UniProtKB - O14746 (TERT_HUMAN)

Protein	**Telomerase reverse transcriptase**
Gene	**TERT**
Organism	*Homo sapiens (Human)*
Status	Reviewed - Annotation score: ●●●●● - Experimental evidence at protein level

Function

Telomerase is a ribonucleoprotein enzyme essential for the replication of chromosome termini in most eukaryotes. Active in progenito and cancer cells. Inactive, or very low activity, in normal somatic cells. Catalytic component of the teleromerase holoenzyme complex whose main activity is the elongation of telomeres by acting as a reverse transcriptase that adds simple sequence repeats to chromosome ends by copying a template sequence within the RNA component of the enzyme. Catalyzes the RNA-dependent extension of 3'-chromosomal termini with the 6-nucleotide telomeric repeat unit, 5'-TTAGGG-3'. The catalytic cycle involves primer binding, primer extension and release of product once the template boundary has been reached or nascent product translocation followed by further extension. More active on substrates containing 2 or 3 telomeric repeats. Telomerase activity is regulated by a number of factors including telomerase complex-associated proteins, chaperones and polypeptide modifiers. Modulates Wnt signaling. Plays important roles in aging and antiapoptosis. Evidence: 12 Publications

Catalytic activity

Deoxynucleoside triphosphate + DNA(n) = diphosphate + DNA(n+1). Evidence: PROSITE-ProRule annotation

Sites

Feature key	Position(s)	Description	Graphical view
Site	169	Required for optimal binding of telomeric ssDNA and incorporation of nucleotides at the second position of the template	
Metal binding	712	Magnesium; catalytic Evidence: PROSITE-ProRule annotation	
Site	867	Required for nucleotide incorporation and primer extension rate	
Metal binding	868	Magnesium; catalytic Evidence: PROSITE-ProRule annotation	
Metal binding	869	Magnesium; catalytic Evidence: PROSITE-ProRule annotation	

GO - Molecular function

- chaperone binding Evidence: Source: BHF-UCL
- DNA binding Evidence: Source: BHF-UCL
- identical protein binding Evidence: Source: IntAct
- metal ion binding Evidence: Source: UniProtKB-KW
- nucleotidyltransferase activity Evidence: Source: BHF-UCL
- protein C-terminus binding Evidence: Source: BHF-UCL
- protein homodimerization activity Evidence: Source: BHF-UCL
- protein N-terminus binding Evidence: Source: BHF-UCL
- RNA binding Evidence: Source: BHF-UCL
- RNA-directed DNA polymerase activity Evidence: Source: BHF-UCL
- telomerase activity Evidence: Source: UniProtKB
- telomerase RNA binding Evidence: Source: BHF-UCL
- telomerase RNA reverse transcriptase activity Evidence: Source: BHF-UCL

- telomeric DNA binding Evidence: Source: ProtInc
- transcription coactivator binding Evidence: Source: BHF-UCL
- tRNA binding Evidence: Source: BHF-UCL

GO - Biological process

- beta-catenin-TCF complex assembly Evidence: Source: Reactome
- cellular response to hypoxia Evidence: Source: BHF-UCL
- DNA biosynthetic process Evidence: Source: BHF-UCL
- DNA strand elongation Evidence: Source: BHF-UCL
- establishment of protein localization to telomere Evidence: Source: BHF-UCL
- mitochondrion organization Evidence: Source: BHF-UCL
- negative regulation of cellular senescence Evidence: Source: BHF-UCL
- negative regulation of endothelial cell apoptotic process Evidence: Source: Ensembl
- negative regulation of extrinsic apoptotic signaling pathway in absence of ligand Evidence: Source: BHF-UCL
- negative regulation of gene expression Evidence: Source: BHF-UCL
- negative regulation of glial cell proliferation Evidence: Source: Ensembl
- negative regulation of neuron apoptotic process Evidence: Source: Ensembl
- negative regulation of production of siRNA involved in RNA interference Evidence: Source: BHF-UCL
- positive regulation of angiogenesis Evidence: Source: Ensembl
- positive regulation of G1/S transition of mitotic cell cycle Evidence: Source: Ensembl
- positive regulation of glucose import Evidence: Source: Ensembl
- positive regulation of hair cycle Evidence: Source: BHF-UCL
- positive regulation of nitric-oxide synthase activity Evidence: Source: BHF-UCL
- positive regulation of pri-miRNA transcription from RNA polymerase II promoter Evidence: Source: BHF-UCL
- positive regulation of protein binding Evidence: Source: BHF-UCL
- positive regulation of protein localization to nucleolus Evidence: Source: BHF-UCL
- positive regulation of stem cell proliferation Evidence: Source: BHF-UCL
- positive regulation of transdifferentiation Evidence: Source: Ensembl
- positive regulation of vascular associated smooth muscle cell migration Evidence: Source: Ensembl
- positive regulation of vascular smooth muscle cell proliferation Evidence: Source: Ensembl
- positive regulation of Wnt signaling pathway Evidence: Source: BHF-UCL
- production of siRNA involved in RNA interference Evidence: Source: BHF-UCL
- regulation of protein stability Evidence: Source: BHF-UCL
- replicative senescence Evidence: Source: BHF-UCL
- response to cadmium ion Evidence: Source: Ensembl
- RNA biosynthetic process Evidence: Source: BHF-UCL
- RNA-dependent DNA biosynthetic process Evidence: Source: BHF-UCL
- telomere maintenance Evidence: Source: UniProtKB
- telomere maintenance via telomerase Evidence: Source: BHF-UCL
- transcription, RNA-templated Evidence: Source: BHF-UCL

Keywords

Molecular function	DNA-binding, Nucleotidyltransferase, Ribonucleoprotein, RNA-directed DNA polymerase, Transferase
Ligand	Magnesium, Metal-binding

Enzyme and pathway databases

Reactome	R-HSA-171319. Telomere Extension By Telomerase. R-HSA-201722. Formation of the beta-catenin:TCF transactivating complex.
SIGNOR	O14746.

