Supplementary Methods and Results

Supplemental Table 1: Diagnostic categories based on clinical features^

Category	Description	# patients
1	Dyskeratosis congenita (DC) diagnosis solely based on the presence of at least 2/3 features of the diagnostic triad without telomere length assay or genetic testing report.	1
2	Any one feature of the triad plus bone marrow hypoplasia plus presence of at least one other physical finding consistent with DC related telomere biology disorders (DC/TBD) without telomere length assay or genetic testing report.	5
3	Patients meeting the clinical criteria of Hoyeraal Hreidarsson syndrome, Revesz syndrome or Coats plus based on medical, personal or family member report. Five were included based on personal or family member report only, not specific medical record review.	32
4	Individuals with two or more features seen in DC/TBDs associated with very short telomeres.	24
5	Individuals with one or more features (any triad feature, bone marrow failure, pulmonary fibrosis, liver disease) seen in DC (+/- telomere length result) and the presence of a pathogenic variant in a DC/TBD-associated gene. Three were included based on personal or family member report only.	110
6	Individuals with a heterozygous pathogenic variant in a DC/TBD-associated gene in the absence of any reported clinical features (any triad feature, bone marrow failure, pulmonary fibrosis, liver disease).* The clinical information for 22 Field Cohort participants was incomplete. Therefore, they were included in this category but may have had unreported TBD-associated features. Twenty-five family members with heterozygous pathogenic variants and the index case having autosomal recessive disease were included, provided the affected genes had previously been implicated in autosomal dominant disease according to OMIM (https://www.omim.org/) and literature review.	47
7	Family members with the DC triad and/or pulmonary fibrosis and/or bone marrow failure (with or without other DC/TBD related features) were included if a pathogenic variant was proven in a first-degree family member. Five were included based on personal or family member report only, not specific medical record review.	12

^ Modified from Dokal et al, Eur J Hum Genet 2015.[1]

Clinical diagnoses were confirmed through physical examination (Clinic Cohort), or based on medical records, photographs of participants, and/or personal reports by participants or family members through the Individual Information Questionnaire (Field Cohort).

* Exclusion: Carriers of heterozygous variants in genes associated exclusively with AR disease (*WRAP53, NOP10, NHP2, STN1, CTC1, POT1)* according to OMIM (https://www.omim.org/) and literature review at time of data freeze (05/31/2019).

Hoyeraal Hreidarsson syndrome: Cerebellar hypoplasia, immunodeficiency, developmental delay, progressive bone marrow failure, and intrauterine growth restriction (IUGR), possibly intracranial calcifications, nonspecific enteropathy; Revesz syndrome: Bilateral exudative retinopathy, IUGR, intracranial calcification, cerebellar hypoplasia, psychomotor retardation; Coats plus: Bilateral exudative retinopathy, retinal telangiectasias, IUGR, intracranial calcifications , osteopenia with tendency to fracture with poor bone healing, gastrointestinal vascular ectasias.

Supplemental Table 2: Study subjects with inferred genotype (n=24). All individuals were Field Cohort participants. Genotype was inferred by mode of inheritance and reported clinical information (presence of very short telomeres, pulmonary fibrosis, bone marrow failure, and/or hematologic malignancies)

Gene	Number of inferred genotype carriers (number of obligate carriers)	Inferred inheritance pattern
DKC1	5 (2)	XLR
RTEL1	2 (0)	AD
TERC	9 (4)	AD
TERT	5 (1)	AD
TINF2	3 (3)	AD

Supplemental Table 3: Definitions of clinical features used in this study. Data based on self-report (questionnaires), medical report, and/or clinical assessment at the NIH Clinical Center by the IBMFS study team

Assessed clinical feature	Evaluation details for review of phenotype features
Consanguinity	Based on self-report and evaluation of family pedigree.
Prematurity	Born < 37 gestational weeks.
Small for gestational age	• < 37 gestational weeks: birthweight < 10th percentile (www.cdc.gov) • ≥ 37 gestational weeks: birthweight < 2500g
Short stature	Defined as height < 3rd percentile for age • < 2 years of age: percentiles according to https://www.who.int/childgrowth/standards/height_for_age/en/ • 2-19 years of age: percentiles according to https://www.cdc.gov/growthcharts/who_charts.htm
Mucocutaneous triad	Lacy skin pigmentation, nail dysplasia, and oral leukoplakia: • Non severe: 0-1 triad features • Severe: 2-3 triad features
Microcephaly	Head circumference < 5th percentile for age: • < 2 years at time of measurement: Percentiles according to https://www.who.int/childgrowth/standards/height_for_age/en/ • ≥ 2 years at time of measurement. Utilized webtool: https://simulconsult.com/resources/measurement.html
Cerebellar hypoplasia	Diagnosis based on brain MRI reports.
Development delay	Evaluation according to physical exam at time of NIH visit (Clinic Cohort).
Ataxia	Evaluation according to physical evaluation at time of NIH visit (Clinic Cohort).
Lacrimal duct stenosis	According to ophthalmologic consult at time of NIH visit (Clinic Cohort).
Epiphora	Self-report, medical reports or physical exam at time of NIH visit (Clinic Cohort).
Retinopathy	According to ophthalmologic consultant at time of NIH visit (Clinic Cohort).
Dental: Short roots	Diagnosed by dental consultant at time of NIH visit (Clinic Cohort).

Hearing loss	Reported non-age-related hearing loss considered, if available corroborated by audiogram at time of NIH visit (Clinic Cohort).
Congenital heart disease	Positive history and/or abnormal echocardiogram at time of NIH visit (Clinic Cohort).
Pulmonary fibrosis	For individuals evaluated at NIH (Clinic Cohort) based on physical exam and diagnostics at time of NIH visit. For follow-up period of Clinic Cohort patients and for additional individuals included in study (Field Cohort): Family or self-report of established diagnosis of pulmonary fibrosis and/or (if available) medical records stating pulmonary fibrosis as the diagnosis. A central review of pulmonary CT images was beyond the scope of this study.
Pulmonary arteriovenous malformations (PAVM)	If reported as established diagnosis by self-report and/or medical reports (bubble contrast echocardiography, CT angiogram, cardiac catheterization, or lung perfusion scan).
Hepatopulmonary syndrome (HPS)	If reported as established diagnosis by self-report and/or medical report based on positive bubble echocardiography and/or pulmonary scan with dilated pulmonary vessels in the context of severe liver disease with portal hypertension.
Severe liver disease	Reported liver cirrhosis/ fibrosis diagnosed by biopsy, and/or portal hypertension diagnosed by ultrasound and/or esophageal varices diagnosed by endoscopy in the context of liver disease.
Esophageal web/stricture	Considered if established diagnosis by self-report, endoscopy, and/or other medical record report.
Gastrointestinal telangiectasias	Diagnosed abnormalities based on self-reported diagnosis by endoscopy, and/or by original endoscopy reports.
Gastrointestinal abnormalities	Any reported gastrointestinal abnormality was collected based on self-report or medical report, only applicable for individuals evaluated at NIH visit (Clinic Cohort).
Kidney disease	Any reported structural renal abnormality based on self-report and/or medical report and/or ultrasound report at time of NIH visit (Clinic Cohort).
Males: urethral stenosis, strictures, or phimosis	Reported diagnosis at time of NIH visit and/or physical exam at NIH visit (Clinic Cohort).
Males: undescended testis	Reported diagnosis at time of NIH visit and/or physical exam at NIH visit (Clinic Cohort).

