

World Journal of *Clinical Cases*

World J Clin Cases 2022 November 26; 10(33): 12066-12461



Contents

Thrice Monthly Volume 10 Number 33 November 26, 2022

MINIREVIEWS

- 12066** Review of risk factors, clinical manifestations, rapid diagnosis, and emergency treatment of neonatal perioperative pneumothorax
Zhang X, Zhang N, Ren YY

ORIGINAL ARTICLE

Clinical and Translational Research

- 12077** Integrative analysis of platelet-related genes for the prognosis of esophageal cancer
Du QC, Wang XY, Hu CK, Zhou L, Fu Z, Liu S, Wang J, Ma YY, Liu MY, Yu H
- 12089** Comprehensive analysis of the relationship between cuproptosis-related genes and esophageal cancer prognosis
Xu H, Du QC, Wang XY, Zhou L, Wang J, Ma YY, Liu MY, Yu H
- 12104** Molecular mechanisms of Baihedihuang decoction as a treatment for breast cancer related anxiety: A network pharmacology and molecular docking study
Li ZH, Yang GH, Wang F
- 12116** Single-cell RNA-sequencing combined with bulk RNA-sequencing analysis of peripheral blood reveals the characteristics and key immune cell genes of ulcerative colitis
Dai YC, Qiao D, Fang CY, Chen QQ, Que RY, Xiao TG, Zheng L, Wang LJ, Zhang YL

Retrospective Study

- 12136** Diagnosis and treatment of tubal endometriosis in women undergoing laparoscopy: A case series from a single hospital
Jiao HN, Song W, Feng WW, Liu H
- 12146** Different positive end expiratory pressure and tidal volume controls on lung protection and inflammatory factors during surgical anesthesia
Wang Y, Yang Y, Wang DM, Li J, Bao QT, Wang BB, Zhu SJ, Zou L
- 12156** Transarterial chemoembolization combined with radiofrequency ablation in the treatment of large hepatocellular carcinoma with stage C
Sun SS, Li WD, Chen JL
- 12164** Coexistence of anaplastic lymphoma kinase rearrangement in lung adenocarcinoma harbouring epidermal growth factor receptor mutation: A single-center study
Zhong WX, Wei XF

Observational Study

- 12175** Prognostic values of optic nerve sheath diameter for comatose patients with acute stroke: An observational study

Zhu S, Cheng C, Wang LL, Zhao DJ, Zhao YL, Liu XZ

- 12184** Quality of care in patients with inflammatory bowel disease from a public health center in Brazil

Takamune DM, Cury GSA, Ferrás G, Herrerias GSP, Rivera A, Barros JR, Baima JP, Saad-Hossne R, Sasaki LY

- 12200** Comparison of the prevalence of sarcopenia in geriatric patients in Xining based on three different diagnostic criteria

Pan SQ, Li XF, Luo MQ, Li YM

Prospective Study

- 12208** Predictors of bowel damage in the long-term progression of Crohn's disease

Fernández-Clotet A, Panés J, Ricart E, Castro-Pocheiro J, Masamunt MC, Rodríguez S, Caballol B, Ordás I, Rimola J

Randomized Controlled Trial

- 12221** Protective effect of recombinant human brain natriuretic peptide against contrast-induced nephropathy in elderly acute myocardial infarction patients: A randomized controlled trial

Zhang YJ, Yin L, Li J

META-ANALYSIS

- 12230** Prognostic role of pretreatment serum ferritin concentration in lung cancer patients: A meta-analysis

Gao Y, Ge JT

CASE REPORT

- 12240** Non-surgical management of dens invaginatus type IIIB in maxillary lateral incisor with three root canals and 6-year follow-up: A case report and review of literature

Arora S, Gill GS, Saquib SA, Saluja P, Baba SM, Khateeb SU, Abdulla AM, Bavabeedu SS, Ali ABM, Elagib MFA

- 12247** Unusual presentation of Loeys-Dietz syndrome: A case report of clinical findings and treatment challenges

Azrad-Daniel S, Cupa-Galvan C, Farca-Soffer S, Perez-Zincer F, Lopez-Acosta ME

- 12257** Peroral endoscopic myotomy assisted with an elastic ring for achalasia with obvious submucosal fibrosis: A case report

