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IN A NUTSHELL

Different phenotypes with different endings—Telomere biology disorders and cancer predisposition with long telomeres

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Summary
Rare germline pathogenic variants (GPVs) in genes essential in telomere length maintenance and function have been implicated in two broad classes of human disease. The telomere biology disorders (TBDs) are a spectrum of life-threatening conditions, including bone marrow failure, liver and lung disease, cancer and other complications caused by GPVs in telomere maintenance genes that result in short and/or dysfunctional telomeres and reduced cellular replicative capacity. In contrast, cancer predisposition with long telomeres (CPLT) is a disorder associated with elevated risk of a variety of cancers, primarily melanoma, thyroid cancer, sarcoma, glioma and lymphoproliferative neoplasms caused by GPVs in shelterin complex genes that lead to excessive telomere elongation and increased cellular replicative capacity. While telomeres are at the root of both disorders, the term TBD is used to convey the clinical phenotypes driven by critically short or otherwise dysfunctional telomeres and their biological consequences.

KEYWORDS
cancer, genetics, telomere

Rare germline pathogenic variants (GPVs) in genes essential for telomere length maintenance (TLM) and function cause a broad spectrum of disorders. The biological consequences of these GPVs range from short or dysfunctional telomeres and reduced cellular replicative potential to long telomeres and increased cellular replicative capacity.

DYSKERATOSIS CONGENITA WAS THE FIRST DISORDER TO LINK GERMLINE GENETICS, TELOMERE DYSFUNCTION AND HUMAN DISEASE

X-linked recessive GPVs in *DKC1* were the first identified connection between dyskeratosis congenita (DC) and very short telomeres, making DC the prototypic telomere biology disorder (TBD).[1,2] DC is diagnosed clinically by the mucocutaneous triad of oral leukoplakia, nail dysplasia and abnormal skin pigmentation or the presence of two of the triad and bone marrow failure.[3] Individuals with DC are also at high risk of pulmonary fibrosis, acute myeloid leukaemia, myelodysplastic syndrome, head and neck squamous cell carcinoma (HNSCC), cryptogenic liver disease, oesophageal and lacrimal duct stenosis and avascular necrosis, among other complications.[4–8]

TBDs ARE A SPECIFIC SPECTRUM OF ILLNESSES CAUSED BY TELOMERE DYSFUNCTION

Several subtypes of TBDs present early in childhood and are caused by GPVs in the same genes as DC. Features of

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Hoyeraal–Hreidarsson syndrome include cerebellar hypoplasia, immunodeficiency and intrauterine growth restriction. Bilateral exudative retinopathy, intracranial calcifications and intrauterine growth restriction are features of Revesz syndrome and Coats plus.[9–11] Additionally, individuals with Coats plus typically have cerebral cysts, a tendency to fractures and telangiectasia-associated gastrointestinal bleeding.[10]

The identification of GPVs in TLM genes in individuals and families with only one or two clinical or overt features of DC (e.g. pulmonary fibrosis) and the development of lymphocyte telomere length (TL) measurement as a diagnostic test led to the recognition of variable penetrance and expressivity and the term 'telomere biology disorder'.[12] Individuals with TBDs generally have median lymphocyte TL <10th percentile for age, with the shortest telomeres (<1st percentile) correlating with earlier age at onset, autosomal or X-linked recessive or heterozygous *TINF2* PGVs.[6,13] GPVs in >17 genes are associated with TBDs.[4–8]

TBD PHENOTYPES RESULT FROM LIMITED STEM CELL RENEWAL INDUCED BY CRITICALLY SHORT TELOMERES

Telomeres consist of kilobase pairs of TTAGGG repeats at chromosome ends coated with a six-protein complex called shelterin. They are essential for maintaining chromosomal integrity yet shorten with each cell division in cells lacking or with limited levels of telomerase (most human somatic cells). Cellular senescence or apoptosis is triggered when telomeres reach a critically short length (the Hayflick limit). The mechanisms causing short telomeres vary in TBDs.[14] In individuals without TBDs, in addition to age, telomere shortening is associated with oxidative stress such as from smoking or other lifestyle factors.[15] GPVs in components of the telomerase complex or proteins involved in the maturation of the telomerase RNA subunit compromise telomerase catalytic activity, thereby reducing the extension of TTAGGG repeats. Without affecting telomerase activity per se, GPVs in factors required for telomerase trafficking within the nucleus or its recruitment to telomeres also reduce TL. Alternatively, GPVs may impact factors required for telomere stability by impairing telomere replication. For *TINF2* exon 6 GPVs, the precise molecular mechanism causing extremely short telomeres remains incompletely understood.