Other genitourinary abnormalities (*e.g.,* hypospadias)	Reported diagnosis at time of NIH visit and/or physical exam at NIH visit (Clinic Cohort).
Infertility	Any self-reported infertility issues at time of NIH visit (Clinic Cohort).
Any endocrine abnormality	Any endocrine abnormality reported at time of NIH visit (Clinic Cohort). Abnormal lipid profiles were not specifically considered since we have shown in a previous study the association of androgens and changes in lipid profiles.[2] Low vitamin D levels were not separately considered.
Avascular osteonecrosis (AVN)	Established diagnosis according to MRI, reported either by questionnaire and/or medical reports.
DEXA scan	DEXA scans performed at the NIH (Clinic Cohort).
Dysmorphia	Based on physical exam at time of NIH visit (Clinic Cohort). Self-reported dysmorphic features or features reported by medical reports were not considered.
Immunologic abnormality	Decreased immunoglobulins and/or lymphocyte subsets according to laboratory diagnostics performed for patients evaluated at NIH visit (Clinic Cohort).
Bone marrow failure (BMF)	For evaluation all provided laboratory and patient history data was reviewed in detail. • Non-severe: ANC 500-<1500/mm^3, platelets 20.000-<150.000/mm^3, and/or Hb ≥8g/dl-less than normal for age • Severe: ANC < 500/mm^3, platelets < 20.000/mm^3, and/or Hb < 8.0 g/dl BMF was always considered severe (irrespective of available laboratory data) if • Hematopoietic cell transplantation had been performed • Regular red cell or platelet transfusions were necessary • Androgen treatment had been initiated due to bone marrow failure • MDS or leukemia had been diagnosed Hemoglobin levels according to age were defined according to https://www.uptodate.com/contents/approach-to-the-child-with-anemia (accessed 06/30/2020).

Myelodysplastic syndrome	All reported diagnoses by self-report and/or medical report were considered. In all reported cases it was attempted to retrieve medical reports to corroborate the diagnosis. If available, diagnoses were verified according to the following criteria: Pathogenic abnormality by original cytogenic report and/or morphological sign of MDS by original pathology report.
Leukemia	Reported leukemia or lymphoma by pathology report and/or medical report and/or self-report.
Solid tumor	Any reported solid tumor or carcinoma in situ, including lymphomas and melanomas, by pathology report and/or medical report and/or self-report.
Non-melanoma skin cancer	Basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) reported by pathology report and/or medical report and/or self-report. In all reported cases it was attempted to retrieve pathology reports to corroborate the diagnosis.

NIH, National Institutes of Health; CT, Computer Tomography; MRI, Magnetic resonance imaging; ANC, absolute neutrophil count; Hb, hemoglobin; MDS, myelodysplastic syndrome

Supplemental Table 4: ACMG/AMP variant classification specifications

Variants were classified using The American College of Medical Genetics and Genomics/The Association for Molecular Pathology guidelines (ACMG/AMP). The software VarSeq™ v2.2.0 (Bozeman, MT: Golden Helix, Inc., available from http://www.goldenhelix.com)[3] and Varsome[4] were used during the variant classification process. No ACMG/AMP criteria were applied for TERC (RNA component of the telomerase). *TERC* gene variant evaluation was based on critical regions of the TERC secondary structure, absence in gnomAD, disease segregation, the variant's presence in several unrelated individuals with a consistent phenotype, and previous publications.[5]

The following tables lists the ACMG/AMP criteria and the adjustments applied in the context of evaluating variants in TBD-associated genes for our study cohort. Special consideration was given to varying modes of inheritance in TBD associated genes (*TERT, ACD, RTEL1, PARN).*

ACMG/ AMP criteria	ACMG criteria summary	Comments on usage	strength-level
PVS1	Null variant in a gene where LOF is a known mechanism of disease	Application based on SVI recommendations regarding predicted nonsense-mediated mRNA decay, presence in biologically relevant transcript, importance of the truncated protein domain, clinical significance of exons, identification of cryptic or newly generated splice sites. [6] Clinical validity of gene-disease associations defined according to Strande et al. 2017.[7] All currently with DC associated genes meet evidence level of definite or strong. Strength-level adjusted based on SVI recommendations.[6] For evaluation the publicly available tool AutoPVS1 (http://autopvs1.genetics.bgi.com/) was used. PVS1 ruled out PM4 to avoid double counting of evidence.	Supporting to very strong
PS1	Same amino acid change as a previously established pathogenic variant regardless of nucleotide change	Variants with an entry in ClinVar as likely pathogenic/pathogenic if criteria were available by the submitter and could be reviewed. [8,9] Evidence was based on the variants review status in ClinVar • Supporting: Criteria provided, single submitter or multiple submitters, conflicting interpretations • Moderate: Criteria provided, multiple submitters, no conflict • Strong: Reviewed by expert panel • Very strong: Practice guidelines	Supporting to very strong
PS2	De novo (both maternity and paternity confirmed) in a patient	PS2 was not applied in the context of our study evaluation, since maternity and paternity confirmation is not routinely available in the setting of an observational study. Instead PM6 was applied.	N/A

	with the disease and no family history		
PS3	Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product	Telomere length assays were not accepted as sole functional study evidence since telomere length (leukocyte flow FISH or other testing) can vary by the specific gene. Short telomeres could be caused by deleterious variants in any of the TBD genes. Additionally, it has previously been shown, that the absence of very short telomeres (<1st percentile) does not indicate the absence of a deleterious TBD gene variant– specifically in the context of AD disease. Therefore, only the combination of telomere length testing and other functional testing of a specific variant (for example telomerase activity measured by the fluorescent telomeric repeat-amplification protocol (TRAP) assay) justified the application of different strength levels of PS3.[10] Evidence was based on the framework published in Brnich et al. 2019.[10] Since only published functional studies were taken into consideration, evidence levels applied were exclusively supporting to moderate.	Supporting to very strong
PS4	The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls	Only applied for variants absent from gnomAD (meeting PM2), or described to be founder mutations in certain populations, but repeatedly described in unrelated probands with a phenotype consistent with TBD (pulmonary fibrosis, BMF, MDS or hematologic malignancies, with short/very short telomeres). Evidence level based on ClinGen's RASopathy Expert Panel Consensus Methods for Variant Interpretation.[11] • Supporting: 1-2 independent • Moderate: 3-4 independent occurrences • Strong: ≥5 independent occurrences	Supporting to strong
PM1	Located in a mutational hot spot and/or critical and well-established functional domain	Applied only to missense/in-frame variants located within functional domains. LoF variants are generally deemed to damage the function of the entire protein, irrespective of their location.[12]	Supportive to Moderate

