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Gene Section
Review

TERF2 (telomeric repeat binding factor 2)

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Identity

Other names: TRBF2, TRF2

HGNC (Hugo): TERF2

Location: 16q22.1

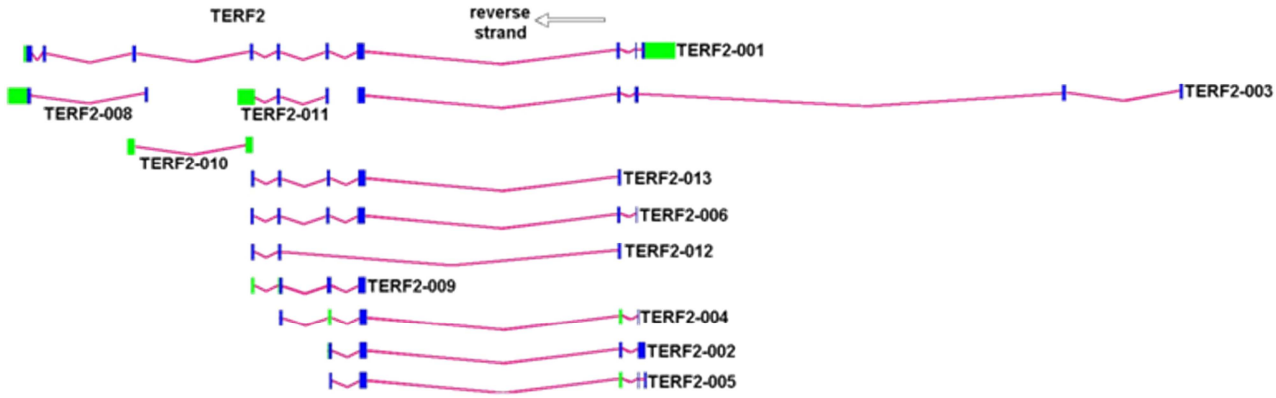
DNA/RNA

Description

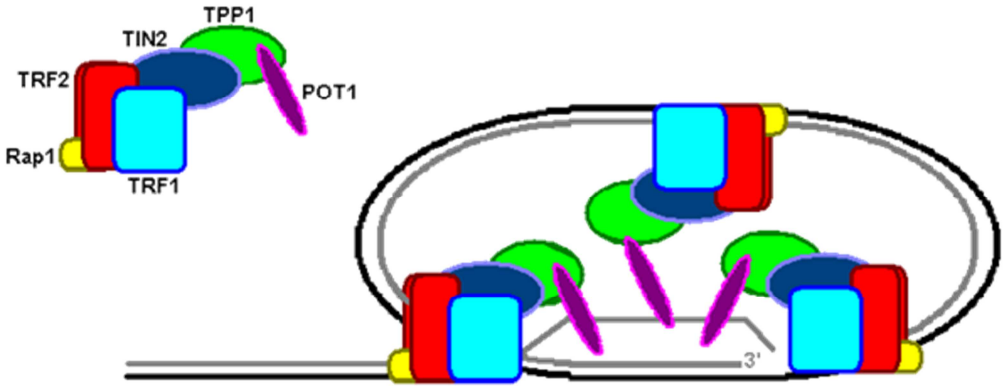
The human TERF2 gene spans a length of 53011 bp. The TERF2 structural gene is composed of 10 exons.

Transcription

Human TERF2 is alternatively spliced, resulting in 12 transcripts, 8 of which are protein encoding.
TERF2-001: 2951 bp in length, with a translational length of 500 residues.
TERF2-002: 1112 bp in length, with a translational length of 251 residues.
TERF2-003: 554 bp in length, with no protein product.
TERF2-004: 556 bp in length, with no protein product.
TERF2-005: 513 bp in length, with a translational length of 60 residues; transcript undergoes nonsense-mediated decay.
TERF2-006: 917 bp in length, with a translational length of 283 residues.
TERF2-008: 791 bp in length, with a translational length of 49 residues.
TERF2-009: 573 bp in length, with a translational length of 99 residues; transcript undergoes nonsense mediated decay.
TERF2-010: 316 bp in length, with no protein product.
TERF2-011: 1107 bp in length, with no protein product.
TERF2-012: 431 bp in length, with a translational length of 144 residues.
TERF2-013: 669 bp in length, with a translational length of 206 residues.
(Flicek et al., 2012).



