Bone Marrow Failure Syndromes: *TERT*-associated Dyskeratosis Congenita

Ido Somekh MD PhD[1,2,7], Amarilla B. Mandola MD[1,2,6], Shirly Frizinsky MD[1,2,6], Atar Lev PhD[1,2], Ben Pode-Shakked MD[5,6], Nurit Loberman Nachum MD[3,6], Raz Somech MD PhD[1,2,6,8], and Amos J. Simon BA[4]

[1]Department of Pediatrics A, [2]Pediatric Immunology Services, Jeffrey Modell Foundation Center, and [3]Division of Pediatric Gastroenterology and Nutrition, Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel
[4]Hemato-Immunology unit, Hematology Lab, and Cancer Research Center and [5]Institute for Rare Diseases, Sheba Medical Center, Tel Hashomer, Israel
[6]Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel
[7]Recanati School of Medicine, Reichman University, Herzliya, Israel
[8]Israel Association of Allergy and Clinical Immunology, Israel Medical Association, Ramat Gan, Israel

ABSTRACT **Background:** Bone marrow failure syndromes (BMFs) comprise a heterogeneous group of genetic disorders characterized by impaired hematopoiesis and multisystem involvement. Dyskeratosis congenita (DC) is a telomere biology disorder caused by defects in telomerase or telomere maintenance, leading to progressive BMF and variable extra-hematopoietic manifestations.

Objectives: To describe the clinical, immunologic, genetic, and telomere biology findings in a patient with DC caused by a novel biallelic telomerase reverse transcriptase (TERT) mutation, and to highlight diagnostic and therapeutic considerations in telomere-associated BMFs.

Methods: We assessed cellular and humoral immune functions. Genetic analysis was conducted using whole-exome sequencing (WES) with segregation analysis. Telomere length was assessed by flow-FISH. Functional and radiologic evaluations were performed to define disease extent.

Results: A 2-year old male born to consanguineous parents presented with multisystemic clinical features, and hypocellular bone marrow. WES identified a novel homozygous TERT missense variant (c.3052G>A; p.Ala109Thr) supported by markedly shortened telomeres. Neuroimaging revealed cerebellar hypoplasia consistent with Hoyeraal-Hreidarsson syndrome. Immunologic evaluation demonstrated skewed CD4:CD8 ratios. An incidental heterozygous MEN1 variant was also detected.

Conclusions: We expand the clinical and genetic spectrum of TERT-associated DC and illustrate the critical role of genomic diagnostics and telomere assessment in BMFs. Early molecular diagnosis enables targeted evaluation, informs prognosis, and guides personalized management in telomere biology disorders. In addition, the identification of actionable secondary variants further highlights both the power and complexity of comprehensive genomic testing.

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KEY WORDS: bone marrow failure (BMF) syndromes, dyskeratosis congenita-Hoyeraal–Hreidarsson syndrome (DC-HHS), hematopoietic stem cell transplantation (HSCT), telomeres, telomerase reverse transcriptase (TERT) mutations

Hematopoiesis is a tightly regulated process in which hematopoietic stem cells (HSCs) self-renew and differentiate into mature, functional blood cells across specific lineages [1]. Bone marrow failure syndromes (BMFs) comprise a heterogeneous group of genetic disorders characterized by impaired hematopoiesis, leading to cytopenias that may affect one or multiple blood cell lineages. Classical BMFs often involve defects in DNA repair (e.g., Fanconi anemia), telomere maintenance (e.g., dyskeratosis congenita), or ribosome biogenesis (e.g., Schwachman-Diamond syndrome) [2,3].

The diagnostic and therapeutic landscape of inherited BMFs has advanced significantly with the implementation of next-generation sequencing (NGS). Currently, 47 genetically defined BMFs are included in the latest International Union of Immunological Societies (IUIS) classification [4,5]. Recently identified BMFs, including mutations in *SNM1B/DCLRE1B*, further illustrate the expanding spectrum of BMFs [6]. In addition, advances in treatment approaches, such as improved hematopoietic stem cell transplantation (HSCT), molecularly targeted therapies, and experimental gene therapies underscore the progress made in this field [1-3].

