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# Syndromes Associated with Telomere Shortening

*Snehasish Nag*

## Abstract

We know that chromosomes are threadlike structures of nucleic acids and proteins, which are found in the nucleus of most living cells. They carry genetic information in the form of genes. Chromosomes are protected at their ends by a specialized structure called telomere. With each replicative cycle, the telomeres get shortened preventing uncontrolled replications. Telomeres perform several functions like protect the chromosome ends from sticking together, solve the end of replication problem, and limit the number of cell divisions. It is considered that telomeres are associated with cancer incidence and mortality. Telomere DNA has repetitive sequences (5'-TTAGGG-3' in human), which is lengthened at the 3' end by a special ribonucleoprotein enzyme called telomerase. Short telomeres are associated with early senescence, genomic instability, and apoptosis of cells. Short telomeres can result due to several factors including environmental factors, external factors like smoking, stress, as well as due to mutations in the components of telomere or telomerase. Short telomeres are associated with several disorders and diseases, such as dyskeratosis congenita, aplastic anemia, pulmonary fibrosis, and even cancer. Thus, it is important to understand how telomeres are associated with these diseases and what can be done to prevent such conditions.

**Keywords:** aplastic anemia, dyskeratosis congenita, idiopathic pulmonary fibrosis, telomere, telomerase

## 1. Introduction

Over the years, it has been observed that many degenerative disorders are associated with telomere dysfunction. Telomeres are present at the end of chromosomes. They protect the chromosome ends and critical genetic information in the chromosome from degradation by acting as caps from fusing with other chromosomes [1]. We know that the replication machinery cannot completely copy the chromosome ends, which is called end replication problem. As a result, the telomeres get shorter with each replicative cycle that leads to cell senescence [2]. Short telomeres are associated with genome instability. Telomere dysfunction caused by defects in telomerase proteins is associated with genomic instability that increases genetic mutations characterized by an increased incidence of cancer and also high sensitivity to genotoxic compounds. Short telomeres activate a p53-dependent checkpoint, which leads to senescence and apoptosis of the cells [3–6]. Telomere shortening can be caused by some external factors also such as smoking, stress, poor health such as obesity, inflammation [7]. Telomere shortening is also accelerated due to chemical and physical environmental agents. Reactive oxygen species can produce modified

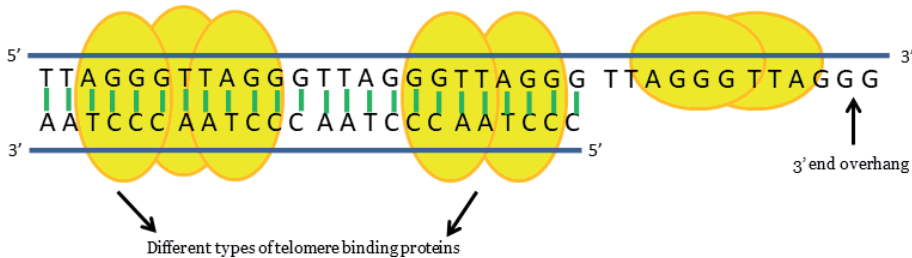
bases (mainly 8-oxoG) and single strand breaks in the genome. Oxidative damage can result from high incidence of guanine residues in telomeric DNA sequences [8]. Telomere shortening has been recognized as one of the important determinants behind senility and some diseases including—dyskeratosis congenita (DC), idiopathic pulmonary fibrosis (IPF) [9]. Telomere length is maintained by an enzyme called telomerase that adds telomeric repeats to the chromosome 3'-end using an RNA template. The enzyme is a ribonucleoprotein complex, which is inactive in somatic cells but active in stem cells and most cancer cells [10, 11]. Dysfunctional telomeres are recognized by many DNA damage response proteins leading to chromosome fusions, genome instability and altered gene expression patterns [12, 13]. Several cellular processes including apoptosis, aging, carcinogenesis, and chromosome instability are caused as consequences of loss of telomeres [14, 15].

## 2. Telomeres

Hermann J. Muller and Barbara McClintock in the 1930s described the telomere as a protective structure of DNA present at the end of the chromosome [16]. It protects the chromosome structure. The human telomeres have repetitive 5'-TTAGGG-3' subunits, associated with a variety of telomere-associated proteins. The structure consists of a portion of the double-stranded DNA with an overhanging 3' G-rich end (**Figure 1**) [1, 16].

Human somatic cells enter replicative senescence after a limited number of replications. This occurs due to the end replication problem leading to shortening of telomeres [17]. In absence of this structure, the replication cycle stops and the end-to-end fusion of chromosomes may occur [18–20]. Telomeres are bound by a specialized protein complex called shelterin [21–24]. Due to the end replication problem, the telomeres shorten with each cell cycle, and these short telomeres induce the DNA damage response and activate the  $p^{53}$  dependent checkpoint, leading to apoptosis or senescence (**Figure 2A**) [21]. But in case of germ cells or in cancer cells, telomere maintenance is observed likely due to the expression or reactivation of telomerase, thus the replicative cycle of the cells continue.

