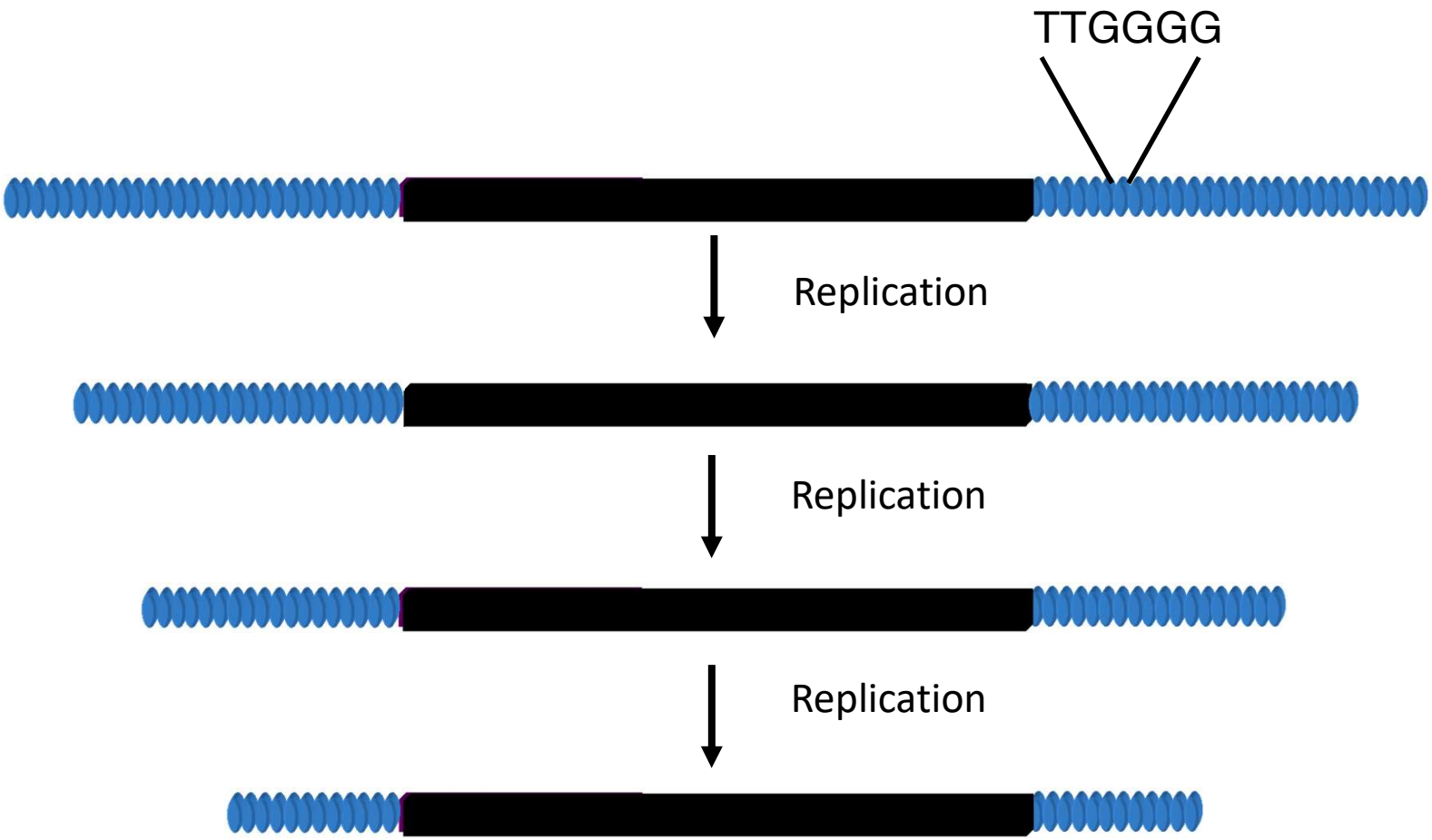
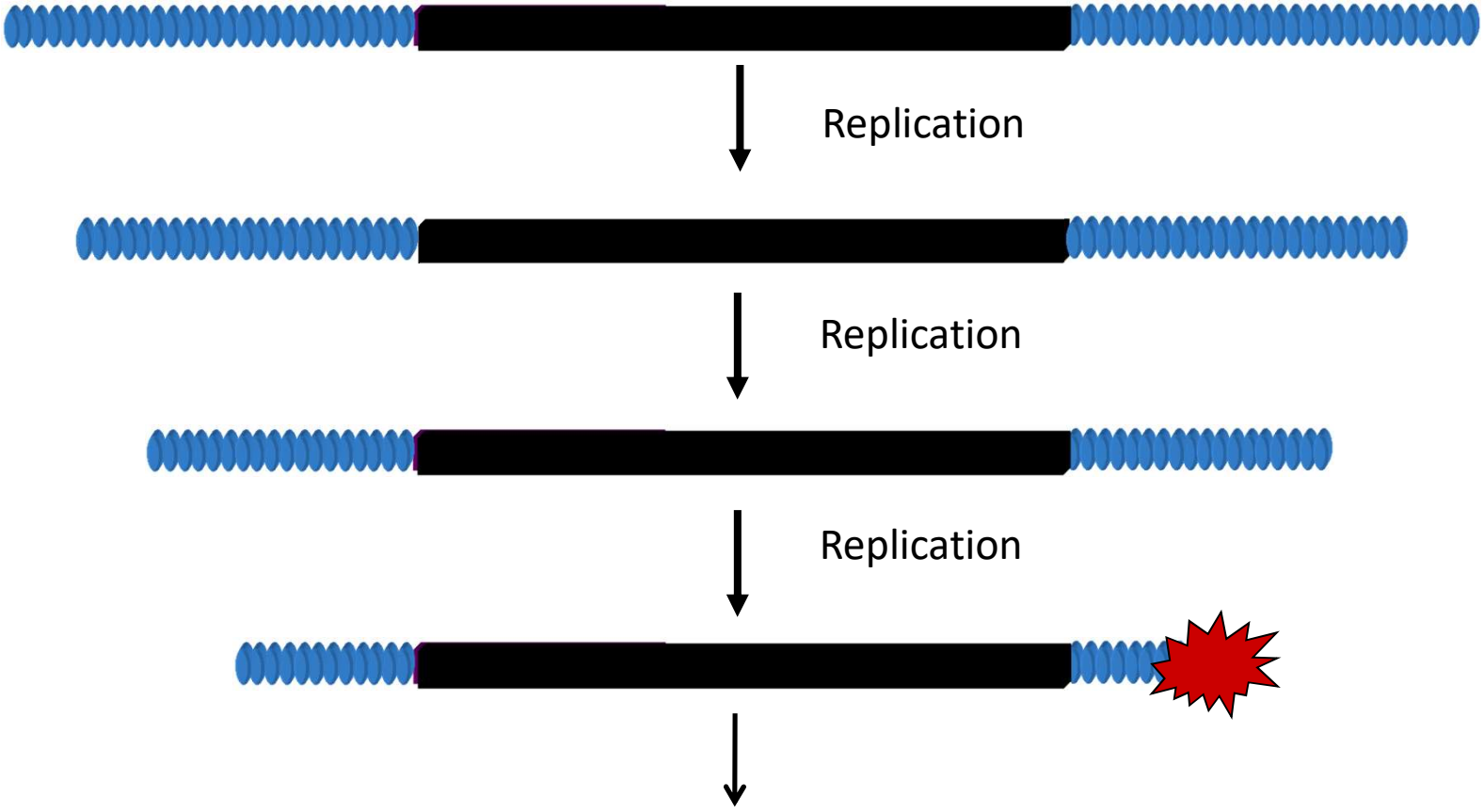
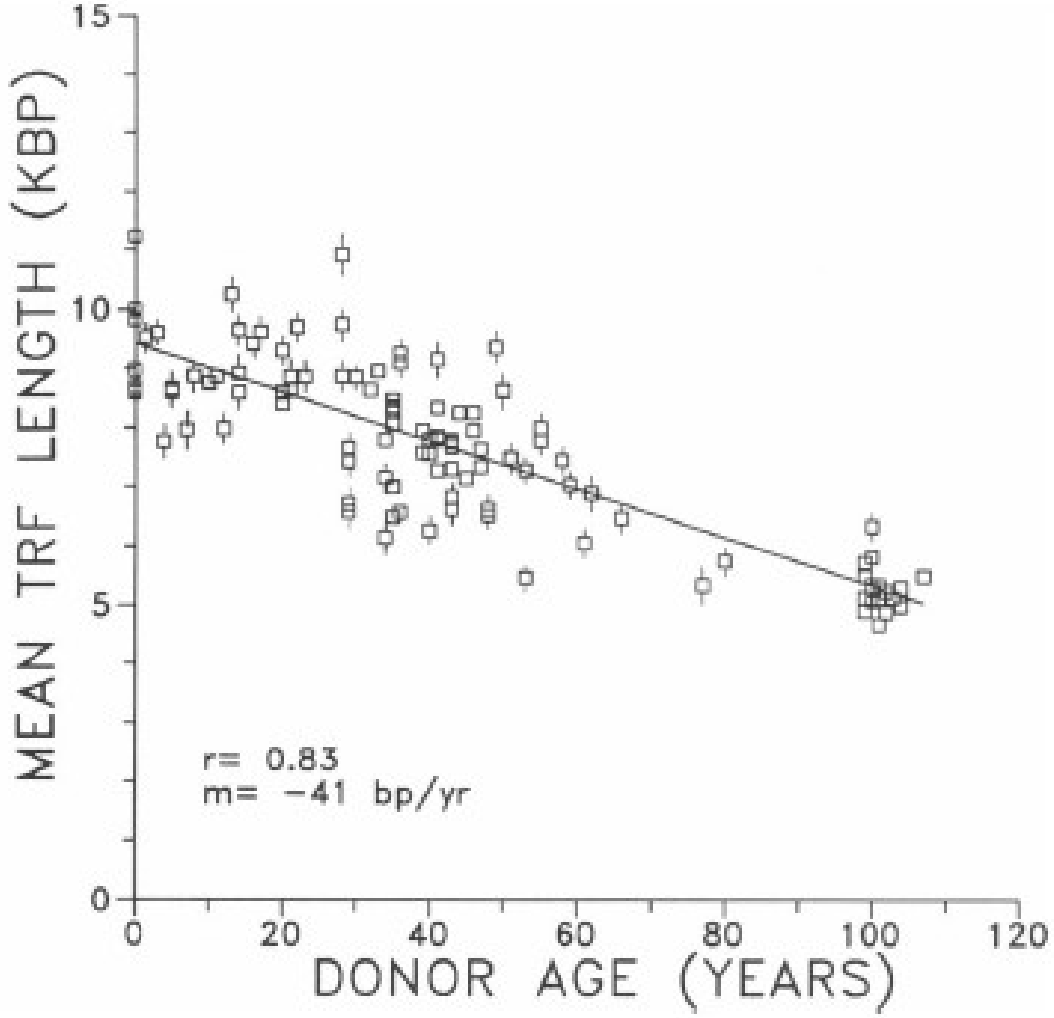
Telomeres shorten as cells divide