	(e.g., active site of an enzyme) without benign variation	PM1 scoring was applied with the following criteria (based on Kopanos et al. 2019[4] and Ellard et al. 2020: ACGS Best Practice Guidelines for Variant Classification in Rare Disease 2020, accessible at https://www.acgs.uk.com/quality/best-practice-guidelines/). • Supporting: Functional protein domains based on UniProt (www.uniprot.org), was conserved, and no benign variants within 3 amino acid positions of the variant • Moderate: Hotspots as a region of 25 base-pairs on both sides of the evaluated variant, with at least 6 reported pathogenic variants within this region.	
PM2	Absent from controls (or at extremely low frequency if recessive)	Population databanks considered: gnomAD exome (or genome if insufficient coverage) and 1000 Genomes. SVI recommendations have considered reducing the evidence of PM2 to supportive (https://clinicalgenome.org/working-groups/sequence-variant-interpretation/). In the context of this study, we considered PM2 with moderate weight given the following adjustments (modified from criteria in Nykamp et al. 2017)[13]: • Supportive evidence: Applied only if present below the following MAF. For dominant and dominant/recessive inherited genes MAF<0.1%. For recessive inherited genes MAF<0.3%. • Moderate: If absent in population databanks or if <8 alleles total in gnomAD exomes (both AD and AR disease).	Supporting to Moderate
PM3	For recessive disorders, detected in trans with a pathogenic variant	Based on the recommendations by: ClinGen. (https://clinicalgenome.org/site/assets/files/3717/svi_proposal_for_pm3_criterion_-_version_1.pdf) only applied in recessive disorders, if detected in trans with a pathogenic or likely pathogenic variant in an affected patient.	Supporting to Moderate

		Was applied for all recessive variants and for variants in *TERT, PARN, RTEL1,* and *ACD*, which occurred in AD and in AR disease. • Supporting evidence if homozygous occurrence • Moderate evidence if in trans to a pathogenic/likely pathogenic variant	
PM4	Protein length changes as a result of in-frame deletions/insertions in a non-repeat region or stop-loss variants	Was not applied if PVS1 was used.[6]	Moderate
PM5	Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before	Variants with an entry in ClinVar as likely pathogenic/pathogenic if criteria were available by the submitter and could be reviewed. [8,9] Evidence was based on review status in ClinVar • Supporting: Criteria provided, single submitter or multiple submitters, conflicting interpretations • Moderate: Criteria provided, multiple submitters, no conflict • Strong: Reviewed by expert panel • Very strong: Practice guidelines	Supporting to very strong
PM6	Assumed de novo, but without confirmation of paternity and maternity	Applied in cases in which variant was identified in the index case and genotype data of the parents could be obtained. Only supporting evidence applied, since the TBD phenotype is consistent with gene but not highly specific (since other TBD associated genes also potentially cause similar disease). Based on the recommendations by: ClinGen. ClinGen sequence variant interpretation recommendation for de novo criteria (PS2/PM6) version 1.0, 2018. Available at	Supporting

		https://clinicalgenome.org/site/assets/files/3461/svi_proposal_for_de_novo_criteria_v1_0.pdf	
PP1	Cosegregation with disease in multiple affected family members in a gene definitively known to cause the disease	Applied genotype-positive individuals (or obligate carriers) within one or across multiple families with the following strength levels (modified from Nykamp et al. 2017).[13] A positive phenotype was considered as the presence of pulmonary fibrosis, moderate to severe BMF, liver disease, triad features with short telomeres.[5,14] Supportive: Minimum of 3 individuals with dominant or 2 individuals with 2 rare variants in trans and affected with a recessive condition Moderate: Six dominant or 3 recessive affected individuals from at least 2 families Strong: 10 dominant or 5 recessive affected individuals from 2 or more families	Supporting to strong
PP2	Missense variant in a gene that has a low rate of benign missense variation and in which missense variants are a common mechanism of disease	Only applied in genes with a missense constraint score (gnomAD) ≥3.09.[15] For the evaluated genes within this study, this was only true for *TERT* and *DKC1.*	Supporting
PP3	Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc.)	Applied for missense variants REVEL, MetaSVM and BayesDel (applied score BayesDel_noAF) were used as in silico prediction tools.[16-18] The binary threshold applied for REVEL was set at 0.5 (with >0.5 for deleterious). If at least 2 of the in silico tools agreed as being deleterious, PP3 was applied. Only supportive evidence was applied since there is currently not a consensus-based approach for the application of in silico prediction tools.[16]	Supporting
PP4	Patient's phenotype or family history is highly specific for a	For the Inherited Bone Marrow Failure Syndrome study at the National Cancer Institute, each participant is enrolled based on clinical, family history and	Supporting

	disease with a single genetic etiology	diagnostic findings. For the current study, all study subjects were participating in the same study. In this context, PP4 was therefore scored as supporting evidence.	
PP5	Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation	According to the recent SVI recommendations PP5/BP6 should not be applied.[19]	N/A
BS2	Observed in a healthy adult individual for a recessive (homozygous), dominant (heterozygous), or X-linked (hemizygous) disorder, with full penetrance expected at an early age	Not applicable in the context of the current evaluation. TBD associated variants have been described previously to have incomplete penetrance.[20]	N/A
BS3	Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing	See PS3	Supporting to strong
BS4	Lack of segregation in affected members of a family	Since the presented study cohort of a pre-selected group of probands clinically determined to be TBD affected, BS4 was not applied. PP1 was considered. Additional information for scoring of segregation see PP1.	N/A
BP1	Missense variant in a gene for which primarily truncating variants are known to cause disease	Was not applied since despite a missense constraint score (gnomAD) ≤3.09 in *ACD*, *RTEL1, CTC1, WRAP53, TINF2* and *PARN*, all the mentioned genes do not have only truncating variants as cause of disease. In all genes, missense variants have also been reported as disease causing.	Supporting
BP2	Observed in trans with a pathogenic variant for a fully	See PM3	N/A

