also found that the telomerase of fishes is involved in the synthesis of telomeric repeats at non-chromosomal termini regions in some species; such sequences are called Interstitial Telomeric Sequences, which serve as "hotspots" for recombination [50]. Experiments conducted on *Mus musculus* (mouse) have proven that TTAGGG is their telomeric repeat sequence. Furthermore, it has been indicated that the telomeres of mice are longer than those of humans [51]. Unlike humans, where somatic cells lack telomerase activity, telomerase is active in mouse somatic cells [52]. Age-related shortening of telomeres has also been studied in chickens. Telomerase activity was detected in all preorganogenesis stages of development, with upregulation to strong levels in gastrula and neurula embryos. Activity decreased postnatally in the brain, liver, heart, muscle, lung, and kidney but remained strong in the intestine, reproductive system, immune organs, and terminal organs.

## 7.2. Insects

Although there are some variations in the telomeric repeat sequences of insect species, one of the characteristic telomeric repeat sequence is TTAGG. This repeat sequence is found in species such as *Apis mellifera* (honey bee) [53], *Ephestia kuehniella* (Mediterranean flour moth), *Manica yessensis* (ant) and Lepidoptera species like *Bombyx mori* (domestic silkworm), and *Papilio xuthus* (butterfly) [54]. The conservation of TTAGG repeat sequence in these organisms has been confirmed by FISH of insect chromosomes with $(TTAGG)_n$ probes [54]. Unlike other insect orders, beetles exhibit heterogeneity in the occurrence of TTAGG repeats, and this pattern was not consistently linked to phylogenetic relationship. Some species of beetles such as Palorus, Pimelia, Tenebrio, and Tribolium have "TCAGG" repeat sequence [55]. The hypothesis proposed is that TCAGG telomeric sequences in insects result from telomerase with a mutated RNA template. Telomere length in insects is maintained by either a telomerase-dependent mechanism or a telomerase-independent mechanism. In the previous research conducted on the terminal fragment of an intact Drosophila melanogaster telomere, the telomere does not include the short tandem terminal repeat motif, which is a characteristic feature of all eukaryotic telomeres. Rather, they are made up of two main retrotransposons classes, HeT-A and TART, which are involved in telomere length maintenance [56].

## 7.3. Plant species

Plants predominantly contain TTTAGGG repeats at their telomeres [57]. The evolution of TTTAGGG repeats occurred earlier than the origin of land plants [58]. However, in some members of Alliaceae and Aloe spp. (Asphodelaceae), TTTAGGG repeats were not found. The examination of Aloe telomere composition through PCR and FISH, employing an Arabidopsis-type DNA probe and a vertebrate-type DNA probe, along with a $(C_3TA_2)_3$ peptide nucleic acid probe, indicates the existence of telomeric sequences in Aloe spp. chromosomes that resemble those found in vertebrates. It has been revealed that species within the order Asparagales lack the Arabidopsis-type telomeric sequence, which has been partly or entirely replaced by the $(TTAGGG)_n$ sequence. Initially, it was proposed that the majority of studied genera within Solanaceae including the genera Nicotiana and Solanum exhibit telomeric repeats of $(TTTAGGG)_n$. Nevertheless, further research showed that these particular telomeric repeats are absent from three closely related genera such as Cestrum, Vestia, and Sessea [59]. From recent experiments conducted, it was reported that the plant *Cestrum elegans* has $(TTTTTTAGGG)_n$ sequences at their telomeric region [60]. This divergence in telomeric repeat sequences may be attributed to several potential mutations in the telomerase RNA (TR) subunit.