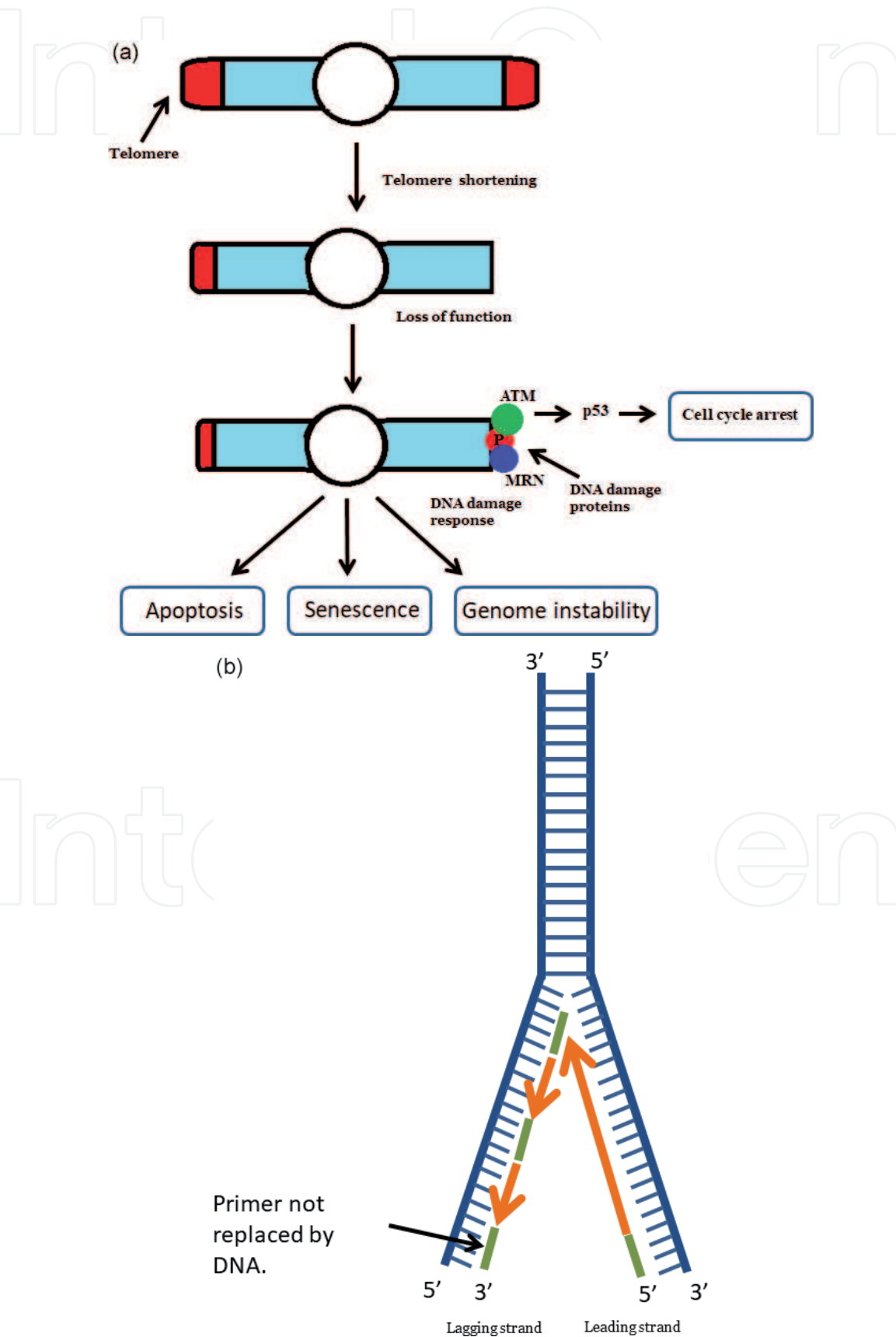
The telomere shortening takes place as the eukaryotic DNA polymerases have no mechanism for synthesizing the final nucleotides present on the “lagging strand” of the double-stranded DNA. DNA polymerase synthesizes new DNA only from the 5' → 3' direction. The two strands of DNA are complementary, one strand is in 5' → 3' direction, while the other is in 3' → 5'. DNA polymerase cannot synthesize DNA in the 3' → 5' direction. The process is compensated by the use of Okazaki fragments. Okazaki fragments are short pieces of DNA that are synthesized in the 5' → 3' direction from the 3' → 5' end as the replication fork moves. As RNA primer is required by DNA polymerase to synthesize new strand, each Okazaki fragment consists of an RNA primer followed by short DNA sequence. When the DNA polymerase reaches the chromosome end, the RNA primer is again placed, which