Wang BH, Li RY

- 12261** Subclavian brachial plexus metastasis from breast cancer: A case report

Zeng Z, Lin N, Sun LT, Chen CX

- 12268** Case mistaken for leukemia after mRNA COVID-19 vaccine administration: A case report

Lee SB, Park CY, Park SG, Lee HJ

- 12278** Orthodontic-surgical treatment of an Angle Class II malocclusion patient with mandibular hypoplasia and missing maxillary first molars: A case report

Li GF, Zhang CX, Wen J, Huang ZW, Li H

- 12289** Multiple cranial nerve palsies with small angle exotropia following COVID-19 mRNA vaccination in an adolescent: A case report
Lee H, Byun JC, Kim WJ, Chang MC, Kim S
- 12295** Surgical and nutritional interventions for endometrial receptivity: A case report and review of literature
Hernández-Melchor D, Palafox-Gómez C, Madrazo I, Ortiz G, Padilla-Viveros A, López-Bayghen E
- 12305** Conversion therapy for advanced penile cancer with tislelizumab combined with chemotherapy: A case report and review of literature
Long XY, Zhang S, Tang LS, Li X, Liu JY
- 12313** Endoscopic magnetic compression stricturoplasty for congenital esophageal stenosis: A case report
Liu SQ, Lv Y, Luo RX
- 12319** Novel *hydroxymethylbilane synthase* gene mutation identified and confirmed in a woman with acute intermittent porphyria: A case report
Zhou YQ, Wang XQ, Jiang J, Huang SL, Dai ZJ, Kong QQ
- 12328** Modified fixation for periprosthetic supracondylar femur fractures: Two case reports and review of the literature
Li QW, Wu B, Chen B
- 12337** Erbium-doped yttrium aluminum garnet laser and advanced platelet-rich fibrin+ in periodontal diseases: Two case reports and review of the literature
Tan KS
- 12345** Segmental artery injury during transforaminal percutaneous endoscopic lumbar discectomy: Two case reports
Cho WJ, Kim KW, Park HY, Kim BH, Lee JS
- 12352** Pacemaker electrode rupture causes recurrent syncope: A case report
Zhu XY, Tang XH, Huang WY
- 12358** Hybrid intercalated duct lesion of the parotid: A case report
Stankevicius D, Petroska D, Zaleckas L, Kutanovaite O
- 12365** Clinical features and prognosis of multiple myeloma and orbital extramedullary disease: Seven cases report and review of literature
Hu WL, Song JY, Li X, Pei XJ, Zhang JJ, Shen M, Tang R, Pan ZY, Huang ZX
- 12375** Colon mucosal injury caused by water jet malfunction during a screening colonoscopy: A case report
Patel P, Chen CH
- 12380** Primary malignant pericardial mesothelioma with difficult antemortem diagnosis: A case report
Oka N, Orita Y, Oshita C, Nakayama H, Teragawa H
- 12388** Typical imaging manifestation of neuronal intranuclear inclusion disease in a man with unsteady gait: A case report
Gao X, Shao ZD, Zhu L

- 12395** Multimodality imaging and treatment of paranasal sinuses nuclear protein in testis carcinoma: A case report
Huang WP, Gao G, Qiu YK, Yang Q, Song LL, Chen Z, Gao JB, Kang L
- 12404** T1 rectal mucinous adenocarcinoma with bilateral enlarged lateral lymph nodes and unilateral metastasis: A case report
Liu XW, Zhou B, Wu XY, Yu WB, Zhu RF
- 12410** Influence of enhancing dynamic scapular recognition on shoulder disability, and pain in diabetics with frozen shoulder: A case report
Mohamed AA
- 12416** Acute myocardial necrosis caused by aconitine poisoning: A case report
Liao YP, Shen LH, Cai LH, Chen J, Shao HQ
- 12422** Danggui Sini decoction treatment of refractory allergic cutaneous vasculitis: A case report
Chen XY, Wu ZM, Wang R, Cao YH, Tao YL
- 12430** Phlegmonous gastritis after biloma drainage: A case report and review of the literature
Yang KC, Kuo HY, Kang JW
- 12440** Novel *TINF2* gene mutation in dyskeratosis congenita with extremely short telomeres: A case report
Picos-Cárdenas VJ, Beltrán-Ontiveros SA, Cruz-Ramos JA, Contreras-Gutiérrez JA, Arámbula-Meraz E, Angulo-Rojo C, Guadrón-Llanos AM, Leal-León EA, Cedano-Prieto DM, Meza-Espinoza JP
- 12447** Synchronous early gastric and intestinal mucosa-associated lymphoid tissue lymphoma in a *Helicobacter pylori*-negative patient: A case report
Lu SN, Huang C, Li LL, Di LJ, Yao J, Tuo BG, Xie R