In this study, we focused on dyskeratosis congenita (DC), specifically evaluating clinical, immunologic, and genetic features as well as telomere biology in a patient with a novel biallelic telomerase reverse transcriptase (*TERT*) mutation. We illustrate the multi-systemic clinical features of DC, present functional validation of a novel disease-causing mutation, and discuss current and emerging therapeutic strategies in BMFs.

BACKGROUND

Bone marrow failure syndromes

The IUIS classification currently lists 47 distinct genetic causes of BMFs [Table 1]. Fanconi anemia (FA) is the

most common and well characterized entity. It is caused by defects in DNA interstrand cross-link repair. FA is typically inherited in an autosomal recessive manner, with rare X-linked and autosomal dominant forms. Hematologic manifestations commonly include childhood cytopenias, typically presenting in the first decade of life, myelodysplastic syndrome (MDS), and acute myeloid leukemia (AML). Two-thirds of patients exhibit extra-hematopoietic features, such as radial hypoplasia, short stature, café au lait pigmentation, developmental delay, and predisposition to solid tumors of the head and neck. Diagnostic confirmation typically requires chromosomal breakage tests followed by molecular genetic testing. Treatment options include fludarabine-based HSCT. Experimental therapies, such as TGF-β inhibitors and gene therapy, show promise as potential future management strategies [7,8]. Other BMFs include genetic defects associated with diverse extra-hematopoietic manifestations, such as congenital nerve deafness (*SRP72*), microcephaly and learning difficulties (*ERCC6L2*), adrenal hypoplasia, growth restriction, enteropathy (MIRAGE syndrome, *SAMD9*), and ataxia pancytopenia syndrome (*SAMD9L*) [Table 1] [9].

Dyskeratosis congenita: a telomere biology disorder

Telomeres are protective nucleoprotein structures consisting of TTAGGG repeat sequences located at the ends of chromosomes. They shorten with each cell division, and critically shortened telomeres inhibit further cellular proliferation, leading to senescence or apoptosis. This process is counteracted by telomerase, a reverse transcriptase that is particularly active in rapidly dividing cells, including hematopoietic and immune cells, as well as cells in the intestinal, liver, skin, and lung tissues [10,11].

Pathogenic variants affecting telomerase components (e.g., *DKC1, TERC, TERT, NHP2, NOP10, GAR1, WRAP53/TCAB1*), the shelterin complex (e.g., *TERF, TINF2, RAP1, ACD/TPP1, POT1*), and telomere maintenance complexes (e.g., *CTC1, STN1, TEN1, RTEL1, PARN, NAF1, ZCCHC8, DCLRE1B*) result in telomere biology disorders, which leads to DC [Figure 1] [10-13].

DC, initially described by Zinsser in 1910, presents a heterogeneous clinical phenotype. The classical triad includes nail dystrophy, abnormal skin pigmentation, and oral leukoplakia. Additional features include premature