Human TERF2 is alternatively spliced, resulting in 8 protein encoding transcripts. Figure adapted from Flicek et al. 2012.



Homodimer. Component of the shelterin complex (telosome) composed of TERF1, TERF2, TIN2, TPP1, RAP1 and POT1. Figure adapted from de Lange 2005, and Oeseburg et al. 2010.

Pseudogene

This gene has a pseudogene, TERF2IPP1, telomeric repeat binding factor 2 interacting protein pseudogene 1, located on chromosome 22q11.2 (Seal et al., 2011).

Protein

Description

Of the 12 TERF2 transcripts, 8 encode for proteins, and 2 of these are subject to nonsense-mediated decay. Among splice variants: isoform 1 is 500 aa in length, mass 55.6 kDa; isoform 2 is 251 aa in length, mass 28.3 kDa; isoform 6 is 283 aa in length, mass 31.5 kDa; and isoform 13 is 206 aa in length, mass 22.9 kDa (Uhlen et al., 2010).

Expression

Ubiquitous.
There are high levels of TERF2 expression in spleen, thymus, prostate, uterus, testes, brain, kidney, lung, liver, small intestine, colon, and peripheral blood leukocytes (Jung et al., 2004; Sugiura et al., 2003; UniProt, 2012).

Localisation

TERF2 colocalizes with telomeric DNA in the nucleus of cells at interphase, and is located at telomeres on chromosome ends during metaphase (Ye et al., 2010). TERF2 has also been found in peripheral nerve axons (Jung et al., 2004).

Function

TERF2 is a component of the telomere-specific protein complex called shelterin or telosome, which coats mammalian telomeric DNA (Kim et al., 2009). TERF2 is a homodimer, which binds to the double-stranded 5'-TTAGGG-3' repeat in telomeres (van Steensel et al., 1998).
Its primary role is the maintenance of telomere length, structure, and protection against end-to-end fusion of chromosomes. TERF2 induces the formation of telomere-loops (t-loops); without its protection, telomeres are no longer hidden from DNA repair pathways and these ends could be
subject to non-homologous end joining (NHEJ) of chromosomes during metaphase (Wang et al., 2004). TERF2 causes the 3' single-stranded overhang to tuck under the double stranded TTAGGG repeat, thus shielding chromosomes from incorrect processing.
TERF2 also works together with the exonuclease Apollo as a negative regulator of telomere length (Ye et al., 2010).
TERF2 differs from TERF1 in that its N terminus is basic rather than acidic (provided by RefSeq, Jul 2008).

Homology

Significant TERF2 sequence homology is shared among human (H.sapiens), chimpanzee (P.troglodytes), Rhesus monkey (M.mulatta), dog (C.lupus), cow (B.taurus), mouse (M.musculus), and rat (R.norvegicus).
Conserved domains in protein sequences include: the Telomeric Repeat binding Factor domain, the RAP1 binding motif of telomere repeat binding factor, and the 'SWI3, ADA2, N-CoR and TFIIIB' DNA-binding domains, which consist of repeats containing the G/C rich motif (Geer et al., 2010).

Mutations

Note

According to the January 2013, NCBI dbSNP database, there are 488 known SNPs in the human TERF2 gene.
SNPs associated with TERF2 affect telomere length and chromosomal stability by influencing gene expression or protein configuration at telomeres.

Implicated in

Various pathological conditions

Note

The dysregulation of TERF2 has been implicated in the susceptibility of a number of human diseases and pathological disorders.

Such implications include age- and cancer-related conditions.

Adult T-cell leukemia

Note

TERF2 was found to be overexpressed in T-cell leukemia cell lines. TERF2 expression levels were found to be highest in primary leukemia cells from patients with M0 and M1 subtypes of acute myelogenous leukemia (AML) compared with normal controls and other subtypes of AML (Chen et al., 2008; Jiao et al., 2007).