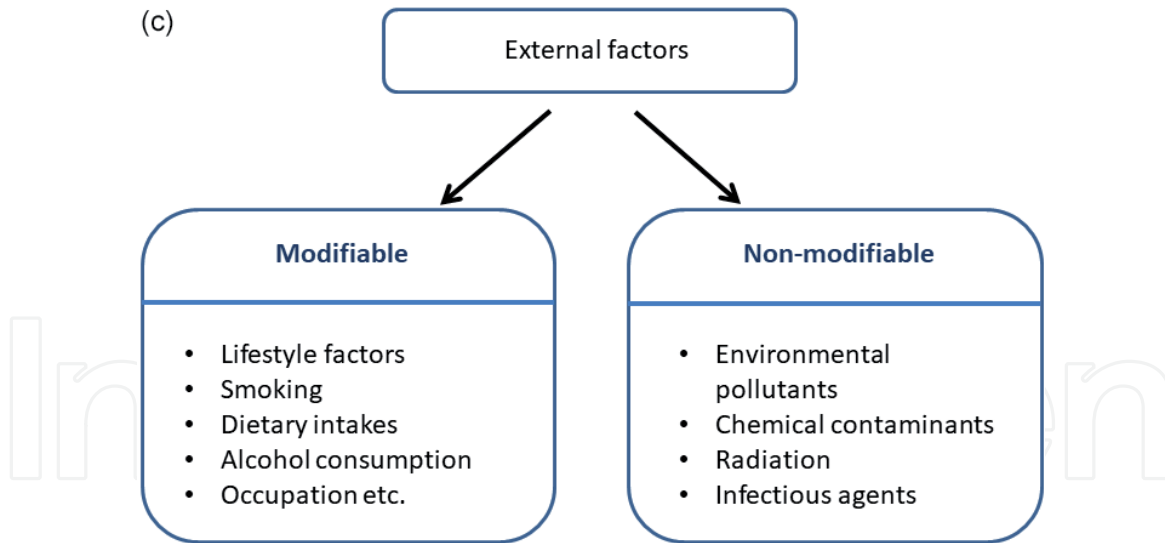


**Figure 1.**  
3' overhanging of telomere.

is inevitably removed. But as the primer is removed, the DNA polymerase cannot synthesize the remaining bases leading to telomere shortening with each replicative cycle (**Figure 2B**) [16, 25, 26].

In addition to that several external factors can also affect telomere length and maintenance. Factors such as smoking, alcohol consumption, chemical and environmental pollutants, radiation and many more can affect telomere length (**Figure 2C**).





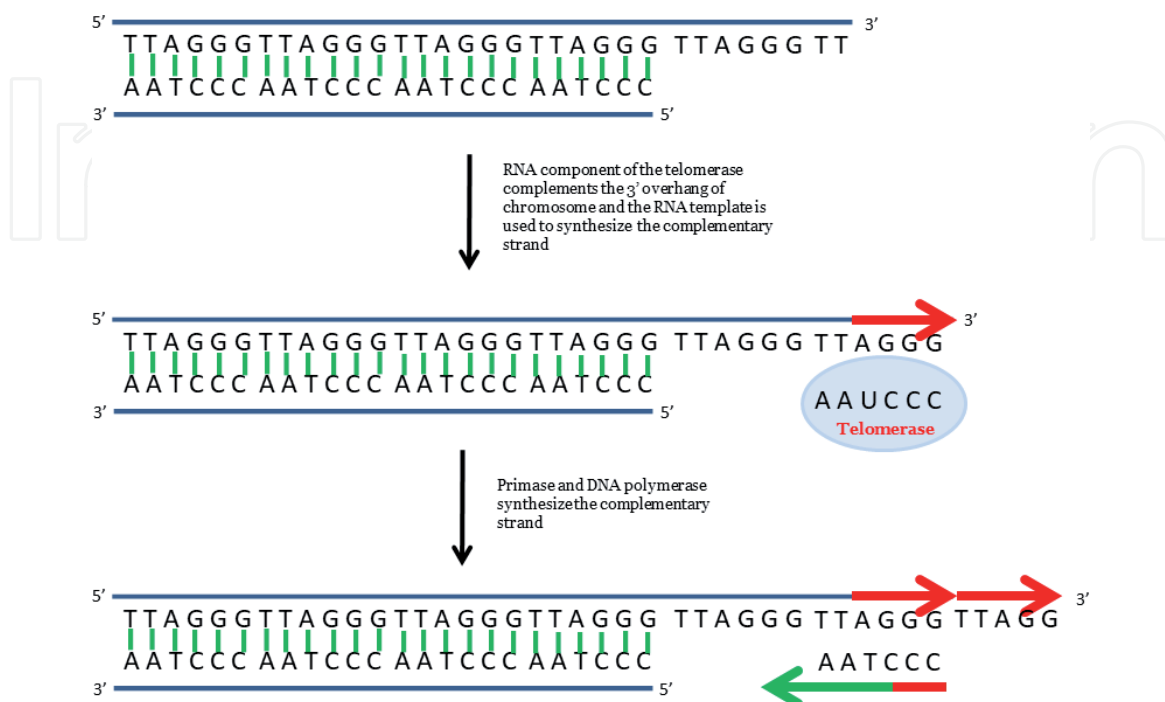
**Figure 2.**

(A) Telomere shortening leads to DNA damage response. The DNA damage responses include apoptosis, senescence of the cell or genomic instability that can lead to cancer. (B) “Lagging strand” end-replication problem. With each replication cycle the ends of the chromosome get shortened as the final RNA primer at the 3'-end cannot be replaced with DNA. (C) External factors associated with telomere shortening and maintenance.