## 7.4. Fungus

In the fungus genus Candida, variations are observed in telomeric repeat sequences. For example, the *Candida albicans* has 23 bp long telomeric repeat sequence ACTTCTTGGTGTACGGATGTCTA [61]. Diversity exists among telomeric repeat sequences of the genus Saccharomyces. The fungus *Saccharomyces cerevisiae* has the telomeric repeat sequence $TG_{2\text{-}3}(TG)_{1\text{-}6}$, while the fungi *Saccharomyces castellii* and *Saccharomyces dairenensis* have TCTGGGTG as their telomeric repeat sequence [61]. In budding yeast, telomere protection relies on the CST complex containing Cdc13, Stn1, and Ten1. Investigations in *Saccharomyces cerevisiae* have elucidated the precise binding characteristics of CST complex subunits. Cdc13 exhibits a high-affinity, sequence-specific binding affinity to telomeric G overhangs, while Stn1 and Ten1 exhibit a preference for binding G-rich DNA with reduced affinity. Additionally, Stn1 and Ten1 are capable of recruiting to telomeres through protein-protein interactions within the CST complex subunits. TTAGGG telomeric repeats were found in *Aspergillus nidulans, Aspergillus fumigatus, Neurospora crassa,* and *Cladosporium fulvum* [62]. The genomic DNA of *Aspergillus nidulans* undergoes cleavage by EcoRI, followed by a Southern blot analysis using $(TTAGGG)_4$ probe. The findings validated the existence of telomeric DNA fragments displaying robust hybridization to the probe. The identification of telomere-binding proteins in *Neurospora crassa* has made it an ideal model for understanding human telomere biology [62].

## 7.5. Algae

Diversity in telomeric repeat sequences exists among algae. From previous studies, it has been inferred that two types of telomeric repeats were identified in green algae: the Arabidopsis-type telomeric repeats (TTTAGGG) and the repeat that was reported in *Chlamydomonas reinhardtii* (TTTTAGGG). In Mamiellophyceae, Chlorodendrophyceae, Trebouxiophyceae (e.g., *Chlorella vulgaris*), Sphaeropleales, and most Chlamydomonadales, the TTTAGGG repeats were found to be conserved and it is said to be the ancestral motif. In the case of Chlamydomonadales, there have been occurrences of evolutionary shifts in the subgroup of the Reinhardtinia clade and the Chloromonadinia clade [63]. Within the clades Dunaliellinia and Stephanosphaeria, the emergence of TTAGGG motif represents evolutionary changes among green algae [64]. This results in template utilization caused by mutation of catalytic telomerase component TERT or single nucleotide alterations in RNA telomerase template region. In brown algae, the telomeric repeat sequence of *Saccharina japonica* was identified as TTTAGGG. In red algae, the telomeric repeat sequence of *Cyanidioschyzon merolae* was identified as AATGGGGGG through restriction fragment analysis using the $(CCCCCCATT)_3$ probe [65].

## 7.6. Nematodes

Telomeric repeat sequences in nematodes, a diverse phylum of roundworms, vary across different species. TTAGGC sequence was found as a telomeric repeat sequence in *Ascaris lumbricoides*, *Ascaris suum* [66], and *Caenorhabditis elegans* [67]. It was identified as a canonical telomeric repeat sequence of nematodes. In pre-somatic cells of *Ascaris suum*, the fragmentation of chromosomes at chromosomal breakage region is followed by the addition of TTAGGC repeats to maintain the stability of chromosomes. Recent research suggests that another telomeric repeat sequence (TTAGAC) has evolved from the canonical telomeric repeat due to a single nucleotide mutation in the TERC gene [68]. It has been identified in the family Panagrolaimidae. The organism *Parascaris univalens* has the telomeric repeat sequence $(TTGCA)_n$/ $(TTAGGC)_n$ [69].

## 7.7. Ciliates

Ciliates are a group of organisms that belong to the phylum Protista, and they possess short, hairlike organelles called cilia.

