

Telomeres in dyskeratosis congenita

Jerry W Shay & Woodring E Wright

A new study shows that 'anticipation' occurs in the autosomal dominant form of dyskeratosis congenita and is due to inheritance of short telomeres and mutations in *TERC* (encoding telomerase RNA).

The diagnostic features of dyskeratosis congenita are nail dystrophy, abnormal skin pigmentation and mucosal leukoplakia¹. Bone marrow failure and pulmonary complications are the primary cause of death. There are multiple patterns of inheritance, and the autosomal dominant form (AD-DC) generally has a later age of onset. The X-linked form is due to mutations in the gene encoding dyskerin, which is involved in processing the template RNA component of telomerase (*TERC*). Individuals with X-linked dyskeratosis congenita have low levels of *TERC* (and less telomerase activity). Direct experimental evidence that dyskeratosis congenita is due to dysfunction of telomere maintenance comes from the observation that deletion or mutation of *TERC* itself is associated with AD-DC. It is thought that haploinsufficiency can cause dyskeratosis congenita (e.g., when one copy of *TERC* is mutated to an unstable form, it produces cells having less *TERC* and thus less telomerase activity to maintain highly proliferative stem-like cells)¹⁻⁵. Because the telomerase RNP enzyme may be a functional dimer, mutations in one *TERC* allele may also result in a greater overall impact on telomerase activity by a dominant negative effect.

On page 447 of this issue, Tom Vulliamy and colleagues report³ disease anticipation (the onset of disease occurs at progressively younger ages in successive generations) in eight families with AD-DC, and this correlates with progressive telomere shortening in later generations (Fig. 1). Siblings that did not inherit a mutated copy of *TERC* did not have

early-onset symptoms even though they inherited shorter telomeres from the affected parent. Thus, individuals with dyskeratosis congenita must both inherit short telomeres and be heterozygous with respect to *TERC* (*TERC*^{+/-}) to show anticipation. This is a new mechanism of disease anticipation. Instead of amplification of triplet repeats, as occurs in neurodegenerative disorders, there is a reduction of telomere repeats in dyskeratosis congenita.

Repeat inheritance

The results of these new studies show that individuals with AD-DC in later generations

inherit a set of chromosomes with short telomeres from the parent who carried the *TERC* mutation and that this is sufficient to cause anticipation. Studies in the telomerase-knockout mouse previously indicated that this could occur. Heterozygous mice derived from crossing *TERC*^{+/+} and *TERC*^{-/-} mice did not fully elongate the shorter telomeres⁶. This suggests that haploinsufficiency with respect to *TERC* may reduce telomerase activity enough that telomeres cannot be fully elongated in one generation.

Reports based on twin studies show that telomere length is familial^{7,8}. In one recent

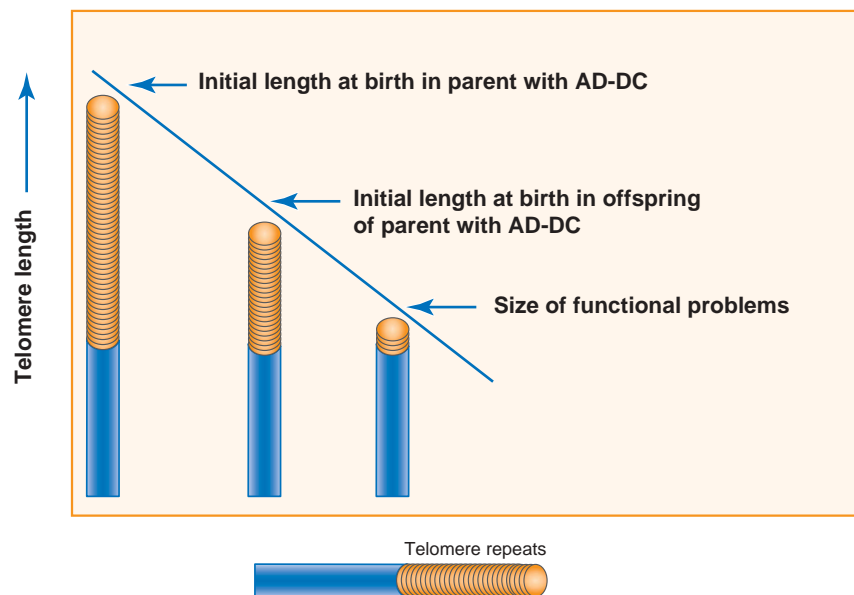


Figure 1 In humans, telomeres progressively shorten with increased age. A parent with AD-DC provides all his children with shorter telomeres. But only children who inherit both the shorter telomeres and a *TERC* mutation will have accelerated disease. It is not yet known whether children who inherit shorter telomeres without the *TERC* mutation develop any symptoms very late in life due to normal age-associated telomere shortening.