Telomere shortening leads to cell death



Telomeres shorten with age



Telomerase is limiting in cells

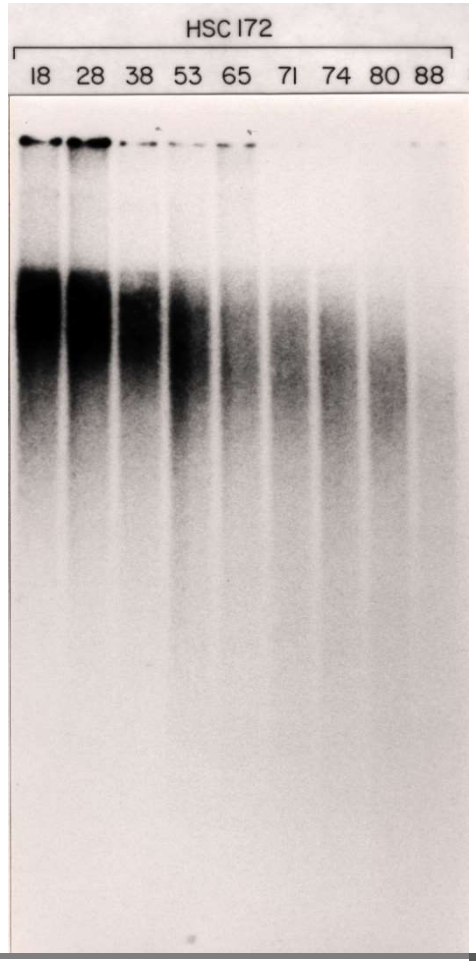
Vaziri et al. *AJHG* (1995)

Telomere shortening in cellular senescence

Telomeres shorten during ageing of human fibroblasts

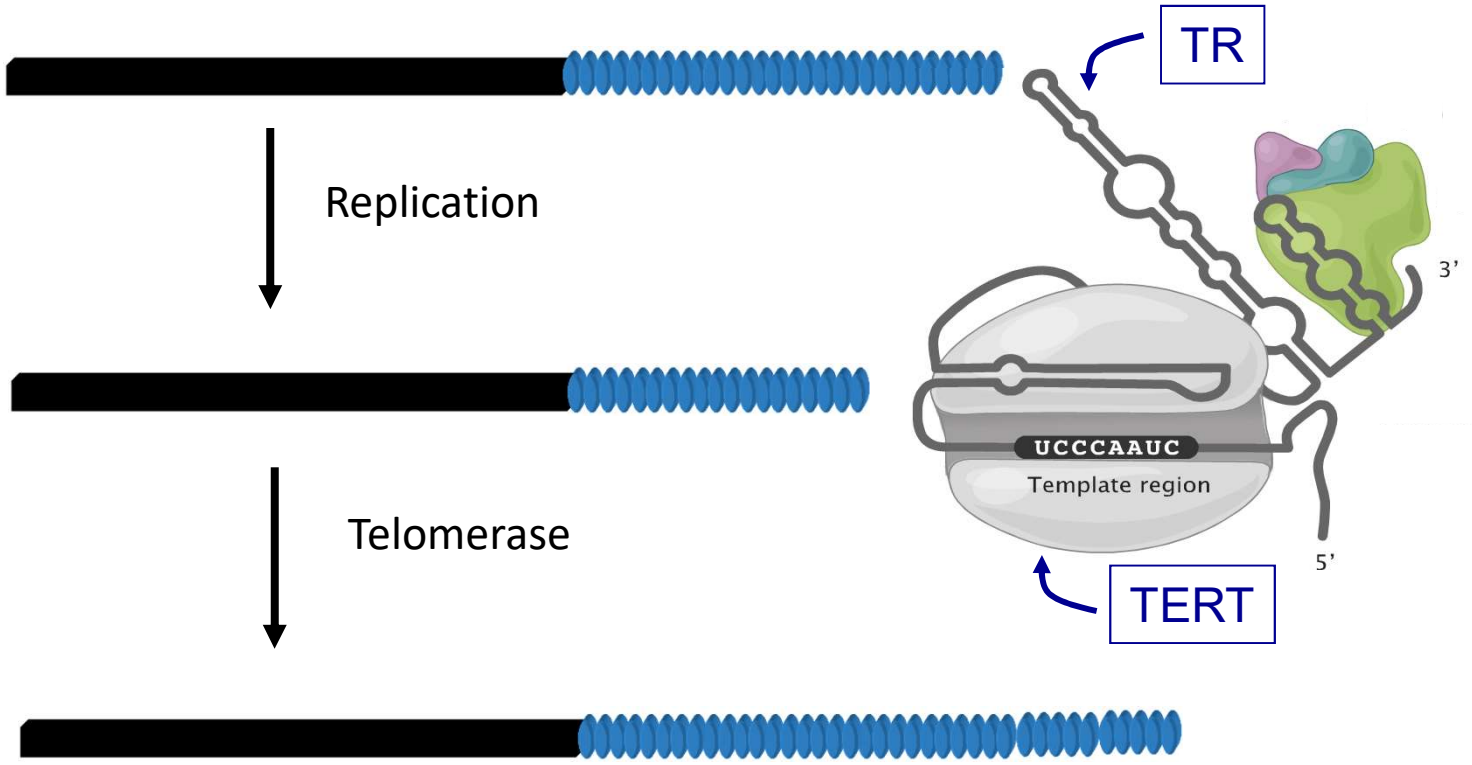
Calvin B. Harley*, A. Bruce Futcher† & Carol W. Greider†