These cilia are used for both locomotion and food gathering. *Tetrahymena thermophila* is the first ciliated organism discovered with telomeric repeat sequence as TTGGGG [70]. In *Tetrahymena thermophila*, Pot1a assists in the negative regulation of telomerase activity and binds with Tpt1 to cap macromolecular telomeres. Both are orthologs of proteins POT1 and TPP1, respectively. The subunits of Tetrahymena telomerase TERT, TER, p65, Teb1, p50, p75, p45, and p19 are essential for the synthesis of telomeric repeats [71]. At first, it was believed that there would be involvement of two telomerase enzymes, but experimental research found that a single telomerase was responsible for the production of variable repeats. The template region of the telomerase RNA is not edited, so there is a chance of different mechanisms involved in synthesizing telomeric repeats in Paramecium. It has been found that the telomeric repeat sequence of the genera Euplotes and Oxytricha is TTTTGGGG, an octamer repeat. Telomere-binding proteins in Oxytricha and Euplotes play a crucial role in telomere function. The telomere-binding protein of Oxytricha, a heterodimer with two subunits: α and β subunits, having a molecular weight of 56 kD and 41 kD respectively, binds to the G-rich 3'-overhang of telomeres. The α-subunit is primarily responsible for DNA binding, while the β-subunit, with a lysine-rich carboxy-terminus, accelerates G-quartet formation and inhibits telomerase activity. Table 1 summarizes the organisms and associated telomeric repeat sequences.

## 8. Comparative Genomics

Through genome comparisons, biologists are able to determine genetic variants, reconstruct the evolutionary history, and deduce the functional relevance of divergent and conserved sequences. The development of centromeres and telomeres, as well as the construction of genome architecture, is further elucidated by comparative genomics. This research provides important new insights into species adaptability, genome evolution, and the molecular underpinnings of complex behaviors. A study compared several Chlamydomonas species, including *C. reinhardtii*, *C. schloesseri*, and *C. incerta*, revealing complex gene structures with an average of 7.7 to 9.3 introns per gene, suggesting early intron expansion in chlorophyte evolution. Intron lengths and densities varied among species, reflecting differences in regulatory sequences. Hundreds of highly conserved genes, particularly for photosynthesis like PsbW, were identified. The study also uncovered over 400 new gene models and explored the role of

**Table 1. Organisms and their associated telomeric repeat sequences**

| S.No | Group | Source organism | Telomeric repeat sequence | References |
|---|---|---|---|---|
| 1. | Vertebrates | Human | TTAGGG/ CACAGA/ TCTCTGCGCCTGCGCCGGCGCGGCGCGCC | [47] |
| 2. | Insects | *Apis mellifera* | TTAGG | [53] |
| | | *Papilio xuthus* | TTAGG | [54] |
| | | *Bombyx mori* | d[TAGG(TTAGG)$_3$] | [72] |
| | | *Odonata* | TTAGG | [73] |
| | | *Malachius bipustulatus* | TCAGG | [74] |
| | | *Pyrochroa serraticornis* | TCAGG | [74] |
| | | *Gryllus campestris* | (TTAGG)$_n$ | [75] |
| | | *Palorus, Pimelia, Tenebrio* and *Tribolium* species | TCAGG | [55] |
| | | *Monochamus alternatus* | AACCT | [76] |
| | | *Bombus sylvestris* | TTAGGTTGGGC | [77] |
| | | *Nasonia vitripennis* | (TTATTGGG)$_n$ | [78] |
| | | *Parasitoid wasps* | (TTATTGGG)$_n$ | [79] |
| | | *Cestrum elegans* | TTTTTTAGGG | [60] |
| | | *Genlisea hispidula* *Genlisea nigrocaulis* | TTCAGG/TTTCAGG | [80] |
| | | *Convolvulus arnensis* | TTTAGGG | [80] |
| | | *Arachis hypogaeo* | TTTAGGG | [81] |
| | | *Physcomitrium patens* | GGCCCA | [82] |
| | | *Allium species* | CTCGGTTATGGG | [77] |
| | | *Hibiscus mutabilis* | AGGGTTT | [83] |
| | | *Juglans regia* | AGGGTTT | [83] |
| | | *Hippophaë rhamnoides* | (AGGGTTT)$_3$ | [84] |
| | | *Berberis diaphana* | (AGGGTTT)$_3$ | [85] |
| | | *Robinia pseudoacacia* | (AGGGTTT)$_3$ | [86] |
| | | *Amorpha fruticose* | (AGGGTTT)$_3$ | [86] |
| | | *Corydalis yanhusuo* | (TTTCGG)$_n$ | [87] |
| | | *Dioon edule* *Stangeria eriopus* | TTTAGGG | [88] |
| 4. | Fungi | *Candida albicans* | ACTTCTTGGTGTACGGATGTCTA | [61] |
| | | *Saccharomyces cerevisiae* | TG$_{2\text{-}3}$(TG)$_{1\text{-}6}$ | [61] |
| | | *Aspergillus nidulans* *Aspergillus fumigatus* *Cladosporium fulvum* *Neurospora crassa* | TTAGGG | [62] |