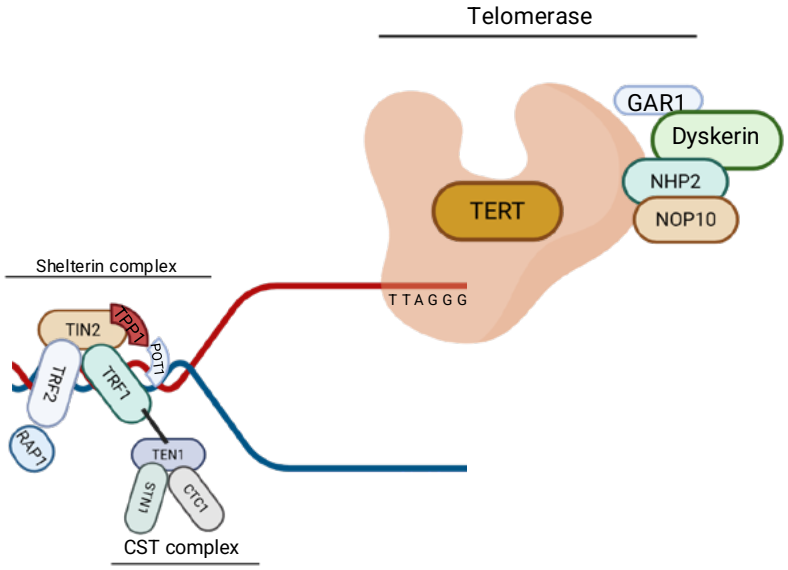
Table 1. Bone marrow failure syndromes

Disease	Genetic defects	Inheritance	Clinical manifestations
Fanconi anemia (A-W, 22 subtypes)	*FANCA, FANCB, FANCC, BRCA2, FANCD2, FANCE, FANCF, FANCG, FANCI, BRIP1, FANCL, FANCM, PALB2, RAD51C, SLX4, ERCC4, RAD51, BRCA1, UBE2T, XRCC2, MAD2L2, RFWD3*	AR, AD, XL	Cytopenias, MDS, AML, duodenal atresia, single kidney, radial hypoplasia, short stature, café au-lait, developmental delay, solid tumors of head and neck, female genitalia
Dyskeratosis congenita (14 subtypes)	*DKC1, TERC, TERT, TINF2, RTEL1, ACD, NOP10/ NOLA3, NHP2/NOLA2, WRAP53, PARN*	AR, AD, XL, De- Novo	BMF, premature aging pulmonary and hepatic fibrosis, nail dystrophy, oral leukoplakia, skin pigmentation; microcephaly, neurodevelopmental delays
BMFS1 (SRP72 deficiency)	*SRP72*	AD	BMF, congenital nerve deafness
BMFS2	*ERCC6L2*	AR	BMF, genomic instability, learning difficulties, microcephaly
BMFS5	*TP53*	AR	BMF, malignancies, developmental disorders
MECOM deficiency	*MECOM*	AD	Bone marrow failure, skeletal anomalies, cardiac, and renal malformations, hearing loss
COAT plus syndrome	*CTC1, STN1*	AR	IUGR, premature aging, pancytopenia, hypocellular bone marrow, GI hemorrhage due to vascular ectasia, intracranial calcification, abnormal telomeres
DC, Hoyeraal Hreidarsson syndrome	*DCLRE1B*	AR	Early onset BMF, cerebellar hypoplasia, B-cell and NK-cell lymphopenia, IUGR
BMFDMS	*DUT*	AR	BMF, diabetes mellitus, short stature, skin pigmentation
Nijmegen breakage syndrome-like disorder	*RAD50*	AR	BMF, microcephaly, immunodeficiency, microcephaly, mental retardation, bird-like face, short stature, breast and ovarian cancers
MIRAGE syndrome	*SAMD9*	AD	Intrauterine growth retardation, gonadal abnormalities, adrenal hypoplasia, MDS with chromosome 7 aberrations, predisposition to infections, enteropathy
Ataxia pancytopenia syndrome	*SAMD9L*	AD	MDS, cerebellar ataxia, B-cell lymphopenia, severe infections

AML = acute myeloid leukemia, BMF = bone marrow failure syndromes, IUGR = intra-uterine growth retardation, MDS = myelodysplastic syndrome

Figure 1. Schematic illustration of the Telomere machinery

Key components involved in telomere function are shown, including the telomerase complex, the Shelterin complex, and the CST complex. The major proteins constituting each complex are indicated.



aging, growth failure, developmental delays, osteoporosis, esophageal strictures, pulmonary fibrosis, liver disease, and increased cancer risk. Severe variants include Hoyeraal–Hreidarsson syndrome (HHS), characterized by early onset disease and cerebellar hypoplasia, and Revesz syndrome, associated with exudative retinopathy. Diagnostic confirmation relies on demonstration of shortened telomeres, typically by flow-FISH, and identification of causative mutations [14,15].

In this article, we present the clinical and genetic findings of a patient with DC caused by a novel biallelic *TERT* mutation, confirmed through whole-exome sequencing (WES) and functional validation, exhibiting shortened telomeres alongside multi-systemic manifestations characteristic of DC-HHS.