* Department of Biochemistry, McMaster University, 1200 Main Street West, Hamilton, Ontario L8N 3Z5, Canada
† Cold Spring Harbor Laboratory, Cold Spring Harbor, New York 11724, USA



Nature May 1990

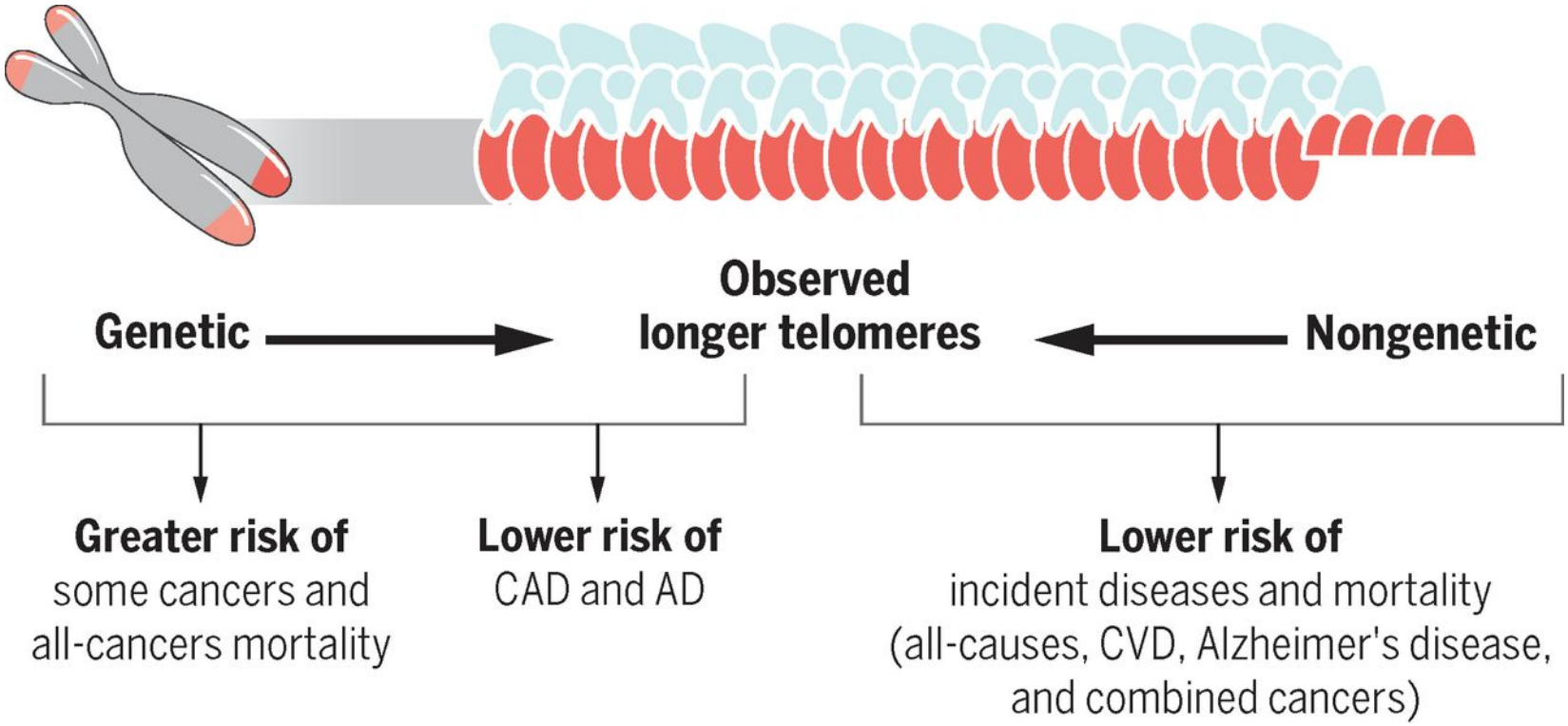
Telomerase allows telomere length equilibrium maintenance



In somatic cells, telomeres shorten with each division (a phenomenon termed the end-replication problem) to a minimal threshold of telomere length known as the Hayflick Limit.
Once this threshold is breached, telomeres lose their protective capacity resulting in two critical outcomes [1].
Either the cell detects the threat posed by such shortened telomeres, resulting in the initiation of a p53 dependent signaling cascade that induces replicative senescence, a state of permanent cell growth arrest

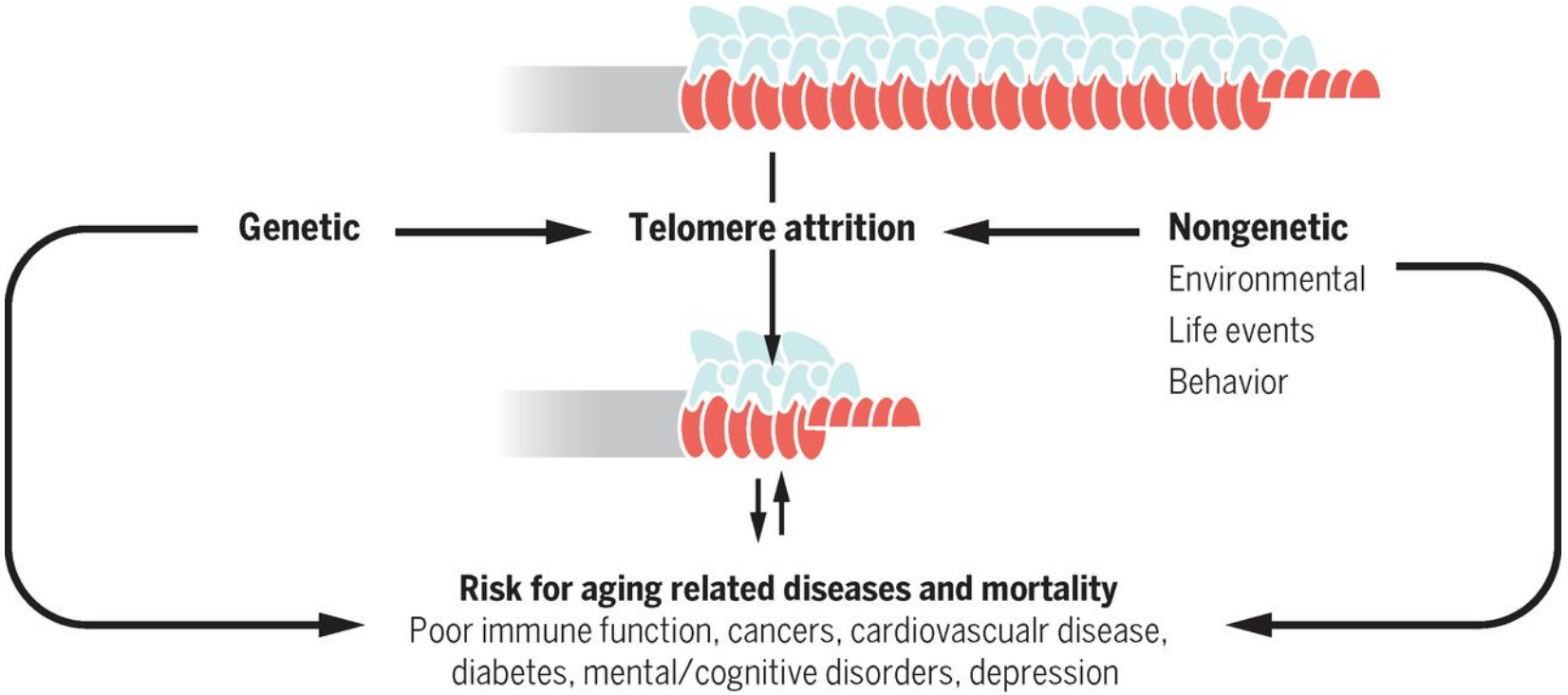
If the cell continues to proliferate, telomere shortening will eventually kill the cell at crisis

Different inputs to telomere maintenance have disease-specific consequences.