(*Continued*)

**Table 1.** (*Continued*)

| S.No | Group | Source organism | Telomeric repeat sequence | References |
|---|---|---|---|---|
| | | *Colletotrichum fructicola* | TTAGGG | [89] |
| | | *Fusarium oxysporum* | $(TTAGGG)_n$ | [90] |
| | | *Pyricularia oryzae* | $(TTAGGG)_n$ | [91] |
| | | *Schizosaccharomyces japonicus* | GTCTTA | [92] |
| | | *Yarrowia lipolytica* | TTagtcAGGG | [93] |
| | | *Drechmeria coniospora* | CCGTTGCTGTTG | [94] |
| | | *Penicillium oxalicum* | TTAGGG/CCCTAA | [95] |
| 5. | Protozoan parasite | *Hamiltosporidium tvaerminnensis* | $(TTAGGG)_n$ | [96] |
| | | *Encephalitozoon cuniculi* | TTAGG | [97] |
| | | *Cryptosporidium parvum* | CCTAAA/AGGTTT | [98] |
| | | *Theileria annulata* | TTTAGGG/TTTTAGGG | [99] |
| 6. | Algae | *Chlamydomonas reinhardtii* | TTTTAGGG | [63] |
| | | *Chlorella vulgaris* | TTTAGGG | [63] |
| | | *Saccharina japonica* | TTTAGGG | [65] |
| | | *Cyanidioschyzon merolae* | AATGGGGGG | [100] |
| | | *Chlorella sorokiniane* | CCCTAAA | [101] |
| | | *Chlorella pyrenoidosa* | TTTAGGG | [101] |
| 7. | Ciliates | *Tetrahymena thermophila* | TTGGGG | [70] |
| | | *Giardia duodenalis* | TAGGG/TAAGG | [102] |
| 8. | Nematodes | *Panagrolaimidae* | TTAGAC | [68] |
| | | *Parascaris univalens* | $(TTGCA)_n/(TTAGGC)_n$ | [69] |
| | | *Litomosoides sigmodontis* | TTAGGC | [103] |
| | | *Caenorhabditis elegans* | GGCTTA/ TTAGGC | [67] |
| 9. | Coral | *Orbicella faveolata* | TTAGGG | [104] |
| | | *Nephrops norvegicus* | $(TTAGG)_n$ | [105] |
| | | *Procambarus clarkii* | | |
| | | *Scyllarus arctus* | | |
| | | *Scomber japonicus* | AACCCT | [106] |

transposable elements in centromere formation, showing variability in genome organization across green algae species like *C. subellipsoidea* which utilize certain repeat elements in centromere formation, and others like *Volvox carteri* do not reflect variability [107]. While many species, such as beetles and butterflies, rely on the canonical TTAGG telomeric repeat sequence, some insects like Drosophila have evolved telomerase-independent mechanisms. These species use transposable elements or long repeat sequences to elongate their telomeres. Additionally, subtelomeric regions, located adjacent to telomeres, show considerable variability across insect species. These regions consist of repeated sequences that influence genome stability and gene regulation, reflecting the insects' diverse evolutionary histories [74]. The study highlighted a high degree of polymorphism in *Agaricus bisporus* at chromosome ends, indicating significant genetic variation in telomeric regions across individuals and subspecies. This variation suggests unique evolutionary pressures and potential roles in mushroom biology. These findings could inform breeding programs for improved strains, while the advancements in assembly and annotation techniques mark a significant step in accurately characterizing complex genomic regions [108]. A study revealed that Gomphocerine grasshoppers with larger genomes exhibit a significant expansion of satellite DNA and Helitrons. Satellite DNA, often located in centromeric and pericentromeric regions, and Helitrons, which are transposable elements, are both linked to genome size increase. The proliferation of these repetitive sequences suggests their critical role in driving genome expansion and the evolutionary dynamics of grasshoppers with unusually large genomes [109]. A study compared cnidarians such as *Turritopsis dohrnii* and *Turritopsis rubra*, where *T. dohrnii* exhibit continuous regeneration and extended lifespans with unique genomic features than *T. rubra*. The identification of unique genes and network patterns enhanced cellular mechanism, DNA repair, and stress response [110].