	penetrant dominant gene/disorder or observed in cis with a pathogenic variant in any inheritance pattern		
BP4	Multiple lines of computational evidence suggest no impact on gene or gene product (conservation, evolutionary, splicing impact, etc.)	Applied for missense variants. True if 3 selected in silico prediction scores (BayesDel_noAF, REVEL, and MetaSVM) predicted variant to be tolerated (REVEL <0.5), or if 2 predicted tolerated and the position was not conserved.	Supporting
BP5	Variant found in a case with an alternate molecular basis for disease	Individuals with an identified possible alternate molecular base for disease (or a gene not considered a TBD associated gene as of May 2019) were excluded from this study.	N/A
BP7	A synonymous (silent) variant for which splicing prediction algorithms predict no impact to the splice consensus sequence nor the creation of a new splice site AND the nucleotide is not highly conserved	Carriers of synonymous variants in TBD-associated genes were not considered in the context of the here presented study.	N/A

Supplemental Table 5: variants in telomere biology disorder-associated genes in study participants and variant curation using adapted ACMG/AMP criteria

Gene	Zygosity	cDNA change	AA change	functional classification	ACMG classification	Applied ACMG/AMP criteria	# of affected families in this cohort
ACD	Comp Het	c.1213C>A	p.P405T	missense	VUS-P (evidence for modifier in functional studies)	PM2_Supporting PM3 PP4 BP4_Supporting	1
ACD[§]	Comp. Het, Het	c.250_252del	p.K84del	Inframe deletion	LP	PS3 PS4_Supporting PM2 PM4 PP4	1
CTC1[#]	Comp. Het	c.2959C>T	p.R987W	missense	LP	PS3_Supporting PS1_Supporting PM2_Supporting PM3 PP1 PP3 PP4	1
CTC1[#]	Comp. Het	c.1270T>G	p.C424G	missense	LP	PM2_Supporting PM3 PP1 PP3 PP4	1
CTC1	Comp. Het	c.2954_2956del	p.C985del	Inframe deletion	LP	PS3_Supporting PM2 PM3 PM4 PP4	4
CTC1	Comp. Het	c.1186C>T	p.R396*	stop gained	P	PVS1 PM2 PP4	1
CTC1	Comp. Het	c.724_727del	p.K242Lfs*?	frameshift	P	PVS1 PS3_Supporting PM2_Supporting PM3 PP1 PP4	3
DKC1	Hemiz	c.103_105del	p.E35del	Inframe deletion	LP	PM1 PM2 PM4 PP4	1
DKC1	Hemiz	c.1058C>T	p.A353V	missense	LP	PS1_Supporting PS3_Moderate PS4_Moderate PM1 PP2 PP3 PP4	4
DKC1	Hemiz	c.109_111del	p.Leu37del	Inframe deletion	LP	PS3_Supporting PS4_Supporting PM1 PM2 PM4 PP2 PP3 PP4	1
DKC1	Hemiz	c.1168A>C	p. K390Q	missense	LP	PS3_Supporting PM2 PP2 PP3 PP4	1
DKC1	Hemiz	c.1178T>A	p.I393N	missense	LP	PM1_Supporting PM2 PP2 PP3 PP4	1
DKC1	Hemiz	c.1223C>T	p.T408I	missense	LP	PS4_Supporting PM2 PP2 PP3 PP4	1
DKC1	Hemiz	c.1345C>G	p.R449G	missense	LP	PS1_Supporting PM2 PP2 PP3 PP4	1
DKC1	Hemiz	c.146C>T	p.T49M	missense	P	PS1_Moderate PS3_Supporting PS4_Moderate PM1 PM2 PM6_Supporting PP2 PP3 PP4	1
DKC1	Hemiz	c.160C>G	p.L54V	missense	LP	PS3_Supporting PS4_Supporting PM2 PM1 PP1 PP2 PP3 PP4	2
DKC1	Hemiz	c.191T>G	p.V64G	missense	LP	PM1 PM2 PP2 PP3 PP4	1

DKC1	Hemiz	c.196A>G	p.T66A	missense	LP	PS3_Supporting PM1 PM2 PP2 PP3 PP4	1
DKC1	Hemiz	c.209C>T	p.T70I	missense	LP	PS3_Supporting PM1 PM2 PP2 PP3 PP4	1
DKC1	Hemiz	c.277A>T	p.N93Y	missense	VUS-P (has evidence for pathogenicity but does not completely fulfill ACMG/AMP criteria)	PM2 PP2 PP3 PP4	1
DKC1	Hemiz	c.5C>T	p.A2V	missense	LP	PS4_Moderate PM1 PM2 PP2 PP3 PP4	1
DKC1	Hemiz	c.941A>G	p. K314R	missense	LP	PS3_Supporting PS4_Supporting PM1 PM2 PP1 PP2 PP3 PP4	1
DKC1	Hemiz	c.949C>T	p. L317F	missense	LP	PS4_Moderate PM1 PM2 PP2 PP3 PP4	1
DKC1	Hemiz	c.965G>A	R322Q	missense	LP	PS4_Supporting PM1 PM2 PP1 PP2 PP3 PP4	1
PARN#§	Comp. Het, Het	c.260C>T	p.S87L	missense	LP	PS3_Supporting PM1 PM2 PP4	1
PARN#§	Comp. Het, Het	c.19A>C	p.N7H	missense	LP	PS3_Supporting PS4_Supporting PM2 PM3_Supporting PP4	1
PARN	Comp. Het	c.-63C>T	-	5 prime UTR	VUS-P (deemed to contribute to disease when compound heterozygote state)	PM2 PM3 PP4	1
PARN§	Comp. Het	c.709C>T	p.R237*	stop gained	P	PVS1 PS4_Moderate PM2 PP4	1
PARN#§	Comp. Het, Het			deletion encompassing PARN locus per SNP array: chr16:14,037,911 - 15,319,123	NA		1
PARN#	Comp. Het, Het			noncoding defect affecting accumulation of PARN	NA		1
RTEL1#§	Comp. Het, Het	c.1675T>A	p.F559I	missense	LP	PS4_Supporting PM1_Supporting PM2 PM3 PP3 PP4	1
RTEL1	Het	c.3506C>A	p.S1169*	stop gained	LP	PVS1 PM2 PP4	1
RTEL1§	Comp. Het, Het	c.3289del	p.A1097Lfs*6	frameshift	P	PVS1 PM2 PM3 PP1 PP4	1
RTEL1	Het	c.1861G>A	p.A621T	missense	LP	PM1_Supporting PM2 PP1 PP3 PP4	1

