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The short and long telomere syndromes: paired paradigms for molecular medicine

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Recent advances have defined a role for abnormally short telomeres in a broad spectrum of genetic disorders. They include rare conditions such as dyskeratosis congenita as well pulmonary fibrosis and emphysema. Now, there is new evidence that some familial cancers, such as melanoma, are caused by mutations that lengthen telomeres. Here, we examine the significance of these short and long telomere length extremes for understanding the molecular basis of age-related disease and cancer.

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The origins of telomere human genetics

Telomeres and telomerase were first discovered in *Tetrahymena thermophila*, a protozoan of no obvious clinical significance [1,2]. Genetic models in yeast, mice, and human cells subsequently established a framework for how chromosome ends are maintained before disease connections crystallized [3]. Now, abnormally short telomeres are appreciated to mediate common age-related disorders such as pulmonary fibrosis and emphysema [4]. While the connection between short telomeres and degenerative disease may have suggested a hypothetical benefit for long telomeres, new discoveries have uncovered a potential link between *long* telomeres and familial cancer syndromes [5••,6,7]. Here, we review how extreme telomere length abnormalities, both short and long, inform understanding the molecular basis of degenerative disease associated with aging as well as cancer.

Telomere length is a 'molecular clock' mechanism

Telomere shortening is considered one of the best-characterized mechanisms of cellular aging [4]. This claim builds on the fact that telomere length predicts the onset of replicative senescence [8,9]. Telomeres also shorten in humans with age, and in the last decade, it has become clear that abnormally short telomeres recapitulate several premature aging phenotypes [4]. The progressive shortening of the TTAGGG telomeric sequence occurs because DNA polymerases cannot fully copy to chromosome ends [10]. Telomerase offsets this end-replication problem by synthesizing new telomere sequences [2,11,12]. When telomeres become critically short, they activate a DNA damage response [13], which provokes cellular senescence and apoptosis [14–18]; these responses underlie the progressive disease phenotypes seen in disorders that share the short telomere defect as a driving mechanism.

Several safeguards restrict telomere elongation in favor of net shortening with aging. They include a tight regulation of telomerase levels, as well as intrinsic factors at telomeres that limit excessive elongation by telomerase [19–21]. The expression of the reverse transcriptase component of telomerase, TERT, is also repressed in most adult tissues. In hematopoietic as well as other somatic stem cells, even though telomerase is expressed, its low levels do not offset the telomere shortening that normally occurs with aging [19,22–24]. As we will discuss here, genetic defects that disturb this telomere length homeostasis cause highly penetrant disease phenotypes.

The mammalian short telomere phenotype was first studied in telomerase null mice [14,15,25]. While telomerase loss alone has no clinical consequences in the first generation, late-generation telomerase null mice accumulate short telomeres [14,15,18,25,26]. The short telomeres cause degenerative organ failure indicating that the telomere length, and not telomerase loss, is the primary determinant of the phenotype. Late-generation mice with short telomeres develop a stem cell failure phenotype, which is prominent in highly proliferative tissues such as the bone marrow and intestinal tract where stem cell replicative potential is crucial for homeostasis [14,15,18,25,26]. The human short telomere syndromes recapitulate these phenotypes [21,27].