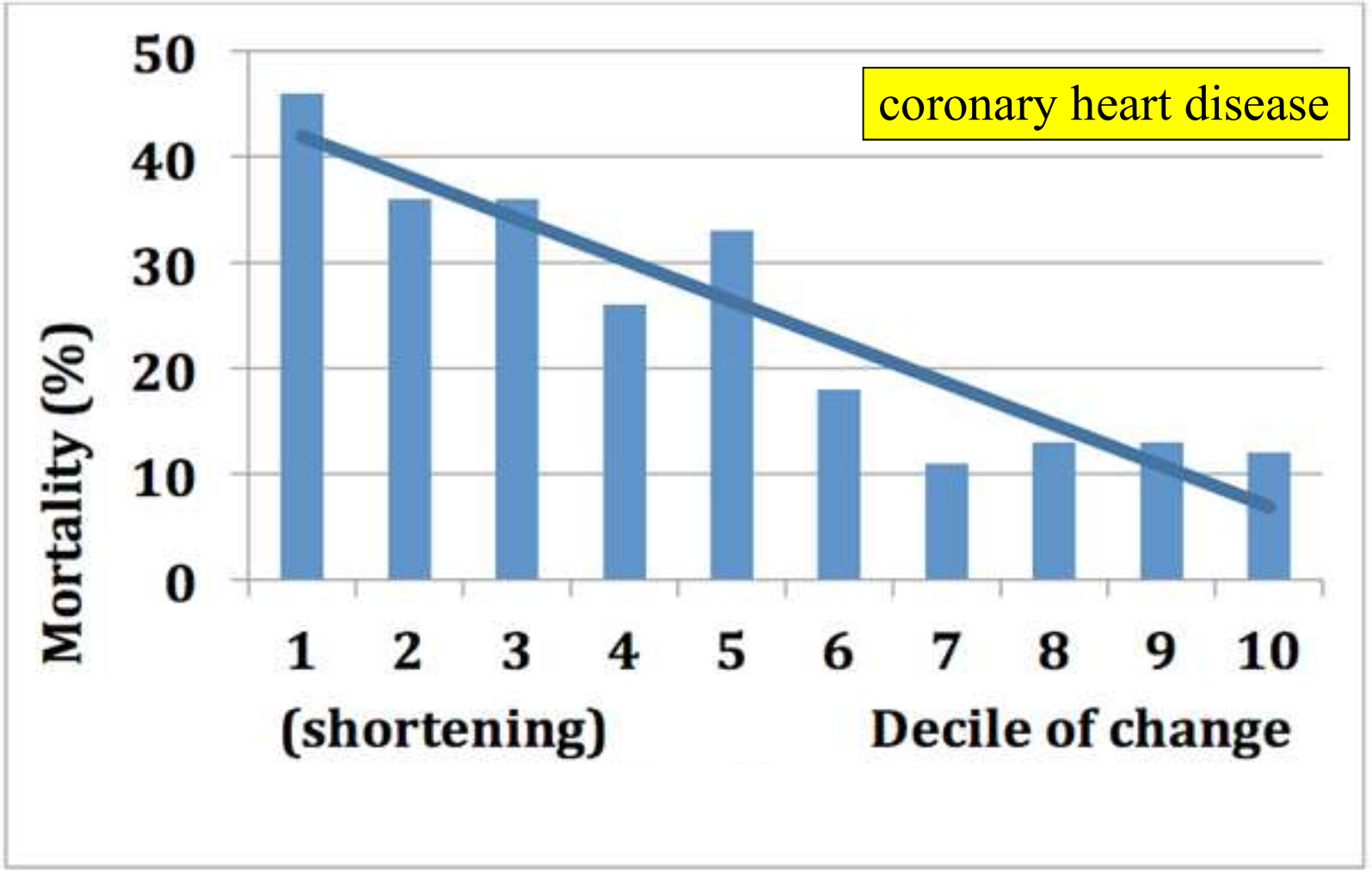
Elizabeth H. Blackburn et al. Science 2015;350:1193-1198

Relationship of telomere attrition to human aging-related diseases.



Elizabeth H. Blackburn et al. Science 2015;350:1193-1198

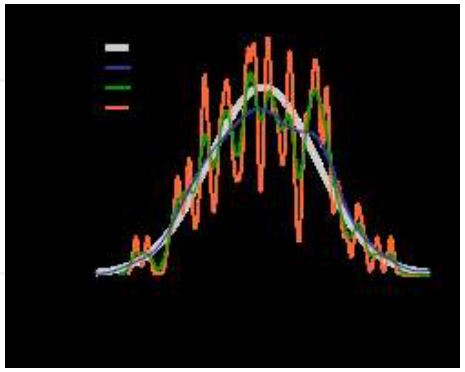
Fig 1. Mortality by decile of 5-year change in telomere length (p for trend <0.001).



Goglin SE, Farzaneh-Far R, Epel ES, Lin J, Blackburn EH, et al. (2016) Change in Leukocyte Telomere Length Predicts Mortality in Patients with Stable Coronary Heart Disease from the Heart and Soul Study. PLoS ONE 11(10): e0160748. doi:10.1371/journal.pone.0160748
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0160748

Distribution of telomere length by exclusive breastfeeding status at 4–6 wk of age

The American Journal of Clinical Nutrition



kdensity, kernel density

Janet M Wojcicki et al. Am J Clin Nutr 2016;104:397-405

MUTAZIONII nei geni dei complessi dei TELOMERI

Technology Corporation for support. This work was also funded in part by the Ralph Hochstetter Medical Research Fund.

Correspondence and requests for materials should be addressed to F.S. (e-mail: sachs@buffalo.edu).

The RNA component of telomerase is mutated in autosomal dominant dyskeratosis congenita

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† Department of Pediatrics, The University of Iowa Hospitals and Clinics, Iowa City, Iowa 52242-1083, USA
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Dyskeratosis congenita is a progressive bone-marrow failure syndrome that is characterized by abnormal skin pigmentation, leukoplakia and nail dystrophy[1,2]. X-linked, autosomal recessive and autosomal dominant inheritance have been found in different pedigrees. The X-linked form of the disease is due to mutations in the gene *DKC1* in band 2, sub-band 8 of the long arm of the X chromosome (ref. 3). The affected protein, dyskerin, is a nucleolar protein that is found associated with the H/ACA class of small nucleolar RNAs and is involved in pseudo-uridylation of specific residues of ribosomal RNA[4]. Dyskerin is also associated with telomerase RNA (hTR)[5], which contains a H/ACA consensus sequence[6,7]. Here we map the gene responsible for dyskeratosis congenita in a large pedigree with autosomal dominant inheritance. Affected members of this family have an 821-base-pair deletion on chromosome 3q that removes the 3′ 74 bases of hTR. Mutations in hTR were found in two other families with autosomal dominant dyskeratosis congenita.