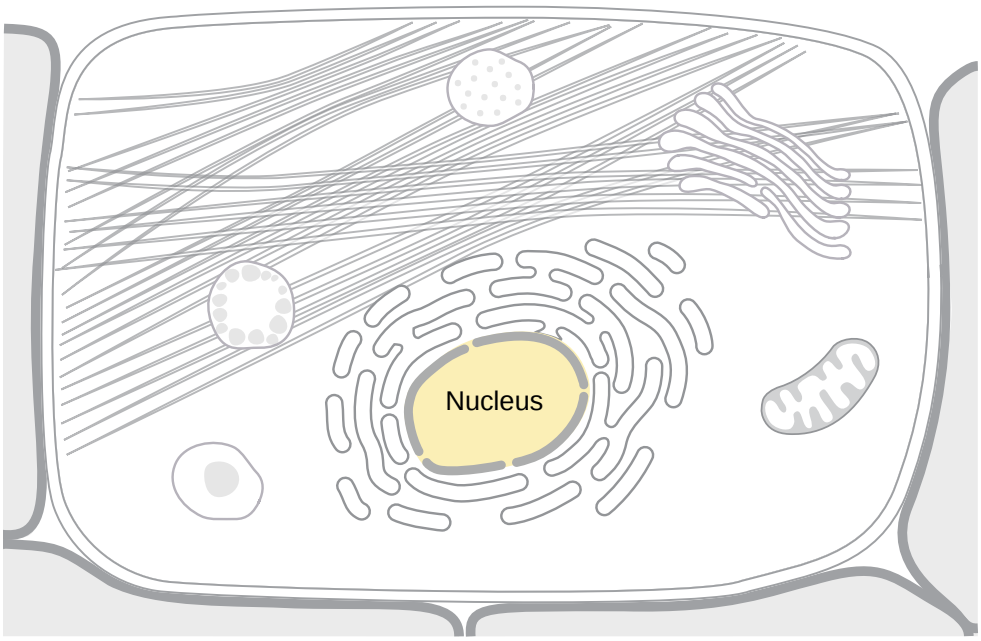
Names & Taxonomy

Protein names	*Recommended name:* **Telomerase reverse transcriptase** (EC:2.7.7.49) *Alternative name(s):* • HEST2 • Telomerase catalytic subunit • Telomerase-associated protein 2 ▪ *Short name:*TP2
Gene names	*Name:*TERT Synonyms:EST2, TCS1, TRT
Organism	Homo sapiens (Human)
Taxonomic identifier	9606 [NCBI]
Taxonomic lineage	Eukaryota › Metazoa › Chordata › Craniata › Vertebrata › Euteleostomi › Mammalia › Eutheria › Euarchontoglires › Primates › Haplorrhini › Catarrhini › Hominidae › Homo
Proteomes	UP000005640 Component: Chromosome 5

Organism-specific databases

EuPathDB	HostDB:ENSG00000164362.18.
HGNC	HGNC:11730. TERT.
MIM	187270. gene+phenotype.

Subcellular location



Graphics by Christian Stolte; Source: COMPARTMENTS

Manual annotation Automatic computational assertion

UniProt annotation GO (Gene Ontology) annotation

Nucleus

nucleolus Evidence: 1 Publication
nucleoplasm
Nucleus
PML body

Other locations

telomere

Cytoplasm

Note: Shuttling between nuclear and cytoplasm depends on cell cycle, phosphorylation states, transformation and DNA damage. Diffuse localization in the nucleoplasm. Enriched in nucleoli of certain cell types. Translocated to the cytoplasm via nuclear pores in a CRM1/RAN-dependent manner involving oxidative stress-mediated phosphorylation at Tyr-707. Dephosphorylation at this site by SHP2 retains TERT in the nucleus. Translocated to the nucleus by phosphorylation by AKT.

Keywords - Cellular component

Chromosome, Cytoplasm, Nucleus, Telomere

Pathology & Biotech

Involvement in disease

Activation of telomerase has been implicated in cell immortalization and cancer cell pathogenesis.

Aplastic anemia (AA) Evidence: 4 Publications

Disease susceptibility is associated with variations affecting the gene represented in this entry.

Disease description: A form of anemia in which the bone marrow fails to produce adequate numbers of peripheral blood elements. It is characterized by peripheral pancytopenia and marrow hypoplasia.

See also OMIM:609135

Feature key	Position(s)	Description	Graphical view
Natural variant (VAR_036863)	202	A → T in PFBMFT1 and AA; severe and moderate; associated with disease susceptibility; shorter telomeres. Evidence: 3 Publications Corresponds to variant dbSNP:rs121918661	
Natural variant (VAR_025149)	412	H → Y in PFBMFT1, AA and DKCB4; severe and moderate; associated with susceptibility to acute myelogenous leukemia; the mutant protein has 36% residual activity. Evidence: 5 Publications Corresponds to variant dbSNP:rs34094720	
Natural variant (VAR_036865)	441	Missing in AA; associated with susceptibility to acute myeloid leukemia. Evidence: 3 Publications	
Natural variant (VAR_062536)	570	K → N in AA; abolishes telomerase catalytic activity but no effect on binding to TERC. Evidence: 2 Publications	
Natural variant (VAR_062783)	631	R → Q in AA. Evidence: 1 Publication Corresponds to variant dbSNP:rs199422294	
Natural variant (VAR_062537)	682	G → D in AA; non-severe; abolishes telomerase catalytic activity but little effect on binding to TERC. Evidence: 2 Publications Corresponds to variant dbSNP:rs199422295	
Natural variant (VAR_036866)	694	V → M in PFBMFT1 and AA; moderate. Evidence: 2 Publications Corresponds to variant dbSNP:rs121918662	
Natural variant (VAR_062539)	726	T → M in AA; very severe; no effect on telomerase catalytic activity but shortened telomeres. Evidence: 2 Publications Corresponds to variant dbSNP:rs149566858	
Natural variant (VAR_062784)	785	P → L in AA. Evidence: 1 Publication	

Genetic variations in TERT are associated with coronary artery disease (CAD).