Prognosis

Increased TERF2 expression levels were found in T-cell leukemia cell lines and AML patients with poor prognosis, suggesting that TRF2 expression might be related to the prognosis of leukemia (Chen et al., 2008; Jiao et al., 2007).

Breast cancer

Note

In vitro models suggest that expression of TERF2 protein increases during mammary cancer progression. However, some data indicate that elevated expression of TERF2 is not a frequent occurrence during the transformation of breast cancer cells in vivo.

Conversely, higher levels of TERF2 protein may protect advanced cancer cells with critically short telomeres, and shorter telomeres in breast cancer cells correlate with a higher TNM stage (Diehl et al., 2011).

Prognosis

Shorter telomeres correlate with advanced stages in breast cancer.

Furthermore, elevated TERF2 levels are found in advanced breast cancer with short telomeres, suggesting TERF2 levels may correlate with breast cancer progression and prognosis (Diehl et al., 2011).

Werner syndrome

Note

Telomere dysfunction has been proposed to contribute to the pathogenesis of Werner syndrome. The Werner syndrome protein (WRN) is a nuclear protein with helicase and exonuclease activities, whose loss-of-function mutations are associated with the premature aging and the cancer-prone disease, Werner syndrome. WRN functions at telomeres and interacts with TERF2.

TERF2 has an N-terminal domain which plays a key role in the prevention of telomere shortening. Expression of TRF2(DeltaB), lacks this key domain, and leads to the formation of telomeric circles, telomere shortening, and cell senescence. The TRF2(DeltaB) pathway requires WRN helicase (Jog et al., 2011; Li et al., 2008).

Prognosis

Expression of TRF2(DeltaB) leads to excessive telomere shortening and cellular senescence, thus contributing to the pathogenesis of Werner syndrome (Jog et al., 2011; Li et al., 2008).

Lung and bronchial cancer

Note

Telomere shortening is an early event in lung and bronchial carcinogenesis, leading to DNA damage responses (DDR).

As telomere attrition occurs, genetic instability increases, thus facilitating malignant progression. When telomeres reach a critical length, expression of TERF2 increases progressively and correlates with progression from dysplasia to squamous invasive carcinoma and from atypical alveolar hyperplasia to invasive adenocarcinoma (Frias et al., 2008; Hosgood et al., 2009; Lantuejoul et al., 2010).

Prognosis

Telomere attrition occurs at an early stage of lung carcinogenesis as an initiating event and is preceded by TERF2 overexpression for telomere stabilization.

Evidence suggests that telomere length and genetic variance of TERF2 and other telomere maintenance genes may be associated with an increased risk of developing lung cancer and a poorer prognosis (Frias et al., 2008; Hosgood et al., 2009; Lantuejoul et al., 2010).

Colorectal cancer

Note

Overexpression of TERF2 protein has been observed in colorectal carcinoma tissue. Experimental data suggests that siRNA silencing of TERF2 expression significantly inhibited SW480 cell proliferation and colony formation; moreover, defective TERF2 induced apoptosis and increased chromosomal instability in SW480 cells (Dong et al., 2009).

Prognosis

TERF2 is overexpressed in colorectal carcinoma and siRNA TERF2 inhibition reduced tumorigenesis of colorectal cancer, suggesting a new target for the development of anti-cancer therapy for colorectal carcinoma (Dong et al., 2009).

Age-dependent telomere shortening

Note

TERF2 alterations permit the progressive reduction in the length of telomeres at the termini of eukaryotic chromosomes, which occur as part of cellular aging.

Prognosis

Shortening of telomeres can initiate DNA damage response mechanisms, leading to cell cycle arrest, cell death, or cellular senescence whereby normal cells irreversibly lose their ability to divide (De Boeck et al., 2009; Mikhelson and Gamaley, 2012).

Type 2 - Diabetes mellitus

Note

Leukocyte telomere length shortening has recently been

associated with type 2 diabetes mellitus (T2D). tSNPs within TERF2 were associated with T2D risk (Zee et al., 2011).

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