### 3. Telomerase

The telomerase enzyme is a ribonucleoprotein containing both RNA and protein. It functions as a reverse transcriptase that positively regulates the telomere length [21, 27, 28]. The ribonucleoprotein has two essential components: telomerase reverse transcriptase (hTERT), the catalytic component, and telomerase RNA component (hTERC or hTR) which provides the template for telomere addition. Telomerase synthesizes new telomeres by solving the end-replication problem (**Figure 3**) [29].

Biogenesis of telomerase in somatic cells requires the assembly of hTERT and hTR into a stable complex that can function at telomeres. hTR (RNA component of telomerase) contains a box H/ACA motif which regulates RNA trafficking and



**Figure 3.**

*An image showing how telomerase elongates telomere ends progressively.*





gene	Chromosome no.	function	Mode of Inheritance in dyskeratosis congenita
RTEL1	20	Helicase activity	Autosomal dominant and Autosomal recessive
TINF2	14	Forms part of shelterin complex	Autosomal dominant
hGAR1	4	Stability, maturation, localization	-
Dyskerin	Chromosome X	Stability, maturation, localization	X-linked
hNOP10	15	Telomere maintenance	Autosomal recessive
hNHP2	5	Stability, maturation, localization	Autosomal recessive
hStau	20	Accessibility to telomeres	-
hTERT	5	Synthesize protein component of telomerase	Autosomal dominant and Autosomal recessive
hTR	3	Synthesize RNA component of telomerase	Autosomal dominant

**Table 1.**  
*Human telomere shortening associated genes, their functions and mode of inheritance in dyskeratosis congenita [37].*

life cycle. About 90% of the cancer cells have short telomeres with increased levels of telomerase activity [18]. For example, about 75% cases of oral carcinomas, 80% of lung cancers, 84% of prostate cancers, 85% of liver cancers, 93% of breast cancers, 94% of neuroblastomas, 95% of colorectal cancers, and 98% of bladder cancers have been found to be associated with increased levels of telomerase activity [35].

Telomerase transfection in normal cells can lead to the elongation of telomeres. For example, telomerase-negative normal cells, such as retinal pigment epithelial cells and foreskin fibroblasts, transfected with vectors encoding human hTERT show telomere elongation, but telomerase-negative control cells exhibit both telomere shortening and senescence [36].

Furthermore, mutations in the telomerase and telomere components lead to the syndromes of telomere shortening (**Table 1**).

## 4. Syndromes associated with short telomere

### 4.1 Dyskeratosis congenita (DC)

Dyskeratosis congenita (DC) is a rare progressive congenital disorder having a highly variable phenotype [38]. DC is a rare syndrome of premature aging. The term coined by clinicians based on a triad of mucocutaneous features that they found in male children. These are—leukoplakia of the oral mucosa, skin hyperpigmentation, and dystrophy of nails [39]. This triad was associated with premature mortality of children due to bone marrow failure in aplastic anemia. DC mainly affects the skin. But in nearly 80% of the cases, bone marrow failure also occurs. DC is also characterized by the predisposition of cancer. In serious forms, the life span can be significantly shortened.

4.1.1 Genetics of the syndrome

In 1998, the gene encoding dyskerin, DKC1 was discovered. It was identified in X-linked families with the help of linkage and positional cloning. Dyskerin is a putative box H/ACA telomerase RNA binding protein [40]. The protein links with the telomerase RNA structure. The hTR has a box H/ACA motif and the X-linked DC patients have low levels of telomerase RNA component resulting in short telomeres. It is supported by the fact that mutations in the DKC1 gene disrupt the maturation and stability of hTR. Mutations in the dyskerin complex, NOP10 and NHP2 have also been identified in DC families [41, 42].

The best characterized form of dyskeratosis congenita is a result of one or more mutations in the gene DKC1 present on the long arm of X chromosome. This result in the X-linked recessive form of the disease also called Zinsser-Cole-Engman syndrome wherein the major protein affected is dyskerin [40]. Within the vertebrates, dyskerin is a key component of the telomerase RNA component (hTR) in the form of the H/ACA motif. This X-linked variety, like the NOP10 and NHP2 mutations, demonstrates shortened telomeres as a result of lower hTR concentrations [43, 44].

Recently, heterozygous mutations in the shelterin component TINF2 were identified in several cases of DC. Mutations in the TINF2 results in severe manifestations and usually present in children [34, 45]. Different organs show different types of defects in DC patients (**Table 2**). Many of these cells express telomerase, an enzyme that maintains telomeres.