Dyskeratosis congenita, autosomal dominant, 2 (DKCA2) Evidence: 2 Publications

The disease is caused by mutations affecting the gene represented in this entry.

Disease description: A rare multisystem disorder caused by defective telomere maintenance. It is characterized by progressive bone marrow failure, and the clinical triad of reticulated skin hyperpigmentation, nail dystrophy, and mucosal leukoplakia. Common but variable features include premature graying, aplastic anemia, low platelets, osteoporosis, pulmonary fibrosis, and liver fibrosis among others. Early mortality is often associated with bone marrow failure, infections, fatal pulmonary complications, or malignancy.
See also OMIM:613989

Feature key	Position(s)	Description	Graphical view
Natural variant (VAR_036869)	902	K → N in DKCA2; abolishes telomerase catalytic activity but no effect on binding to TERC. Evidence: 2 Publications Corresponds to variant dbSNP:rs121918665	
Natural variant (VAR_062542)	979	R → W in DKCA2; shortened telomeres but no effect on telomerase catalytic activity nor on binding to TERC. Evidence: 2 Publications Corresponds to variant dbSNP:rs199422305	
Natural variant (VAR_062544)	1127	F → L in DKCA2; severe; shortened telomeres but no effect on telomerase catalytic activity nor on binding to TERC. Evidence: 2 Publications	

Pulmonary fibrosis, and/or bone marrow failure, telomere-related, 1 (PFBMFT1) Evidence: 5 Publications

The disease is caused by mutations affecting the gene represented in this entry.
Disease description: A disease associated with shortened telomeres. Pulmonary fibrosis is the most common manifestation. Other manifestations include aplastic anemia due to bone marrow failure, hepatic fibrosis, and increased cancer risk, particularly myelodysplastic syndrome and acute myeloid leukemia. Phenotype, age at onset, and severity are determined by telomere length.
See also OMIM:614742

Feature key	Position(s)	Description	Graphical view
Natural variant (VAR_068792)	170	V → M in PFBMFT1; the mutant protein is demonstrated to cause decreased telomerase activity. Evidence: 1 Publication Corresponds to variant dbSNP:rs387907248	
Natural variant (VAR_036863)	202	A → T in PFBMFT1 and AA; severe and moderate; associated with disease susceptibility; shorter telomeres. Evidence: 3 Publications Corresponds to variant dbSNP:rs121918661	
Natural variant (VAR_025149)	412	H → Y in PFBMFT1, AA and DKCB4; severe and moderate; associated with susceptibility to acute myelogenous leukemia; the mutant protein has 36% residual activity. Evidence: 5 Publications Corresponds to variant dbSNP:rs34094720	
Natural variant (VAR_036866)	694	V → M in PFBMFT1 and AA; moderate. Evidence: 2 Publications Corresponds to variant dbSNP:rs121918662	
Natural variant (VAR_068794)	716	A → T in PFBMFT1; the mutant protein is demonstrated to cause severely compromised telomerase activity. Evidence: 1 Publication Corresponds to variant dbSNP:rs387907249	
Natural variant (VAR_036867)	772	Y → C in PFBMFT1; moderate. Evidence: 1 Publication Corresponds to variant dbSNP:rs121918663	
Natural variant (VAR_068795)	791	V → I in PFBMFT1; associated with Met-867 in cis on the same allele; the double mutant shows severe defects in telomere repeat addition processivity. Evidence: 1 Publication Corresponds to variant dbSNP:rs141425941	
Natural variant (VAR_068796)	841	L → F in PFBMFT1. Evidence: 1 Publication	
Natural variant (VAR_036868)	865	R → H in PFBMFT1. Evidence: 1 Publication Corresponds to variant dbSNP:rs121918666	
Natural variant (VAR_068797)	867	V → M in PFBMFT1; associated with Ile-791 in cis on the same allele; the double mutant shows severe defects in telomere repeat addition processivity; this mutation causes most if not all of the functional defects. Evidence: 1 Publication Corresponds to variant dbSNP:rs201159197	

Natural variant (VAR_068798)	902	K → R in PFBMFT1. Evidence: 1 Publication Corresponds to variant dbSNP:rs387907250	
Natural variant (VAR_068799)	923	P → L in PFBMFT1. Evidence: 1 Publication Corresponds to variant dbSNP:rs387907251	
Natural variant (VAR_068800)	1025	V → F in PFBMFT1. Evidence: 1 Publication	
Natural variant (VAR_036870)	1090	V → M in PFBMFT1; severe. Evidence: 1 Publication Corresponds to variant dbSNP:rs121918664	

Dyskeratosis congenita, autosomal recessive, 4 (DKCB4) Evidence: 3 Publications

The disease is caused by mutations affecting the gene represented in this entry.
Disease description: A severe form of dyskeratosis congenita, a rare multisystem disorder caused by defective telomere maintenance. It is characterized by progressive bone marrow failure, and the clinical triad of reticulated skin hyperpigmentation, nail dystrophy, and mucosal leukoplakia. Common but variable features include premature graying, aplastic anemia, low platelets, osteoporosis, pulmonary fibrosis, and liver fibrosis among others. Early mortality is often associated with bone marrow failure, infections, fatal pulmonary complications, or malignancy.
See also OMIM:613989

Feature key	Position(s)	Description	Graphical view
Natural variant (VAR_025149)	412	H → Y in PFBMFT1, AA and DKCB4; severe and moderate; associated with susceptibility to acute myelogenous leukemia; the mutant protein has 36% residual activity. Evidence: 5 Publications Corresponds to variant dbSNP:rs34094720	
Natural variant (VAR_068793)	704	P → S in DKCB4; the mutant protein has 13% residual activity. Evidence: 1 Publication Corresponds to variant dbSNP:rs199422297	
Natural variant (VAR_062538)	721	P → R in DKCB4; no effect on telomerase catalytic activity and little effect on binding to TERC. Evidence: 2 Publications Corresponds to variant dbSNP:rs199422299	
Natural variant (VAR_062540)	811	R → C in DKCB4; 50% reduction in telomerase activity. Evidence: 1 Publication Corresponds to variant dbSNP:rs199422301	
Natural variant (VAR_062541)	901	R → W in DKCB4; severe phenotype overlapping with Hoyeraal-Hreidarsson syndrome; very short telomeres and greatly reduced telomerase activity. Evidence: 1 Publication Corresponds to variant dbSNP:rs199422304	