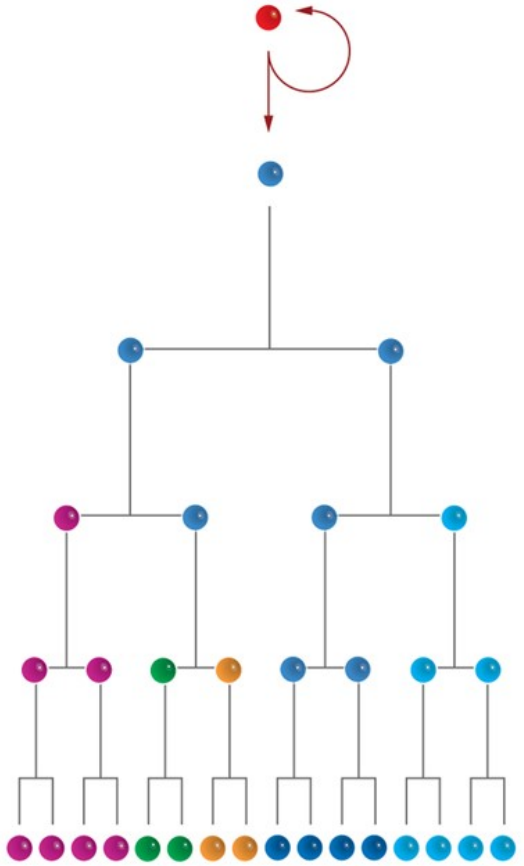
Three other proteins, GAR1, NHP2 and NOP10, are known to be present along with dyskerin in the nucleolar ribonucleoprotein complex and in the telomerase complex[5,8,9]. Telomerase is an RNA–protein complex that is essential for maintaining the nucleoprotein caps at the ends (telomeres) of eukaryotic chromosomes[10,11]. The principal components of telomerase are hTR[6] and a specialized reverse transcriptase (hTERT)[12]. Dyskeratosis congenita is a multisystem disease that affects tissues such as skin, gut and bone marrow, all of which require constant renewal that is dependent on stem-cell activity, and thus may be due to a defect in stem-cell turn over or proliferative capacity[2,13]. Defects in rRNA synthesis and/or in telomere maintenance might affect stem-cell function[14]. Dyskeratosis congenita patients have markedly shorter telomeres than normal individuals and this is apparent from an early age[15]. The relative importance of rRNA processing and telomere maintenance in the pathophysiology of dyskeratosis congenita may be clarified by the nature of the genetic loci causing the autosomal form(s) of the disease. Our finding of mutations in the telomerase RNA component (hTR) in three separate autosomal dominant pedigrees suggests that dyskeratosis congenita is due to defective telomerase activity.

Among the families on the dyskeratosis congenita registry at the Hammersmith Hospital is a large family from Iowa, USA, with a mild form of dyskeratosis congenita and a[illegible] inheritance (DCR101; see Supplementary Info

Nature 2001

Dyskeratosis congentia causes bone marrow failure

- Skin and nail problems
  - Skin hyperpigmentation
  - Rashes
  - Abnormal nail growth
- Mortality
  - Bone marrow failure
  - Cancer
  - other?



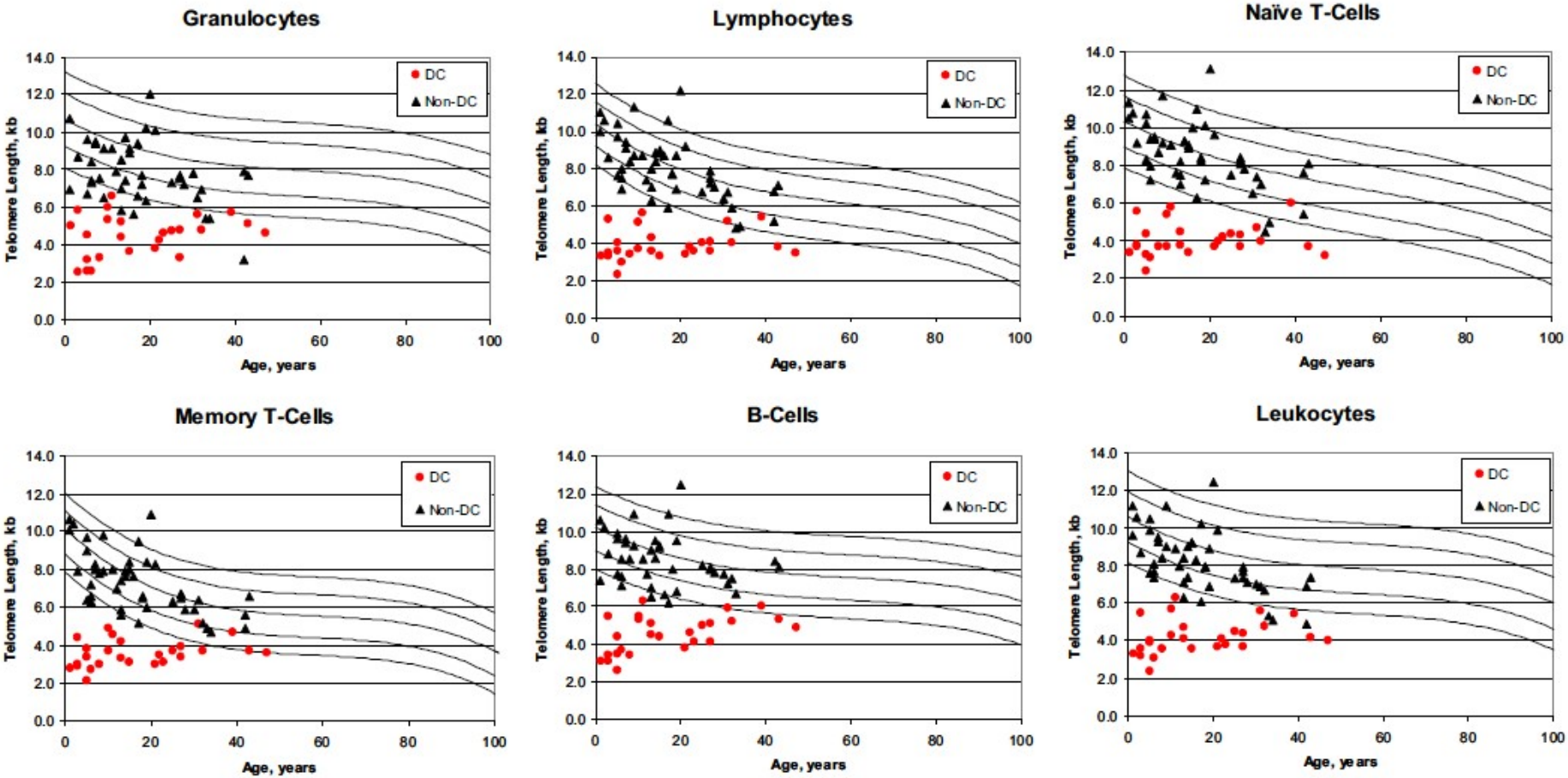


Figure 3. Telomere length according to age in dyskeratosis congenita and non–dyskeratosis congenita patients. The vertical axis represents telomere length ir kilobytes. Lines in the figures indicate the first, tenth, 50th, 90th, and 99th percentiles of results from 400 normal control subjects. Symbols represent subjects: 26 patients with dyskeratosis congenita (red solid circle), 46 non–dyskeratosis congenita patients (black solid triangle).

Short telomeres in lung disease

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Telomerase Mutations in Families with Idiopathic Pulmonary Fibrosis

Mary Y. Armanios, M.D., Julian J.-L. Chen, Ph.D., Joy D. Cogan, Ph.D., Jonathan K. Alder, B.A., Roxann G. Ingersoll, B.S., Cheryl Markin, B.S., William E. Lawson, M.D., Mingyi Xie, B.S., Irma Vulto, B.S., John A. Phillips III, M.D., Peter M. Lansdorp, M.D., Ph.D., Carol W. Greider, Ph.D., and James E. Loyd, M.D.

ABSTRACT

BACKGROUND

Idiopathic pulmonary fibrosis is progressive and often fatal; causes of familial clustering of the disease are unknown. Germ-line mutations in the genes *hTERT* and *hTR*, encoding telomerase reverse transcriptase and telomerase RNA, respectively, cause autosomal dominant dyskeratosis congenita, a rare hereditary disorder associated with premature death from aplastic anemia and pulmonary fibrosis.

METHODS

To test the hypothesis that familial idiopathic pulmonary fibrosis may be caused by short telomeres, we screened 73 probands from the Vanderbilt Familial Pulmonary Fibrosis Registry for mutations in *hTERT* and *hTR*.