Mutations in DKC1 can lead to significant declines in hTR levels, i.e. one fifth of the wild-type [46]. This is consistent with the fact that mutations in the DKC1

Organ System	Telomerase expressing cells	Defects in Dyskeratosis congenita
Hair	Hair follicle	Alopecia
Oral cavity	Squamous epithelium	Leukoplakia
Skin	Basal layer of epidermis	Hyperpigmentation, Nail dystrophy
Lungs	Type 2 alveolar epithelial cells	Fibrosis
Liver	Distributed hepatocytes	Cirrhosis
Intestine	Intestinal crypts	Disorders of gut
Testes	Spermatogonia	Hypogonadism
Bone marrow	Progenitor stem cells	Blood cell production failure

**Table 2.**  
*Defects in DC patients are most often seen in tissues in which cells divide rapidly, and often, many of these cells express telomerase, an enzyme that maintains telomeres.*



lead to accelerated phenotypes because of a loss of greater than half of the available telomerase. Mutations in the shelterin component TINF2 also lead to severe disease. This suggests that telomere defects are alone sufficient to cause dyskeratosis congenita (DC) [40, 42, 43].

Due to aplastic anemia when DC patients undergo bone marrow transplant, they frequently suffer with morbidity and mortality from pulmonary fibrosis and liver failure. This happens even when the patients seem to have intact function in these organs during the time of transplant [47, 48]. This happens due to the limited length of the telomeres in the patient's lung and liver, and also the poor capacity of DNA damage repair after chemotherapy and radiation.

Nonmyeloablative bone marrow transplant should be considered in aplastic anemia, where there is mutation in the telomere or telomerase components [40].

#### *4.1.2 DC patients are cancer prone*

As many as 10% of the DC patients die due to the cancer diagnosis. DC is thought to be a cancer-prone disorder because of the underlying pathology of abnormal telomere maintenance. The link between DC and cancer is very interesting, because DC is associated with defects in telomere biology. Patients with DC have very short telomeres. Mutations have been identified in telomere biology genes. The United Kingdom Dyskeratosis Congenita Registry (DCR) data indicated that the crude rate of malignancy among approximately 300 patients was 10%. DC patients are at increased risk of myelodysplasia and acute leukemia [49]. Since aplastic anemia itself has an associated increased risk for transformation to acute myeloid leukemia, it is unclear whether DC patients with aplastic anemia have an added predisposition. DC patients also have increased incidence of squamous cell cancers of the skin and head and neck. In DC patients, these cancers are diagnosed as early as the 2nd decade of the life. DC patients with cancer have a mean age at cancer diagnosis of 29 and a cumulative incidence of ~40% by the age of 50.

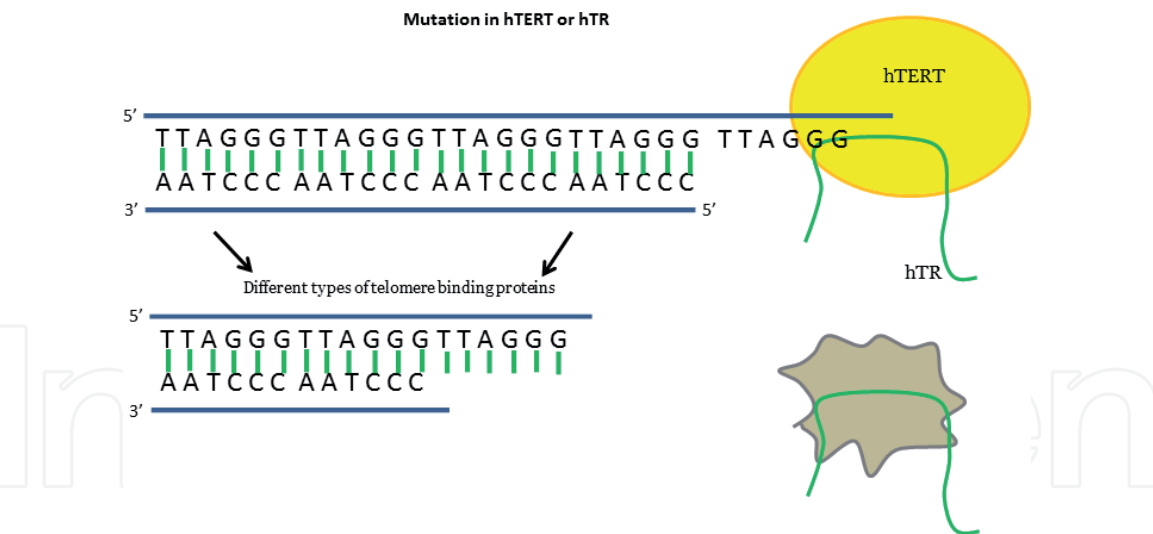
#### *4.1.3 Predisposition to cancer*

Susceptibility to cancer seems counterintuitive due to the fact that in many known cancers reactivation of telomerase is actually a required step for malignancy to evolve however short telomeres do contribute to genome instability. In a disease like DC where telomerase is affected, it does not seem that cancer would be a complication to result. But it is discussed that with critically short or absent telomeres, chromosomes will likely be attached together at their ends through the non-homologous end joining pathway (NHEJ). If this occurrence is common enough, then malignancy even without functional telomerase seems probable.