Pulmonary fibrosis, idiopathic (IPF)

Disease susceptibility is associated with variations affecting the gene represented in this entry.
Disease description: A lung disease characterized by shortness of breath, radiographically evident diffuse pulmonary infiltrates, and varying degrees of inflammation and fibrosis on biopsy. In some cases, the disorder can be rapidly progressive and characterized by sequential acute lung injury with subsequent scarring and end-stage lung disease.
See also OMIM:178500

Melanoma, cutaneous malignant 9 (CMM9) Evidence: 1 Publication

Disease susceptibility is associated with variations affecting the gene represented in this entry.
Disease description: A malignant neoplasm of melanocytes, arising de novo or from a pre-existing benign nevus, which occurs most often in the skin but also may involve other sites.
See also OMIM:615134

Mutagenesis

Feature key	Position(s)	Description	Graphical view

Mutagenesis	137 – 141	WGLLL → AAAAA: Reduced catalytic activity and repeat addition processivity. Complete loss of catalytic activity but no loss of binding to telomeric primers; when associated with 930-A--A-934. Evidence: 1 Publication
Mutagenesis	169	Q → A: About 80% loss of enzymatic activity. Greatly reduced incorporation of second nucleotide. Altered strength of binding to ssDNA. Little effect on repeat addition processivity, nor on TR interaction nor on protein levels. Evidence: 1 Publication
Mutagenesis	169	Q → N: About 85% loss of enzymatic activity. Greatly reduced incorporation of second nucleotide. Altered strength of binding to ssDNA. No effect on protein levels nor on TR interaction. Evidence: 1 Publication
Mutagenesis	169	Q → T: About 90% loss of enzymatic activity. Greatly reduced incorporation of second nucleotide. Altered strength of binding to ssDNA. No effect on protein levels nor on TR interaction. Evidence: 1 Publication
Mutagenesis	457	S → A: Abolishes phosphorylation by DYRK2. Evidence: 1 Publication
Mutagenesis	547	W → A: Defective in high-affinity TERC interactions. Evidence: 1 Publication
Mutagenesis	631	R → A: Abolishes telomerase catalytic activity. Evidence: 1 Publication
Mutagenesis	707	Y → F: Abolishes oxidative stress-induced phosphorylation and RAN binding. Impaired nuclear export and enhanced antiapoptotic activity against ROS-dependent apoptosis induction. Impaired interaction with PTPN11. No dephosphorylation by PTPN11. Evidence: 2 Publications
Mutagenesis	712	D → A: Loss of telomerase activity. In the absence of TR, no loss of binding to telomeric primers. Evidence: 4 Publications
Mutagenesis	866	L → Y: Moderate reduction in telomerase activity, no change in repeat extension rate nor on nucleotide incorporation fidelity. Little further reduction in activity but 13.5-fold increase in nucleotide incorporation fidelity; when associated with M-867. Evidence: 1 Publication
Mutagenesis	867	V → A: About 75% reduction in telomerase activity, about 80% reduction in repeat reduction rate and 3.9-fold increase in nucleotide incorporation fidelity. Evidence: 1 Publication
Mutagenesis	867	V → M: About 75% reduction in telomerase activity, about 50% reduction in repeat extension rate and 5.2-fold increase in nucleotide incorporation fidelity. Little further reduction in activity and 13.5-fold increase in nucleotide incorporation fidelity; when associated with Y-866. Evidence: 1 Publication
Mutagenesis	867	V → T: Severe reduction in telomerase activity, about 50% reduction in repeat extension rate and 2.2-fold increase in nucleotide incorporation fidelity. No further reduction in activity but 2.8-fold increase in nucleotide incorporation fidelity; when associated with Y-866. Evidence: 1 Publication
Mutagenesis	868 – 869	DD → AA: Loss of telomerase activity.
Mutagenesis	868	D → A: Loss of telomerase activity. Evidence: 5 Publications
Mutagenesis	869	D → A: Loss of telomerase activity. Evidence: 2 Publications

Mutagenesis	930 – 934	WCGLL → AAAAA: Completely abolishes telomerase-mediated primer extension and reduced binding to short telomeric primers. Complete loss of catalytic activity but no further loss of binding to telomeric primers; when associated with 137-A--A-141. Evidence: 1 Publication	

Keywords - Disease

Disease mutation, Dyskeratosis congenita

Organism-specific databases

DisGeNET	7015.
GeneReviews	TERT.
MalaCards	TERT.
MIM	178500. phenotype. 187270. gene+phenotype. 609135. phenotype. 613989. phenotype. 614742. phenotype. 615134. phenotype.
OpenTargets	ENSG00000164362.
Orphanet	1775. Dyskeratosis congenita. 618. Familial melanoma. 3322. Hoyeraal-Hreidarsson syndrome. 88. Idiopathic aplastic anemia. 2032. Idiopathic pulmonary fibrosis.
PharmGKB	PA36447.

Chemistry databases

ChEMBL	CHEMBL2916.
DrugBank	DB05036. Grn163l. DB04937. GV1001. DB00495. Zidovudine.

Polymorphism and mutation databases

BioMuta	TERT.