SOME TBDs HAVE TELOMERE INSTABILITY WITHOUT GLOBALLY SHORT TELOMERES

TBDs may result from GPVs in the shelterin component *POT1* that alters the fill-in step of replication at the telomeric end, resulting in dysregulated telomere elongation, instability and stochastic truncations.[14] Biallelic GPVs in *CTC1* and *STN1* similarly affect the structure of the telomere end and telomere stability, whereas those in *DCLRE1B* do so via a different mechanism.[16]

A DISTINCT SET OF CANCER-PRONE INHERITED DISORDERS HAVE LONG TELOMERES

At the opposite end of the TL range are cancer-prone disorders caused by GPVs in some of the same genes as the TBDs but associated with TL >90th percentile for age, without typical TBD-related clinical features and with different effects on telomeres.[15] The first discovery of such GPVs were in *POT1* and associated with long telomeres in familial melanoma.[17,18] Subsequent studies added glioma, angiosarcoma (mainly cardiac) and chronic lymphocytic leukaemia to the cancer spectrum, leading to the designation of '*POT1* tumour predisposition (TPD)' as a specific syndrome.[19] Other sarcomas, thyroid cancer, Hodgkin lymphoma, myeloid malignancies and clonal haematopoiesis have been suggested part of the *POT1*-TPD spectrum.[15,20,21]

GPVs in shelterin components, *ACD*, *TERF2IP*, *TINF2* and *TERF1*, have also been associated with long telomeres and cancers seen in *POT1*-TPD. To date, GPVs in *TERF2*, the sixth shelterin protein, have not been described. *ACD* or *TERF2IP* GPVs are associated with familial melanoma.[15] *TINF2* GPVs were identified in individuals from cancer-prone families, including papillary thyroid cancer and multiple primary melanoma.[15,22] The association of sarcoma with shelterin proteins has also expanded to include *TERF1*, *TERF2IP* and *TINF2*.[15] Notably, although some of the genes with long telomere-GPVs are among those associated with TBDs, none of the individuals with shelterin complex GPVs and long telomeres have been reported to have TBD phenotypes.

LONG TELOMERES CONFER A GREATER REPLICATIVE CAPACITY SINCE MORE CELL DIVISIONS ARE NEEDED BEFORE TELOMERES REACH A CRITICALLY SHORT LENGTH AND TRIGGER APOPTOSIS OR SENESCENCE

Cells with engineered heterozygous *POT1* or *TINF2* variants associated with familial cancer have excessive telomere elongation yet lack a defect in telomere end protection.[23,24] One reported mechanism is that *POT1* mutations weaken its interaction at the telomere, allowing for more telomerase access and telomere lengthening. Thus, the increased risk of cancer conferred by this class of variants is proposed to be via the greater proliferative capacity endowed by the long telomeres, increasing the population of cells that may acquire mutations to drive cancer progression over time.

WE PROPOSE USING THE TERM 'CANCER PREDISPOSITION WITH LONG TELOMERES (CPLT)' TO DEFINE THE CONDITION CAUSED BY GPVs IN TELOMERE BIOLOGY GENES, TO DATE PRIMARILY IN THE SHELTERIN COMPLEX, ASSOCIATED WITH LONGER-THAN-AVERAGE FUNCTIONAL TELOMERES

This distinction from TBDs is important because CPLT is not associated with typical TBD clinical manifestations but with a distinct set of malignancies.

THE TERM TBD IS USED TO REFER TO THE CONDITIONS THAT MANIFEST IN INDIVIDUALS WITH ABNORMALLY SHORT OR OTHERWISE DYSFUNCTIONAL TELOMERES

These conditions include the mucocutaneous triad of DC, bone marrow failure, pulmonary fibrosis, liver disease, HNSCC and additional features related to limited cell renewal capacity provoked by their telomeres. While most TBD-associated GPVs result in very short telomeres, some variants cause clinically significant telomere dysfunction in the context of TLs within the normal range; hence, short telomere syndromes as an alternative falls short as an all-inclusive term, and we support the continued inclusion of *biology* in the TBD name.

UNANSWERED QUESTIONS FOR THE FIELD INCLUDE

- *Do common germline variants mediate TBD or CPLT phenotypes?* Genome-wide association studies of telomere length in large population-based studies have identified numerous single nucleotide polymorphisms associated with telomere length and allowed for the creation of polygenic scores.[25] These have not been studied in individuals with highly penetrant TBD or CPLT germline variants but could contribute to phenotypic heterogeneity.
- *How do somatic mutations affect phenotypes and outcomes?* Limited studies suggest that somatic mutations in blood of individuals with TBDs is associated with haematopoietic rescue and with progression to MDS.[21,26–29] Additional large, longitudinal studies are required to understand the clinical consequences and to develop precision management approaches.
- *What are the biological consequences of rare germline variants in TBDs and CPLT?* Most of the variants in genes associated with TBDs and CPLTs have had limited studies of the biological consequences. Comprehensive functional studies focused on disease-associated variants are required to thoroughly understand genotype–phenotype relationships and to improve clinical management. For some genes, such as *TERT*, in which a large proportion of the variants detected in patients are novel and classified as variants of uncertain significance, saturation mutagenesis approaches may be needed to broadly impact patient care.

AUTHOR CONTRIBUTIONS

SAS and AAB developed the concept and wrote the manuscript. All individuals listed in the acknowledgements read and approved the final version.

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DATA AVAILABILITY STATEMENT

The data herein are based current scientific literature and referenced accordingly.

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