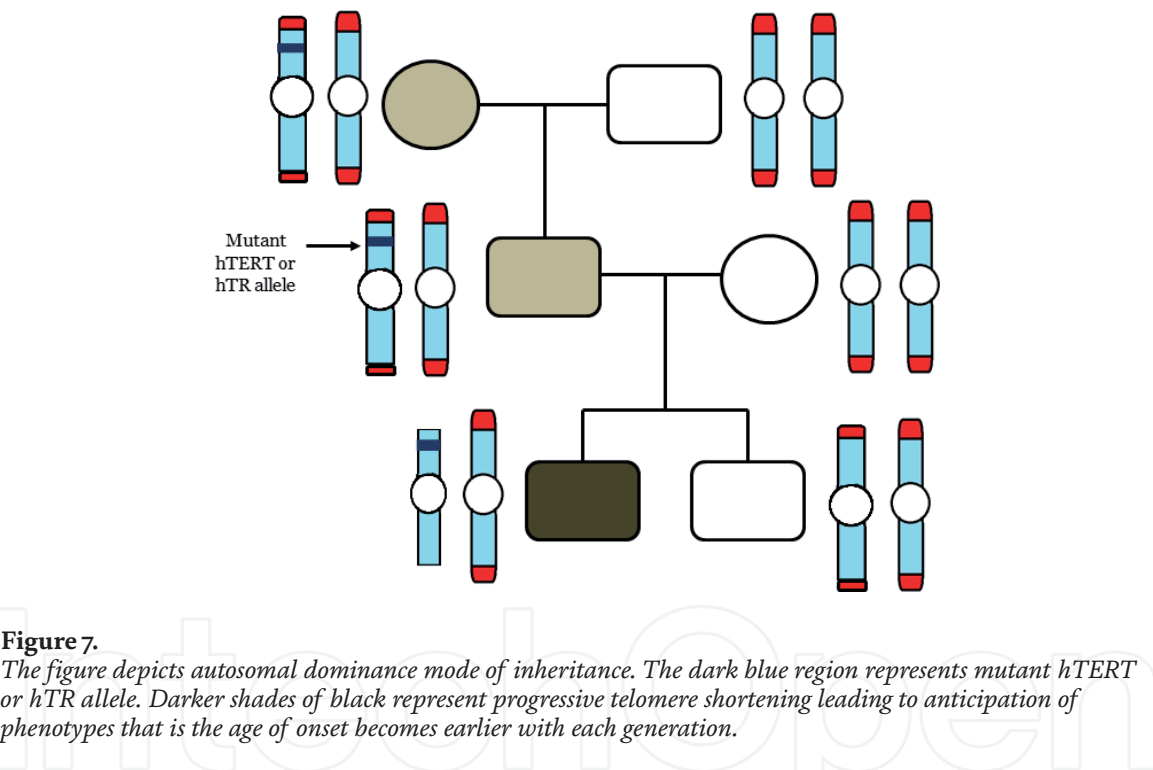
#### *4.1.4 Haploinsufficiency of telomerase*

Families with autosomal dominant dyskeratosis congenita show anticipation and have mutations in the telomerase RNA gene. A null mutation in motif D of the hTERT domain is associated with this phenotype. This mutation leads to haploinsufficiency of telomerase, and telomere shortening occurs despite the presence of telomerase (**Figure 6**) [50].

This finding shows the importance of telomere maintenance and telomerase dosage for maintaining tissue proliferative capacity. It has also relevance for understanding mechanisms of age-related changes. Telomere length limits the number of replication cycle of primary fibroblasts and has been associated with



**Figure 6.**  
Telomere shortening despite the presence of telomerase. Mutations in the hTERT or hTR components of telomerase prevent them from extending the telomere length.



**Figure 7.**  
The figure depicts autosomal dominance mode of inheritance. The dark blue region represents mutant hTERT or hTR allele. Darker shades of black represent progressive telomere shortening leading to anticipation of phenotypes that is the age of onset becomes earlier with each generation.

cellular aging [50]. Short telomeres activate DNA damage response, which leads to apoptosis. It is the shortest telomere and not the average telomere length within a cell that is responsible for mediating the response that leads to cell death [51]. Mutations in the hTERT component can result in a complex phenotype of stem cell failure. This phenotype shows anticipation; it presents earlier and more severely with successive generations. The anticipation is due to haploinsufficiency of telomerase that results in progressive shortening of telomeres (Figure 7) [52]. The hTERT mutation results in haploinsufficiency of telomerase, which leads to shortening of telomeres across generations [49]. The number of these short telomeres is correlated with the severity of phenotypes expressed. The earlier onset of such phenotypes in later generations implicates that in bone marrow and other solid tissues the telomere length is short and in limiting proliferative capacity. This pattern of anticipation suggests that like aplastic anemia, this disorder might also affect the stem cells within the lung.