PTM / Processing

Molecule processing

Feature key	Position(s)	Description	Graphical view
Chain (PRO_0000054925)	1 – 1132	Telomerase reverse transcriptase	

Amino acid modifications

Feature key	Position(s)	Description	Graphical view
Modified residue	227	Phosphoserine; by PKB/AKT1 Evidence: 1 Publication	
Modified residue	457	Phosphoserine; by DYRK2 Evidence: 1 Publication	
Modified residue	707	Phosphotyrosine; by SRC-type Tyr-kinases Evidence: 2 Publications	

Post-translational modification

Phosphorylation at Tyr-707 under oxidative stress leads to translocation of TERT to the cytoplasm and reduces its antiapoptotic activity. Dephosphorylated by SHP2/PTPN11 leading to nuclear retention. Phosphorylation at Ser-227 by the AKT pathway promotes

nuclear location. Phosphorylation at the G2/M phase at Ser-457 by DYRK2 promotes ubiquitination by the EDVP complex and degradation. Evidence: 4 Publications

Ubiquitinated by the EDVP complex, a E3 ligase complex following phosphorylation at Ser-457 by DYRK2. Ubiquitinated leads to proteasomal degradation. In case of infection by HIV-1, the EDVP complex is hijacked by HIV-1 via interaction between HIV-1 Vpr and DCAF1/VPRBP, leading to ubiquitination and degradation. Evidence: 1 Publication

Keywords - PTM

Phosphoprotein, Ubl conjugation

Proteomic databases

EPD	O14746.
PaxDb	O14746.
PeptideAtlas	O14746.
PRIDE	O14746.

PTM databases

iPTMnet	O14746.
PhosphoSitePlus	O14746.

Expression

Tissue specificity

Expressed at a high level in thymocyte subpopulations, at an intermediate level in tonsil T-lymphocytes, and at a low to undetectable level in peripheral blood T-lymphocytes. Evidence: 2 Publications

Induction

Activated by cytotoxic events and down-regulated during aging. In peripheral T-lymphocytes, induced By CD3 and by PMA/ionomycin Inhibited by herbimycin B. Evidence: 1 Publication

Gene expression databases

Bgee	ENSG00000164362.
CleanEx	HS_TERT.
Genevisible	O14746. HS.

Organism-specific databases

HPA	HPA054641. HPA065897.

Interaction

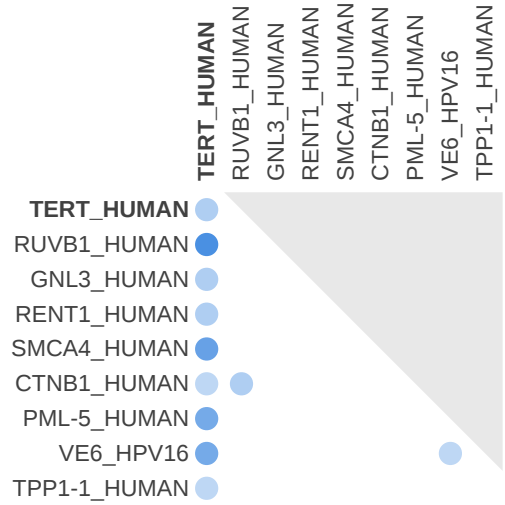
Subunit structure

Homodimer; dimerization is required to produce a functional complex. Oligomer; can form oligomers in the absence of the telomerase RNA template component (TERC). Catalytic subunit of the telomerase holoenzyme complex composed minimally of TERT and TERC The telomerase complex is composed of TERT, DKC1, WDR79/TCAB1, NOP10, NHP2, GAR1, TEP1, EST1A, POT1 and a telomerase RNA template component (TERC). The molecular chaperone HSP90/P23 complex is required for correct assembly and stabilization of the active telomerase. Interacts directly with HSP90A and PTGES3. Interacts with HSPA1A; the interaction occurs in the absence of TERC and dissociates once the complex has formed. Interacts with RAN; the interaction promotes nuclear export of TERT. Interacts with XPO1. Interacts with PTPN11; the interaction retains TERT in the nucleus. Interacts with NCL (via RRM1 and C-terminal RRM4/Arg/Gly-rich domains); the interaction is important for nucleolar localization of TERT. Interacts with SMARCA4 (via the bromodomain); the interaction regulates Wnt-mediated signaling. Interacts with MCRS1 (isoform MCRS2); the interaction inhibits in vitro telomerase activity. Interacts with PIF1; the interaction has no effect on the elongation activity of TERT. Interacts with PML; the interaction recruits TERT to PML bodies and inhibits telomerase activity. Interacts with GNL3L (By similarity). Interacts with isoform 1 and isoform 2 of NVL (PubMed:22226966). Evidence: By similarity Evidence: 1 Publication

Binary interactions

O14746 has binary interactions with 8 proteins

Subcellular location ▾ Diseases ▾



Show more details

GO - Molecular function

- chaperone binding Evidence: Source: BHF-UCL
- identical protein binding Evidence: Source: IntAct
- protein C-terminus binding Evidence: Source: BHF-UCL
- protein homodimerization activity Evidence: Source: BHF-UCL
- protein N-terminus binding Evidence: Source: BHF-UCL
- transcription coactivator binding Evidence: Source: BHF-UCL

Protein-protein interaction databases

BioGrid	112874. 67 interactors.
CORUM	O14746.
DIP	DIP-40646N.
ELM	O14746.
IntAct	O14746. 23 interactors.
MINT	MINT-133963.
STRING	9606.ENSP00000309572.

Chemistry databases

BindingDB	O14746.

Structure

Secondary structure

Legend: Helix Turn Beta strand PDB Structure known for this area

Show more details

3D structure databases

Select the link destinations:
PDBe
RCSB PDB
PDBj

PDB entry	Method	Resolution (Å)	Chain	Positions	PDBsum
2BCK	X-ray	2.80	C/F	461-469	[»]
4B18	X-ray	2.52	B	222-240	[»]
4MNQ	X-ray	2.74	C	540-548	[»]
5MEN	X-ray	2.81	C	540-548	[»]
5MEO	X-ray	1.77	C	540-548	[»]

	5MEP	X-ray	2.71	C/F	540-548	[»]
	5MEQ	X-ray	2.27	C	540-546	[»]
	5MER	X-ray	1.88	C/F	540-546	[»]
	5UGW	X-ray	2.31	A	961-1132	[»]

ProteinModelPortal	O14746.
SMR	O14746.
ModBase	Search...
MobiDB	Search...

Miscellaneous databases

EvolutionaryTrace	O14746.