LETTER TO THE EDITOR

- 12455** Diagnostic value of metagenomics next-generation sequencing technology in disseminated strongyloidiasis
Song P, Li X
- 12458** Diagnostic value of imaging examination in autoimmune pancreatitis
Wang F, Peng Y, Xiao B

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Cornelia Bala, MD, PhD, Professor, Department of Diabetes and Nutrition Diseases, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca 400006, Romania. cbala@umfcluj.ro

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (WJCC, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The WJCC is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for WJCC as 1.534; IF without journal self cites: 1.491; 5-year IF: 1.599; Journal Citation Indicator: 0.28; Ranking: 135 among 172 journals in medicine, general and internal; and Quartile category: Q4. The WJCC's CiteScore for 2021 is 1.2 and Scopus CiteScore rank 2021: General Medicine is 443/826.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; Production Department Director: *Xiang Li*; Editorial Office Director: *Jin-Lei Wang*.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

November 26, 2022

COPYRIGHT

© 2022 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Novel *TINF2* gene mutation in dyskeratosis congenita with extremely short telomeres: A case report

Verónica Judith Picos-Cárdenas, Saúl Armando Beltrán-Ontiveros, José Alfonso Cruz-Ramos, José Alfredo Contreras-Gutiérrez, Eliakym Arámbula-Meraz, Carla Angulo-Rojo, Alma Marlene Guadrón-Llanos, Emir Adolfo Leal-León, Dora María Cedano-Prieto, Juan Pablo Meza-Espinoza

Specialty type: Dermatology

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ishida T, Japan;
Vyshka G, Albania

Received: September 13, 2022

Peer-review started: September 13, 2022

First decision: September 26, 2022

Revised: October 13, 2022

Accepted: October 20, 2022

Article in press: October 20, 2022

Published online: November 26, 2022



Verónica Judith Picos-Cárdenas, Laboratorio de Genética, Facultad de Medicina, Universidad Autónoma de Sinaloa, Culiacán 80018, Sinaloa, Mexico

Saúl Armando Beltrán-Ontiveros, Centro de Investigación y Docencia en Ciencias de la Salud, Hospital Civil de Culiacán, Universidad Autónoma de Sinaloa, Culiacán 80030, Sinaloa, Mexico

José Alfonso Cruz-Ramos, Departamento de Clínicas Médicas, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara 44340, Jalisco, Mexico

José Alfredo Contreras-Gutiérrez, Facultad de Medicina, Universidad Autónoma de Sinaloa, Culiacán 80018, Sinaloa, Mexico

Eliakym Arámbula-Meraz, Emir Adolfo Leal-León, Dora María Cedano-Prieto, Laboratorio de Genética y Biología Molecular, Facultad de Ciencias Químico-Biológicas, Universidad Autónoma de Sinaloa, Culiacán 80010, Sinaloa, Mexico

Carla Angulo-Rojo, Laboratorio de Neurociencias, Facultad de Medicina, Universidad Autónoma de Sinaloa, Culiacán 80018, Sinaloa, Mexico

Alma Marlene Guadrón-Llanos, Laboratorio de Diabetes y Comorbilidades, Facultad de Medicina, Universidad Autónoma de Sinaloa, Culiacán 80018, Sinaloa, Mexico

Juan Pablo Meza-Espinoza, Facultad de Medicina, Universidad Autónoma de Tamaulipas, Matamoros 87349, Tamaulipas, Mexico