PATIENTS AND METHODS

PATIENTS AND CLINICAL EVALUATION

All the procedures were performed following informed consent from the patient's parents, according to the ethical standards of the institutional and/or national research committees and with the current update of the Declaration of Helsinki. Clinical data were collected and reviewed from digital hospital-based data.

IMMUNOLOGICAL EVALUATION

Lymphocyte markers

Cell surface marker expression of peripheral blood mononuclear cells (PBMC) was analyzed by immunofluorescent staining with monoclonal antibodies and flow cytometry (Epics V; Coulter Electronics, Hialeah, FL, USA).

Quantification of T-cell receptor excision circles

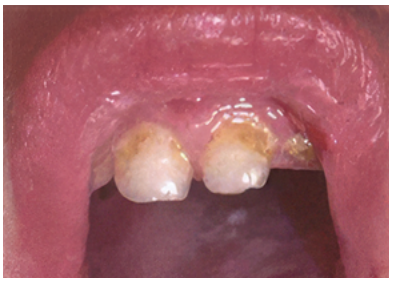
Signal joint T-cell receptor excision circle (TREC) copy numbers were determined by employing quantitative real-time PCR (qRTPCR) of genomic DNA (gDNA, 0.5µg) extracted from patient's PBMCs. Surface expression of individual T-cell receptor Vβ (TCR-Vβ) gene families was assessed using a set of 24 Vβ-specific fluorochrome-labeled monoclonal antibodies (Beckman Coulter, USA) and flow cytometry.

GENETIC EVALUATION

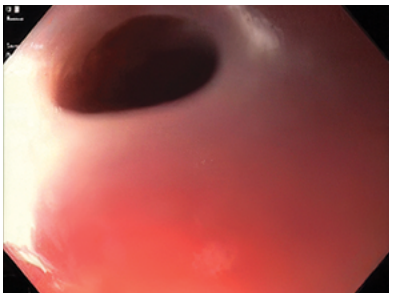
DNA was extracted from whole blood PMBC. DNA was prepared for a generation of whole-exome libraries using the SureSelect XT Human All Exon V5+UTR or V6+UTR kit (Agilent Technologies, USA). Barcoded libraries were sequenced on a NextSeq 500 platform (Illumina, USA) with an average coverage depth of 100x. Bioinformatics analysis and subsequent filtering identified rare sequence

Figure 2. Genetic findings and clinical manifestations in our patient

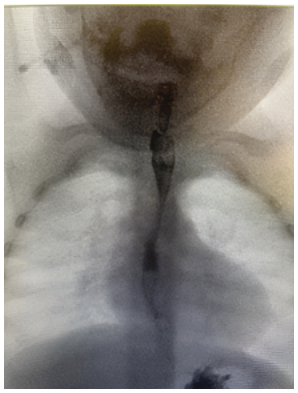
[A] Dental caries



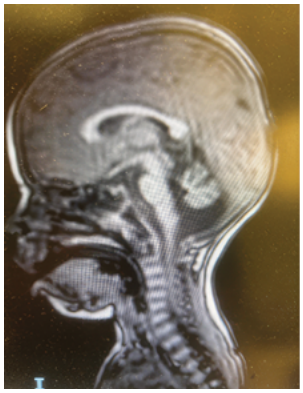
[B] Endoscopic proximal esophageal stricture



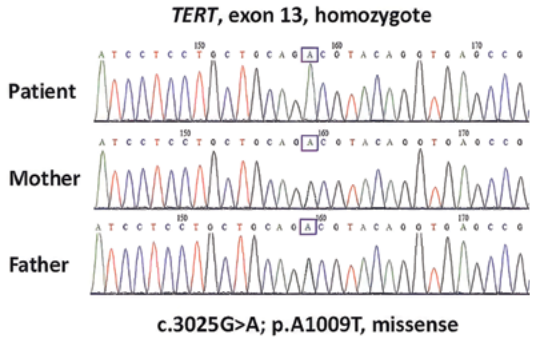
[C] Esophageal stenosis with limited passage of contrast