Family & Domains

Domains and Repeats

Feature key	Position(s)	Description	Graphical view
Domain	605 – 935	Reverse transcriptase Evidence: PROSITE-ProRule annotation	

Region

Feature key	Position(s)	Description	Graphical view
Region	1 – 230	RNA-interacting domain 1	
Region	58 – 197	GQ motif	
Region	137 – 141	Required for regulating specificity for telomeric DNA and for processivity for primer elongation	
Region	231 – 324	Linker	
Region	301 – 538	Required for oligomerization	
Region	325 – 550	RNA-interacting domain 2	
Region	376 – 521	QFP motif	
Region	397 – 417	CP motif	
Region	914 – 928	Required for oligomerization	
Region	930 – 934	Primer grip sequence	
Region	936 – 1132	CTE	

Motif

Feature key	Position(s)	Description	Graphical view
Motif	222 – 240	Bipartite nuclear localization signal	
Motif	328 – 333	TFLY; involved in RNA binding Evidence: By similarity	

Domain

The primer grip sequence in the RT domain is required for telomerase activity and for stable association with short telomeric primers.

The RNA-interacting domain 1 (RD1)/N-terminal extension (NTE) is required for interaction with the pseudoknot-template domain of each of TERC dimers. It contains anchor sites that bind primer nucleotides upstream of the RNA-DNA hybrid and is thus an essential determinant of repeat addition processivity.

The RNA-interacting domain 2 (RD2) is essential for both interaction with the CR4-CR5 domain of TERC and for DNA synthesis.

Sequence similarities

Belongs to the reverse transcriptase family. Telomerase subfamily. Evidence: Curated

Phylogenomic databases

eggNOG	KOG1005. Eukaryota. ENOG410XQJH. LUCA.
GeneTree	ENSGT00390000018531.
HOGENOM	HOG000148780.
HOVERGEN	HBG000460.
InParanoid	O14746.
KO	K11126.
OMA	QCQGIPQ.
OrthoDB	EOG091G04DO.
PhylomeDB	O14746.
TreeFam	TF329048.

Family and domain databases

InterPro	View protein in InterPro IPR000477. RT_dom. IPR021891. Telomerase_RBD. IPR003545. Telomerase_RT.
PANTHER	PTHR12066. PTHR12066. 1 hit.
Pfam	View protein in Pfam PF00078. RVT_1. 1 hit. PF12009. Telomerase_RBD. 1 hit.
PRINTS	PR01365. TELOMERASERT.
SMART	View protein in SMART SM00975. Telomerase_RBD. 1 hit.
PROSITE	View protein in PROSITE PS50878. RT_POL. 1 hit.

Sequences (4)

Sequence status: Complete.
This entry describes **4** isoforms produced by **alternative splicing**.

Isoform 1 (identifier: **O14746-1**) [UniParc]
This isoform has been chosen as the 'canonical' sequence. All positional information in this entry refers to it. This is also the sequenc
that appears in the downloadable versions of the entry.
« Hide