RTEL1§	Comp. Het, Het	c.1773G>T	p.E591D	missense	LP	PM1_Supporting PM2 PM3 PP3 PP4	1
RTEL1§	Comp. Het, Het	c.3370del	p.H1124Tfs*12	frameshift	P	PVS1 PS1_Supporting PM2 PM3 PP1 PP4	1
RTEL1	Comp. Het	c.1274T>C	p.I425T	missense	LP	PS4_Supporting PM2 PM3 PP3 PP4	1
RTEL1#§	Comp. Het, Het	c.1476G>T	p.M492I	missense	LP	PS1_Moderate PS3_Moderate PS4_Moderate PM2_Supporting PP1 PP3 PP4	2
RTEL1§	Comp. Het, Het	c.49C>T	p.P17S	missense	LP	PS1_Supporting PM1_Supporting PM2 PM3 PP1 PP3 PP4	1
RTEL1§	Comp. Het, Het	c.3445del	p.Q1149Rfs*?	frameshift	LP	PVS1_Strong PM2 PM3 PP1 PP4	1
RTEL1§	Comp. Het, Hom, Het	c.3791G>A	p.R1264H	missense	LP	PS1_Moderate PS3_Moderate PS4_Supporting PM2_Supporting PM3 PP1 PP4	2
RTEL1	Comp. Het	c.2920C>T	p.R974*	stop gained	P	PVS1 PS3_Moderate PS4_Moderate PM2_Supporting PM3 PP1_Moderate PP4	2
RTEL1	Het	c.2956C>T	p.R986*	stop gained	P	PVS1 PM2_Supporting PP1 PP4	3
RTEL1#§	Comp. Het, Het	c.137C>T	p.T46I	missense	LP	PM1_Supporting PM2 PM3 PP3 PP4	1
RTEL1§	Comp. Het, Het	c.1266+3A>G	-	splice region	LP	PM2 PP4 PP1 PM3	1
RTEL1	Hom	c.2025+4A>C	-	splice region	VUS-P (evidence of pathogenicity, however lacking family data, so ACMG/AMP criteria not fulfilled)	PM2 PM3_Supporting PP3 PP4	1
RTEL1§	Hom, Het	c.2142-7C>G	-	splice region	LP	PS3_Moderate PM2 PM3_Supporting PP4	1
TERC	Het	n.97_98del	-	TERC	P		1
TERC	Het	n.100T>A	-	TERC	P		1
TERC	Het	n.56_62del	-	TERC	P		1
TERC	Het	n.334_339dupGGGGCG	-	TERC	LP		1
TERC	Het	n.114_115del	-	TERC	P		1
TERC	Het	n.413_417del	-	TERC	LP		1

TERC	Het	n.381G>A	-	TERC	P		1
TERC[#]	Het	n.56_58del	-	TERC	P		1
TERC	Het	n.357_365del	-	TERC	LP		1
TERT	Het	c.416T>G	p.L139R	missense	LP	PS4_Supporting PM1 PM2 PP2 PP3 PP4	1
TERT	Comp. Het	c.2455C>T	p.R819C	missense	LP	PS1_Supporting PS4_Supporting PM2 PM1 PP2 PP4	1
TERT[§]	Comp. Het, Het	c.1990G>A	p.V664M	missense	LP	PM1 PM2 PM3 PM5_Supporting PP2 PP4	1
TERT	Het	c.2935C>T	p. R979W	missense	LP	PS3_Supporting PS4_Moderate PM1 PM2 PP2 PP3 PP4 PP1	2
TERT	Het	c.2947C>T	p.H983Y	missense	LP	PS4_Moderate PM1 PM2 PP2 PP4	1
TERT[#]	Het	c.3257G>A	p.R1086H	missense	VUS-P (has evidence for pathogenicity but does not completely fulfill ACMG/AMP criteria)	PM1 PM2_Supporting PP2 PP4	1
TERT[#]	Het	c.2318T>C	p.M773T	missense	LP	PS4_Supporting PM1 PM2 PP2 PP3 PP4	1
TERT	Het	c.2575C>T	p.R859W	missense	LP	PM1 PM2 PP2 PP4 BP4	1
TERT	Het	c.2593C>T	p.R865C	missense	LP	PM1 PM2 PP2 PP3 PP4	1
TERT	Het	c.2110C>T	p. P704S	missense	LP	PS3_Moderate PS4_Moderate PM1 PM2 PP2 PP3 PS3 PP4	3
TERT[§]	Hom, Het	c.3150G>C	p.K1050N	missense	LP	PS4_Moderate PM3_Supporting PP1 PP2 PP3 PP4	1
TERT	Het	c.2768C>T	p.P923L	missense	LP	PS4_Moderate PM1 PM2 PP1 PP2 PP3 PP4	1
TERT	Het	c.3205G>A	p.A1069T	missense	LP	PS4_Supporting PM1 PM2 PP1 PP2 PP3 PP4	2
TERT	Het	c.2591T>C	p.L864P	missense	LP	PM2 PM1 PP1 PP2 PP3 PP4	1
TERT	Het	c.2603A>G	p.D868G	missense	LP	PM2 PM1 PP2 PP3 PS1_Supporting PP4 PP1	1
TERT	Het	c.2240del	p.V747Afs*20	frameshift	P	PVS1 PS4_Supporting PM2 PP1 PP4	1
TERT	Het	c.320_328del	p.A107_G109del	Inframe deletion	LP	PM1 PM2 PM4 PP1 PP4	1
TERT[#]	Het			1.4 Mb deletion at 5p15.33 including TERT	NA		1