[D] Brain magnetic resonance imaging demonstrating cerebellar and vermis hypoplasia

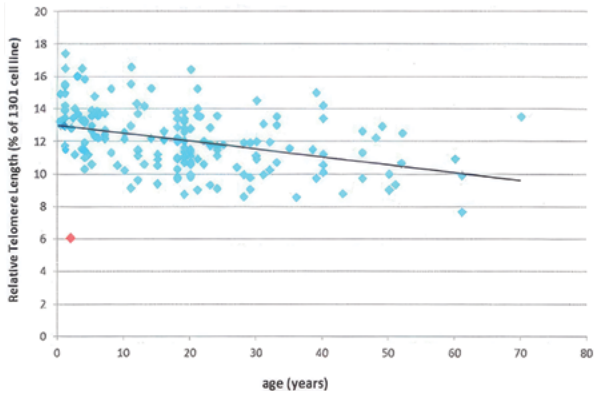


[E] Sanger sequencing chromatograms demonstrating a homozygous *TERT* variant; the homozygous missense *TERT* variant in exon 13 (c. 3025G>A; p.A1009T) identified in the studied patient with segregation analysis confirming heterozygosity in both parents



[F] Telomere length assay

Telomere assay comparing telomere length in the patient and healthy controls, exhibiting shortening of telomeres in our patient are shown, utilizing flow-FISH



variants. Familial segregation for *TERT* and *MEN1* mutations were performed by Sanger sequencing [16].

TELOMERE EVALUATION

Telomere length was assessed by flow-FISH in leukocytes of the patient compared with controls.

RESULTS

CLINICAL EVALUATION

We evaluated a 2-year-old Palestinian male patient born to consanguineous parents (first cousins). Prenatal history was notable for intra-uterine growth retardation, and prematurity at 31 weeks gestation with a very low birth weight (1100 grams). He was referred to our center due to multisystemic clinical manifestations, including failure to thrive, developmental delay, dysphagia, and microcytic anemia, which required blood transfusions at a local hospital. Physical examination revealed severe dental caries and oral leukoplakia [Figure 2A]. Comprehensive immunologic evaluation demonstrated preserved cellular and humoral immune function with normal T-, B-, and NK- cell subsets. A skewed CD4:CD8 ratio was observed, while a polyclonal TCR-Vβ repertoire and normal TREC levels were noted. Serum immune globulin

levels were normal, and vaccine-specific antibody responses were preserved. Both upper endoscopy and barium swallowing studies revealed a proximal esophageal stricture managed with endoscopic dilatation [Figure 2B, 2C]. Bone marrow biopsy demonstrated mild to moderate hypocellularity (50–60%).

GENETIC FINDINGS

Due to the consanguinity and a multisystemic involvement, the patient underwent genetic evaluation employing WES. A novel homozygous *TERT* missense mutation (c.3052G>A; p.Ala109Thr) was identified, classified as a variant of uncertain significance (VUS) according to ACMG criteria. In silico prediction tools (CADD 23.9, REVEL 0.58, AlphaMissense 0.78) predicted the missense mutation to have a deleterious effect, impacting a conserved residue. Both parents and the patient's three unaffected sisters were heterozygous carriers [Figure 2E]. The variant was therefore considered causative for the patient's findings. In addition, a secondary monoallelic novel missense variant in *MEN1* was identified (c.943G>C; p.Asp315His) and classified as likely pathogenic (it lies within a mutational hotspot). The variant was detected in the patient, his mother, and two older sisters.

FUNCTIONAL VALIDATION OF GENETIC FINDINGS

The combination of clinical features and genetic findings supported a diagnosis of biallelic *TERT*-associated DC. Given the genetic findings and developmental delay, the patient underwent additional CNS evaluation including ophthalmic evaluation (to rule out Revesz syndrome) and Brain MRI which demonstrated cerebellar hypoplasia [Figure 2D]. The early age of onset of clinical phenotype and cerebellar hypoplasia suggested the extended spectrum, DC-HHS, in the patient. Endocrinologic evaluation was conducted considering the *MEN1* variant and revealed no evidence of endocrine neoplasia. Genetic consultation was provided, addressing both the primary *TERT*-HHS diagnosis and the incidental maternally inherited *MEN1* variant. Notably, there was no known family history of endocrine tumors on the maternal side.