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study telomere length was linked to the X chromosome⁹. The investigators found a correlation in telomere lengths of fathers and daughters and of mothers and daughters or sons but not of fathers and sons. Perhaps polymorphisms in the gene associated with dyskeratosis congenita on the X chromosome influence telomere maintenance. Thus, the X chromosome would influence telomere length heritability in a manner analogous to the anticipation phenomenon described by Vulliamy *et al.*³.

Several correlative studies support the idea that individuals with telomeres shorter than those of age-matched controls are prone to disease. For example, individuals with atherosclerotic heart disease have significantly shorter telomeres than healthy aged-matched controls¹⁰. Independent of age and mean arterial pressure, arterial stiffness and pulse pressure inversely correlate with TRF length in men¹¹. In a retrospective study of archival cryopreserved white blood cells, telomere length was a primary independent predictor of overall mortality. In this study, mortality due to infectious disease was eight times greater in individuals (over the age of 60 y) whose blood-cell telomere length was in the lowest quartile (shortest telomeres) than in individuals whose telomeres were in the other quartiles¹². Vulliamy *et al.*³ show that genetically inherited short telomeres in dyskeratosis congenita cause anticipation of disease. This supports the hypothesis that short telomeres due to a variety

of causes (increased in cell turnover associated with chronic age-associated diseases, inflammatory processes, oxidative damage, genetic alterations in telomerase components) correlate with disease. Showing cause and effect will require showing that slowing down the rate of telomere loss or resetting the telomere clock reverses or delays the onset of disease¹³.

Because telomerase RNA is limiting *in vivo* in dyskeratosis congenita and telomeres are not maintained to age-appropriate lengths, is dyskeratosis congenita the perfect disease to test the therapeutic value of telomere rejuvenation?

Treatment options

One approach to test if telomere rejuvenation could affect the progression of disease in dyskeratosis congenita would be to isolate hematopoietic stem cells (CD34⁺) from individuals with dyskeratosis congenita, expand them in the laboratory while transiently overexpressing the catalytic protein (TERT) component of telomerase (perhaps using adenoviral TERT that does not integrate into nuclear DNA) until telomeres become sufficiently elongated, and then return the rejuvenated stem-like cells to the affected individual. The obvious advantage of this approach is that these are the person's own cells, which would avoid problems of rejection. In addition, this could be done without ablating the person's own bone marrow cells (skewing of X-chromosome inactivation in

women carrying the X-linked form of dyskeratosis congenita shows that progressive overgrowth of cells with longer telomeres is likely to occur). The ectopic expression of TERT may be sufficient to maintain or elongate telomeres in a wide variety of cells^{14,15}. Safety and efficacy standards, as well as quality and control assurances, will need to be carefully considered before initiating such studies. But if this strategy for engineering telomeres in cells improves the health and longevity of individuals with dyskeratosis congenita, then it could be considered for treatment of other telomere-based proliferative deficiencies produced by disease or aging.

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The spreading influence of chromatin modification

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Specific post-translational histone modifications correlate with distinct patterns of gene activity. A new study of the mouse *Dntt* promoter shows that changes in gene activity are associated with local changes in histone modification that then spread outward in both directions, locking in the altered pattern of transcription.

The mouse genome consists of about 3 billion bp of DNA divided into 20 chromosomes. Stretched out, this DNA would measure nearly a meter in length, but it all fits into a spherical nucleus only several microns in diameter. It is a challenge to understand how the genome can be wrapped so tightly yet remain accessible for precisely regulated gene

expression. Meeting this challenge will require a detailed appreciation of the dynamics of chromatin structure. On page 502 of this issue, a new study by Ruey-Chyi Su and colleagues¹ illustrates how localized changes in chromatin structure influence the regulated expression of a specific gene during mouse lymphocyte development.

Chromatin represses transcription

The most basic element of chromatin structure, the nucleosome, consists of an octamer of histones forming a central core and 146 bp of DNA wrapped nearly twice around it².

Successive nucleosomes are separated by 20–60 bp of DNA, often associated with a linker histone called H1. This 11-nM nucleosome fiber is then wrapped into a 30-nM solenoidal structure. Our understanding of this, and subsequent higher orders of chromatin structure, is rudimentary.

Chromatin structure is a substantial barrier to the transcription machinery. Basal transcription factors, including the essential TFIID complex and RNA polymerase II, cannot recognize promoter sequences packaged in a nucleosome array³. Two processes cooperate to clear the way for gene activation⁴. The

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