TERT	Het	c.258G>C	p.Q86H	missense	LP	PM1 PM2 PP2 PP3 PP4	1
TINF2	Het	c.838A>G	p. K280E	missense	LP	PS3_Supporting PM1 PM2 PP1 PP3 PP4	1
TINF2	Het	c.845G>A	p. R282H	missense	P	PS1_Moderate PS3_Moderate PS4 PM1 PM2 PM5 PM6_Supporting PP1 PP3 PP4	5
TINF2	Het	c.844C>A	p. R282S	missense	P	PS4 PM1 PM2 PM5 PM6_Supporting PP1 PP3 PP4	1
TINF2	Het	c.873G>C	p. R291S	missense	LP	PM1 PM2 PP1 PP3 PP4	1
TINF2	Het	c.830del	p.G277Efs*?	frameshift	P	PVS1 PM2 PP4	1
TINF2	Het	c.860T>C	p.L287P	missense	LP	PS4_Supporting PM1 PM2 PP3 PP4	1
TINF2	Het	c.847C>T	p.P283S	missense	LP	PS1_Supporting PS4_Moderate PM1 PM2 PP2 PP3 PP4	1
TINF2	Het	c.851_852del	p.T284Sfs*7	frameshift	P	PVS1 PM1 PM2 PM6 PP4	1
TINF2	Het	c.815G>A	p.W272*	stop gained	P	PVS1 PM2 PM6_Supporting PP4	1
WRAP53	Comp. Het	c.1126C>T	p.H376Y	missense	LP	PS3_Moderate PM2 PM3 PP4	1
WRAP53	Comp. Het	c.492C>A	p.F164L	missense	LP	PS1_Supporting PS3_Moderate PM2 PM3 PP4 BP4_Supporting	1
WRAP53	Comp. Het	c.1303G>A	p.G435R	missense	LP	PS3_Moderate PM2 PM3 PP3 PP4	1
WRAP53	Comp. Het	c.1192C>T	p.R398W	missense	LP	PS3_Moderate PM2 PM3 PP3 PP4	1
WRAP53	Comp. Het	c.1135G>A	p.G379S	missense	LP	PM2 PM3 PP3 PP4	1
WRAP53	Comp. Het	c.438G>A	p.W146*	stop gained	LP	PVS1 PM2 PP4	1

Genome reference consortium human build 37. RefSeq Transcript ID for each gene: *ACD*: NM_001082486.2, *CTC1*: NM_025099.6. *DKC1*: NM_001363.5, *PARN*: NM_002582.4, *RTEL1*: NM_001283009.1 (XM_005260207.1), *TERC*: NR_001566.1, *TERT*: NM_198253.3, *TINF2*: NM_001099274.3, WRAP53: NM_001143992.2

§ variants identified in family members of index cases with AR inheritance.

No original report available, documentation based on research report.

Abbreviations: comp. het, compound heterozygous; hom, homozygous: het, heterozygous.

Supplemental Table 6: Characteristics of participants divided by gene and inheritance pattern.

	AD-*RTEL1*	AD-*TERT*	AD-*TERC*	AD-*PARN/ACD*	AD-*TINF2*	AR-*RTEL1*	AR-others (*TERT, PARN, WRAP53, ACD*)	*DKC1*
# of patients	29	47	30	6	25	15	16	32
Male:Female	12:17	25:22	13:17	2:4	16:9	8:7	13:3	32:0
Median age at diagnosis, range (# of excluded patients)	35.52, 1.32-63.75 (2)	34.72, 0.74-69.44 (6)	31.87, 11.84-58.81 (8)	50.2, 9.41-58.48	8.08, 0-71.58 (1)	5.08, 0.78-16.93 (4)	15.51, 2.59-29.76 (0)	9.99, 0-45.89 (3)
Median age at last follow-up, range	37.68, 2.4-66.5	43.12, 2.68-81.56	43.5, 18.6-82.17	49, 14.61-59.30	19.26, 4.63-79.58	16.2, 2.16-26.33	25.4, 13.42-33.93	27.95, 1.36-54.18
Total number of patients with TL assays available	24	36	19	6	19	8	14	20
• Stratified by inheritance pattern	85				19	42		
TL percentile <1 (% of patients with TL available)	7 (29)	24 (67)	17 (89)	2 (33)	18 (95)	8 (100)	12 (86)	20 (100)
• Stratified by inheritance pattern	50				18	40		
TL percentile ≥1 (% pf patients with TL available)	17 (71)	12 (33)	2 (11)	4 (67)	1 (5)	0	2 (14)	0

AD, autosomal dominant; AR, autosomal recessive; TL, telomere length measured by flow cytometry with *in situ* hybridization in lymphocytes.

Supplemental Table 7. Clinical complications divided by gene and inheritance pattern.

	AD-*RTEL1*	AD-*TERT*	AD-*TERC*	AD-*PARN/ACD*	AD-*TINF2*	AR-*RTEL1*	AR-others	*DKC1*
# of patients	29	47	30	6	25	15	16	32
Deceased [%]	5 [17.2]	12 [25.5]	14 [46.7]	0	14 [56]	7 [46.7]	8 [50]	23 [71.9]
Age at death in years median, range	23.9, 2.4-66.5	64.2, 28.81-81.56	52.5, 24.67-82.17	NA	16.4, 4.63-79.58	7.6, 2.16-25.13	27.2, 13.79-33.93	28.2, 1.36-54.18
Median overall survival, 95% CI	66.5, 52.37-NA	66.6, 57.34-79.47	54.5, 44.45-63.23	NA	37.9, 13.49-47.31	22.9, 4.34-NA	33.2, 16.13-NA	36.6, 20.49-44.48
Causes of death	Cancer (1), pulmonary (2), treatment related (2)	Cancer (2), pulmonary (6), treatment related (2), unknown (2)	Cancer (1), severe BMF (1), pulmonary (4), treatment related (3), other/unknown (5)	NA	Cancer (4), severe BMF (1), hepatic (2), pulmonary (3), treatment related (2), other/unknown (2)	Severe BMF (3), pulmonary (2), treatment related (1), other (1)	Severe BMF (2), treatment related (2), hepatic (1), pulmonary (1), unknown (2)	Pulmonary (6), severe BMF (4), Cancer (4), treatment related (4), unknown (5)
Hematopoietic cell transplant [%]	5 [17.2]	4 [8.5]	11 [36.7]	0	15 [60]	9 [60]	6 [37.5]	12 [37.5]
Lung transplant [%]	0	3 [6.4]	2 [6.7]	0	2 [8]	0	0	0
Liver transplant [%]	0	1 [2.1]	0	0	0	2 [13.3]	1 [6.3]	0
Severe bone marrow failure [%]	4 [13.8]	12 [25.5]	17 [56.7]	0	19 [76]	13 [86.7]	11 [68.8]	20 [62.5]
Pulmonary fibrosis								
• Prior to HCT [%]	1 [3.4]	11 [23.4]	10 [33.3]	0	2 [8]	1 [6.7]	3 [18.8]	2 [6.3]
• Following HCT [%]§	0	0	1 [9.1]	0	5 [33.3]	3 [33.3]	0	3 [25]
Pulmonary arteriovenous malformations								
• Prior to HCT [%]	0	0	0	0	0	0	1 [6.3]	0
• Following HCT [%]§	1 [20]	0	0	0	4 [26.7]	3 [33.3]	2 [33.3]	1 [8.3]