Corresponding author: Juan Pablo Meza-Espinoza, PhD, Researcher, Facultad de Medicina, Universidad Autónoma de Tamaulipas, Sendero Nacional km 3, Matamoros 87349, Tamaulipas, Mexico. sirol1073@yahoo.com.mx

Abstract

BACKGROUND

Dyskeratosis congenita is a rare disease characterized by bone marrow failure and a clinical triad of oral leukoplakia, nail dystrophy, and abnormal skin pigmentation. The genetics of dyskeratosis congenita include mutations in genes involved in telomere maintenance, including *TINF2*.

CASE SUMMARY

Here, we report a female patient who presented thrombocytopenia, anemia, reticulate hyperpigmentation, dystrophy in fingernails and toenails, and leukoplakia on the tongue. A histopathological study of the skin showed dyskeratocytes; however, a bone marrow biopsy revealed normal cell morphology. The patient was diagnosed with dyskeratosis congenita, but her family history did not reveal significant antecedents. Whole-exome sequencing showed a novel heterozygous punctual mutation in exon 6 from the *TINF2* gene, namely, NM_001099274.1:-c.854delp.(Val285Alafs*32). An analysis of telomere length showed short telomeres relative to the patient's age.

CONCLUSION

The disease in this patient was caused by a germline novel mutation of *TINF2* in one of her parents.

Key Words: Dyskeratosis congenita; *TINF2*; Germline mutation; Novel mutation; Short telomeres; Case report

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Dyskeratosis congenita, characterized by a clinical triad of oral leukoplakia, nail dystrophy, and abnormal skin pigmentation, is a rare disease caused by mutations in genes governing telomere maintenance, including *TINF2*. We performed whole-exome sequencing in a female pediatric patient who presented with dyskeratosis congenita, and subsequently, a novel heterozygous mutation in exon 6 of the *TINF2* gene was detected: NM_001099274.1:c.854delp.(Val285Alafs*32). An analysis of telomere length demonstrated short telomeres relative to the girl's age. Patients with *TINF2* mutations have more severe disease, so their detection is necessary to provide timely treatment.

Citation: Picos-Cárdenas VJ, Beltrán-Ontiveros SA, Cruz-Ramos JA, Contreras-Gutiérrez JA, Arámbula-Meraz E, Angulo-Rojó C, Guadrón-Llanos AM, Leal-León EA, Cedano-Prieto DM, Meza-Espinoza JP. Novel *TINF2* gene mutation in dyskeratosis congenita with extremely short telomeres: A case report. *World J Clin Cases* 2022; 10(33): 12440-12446

URL: <https://www.wjgnet.com/2307-8960/full/v10/i33/12440.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v10.i33.12440>

INTRODUCTION

Dyskeratosis congenita is a rare genetic disease whose prevalence in the general population has been estimated at nearly 1/1000000[1]. This disorder is characterized by bone marrow failure and a typical clinical triad comprised of oral leukoplakia, nail dystrophy, and abnormal skin pigmentation. The risk of aplastic anemia, myelodysplastic syndrome, and leukemia is elevated in patients with this condition [2,3]. Other clinical findings in dyskeratosis congenita include pulmonary fibrosis, liver cirrhosis, and premature hair graying[4]. The genetics of dyskeratosis congenita involve mutations in genes that govern the maintenance of telomeres; therefore, this disorder is marked, molecularly, by a progressive shortening of telomeres[5,6]. The genes associated with dyskeratosis congenita are *DKC1*, *TERC*, *TERT*, *TINF2*, *RTEL1*, *PARN*, *ACD*, *NOP10*, *NHP2*, *TERT*, *USB1*, and *WRAP53*[2,3,7] (Table 1). Pathogenic variants in any of these genes have been identified in most individuals who meet diagnostic criteria for dyskeratosis congenita[3]. Because of this locus heterogeneity, there is a wide clinical variation among patients with this syndrome[8]. Here, we report the case of a girl with dyskeratosis congenita who carries a previously undescribed germline mutation in the *TINF2* gene and an extremely short telomere length.