RESULTS

Six probands (8%) had heterozygous mutations in *hTERT* or *hTR*; mutant telomerase resulted in short telomeres. Asymptomatic subjects with mutant telomerase also had

From the Department of Oncology (M.Y.A., C.W.G.), the Graduate Program in Cellular and Molecular Medicine (J.K.A.), the Institute of Genetic Medicine (R.G.I.), and the Department of Molecular Biology and Genetics (C.W.G.), Johns Hopkins University School of Medicine, Baltimore; the Department of Chemistry and Biochemistry (J.J.-L.C., M.X.) and the School of Life Sciences (J.J.-L.C.), Arizona State University, Tempe; the Departments of Pediatrics (J.D.C., J.A.P.) and Medicine (C.M., W.E.L., J.E.L.), Vanderbilt University School of Medicine, Nashville; the Veterans Affairs Medical Center, Nashville (W.E.L.); and the Terry Fox Laboratory (I.V., P.M.L.) and the British Columbia Cancer Agency and the Department of Medicine (P.M.L.), University of British C
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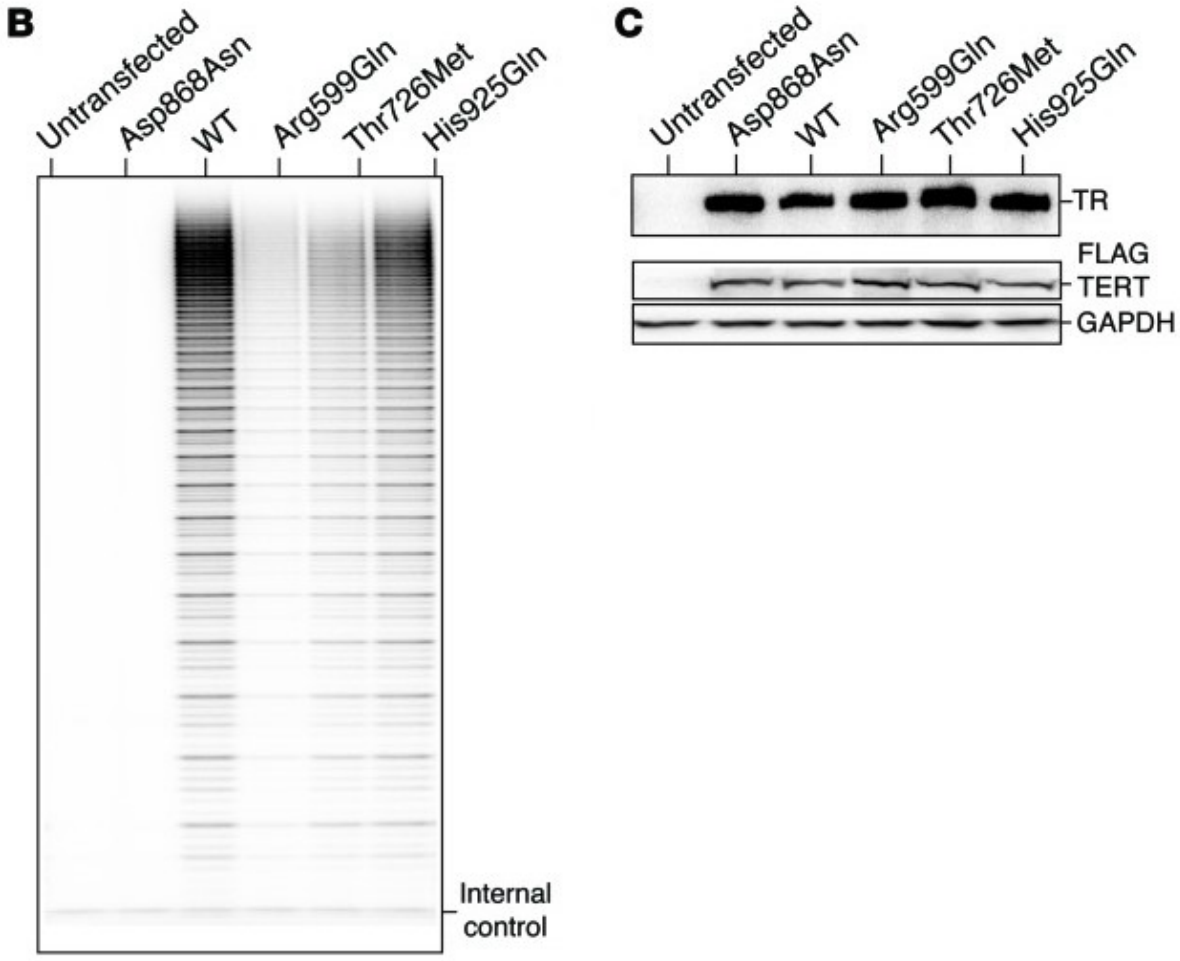
NEJM 357 p1317 (2007)

SUMMARY POINTS

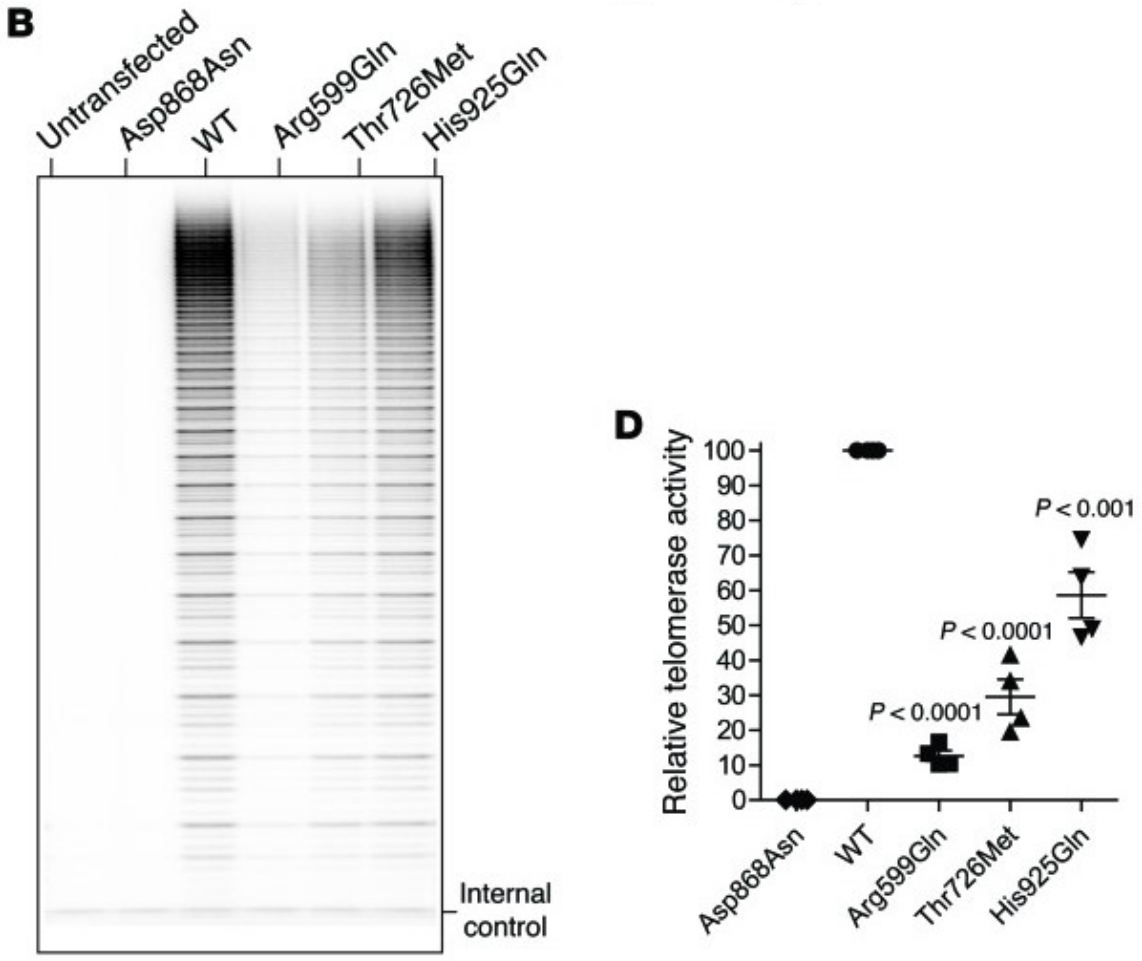
1. Mutations in telomerase and telomere components lead to a broad spectrum of disease that has clinical presentations in children and adults. The extent of telomere shortening determines the onset and severity of these disorders.
2. The study of families with mutations in telomerase components allows the identification of a distinct disease entity marked by organ failure in the bone marrow and a clustering of pulmonary and liver fibrosis. This syndrome frequently appears in adulthood and is distinct from DC, though it falls on the same spectrum.
3. IPF is the most common manifestation of a syndrome of telomere shortening. The causal role implicating short telomeres in IPF provides evidence that short telomeres are sufficient to cause common, age-related disease with its most common manifestation in the lung.
4. Syndromes of telomere shortening are unique among progeroid disorders in that they phenocopy a process that occurs in humans as they age.