The short telomere syndromes

The human short telomere phenotype in high turnover tissues

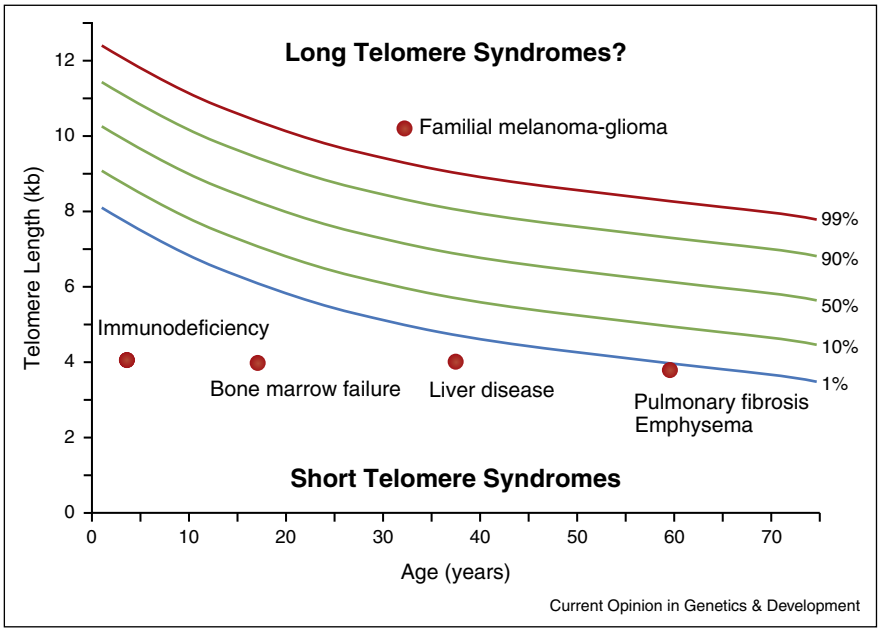
Studies over the last decade have linked the human short telomere phenotype to a broad spectrum of disease [21]; it varies in severity and spans the entire age spectrum from infancy to adulthood (Figure 1). While at onset their clinical and histopathologic classification alone may show few shared features, a growing appreciation for their genetics has highlighted a unified natural history [28]. Their recognition as a single syndromic spectrum is crucial for treatment decisions, because even though a single organ presentation may arise initially, the systemic telomere defect complicates treatment. Because some of these complications can be averted, the molecular grouping of disease across organs under the short telomere syndrome umbrella exemplifies a molecular medicine paradigm that has directly advanced patient care [27,29••,30••].

The short telomere phenotype in children and young adults represents more severe disease [4]. Bone marrow failure is its most common first manifestation, and stem cell transplantation alleviates this condition pointing to a stem cell-autonomous defect in this compartment [21,31–34]. Affected individuals are also prone to developing intestinal villous atrophy, immunodeficiency and infertility [21,27,35]. Pediatric presentations may also be recognized in historically defined syndromic entities. Dyskeratosis congenita was the first disorder to be linked to telomerase mutations and short telomeres [36,37]; it is classically defined by abnormalities in the skin, mucosa and nails [38,39]. Hoyeraal–Hreidarsson syndrome manifests in infancy and is characterized by developmental delay, enterocolitis, and immunodeficiency [27,40–42]. The criteria for recognizing Hoyeraal–Hreidarsson syndrome and dyskeratosis congenita may be specific; but they identify only a small subset of all short telomere syndrome presentations [43].

The slow turnover phenotype in short telomere syndromes

Lung disease is the most common presentation of short telomere syndromes and it represents an attenuated, adult-onset phenotype (Figure 1) [43]. Two types of lung disease have been linked to mutant telomerase and telomere genes. Idiopathic pulmonary fibrosis and the related interstitial diseases are marked by progressive lung scarring. Familial pulmonary fibrosis is a common manifestation of short telomere syndromes [43], and mutant telomere genes explain one third of all cases [44–46,47••,48••,49]. Telomerase mutations have also been recently linked to the risk of emphysema [50••]. The frequency of telomerase mutations in severe emphysema rivals alpha-1 antitrypsin deficiency, which until recently was its only known Mendelian cause [50••]. In families with telomerase mutations, emphysema appears in smokers, while pulmonary fibrosis is the predominant pathology in never smokers [50••]. This apparent phenotypic heterogeneity points to a profound

Figure 1



Telomere length extremes and their predominant clinical manifestations. Telogram showing the decreasing telomere length range across the age spectrum with percentile lines defining the normal range at every age. The short telomere syndromes have typical manifestations that are represented by the red circles at the typical age of onset. Familial melanoma and glioma have been linked to mutations that putatively cause long telomeres.