CASE PRESENTATION

Chief complaints

A 13-year-old Mexican female patient, height 151.0 cm and weight 48.0 kg, was found to have thrombocytopenia, anemia, abnormal skin pigmentation, dystrophic nails, and leukoplakia on the tongue.

Table 1 Genetic spectrum of dyskeratosis congenita[1,3]

| Gene | Chromosome | Inheritance pattern | Frequency, % | Main mutation types |
|---------------|------------|---------------------|------------------|-------------------------|
| <i>DKC1</i> | Xq28 | XLR | Approximately 25 | Missense |
| <i>TINF2</i> | 14q12 | AD | Approximately 12 | Missense |
| <i>TERC</i> | 3q26 | AD | Approximately 5 | Point and deletions |
| <i>TERT</i> | 5p15 | AD, AR | Approximately 5 | Missense |
| <i>USB1</i> | 16q21 | AR | Approximately 2 | Frameshift and nonsense |
| <i>RTEL1</i> | 20q13 | AR, AD | Approximately 2 | Missense |
| <i>CTC1</i> | 17p13 | AR | Approximately 1 | Missense and frameshift |
| <i>NHP2</i> | 5q35 | AR | < 1 | Missense |
| <i>NOP10</i> | 15q14 | AR | < 1 | Missense |
| <i>WRAP53</i> | 17p13 | AR | < 1 | Missense |
| <i>ACD</i> | 16q22 | AD, AR | < 1 | Missense and frameshift |
| <i>PARN</i> | 16p13 | AR, AD | < 1 | Frameshift |

XLR: X-linked recessive; AD: Autosomal dominant; AR: Autosomal recessive.

History of present illness

The patient was the product of the second pregnancy of healthy nonconsanguineous parents (both parents were 31 years old at the time of birth). At the age of 5 years, she was detected to have thrombocytopenia and anemia (platelets 26000/mm³ and hemoglobin 9.0 g/dL); peripheral blood cell smears showed normal morphology and no evidence of blasts. She was thought to have primary immune thrombocytopenia. Prednisone (1 mg/kg/d) was administered as therapy for 21 d. After the administration of prednisone, platelet and hemoglobin counts have fluctuated from 32000/mm³ to 110000/mm³ and 9.5 g/dL to 11.7 g/dL, respectively.

When the patient was 9 years old, she was suspected to have systemic lupus erythematosus and mixed connective tissue disease due to her nail dystrophy and neck pigmentation abnormalities, but an antinuclear antibody test was negative. Methotrexate was administered as prophylaxis regardless. Around this time, an esophagogram was performed due to her difficulty swallowing since childhood; this revealed esophageal stenosis requiring two endoscopies for dilation. At the age of 11, dyskeratosis congenita was suspected due to the progression of reticulate pigmentation to the entire upper trunk, the presence of leukoplakia on the tongue, and the evolution of fingernails and toenails dystrophy; a molecular study was subsequently performed.

History of past illness

The patient had no history of other significant diseases.

Personal and family history

The patient had a healthy older brother, and family history did not indicate any significant morbidities.