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         10          20          30          40          50
MPRAPRCRAV RSLLRSHYRE VLPLATFVRR LGPQGWRLVQ RGDPAAFRAL
         60          70          80          90         100
VAQCLVCVPW DARPPPAAPS FRQVSCLKEL VARVLQRLCE RGAKNVLAFG
        110         120         130         140         150
FALLDGARGG PPEAFTTSVR SYLPNTVTDA LRGSGAWGLL LRRVGDDVLV
        160         170         180         190         200
HLLARCALFV LVAPSCAYQV CGPPLYQLGA ATQARPPPHA SGPRRRLGCE
        210         220         230         240         250
RAWNHSVREA GVPLGLPAPG ARRRGGSASR SLPLPKRPRR GAAPEPERTP
        260         270         280         290         300
VGQGSWAHPG RTRGPSDRGF CVVSPARPAE EATSLEGALS GTRHSHPSVG
        310         320         330         340         350
RQHHAGPPST SRPPRPWDTP CPPVYAETKH FLYSSGDKEQ LRPSFLLSSL
        360         370         380         390         400
RPSLTGARRL VETIFLGSRP WMPGTPRRLP RLPQRYWQMR PLFLELLGNH
        410         420         430         440         450
AQCPYGVLLK THCPLRAAVT PAAGVCAREK PQGSVAAPEE EDTDPRRLVQ
        460         470         480         490         500
LLRQHSSPWQ VYGFVRACLR RLVPPGLWGS RHNERRFLRN TKKFISLGKH
        510         520         530         540         550
AKLSLQELTW KMSVRDCAWL RRSPGVGCVP AAEHRLREEI LAKFLHWLMS
        560         570         580         590         600
VYVVELLRSF FYVTETTFQK NRLFFYRKSV WSKLQSIGIR QHLKRVQLRE
        610         620         630         640         650
LSEAEVRQHR EARPALLTSR LRFIPKPDGL RPIVNMDYVV GARTFRREKR
        660         670         680         690         700
AERLTSRVKA LFSVLNYERA RRPGLLGASV LGLDDIHRAW RTFVLRVRAQ
        710         720         730         740         750
DPPPELYFVK VDVTGAYDTI PQDRLTEVIA SIIKPQNTYC VRRYAVVQKA
        760         770         780         790         800
AHGHVRKAFK SHVSTLTDLQ PYMRQFVAHL QETSPLRDAV VIEQSSSLNE
        810         820         830         840         850
ASSGLFDVFL RFMCHHAVRI RGKSYVQCQG IPQGSILSTL LCSLCYGDME
        860         870         880         890         900
NKLFAGIRRD GLLLRLVDDF LLVTPHLTHA KTFLRTLVRG VPEYGCVVNL
        910         920         930         940         950
RKTVVNFPVE DEALGGTAFV QMPAHGLFPW CGLLLDTRTL EVQSDYSSYA
        960         970         980         990        1000
RTSIRASLTF NRGFKAGRNM RRKLFGVLRL KCHSLFLDLQ VNSLQTVCTN
       1010        1020        1030        1040        1050
IYKILLLQAY RFHACVLQLP FHQQVWKNPT FFLRVISDTA SLCYSILKAK
       1060        1070        1080        1090        1100
NAGMSLGAKG AAGPLPSEAV QWLCHQAFLL KLTRHRVTYV PLLGSLRTAQ
       1110        1120        1130
TQLSRKLPGT TLTALEAAAN PALPSDFKTI LD
```

Length: 1,132
Mass (Da): 126,997
Last modified: January 1, 1998 - v1
Checksum: 94E35469C4CA33A0

Isoform 2 (identifier: **O14746-2**) [UniParc]
The sequence of this isoform differs from the canonical sequence as follows:
764-807: STLTDLQPYM...LNEASSGLFD → LRPVPGDPAG...AGRAAPAFGG
808-1132: Missing.

Show »
Length: 807
Mass (Da): 90,226
Checksum: 199664460CE6D763

Isoform 3 (identifier: **O14746-3**) [UniParc]
The sequence of this isoform differs from the canonical sequence as follows:
885-947: Missing.

Note: May be produced at very low levels due to a premature stop codon in the mRNA, leading to nonsense-mediated mRNA decay experimental confirmation available.
Show »
Length: 1,069
Mass (Da): 120,048
Checksum: BE1E77A653B1C666

Isoform 4 (identifier: **O14746-4**) [UniParc]
The sequence of this isoform differs from the canonical sequence as follows:
711-722: Missing.
764-807: STLTDLQPYM...LNEASSGLFD → LRPVPGDPAG...AGRAAPAFGG
808-1132: Missing.

Show »
Length: 795
Mass (Da): 88,965
Checksum: 6BEAC8A6D1A2E8CB

Experimental Info

Feature key	Position(s)	Description	Graphical view
Sequence conflict	516	D → G in AAC51724 (PubMed:9288757). Evidence: Curated	

Natural variant

Feature key	Position(s)	Description	Graphical view
Natural variant (VAR_062535)	55	L → Q in idiopathic pulmonary fibrosis susceptibility; impaired telomerase activity. Evidence: 1 Publication Corresponds to variant dbSNP:rs387907247	
Natural variant (VAR_062780)	65	P → A Associated with acute myeloid leukemia. Evidence: 2 Publications Corresponds to variant dbSNP:rs544215765	
Natural variant (VAR_068792)	170	V → M in PFBMFT1; the mutant protein is demonstrated to cause decreased telomerase activity. Evidence: 1 Publication Corresponds to variant dbSNP:rs387907248	

Natural variant (VAR_036863)	202	A → T in PFBMFT1 and AA; severe and moderate; associated with disease susceptibility; shorter telomeres. Evidence: 3 Publications Corresponds to variant dbSNP:rs121918661
Natural variant (VAR_036864)	279	A → T Evidence: 1 Publication Corresponds to variant dbSNP:rs61748181
Natural variant (VAR_062781)	299	V → M Associated with acute myeloid leukemia. Evidence: 2 Publications Corresponds to variant dbSNP:rs756624928
Natural variant (VAR_025149)	412	H → Y in PFBMFT1, AA and DKCB4; severe and moderate; associated with susceptibility to acute myelogenous leukemia; the mutant protein has 36% residual activity. Evidence: 5 Publications Corresponds to variant dbSNP:rs34094720
Natural variant (VAR_036865)	441	Missing in AA; associated with susceptibility to acute myeloid leukemia. Evidence: 3 Publications
Natural variant (VAR_062782)	522	R → K Associated with acute myeloid leukemia. Evidence: 2 Publications
Natural variant (VAR_062536)	570	K → N in AA; abolishes telomerase catalytic activity but no effect on binding to TERC. Evidence: 2 Publications
Natural variant (VAR_062783)	631	R → Q in AA. Evidence: 1 Publication Corresponds to variant dbSNP:rs199422294
Natural variant (VAR_062537)	682	G → D in AA; non-severe; abolishes telomerase catalytic activity but little effect on binding to TERC. Evidence: 2 Publications Corresponds to variant dbSNP:rs199422295
Natural variant (VAR_036866)	694	V → M in PFBMFT1 and AA; moderate. Evidence: 2 Publications Corresponds to variant dbSNP:rs121918662
Natural variant (VAR_068793)	704	P → S in DKCB4; the mutant protein has 13% residual activity. Evidence: 1 Publication Corresponds to variant dbSNP:rs199422297
Natural variant (VAR_068794)	716	A → T in PFBMFT1; the mutant protein is demonstrated to cause severely compromised telomerase activity. Evidence: 1 Publication Corresponds to variant dbSNP:rs387907249