## **4.2 Aplastic anemia due to telomere shortening**

Aplastic anemia arises when the body's bone marrow does not make enough new blood cells. It can develop at any age. A number of diseases, conditions and factors can damage the blood-making stem cells in bone marrow and bring about aplastic anemia.

Aplastic anemia patients with shorter chromosome tips, or telomeres, have a lower survival rate and are much more likely to relapse after treatment than those with longer telomeres. Studies identified germline mutations in the hTR and hTERT components of the telomerase in ~3% of the adults with so-called aplastic anemia [52, 53]. In recent years, scientists have found that some patients suffering with severe aplastic anemia have extremely short telomeres in their blood cells. Telomeres are also known as molecular caps that protect the chromosomes ends from erosion. With each cell division they naturally become shorter, but telomeres can be rebuilt by enzymes. Telomere length is affected by genetic factors and environmental stressors. Patients with short telomeres suffer from morbidity and mortality even after the bone marrow transplant for the aplastic anemia [47, 54]. As these short telomeres lead to organ failures.

Patients with the short telomeres are also at greater risk for a conversion to bone marrow cancer (24%).

## **4.3 Idiopathic pulmonary fibrosis due to telomere shortening**

Idiopathic pulmonary fibrosis has a predictable and progressive clinical course that ultimately leads to respiratory failure [55]. Although both genetic and environmental factors have been implicated, the cause of idiopathic pulmonary fibrosis (IPF) is unknown. IPF is the most common manifestation out of the other telomere-mediated disorders [56]. Germ line mutations in the telomerase hTERT and hTR component genes are the reason behind up to one-sixth of pulmonary fibrosis families [57]. The presence of telomerase mutations is significant. As extra-pulmonary complications, affected individuals can suffer from bone marrow failure and cryptogenic liver cirrhosis due to telomere shortening. Evidence suggests that IPF results from autosomal dominant telomere syndromes. Here with successive generations, the condition evolves from pulmonary fibrosis to a disorder of bone marrow failure. It is perhaps the most devastating of the idiopathic disorders in medicine.

IPF is an age-related disease. From the time of diagnosis, IPF patients live on average 3 years. Several clinical factors are known which are associated with the IPF. Age is the biggest with the great majority are diagnosed after the age of 60. It is also most frequently in males with a nearly 2:1 ratio [58].

### **4.3.1 IPF in dyskeratosis congenita patients**

DC represents a more severe presentation of a spectrum of telomere syndromes where IPF represents an attenuated form [40]. Pulmonary fibrosis in case of bone-marrow failure can be precipitated by pulmonary toxic drugs during of bone marrow transplant. For example, fatal pulmonary fibrosis in DC patients is caused by the alkylating agent busulfan used in myeloablative conditioning regimens [59]. Even without precipitating toxins, pulmonary fibrosis is a significant and under-estimated complication of DC. In some DC patients, pulmonary fibrosis is the major cause of premature mortality in the absence of bone marrow failure [60].

#### *4.3.2 IPF is the most frequent manifestation of telomere-associated disease*

In most cases, IPF is associated with telomere maintenance. Mutations in hTERT and hTR are the risk factors in 8–15% of familial cases of IPF [57, 61]. In about 3% of sporadic IPF cases, mutations in the telomerase genes are also found [53]. Here hTERT mutations frequency is higher than hTR mutations, but the mutant genes cannot be identified based on only clinical features [62]. Short telomeres are sufficient to cause the common form of IPF [63].

The hTERT and hTR mutations result in short telomeres because of the loss of functions and the haploinsufficiency [56]. As compared to DC and aplastic anemia, the prevalence of IPF is more common, lung disease is the most common manifestation of telomere-mediated disorders [64, 65]. Thus, although DC is specific for identifying individuals with telomere-mediated disease, it only can identify only a small subset, i.e. nearly 5% of all cases.

#### *4.3.3 IPF patients with short telomeres without any mutations in telomerase*

Although telomerase mutations are found in one-sixth of the families with IPF, short telomeres are found in other IPF patients without any mutations in the telomerase genes [58]. Significantly shorter telomeres are seen in case of sporadic IPF cases (those who report no family history) [61, 65]. Telomere shortening can be found in immune cells such as lymphocytes, granulocytes and also alveolar epithelial cells, which implicate global telomere defect in such individuals. The observation suggests that individuals with shortest telomeres are more likely to develop IPF than normal individuals in the population [66]. These patients with short telomeres may be a risk factor for disease outside the lung. A subset of sporadic IPF that lack an apparent telomerase mutation also develops cryptogenic liver cirrhosis [57]. There is also relation between IPF and incidence of diabetes. IPF patients have about 3-fold increased incidence of diabetes compared to the age-matched controls [67]. In case of telomerase deficient mice, short telomeres cause defects in insulin secretion resulting in glucose intolerance. Therefore alongside IPF, short telomeres can be a risk factor for diabetes development [68]. Thus in sporadic IPF cases, the defect in telomere length may cause telomere-associated diseases outside of lung.