	AD-*RTEL1*	AD-*TERT*	AD-*TERC*	AD-*PARN/ACD*	AD-*TINF2*	AR-*RTEL1*	AR-others	*DKC1*
# of patients	29	47	30	6	25	15	16	32
Severe liver disease								
○ Prior to HCT [%]	0	2 [4.3]	0	0	0	0	4 [25]	2 [6.3]
○ Following HCT [%][§]	0	1 [25]	1 [9.1]	0	3 [20]	2 [22.2]	1 [16.7]	0
Gastrointestinal complications								
• Esophageal strictures [%]	0	1 [2.1]	1 [3.3]	0	0	7 [46.7]	3 [18.8]	4 [12.5]
• GI telangiectasias								
○ Prior to HCT [%]	0	2 [4.3]	0	0	0	0	4 [25]	1 [3.1]
○ Following HCT [%][§]	0	0	1 [9.1]	0	2 [13.3]	1 [11.1]	1 [16.7]	0
Avascular osteonecrosis								
○ Prior to HCT [%]	0	8 [17]	2 [6.7]	0	2 [8]	0	3 [18.8]	4 [12.5]
○ Following HCT [%][§]	2 [40]	1 [25]	0	0	2 [13.3]	2 [22.2]	1 [16.7]	1 [8.3]
Myelodysplastic syndrome [%]	0	4 [8.5]	8 [26.7]	0	0	0	1 [6.3]	3 [9.4]
Cancer								
○ Prior to HCT [%]	1 [3.4]	6 [12.8]	6 [20]	0	1 [4]	0	1 [6.3]	7 [21.9]
○ Following HCT [%][§]	0	0	0	0	3 [20]	1 [11.1]	0	1 [8.3]

[§] % of patients with HCT; AD, autosomal dominant; AR, autosomal recessive; HCT, hematopoietic cell transplantation; CI confidence interval; BMF, bone marrow failure

Supplemental Table 8: Transplantation data and details on mortality in study participants stratified by inheritance pattern groups

	Total	AD-non*TINF2*	AR/XLR	*TINF2*	Unknown
Transplanted patients*					
Hematopoietic cell transplant (HCT)					
• # of patients,	70	20	27	15	8
median age in years (range)	15.44 (0.9-63.1)	26.1 (2.2-63.1)	16.8 (0.9-34.7)	5.7 (2.1-47.3)	9.4 (2.5-31.5)
○ HCT type					
▪ MSD	9				
▪ MUD	51				
▪ MMUD	1 (8/10)				
▪ CB	5				
▪ No information	4				
○ Reason for transplant					
▪ BMF	57				
▪ BMF/AML	3				
▪ BMF/MDS	8				
▪ BMF/Immunodeficiency	2				
Lung transplant					
• # of patients,	8	5	0	2	1
• median age in years (range)	51.4 (13.1-62.4)	53.7 (32.5-62.4)	NA	29.3 (13.1-45.5)	52.1
○ Reason for transplant	PF, PF/HPS				
○ Previous HCT	2	1	0	1	0
Liver					
• # of patients	4	1	3	0	0
• median age in years (range)	27.8 (21-56.7)		25.8 (21-29.8)		
○ Reason for transplant**	HPS , HPS/LF				
○ Previous HCT	2	0	2	0	0

Deceased patients					
# of patients deceased at last follow up	97	31	38	14	14
Bone marrow failure	15	1	9	1	4
Pulmonary	27	12	9	3	3
Liver	3 (2 HPS)	0	1	2	0
Cancer	15	4	4	4	3
Treatment related	19	7	7	2	3
Other	3	1	1	1	0
Missing data	15	6	7	1	1

* One patient received kidney transplant for chronic kidney disease stage 4 due BK virus nephropathy with severe nephrosclerosis.

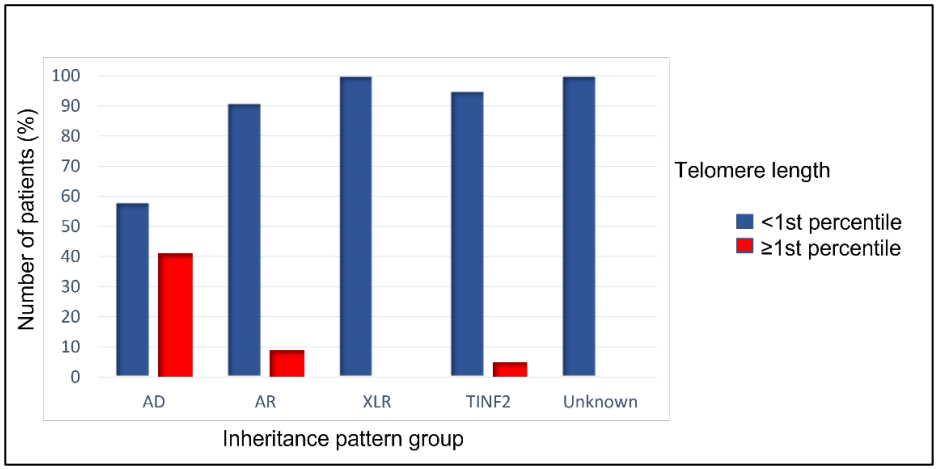
** In one patient final diagnosis leading to liver transplant not documented.

Abbreviations: HCT, hematopoietic cell transplantation; MSD, matched sibling donor; MUD, matched unrelated donor; MMUD, mismatched unrelated donor; CB, cord blood; BMF, bone marrow failure; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; HPS, hepatopulmonary syndrome; LF, liver fibrosis; PF, pulmonary fibrosis.