TELOMERE ANALYSIS

In view of the identified *TERT* mutation and clinical phenotype, telomere length assessment was performed. Flow-FISH analysis demonstrated markedly shortened telomeres in peripheral blood leukocytes [Figure 2F].

DISCUSSION

We highlighted the critical role of genetic diagnosis in BMFs, illustrating the phenotypic spectrum associated with *TERT*-related DC. BMFs encompass an expanding group of genetically heterogeneous disorders. Precise molecular diagnosis is essential for accurate classification, prognostication, and personalized clinical management.

TERT encodes the catalytic subunit of the telomerase complex. Pathogenic variants disrupt telomere maintenance, leading to progressive telomere shortening and cellular replicative failure. Both monoallelic and biallelic *TERT* mutations have been reported to cause DC and HHS, with biallelic variants typically associated with earlier onset and more severe multisystem involvement [10-13]. In the present study, the index patient was diagnosed with a homozygous *TERT* missense mutation. The genetic findings were supported by marked telomere shortening, establishing a definitive telomere biology disorder.

Importantly, genetic diagnosis directly informed clinical management. Prompt neurologic evaluation following molecular confirmation revealed cerebellar hypoplasia, consistent with the extended HHS spectrum. This finding highlights the value of early genomic testing in guiding targeted organ-specific assessments and avoiding diagnostic delay in patients with complex multisystem phenotypes.

In addition to the primary diagnosis, a heterozygous *MEN1* variant was identified as a secondary finding in the patient and several family members. While unrelated to the presenting phenotype, this finding has important implications for cancer risk assessment, surveillance, and genetic counseling. The identification of actionable secondary variants illustrates both the power and complexity of genomic testing. Notably, the family declined preimplantation genetic diagnosis (PGD) and prenatal genetic testing for religious reasons, underscoring the ethical, cultural, and psychosocial considerations inherent to genomic medicine and incidental findings [16].

Therapeutically, management of DC remains challenging. HSCT is currently the only curative option for bone marrow failure, yet outcomes are limited by significant transplant-related toxicity. Patients with telomere biology disorders exhibit heightened sensitivity to myeloablative conditioning, particularly with respect to pulmonary fibrosis. Reduced intensity conditioning regimens have

therefore emerged as a safer alternative, improving transplant tolerability and survival outcomes [17]. Additional supportive therapies include androgen derivatives such as danazol, which may improve cytopenias but are limited by endocrine and virilizing side effects, particularly in female patients.

Emerging therapeutic strategies offer promise beyond transplantation. Telomerase gene therapy has shown encouraging results in preclinical models, with adeno-associated virus-mediated *TERT* delivery successfully rescuing telomere length and disease manifestations in DC mouse models [18,19]. Early-phase clinical studies are currently underway. Pharmacologic approaches targeting telomere regulation, including PAPD5 inhibition to restore telomerase activity and telomere stability, represent additional novel therapeutic avenues under investigation [20].

CONCLUSIONS

With this study, we expand the genetic and clinical spectrum of *TERT*-associated DC/HHS by identifying a novel homozygous variant associated with severe systemic disease and HHS features. Advances in NGS and telomere-specific assays enable precise diagnosis, inform risk stratification, and facilitate tailored clinical surveillance. As genomic technologies, diagnostic assays and therapeutic options continue to evolve, their integration into clinical care will be pivotal for improving outcomes in BMFs and telomeropathies.

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Correspondence

Dr. I. Somekh
Dept. of Pediatrics A, Safra Children's Hospital, Jeffrey Modell Foundation Center, Sheba Medical Center, Tel Hashomer 52621, Israel
Phone/Fax: (972-3) 530-3477
Email: ido.somekh@sheba.health.gov.il

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