Mutations in TERT and TR cause familial pulmonary fibrosis



smokers with chronic obstructive pulmonary disease (COPD).

Mutations in TERT and TR cause familial pulmonary fibrosis



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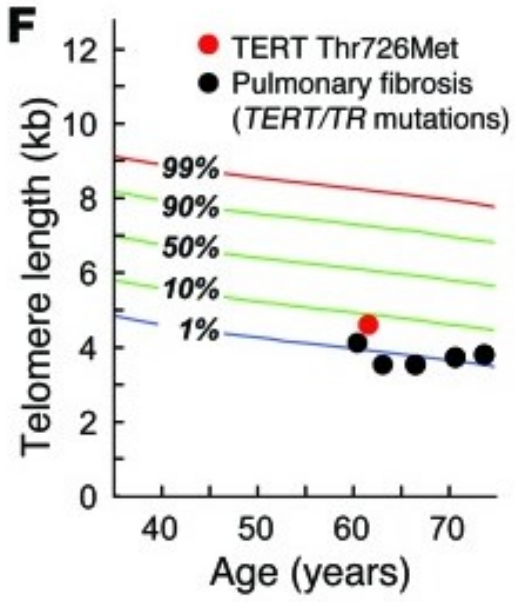


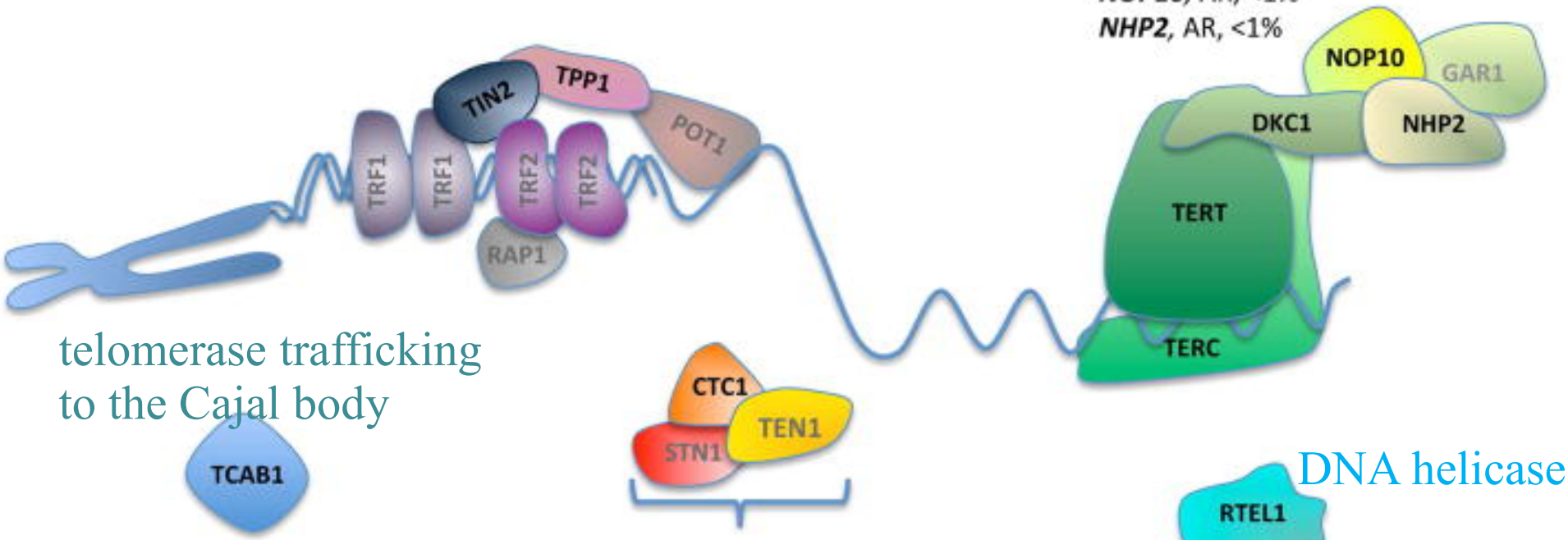
Lymphocyte telomere length by flow cytometry and FISH

Shelterin Complex
Telomerase regulation
Telomere protection

TINF2 (TIN2), AD, 20%
ACD (TPP1), AD/AR, 1%

Telomerase Complex
Telomere elongation

DKC1 (Dyskerin), XLR, 22%
TERC, AD, 6%
TERT, AD & AR, 11%
NOP10, AR, <1%
NHP2, AR, <1%



telomerase trafficking
to the Cajal body

TCAB1

Telomerase trafficking

WRAP53 (TCAB1), AR, 3%

CST complex
Telomerase regulation
Telomere C-strand replication

CTC1, AR,
DC 1-5%
Coats plus syndrome 92%

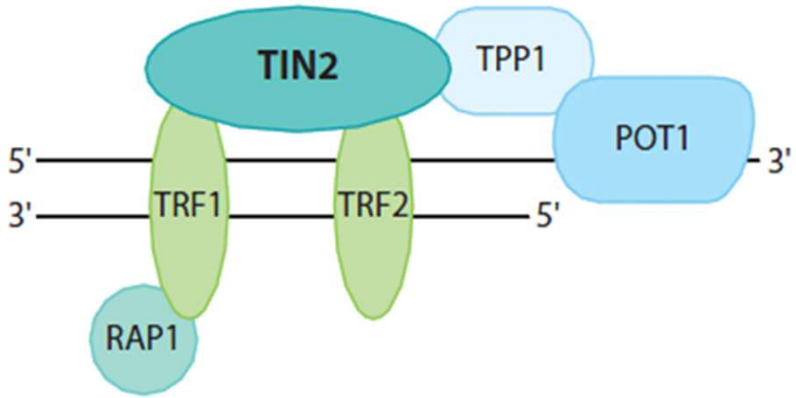
DNA helicase

Telomere stability &
DNA replication /repair

RTEL1, AR & AD, 8%

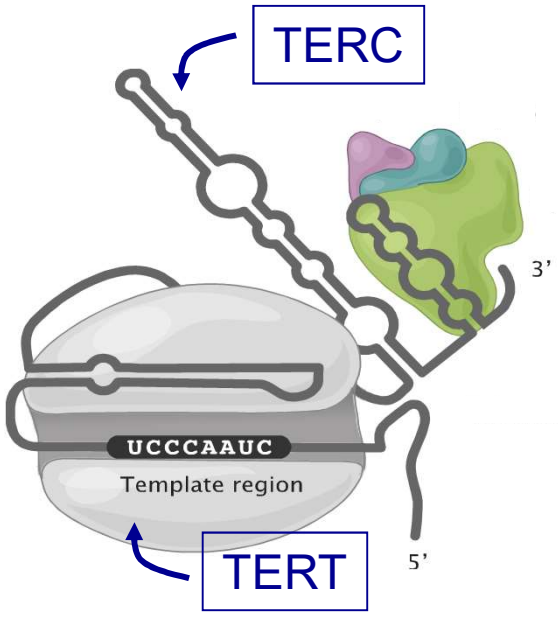
MUTATIONS IN TELOMERIC PROTEINS AND CANCER

Protein	Cancer(s)
Shelterin	
TRF1/TRF2	Gastric
POT1	Leukemia (CLL) Melanoma Glioma
TPP1	DC Melanoma
TIN2	DC
RAP1	Melanoma