Natural variant (VAR_062538)	721	P → R in DKCB4; no effect on telomerase catalytic activity and little effect on binding to TERC. Evidence: 2 Publications Corresponds to variant dbSNP:rs199422299
Natural variant (VAR_062539)	726	T → M in AA; very severe; no effect on telomerase catalytic activity but shortened telomeres. Evidence: 2 Publications Corresponds to variant dbSNP:rs149566858
Natural variant (VAR_036867)	772	Y → C in PFBMFT1; moderate. Evidence: 1 Publication Corresponds to variant dbSNP:rs121918663
Natural variant (VAR_062784)	785	P → L in AA. Evidence: 1 Publication
Natural variant (VAR_068795)	791	V → I in PFBMFT1; associated with Met-867 in cis on the same allele; the double mutant shows severe defects in telomere repeat addition processivity. Evidence: 1 Publication Corresponds to variant dbSNP:rs141425941
Natural variant (VAR_062540)	811	R → C in DKCB4; 50% reduction in telomerase activity. Evidence: 1 Publication Corresponds to variant dbSNP:rs199422301
Natural variant (VAR_068796)	841	L → F in PFBMFT1. Evidence: 1 Publication
Natural variant (VAR_036868)	865	R → H in PFBMFT1. Evidence: 1 Publication Corresponds to variant dbSNP:rs121918666

Natural variant (VAR_068797)	867	V → M in PFBMFT1; associated with Ile-791 in cis on the same allele; the double mutant shows severe defects in telomere repeat addition processivity; this mutation causes most if not all of the functional defects. Evidence: 1 Publication Corresponds to variant dbSNP:rs201159197
Natural variant (VAR_062541)	901	R → W in DKCB4; severe phenotype overlapping with Hoyeraal-Hreidarsson syndrome; very short telomeres and greatly reduced telomerase activity. Evidence: 1 Publication Corresponds to variant dbSNP:rs199422304
Natural variant (VAR_036869)	902	K → N in DKCA2; abolishes telomerase catalytic activity but no effect on binding to TERC. Evidence: 2 Publications Corresponds to variant dbSNP:rs121918665
Natural variant (VAR_068798)	902	K → R in PFBMFT1. Evidence: 1 Publication Corresponds to variant dbSNP:rs387907250
Natural variant (VAR_068799)	923	P → L in PFBMFT1. Evidence: 1 Publication Corresponds to variant dbSNP:rs387907251
Natural variant (VAR_053726)	948	S → R. Corresponds to variant dbSNP:rs34062885
Natural variant (VAR_062542)	979	R → W in DKCA2; shortened telomeres but no effect on telomerase catalytic activity nor on binding to TERC. Evidence: 2 Publications Corresponds to variant dbSNP:rs199422305
Natural variant (VAR_068800)	1025	V → F in PFBMFT1. Evidence: 1 Publication
Natural variant (VAR_025150)	1062	A → T Increased incidence in sporadic acute myeloid leukemia. Evidence: 4 Publications Corresponds to variant dbSNP:rs35719940
Natural variant (VAR_036870)	1090	V → M in PFBMFT1; severe. Evidence: 1 Publication Corresponds to variant dbSNP:rs121918664
Natural variant (VAR_062543)	1110	T → M in idiopathic pulmonary fibrosis susceptibility; impaired telomerase activity. Evidence: 1 Publication Corresponds to variant dbSNP:rs199422306
Natural variant (VAR_062544)	1127	F → L in DKCA2; severe; shortened telomeres but no effect on telomerase catalytic activity nor on binding to TERC. Evidence: 2 Publications

Alternative sequence

Feature key	Position(s)	Description	Graphical view
Alternative sequence (VSP_053369)	711 – 722	Missing in isoform 4. Evidence: 1 Publication	
Alternative sequence (VSP_019587)	764 – 807	STLTD…SGLFD → LRPVPGDPAGLHPLHAALQP VLRRHGEQAVCGDSAGRAAP AFGG in isoform 2 and isoform 4. Evidence: 2 Publications	
Alternative sequence (VSP_019588)	808 – 1132	Missing in isoform 2 and isoform 4. Evidence: 2 Publications	
Alternative sequence (VSP_021727)	885 – 947	Missing in isoform 3. Evidence: 1 Publication	

Sequence databases

Select the link destinations: EMBL GenBank DDBJ	AF018167 mRNA. Translation: AAC51724.1. AF015950 mRNA. Translation: AAC51672.1. AF128894, AF128893 Genomic DNA. Translation: AAD30037.1. AB085628 mRNA. Translation: BAC11010.1. AB086379 mRNA. Translation: BAC11014.1. AB086950 mRNA. Translation: BAC11015.1. AY007685 Genomic DNA. Translation: AAG23289.1. DQ264729 Genomic DNA. Translation: ABB72674.1. AC114291 Genomic DNA. No translation available. CH471102 Genomic DNA. Translation: EAX08167.1.
CCDS	CCDS3861.2. [O14746-1] CCDS54831.1. [O14746-3]
PIR	T03844.
RefSeq	NP_001180305.1. NM_001193376.1. [O14746-3] NP_937983.2. NM_198253.2. [O14746-1]
UniGene	Hs.492203.

Genome annotation databases

Ensembl	ENST00000310581; ENSP00000309572; ENSG00000164362. [O14746-1] ENST00000334602; ENSP00000334346; ENSG00000164362. [O14746-3] ENST00000460137; ENSP00000425003; ENSG00000164362. [O14746-4] ENST00000508104; ENSP00000426042; ENSG00000164362. [O14746-2]
GeneID	7015.
KEGG	hsa:7015.
UCSC	uc003jcb.2. human. [O14746-1]

Keywords - Coding sequence diversity

Alternative splicing, Polymorphism

Similar proteins

100% Identity 90% Identity 50% Identity

Protein	Similar proteins	Organisms	Length	Cluster ID	Cluster name	Size	
O14746	Q9UNR4 Q9UBR6 Q9UNS6	Homo sapiens (Human)	1,132	UniRef100_O14746	Cluster: Telomerase reverse transcriptase	4	

Entry information

Entry name	TERT_HUMAN	
Accession	Primary (citable) accession number: **O14746** Secondary accession number(s): O14783 Q8NG46	
Entry history	Integrated into UniProtKB/Swiss-Prot:	May 30, 2000
	Last sequence update:	January 1, 1998
	Last modified:	October 25, 2017
	This is version 171 of the entry and version 1 of the sequence. See complete history.	
Entry status	Reviewed (UniProtKB/Swiss-Prot)	
Annotation program	Chordata Protein Annotation Program	
Disclaimer	Any medical or genetic information present in this entry is provided for research, educational and informational purposes only. It is not in any way intended to be used as a substitute for professional medical advice, diagnosis, treatment or care.	

Miscellaneous

Keywords - Technical term

3D-structure, Complete proteome, Reference proteome

Documents

- Human chromosome 5
  Human chromosome 5: entries, gene names and cross-references to MIM
- Human entries with polymorphisms or disease mutations
  List of human entries with polymorphisms or disease mutations
- Human polymorphisms and disease mutations
  Index of human polymorphisms and disease mutations
- MIM cross-references
  Online Mendelian Inheritance in Man (MIM) cross-references in UniProtKB/Swiss-Prot
- PDB cross-references
  Index of Protein Data Bank (PDB) cross-references
- SIMILARITY comments
  Index of protein domains and families