#### *4.3.4 IPF patients with extra-pulmonary disorders*

IPF patients and their relatives who carry telomerase mutations can develop telomere-mediated diseases, which are extra-pulmonary [57]. These are, bone-marrow failure including macrocytosis of red blood cells, single lineage cytopenias, aplastic anemia, myelodysplastic syndromes, and acute myeloid leukemia [69, 70, 71]. In case of patients without DC, IPF and bone marrow failure are not considered as related conditions. But occurrence of these two together allows clinical identification of families carrying telomerase mutations. A recent finding suggests that germ line defects in telomerase of a single family are associated with the occurrence of these two disorders together [62]. When present in successive generations, both the IPF and bone marrow failure syndrome together predicted the presence of an hTERT or hTR gene mutation in 10 out of 10 families (100%).

Other than the bone marrow failure, IPF patients with telomerase mutations may also develop other complications of telomere-mediated disease like liver cirrhosis [50]. So, the IPF affected individuals are at a higher risk of developing extra-pulmonary diseases.



4.4 Role of telomeres and telomerase in cancer

Short telomeres due to mutations in telomerase have been proposed to be associated with cancer. The concept seems counterintuitive as we know that telomerase activation is a required step for malignancy to occur in nearly 85% of the cases as it allows unlimited cell cycle without senescence. How telomerase reactivation occurs in case of cancer is not clear till date. Studies suggest mutations in two key positions of hTERT promoter region (C250T and C228T) cause enhanced expression of hTERT leading to enhanced telomerase activation (**Table 3**) [72, 73]. But this information needs to be investigated properly. Short telomeres can lead to genomic instability and also cancer via non-homologous end joining (NHEJ) of chromosomes. Mutations in the hTR or hTERT components of telomerase are associated with abnormally short telomeres leading to cancer. Mutations in several components of telomerase such as DKC1, NOP10, NHP2, GAR1 or shelterin components such as TRF1, TRF2, POT1 can lead to short telomeres [30]. Absence or very short telomeres allow non-homologous chromosomes to join head to head. Syndromes associated with short telomeres such as dyskeratosis congenita, aplastic anemia are associated with cancer. It has been found that DC patients are cancer prone. They have increased risk of acute leukemia and myelodysplasia [49]. Aplastic anemia is also associated with acute myeloid leukemia. Patients also have increased risk of squamous cell cancers. Overexpression of TERT is also associated with increased cell proliferation in epidermal tumors and mammary carcinomas in mice [74].

Thus genomic instability due to loss of telomeres and overexpression of telomerase probably play major roles in such cancer development.

Mutations in the hTERT promoter region	Types of cancer	Occurrence (~)
	melanomas	70 %
	glioblastomas	80-90%
	hepatocellular carcinomas	60%
	bladder cancers	60%
	basal cell carcinomas	70%
	cutaneous squamous cell carcinomas	50%
	thyroid cancers	30%
	oligodendrogliomas	72%

**Table 3.**  
*Types of cancers associated with mutations in the telomerase hTERT promoter region.*

5. Conclusion

Cellular aging eventually leads to cell death. It is the progressive decline of cells in resisting stress and other cellular damages. This leads to gradual loss of cellular functions resulting in cell death. Telomere shortening is a major factor that is related with cellular aging. With age, the telomere length declines due to end replication problem,



leading to cell senescence. It poses a barrier to the tumor growth but also results in the loss of cells with aging. When the caps of the chromosomes which are telomeres become critically short, it prevents cell cycle to continue leading to either cell senescence or apoptosis. This cell cycle arrest occurs due to DNA damage proteins such as ATM, which become activated when telomere becomes critically shortened leading to activation of p53 dependent checkpoint. Mutations in the telomere or the telomerase components such as hTR or hTERT result in a broad spectrum of diseases present in children and adults. The onset and severity of these diseases are determined by the extent of telomere shortening. Usually the onset of cancer is associated with the activity of the telomerase holoenzyme, but with reduced telomeres due to affected telomerase, the chromosomes may join by non-homologous end joining (NHEJ) and can lead to malignancy. This study shows that syndromes such as dyskeratosis congenita (DC), idiopathic pulmonary fibrosis (IPF), and aplastic anemia are caused by the telomere shortening. IPF syndrome is the most common manifestation of the telomere shortening. Thus this provides evidence that short telomeres are sufficient to cause common, age-related diseases. Treatment for these diseases involves organ transplantation such as liver, lung, bone marrow. Although this organ transplantation provides improved physical condition for patients, it does not address the actual cause, which is short telomeres. In recent times, telomerase activators such as TA-65 has gained commercial interest. It is also reported that sex hormones activate TERT transcription.

The understanding of the role of telomere and telomerase in aging and some diseases can open new possibilities in understanding the genetic factors that play important role in the origin and augmentation of several other diseases.

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## Conflict of interest


The author declares no conflict of interest.

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