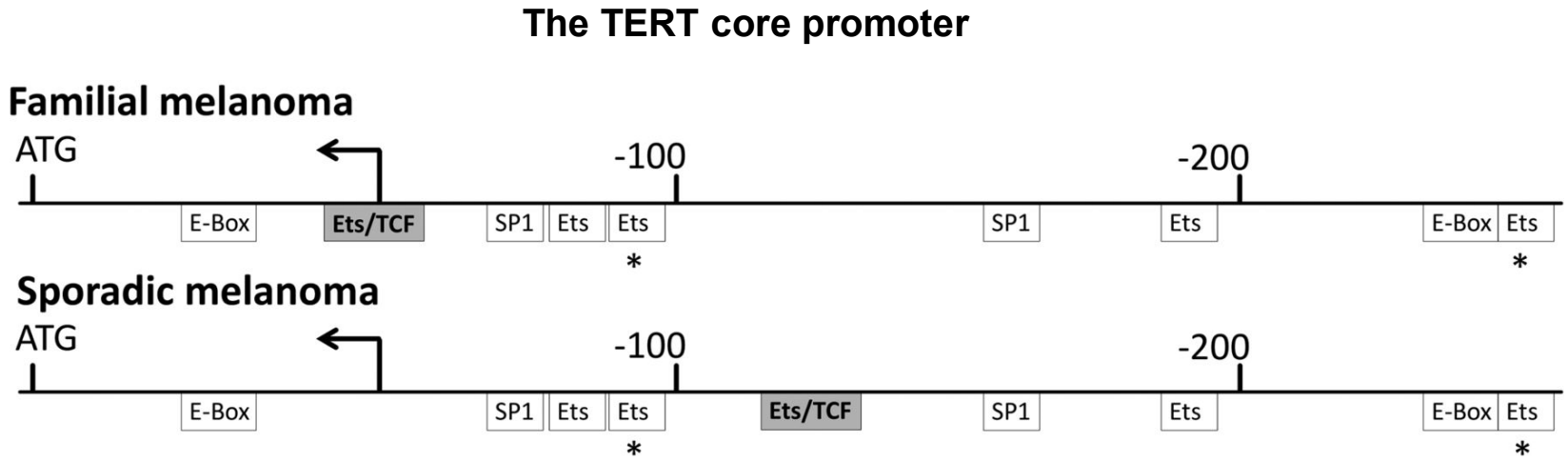


MUTATIONS IN TELOMERIC PROTEINS AND CANCER

Protein	Cancer(s)
Shelterin	
TRF1/TRF2	Gastric
POT1	Leukemia (CLL) Melanoma Glioma
TPP1	DC Melanoma
TIN2	DC
RAP1	Melanoma
Telomere elongation	
TERT	Glioma Bladder Thyroid Melanoma Breast/ovarian
TERC	MDS



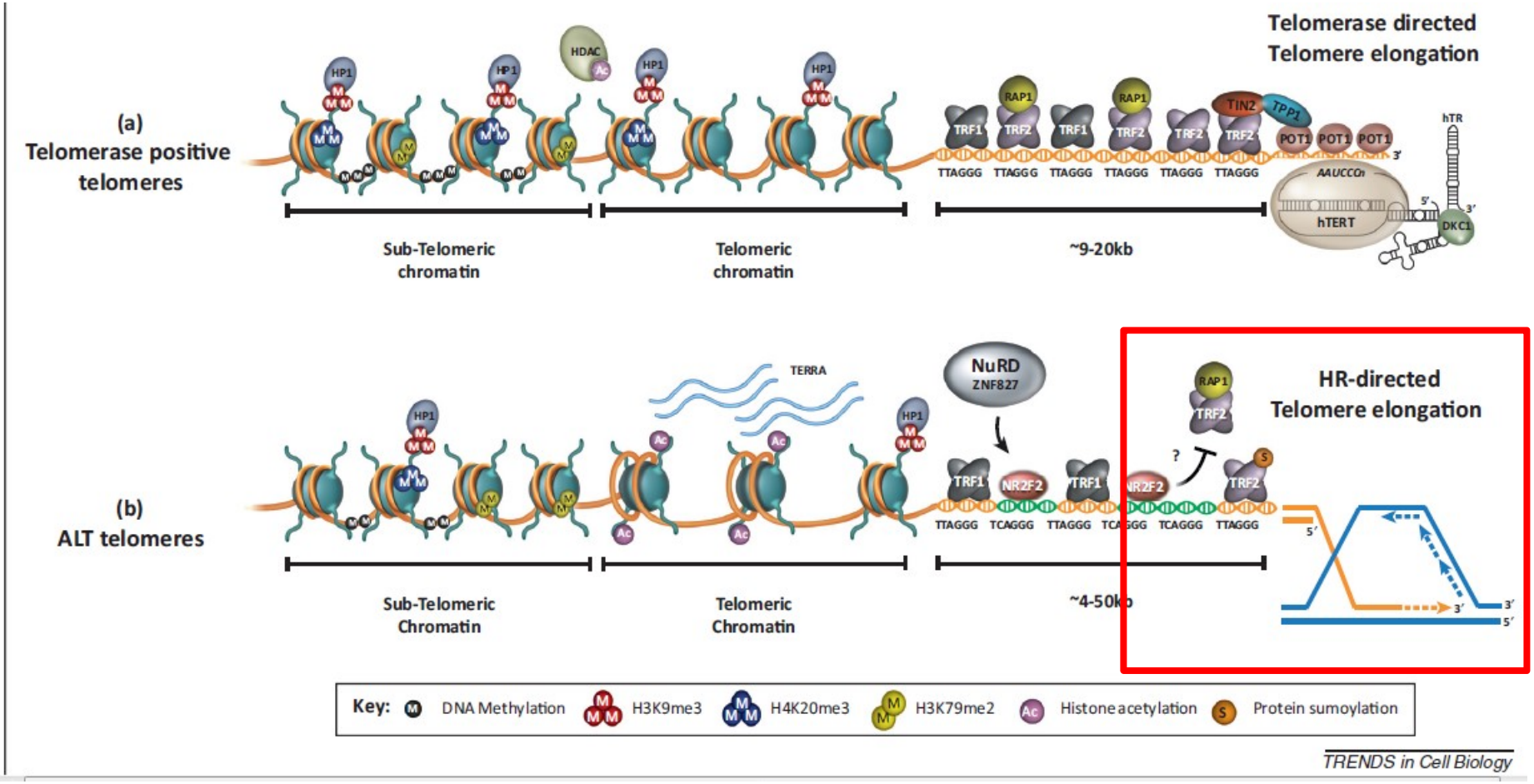
Mutations creating Ets/TCF binding motifs were found in familial and in sporadic metastatic melanoma next to the transcription start site



twofold increase in transcription!!

Susanne Horn et al. Science 2013;339:959-961

Alternative lengthening of telomeres (ALT)


(a)
Telomerase positive telomeres
HDAC
HP1
Telomerase directed
Telomere elongation
RAP1
TRF1
TRF2
TIN2
TPP1
POT1
hTR
TTAGGG
AAUCCCn
hTERT
DKC1
Sub-Telomeric chromatin
Telomeric chromatin
~9-20kb
(b)
ALT telomeres
TERRA
NuRD
ZNF827
NR2F2
HR-directed
Telomere elongation
TCAGGG
Sub-Telomeric Chromatin
Telomeric Chromatin
~4-50kb
Key:
DNA Methylation
H3K9me3
H4K20me3
H3K79me2
Histone acetylation
Protein sumoylation
TRENDS in Cell Biology

ALT telomeres are distinct in that they contain variant C-type TCAGGG repeats and sumoylated TRF2.

These features of ALT telomeres may lead to displacement of TRF2

A small but significant number of cancers do so via the exchange of telomeric DNA between chromosomes by alternative lengthening of telomeres - ALT