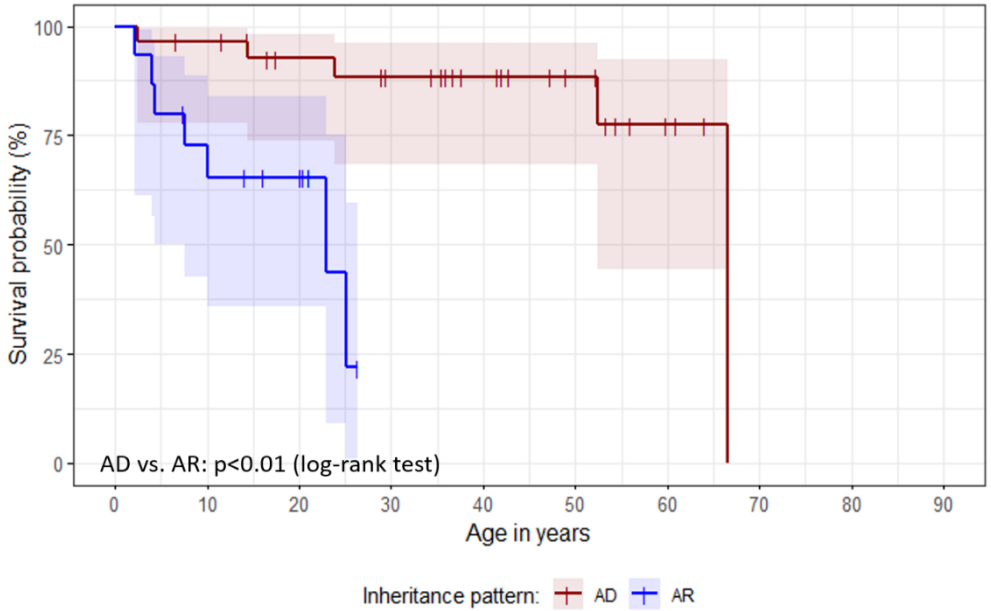
Supplemental Table 9

Association	OR* (p-value) without adjusting for telomere length	OR (p-value) with adjusting for telomere length (<1st vs ≥1st percentile)
Severe bone marrow failure	AR/XLR = 8.7 (<0.001) *TINF2* = 7.5 (<0.001)	AR/XLR = 6.1 (<0.001) *TINF2* = 5.3 (0.004)
Pulmonary fibrosis (adjusted for age at DC diagnosis: pediatric vs adult)	AR/XLR = 1.6 (0.481) *TINF2* =2.1 (0.422)	AR/XLR =1.8 (0.429) *TINF2* = 2.2 (0.388)
Severe liver disease (adjusted for sex and age at DC diagnosis: pediatric vs adult)	AR/XLR = 7.6 (0.063)	AR/XLR = 13.3 (0.048)
Gastrointestinal telangiectasias	AR/XLR = 3.2 (0.214)	AR/XLR= 6.9 (0.108)
Esophageal strictures (adjusted for age at DC diagnosis: pediatric vs adult)	AR/XLR = 3.4 (0.035)	AR/XLR = 4.2 (0.026)
AVN	AR/XLR = 1.3 (0.663)	AR/XLR = 0.9 (0.811)
	HR (p-value) without adjusting for telomere length	**HR (p-value) with adjusting for telomere length (<1st vs ≥1st percentile)**
Cancer risk (adjusted for sex and age at DC diagnosis: pediatric vs adult)	AR/XLR = 10.7 (0.007)	AR/XLR = 5.5 (0.056)
Mortality risk	AR/XLR/*TINF2* = 7.4 (<0.001)	AR/XLR/*TINF2* = 4.8 (<0.001)

All clinical complications with no prior hematopoietic cell transplantation. Reference group is AD-non*TINF2* for all analyses except for esophageal strictures, where AR/XLR is compared with *TINF2* and AD-non*TINF2* combined. OR's and HRs are not equal to the ones reported in the manuscript because those with TL measurements are a subset (n=146 with known genotype and TL measurement available) of the cohort used in the manuscript (n=200 with known genotype). OR, Odds ratio; HR, hazard ratio.

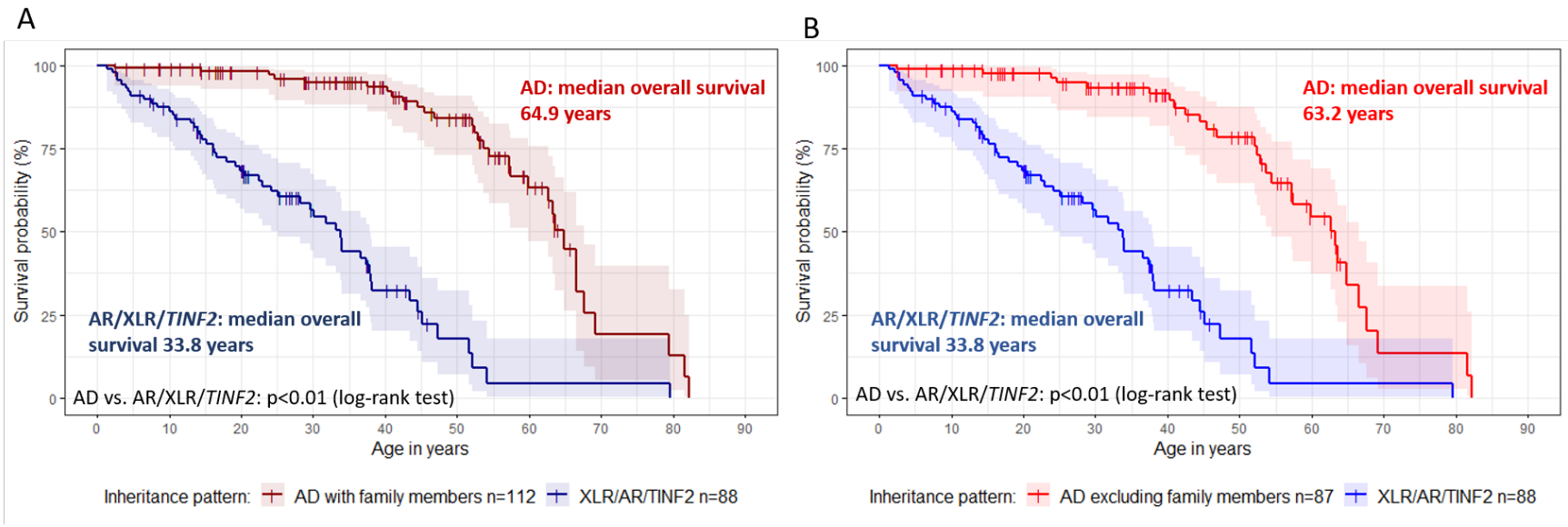


Supplemental Figure 1: Lymphocyte telomere length percentiles of 171 patients with DC/TBDs grouped by inheritance pattern. Depicted are the number of patients (%) in each category of lymphocyte telomere length from flow cytometry with fluorescent *in situ* hybridization (flow FISH). Lymphocyte telomere length categories: <1st percentile (blue) versus ≥ 1st percentile (red). AD: autosomal dominant/non-*TINF2*, n= 85; AR: autosomal recessive, n= 22; XLR: X-linked recessive, n=20; TINF2: autosomal dominant *TINF2* disease, n=19; Unknown: unknown genotype, n=25.



Supplemental Figure 2: Overall survival of individuals with *RTEL1* variants (total n=44): autosomal dominant (n=29, red) versus autosomal recessive (n=15, blue) inheritance pattern group.

Supplemental Figure 3: Overall survival of individuals with autosomal dominant (AD) telomere biology disorders versus individuals with either autosomal recessive (AR), X-linked (XLR) or *TINF2* associated telomere biology disorders. AD group including (A) or excluding (B) 25 family members with heterozygous pathogenic variants and the index case having autosomal recessive disease.



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