## 9. Future Directions

With the advancement of technology, various techniques like Single telomere length analysis, Telomere Length Combing Assay, Single telomere absolute-length rapid assay, and Telomere Shortest Length Assay are available for the determination of telomere length [111]. These advanced technologies could help scientists to further correlate different-diseased states and telomere length. The techniques including qPCR, Flow FISH, qFISH, and TeRF have its own advantages and are appropriate for determining the shortest or average telomere length and even telomeric repeat sequence. The specific study areas will determine which approach is best for usage [112]. Additionally, new drugs have been formulated to target telomere maintenance mechanisms for the treatment of cancer. One such drug is GRN163L (Imetelstat), a 13-mer oligonucleotide that can bind to the template RNA of telomerase to inhibit its activity [113]. In its preclinical studies, it showed good results in the inhibition of cell proliferation of several cancer cell lines, and it has been approved by the FDA for the treatment of myelofibrosis [114]. Another drug that is found to inhibit telomerase activity is Telomestatin, which is derived from the bacterium *Streptomyces anulatus*. Unlike Imetelstat, which binds to the telomerase, Telomestatin does not directly interact with telomerase. Instead, it stabilizes

G-quadruplexes to prevent telomere extension and shelterin binding, leading to replication stress. With IC50 values ranging from 0.1 to 5 μM, it is more effective in causing apoptosis compared to simple telomerase inhibitors. Although the drug is found to be effective, it has some drawbacks including poor water solubility and difficulty in large-scale production [115]. Further exploration of these potential novel therapeutic agents may help diagnose various cancer types. It is noteworthy that treating telomere genetic disorders can be proposed by employing telomerase to lengthen short telomeres, in individuals with mutation that predict the onset of disease or potentially outside the body. The changes of telomerase activation in premalignant cell would be minimal in young individuals when weighed against the possibility of telomere dysfunction [116]. Moreover, the development of personalized medicine approaches based on telomere length and telomerase activity could revolutionize cancer treatment strategies, offering targeted therapies tailored to individual patient profiles.

## 10. Conclusion

In this review, we revealed the telomeric repeat sequences present in different organisms. We also interpreted that telomeric repeat sequence is conserved in all vertebrates but varies among invertebrate organisms. Two evolutionary shifts in telomeric repeat sequences occurred in plant species, one is a change from the canonical TTTAGGG repeat sequence to vertebrate repeat sequence whereas the other one is divergence among three genera of plants, which resulted in an evolution of a different telomeric repeat sequence. Several species have the same telomeric repeat sequence as vertebrates, while other organisms have developed different telomeric repeat sequences due to mutations in telomerase RNA and selection pressures. The binding specificity of telomere-binding proteins plays an important role in the determination of telomeric repeat sequences. Fungus demonstrates diversity in telomeric repeats, and algae exhibit shifts in motifs across clades. Briefly, studying telomeric repeat sequences in a variety of organisms uncovers an intriguing patchwork of evolutionary adaptations, laying the foundation for future study and applications in a range of fields.

## Conflicts of Interest

The authors declare that they have no conflicts of interest to this work.

## Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

## Author Contribution Statement

**Monish Prasanna:** Writing – original draft, Writing – review & editing. **Kousik Varadan:** Writing – original draft, Writing – review & editing. **Achsha Babu:** Writing – original draft, Writing – review & editing, Visualization, Supervision. **Arun Arumugaperumal:** Conceptualization, Supervision.

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