Physical examination

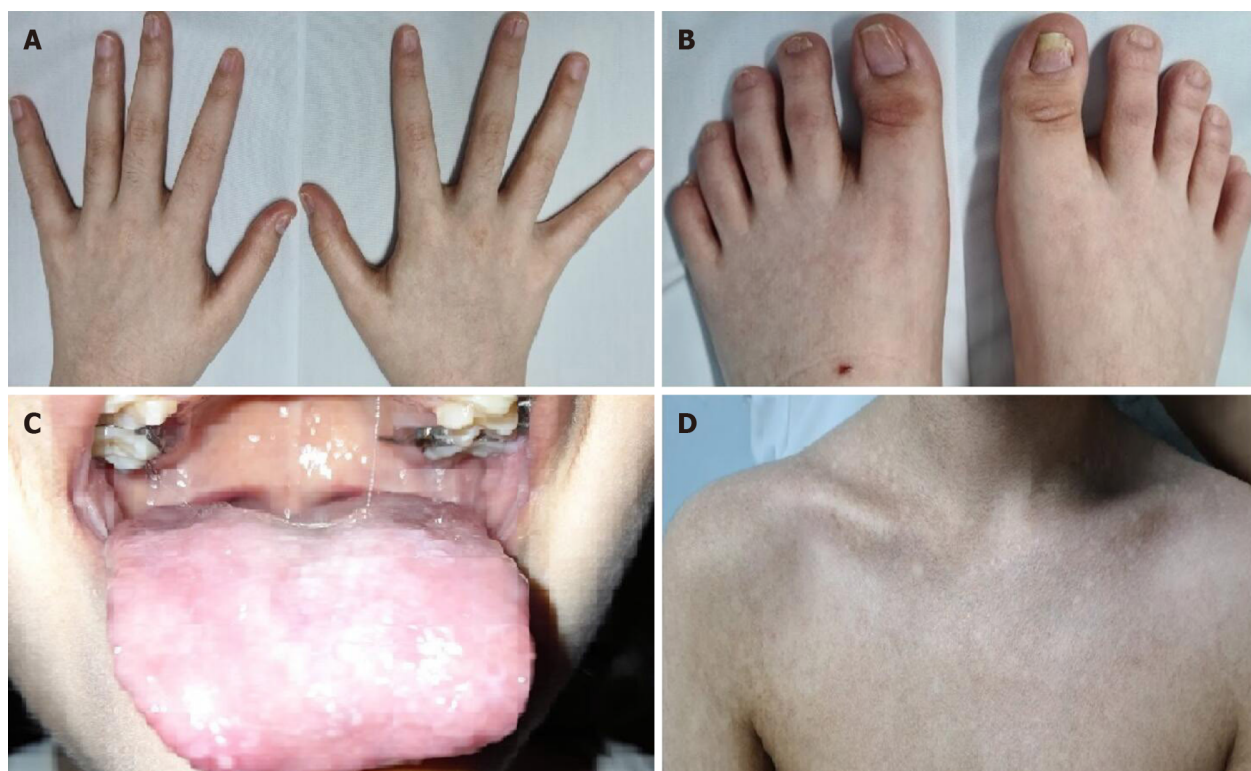
At the age of 6, the patient presented with microcephaly, reticulate pigmentation in the neck, neckline, and axillae, dystrophic nails on hands and feet (Figure 1A and B), and lacrimal obstruction in the right eye. At the age of 11, she showed leukoplakia on the tongue (Figure 1C), and her reticulate pigmentation progressed to the entire upper trunk (Figure 1D).

Laboratory examinations

A histopathological study of the skin showed dyskeratocytes (Figure 2). Although previous peripheral blood smears showed normal leukocyte counts and the absence of blasts throughout the disease, a bone marrow biopsy was performed, which revealed normal cellularity.

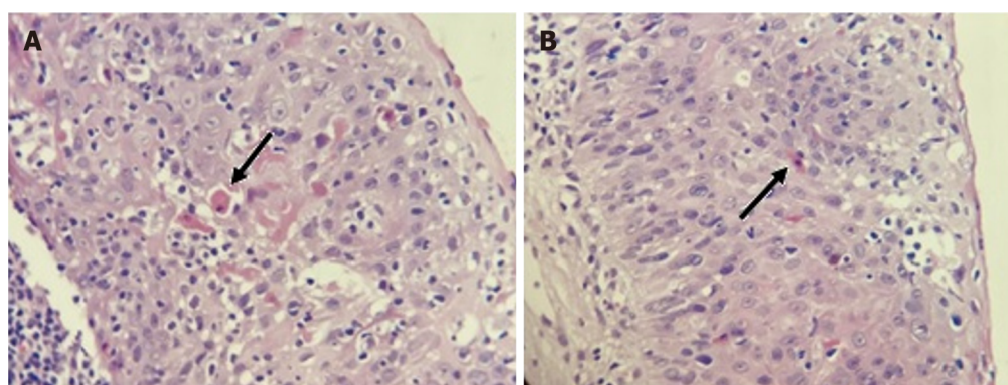
Whole-exome sequencing

Whole-exome sequencing analysis was performed according to the manufacturer's protocol. DNA was enzymatically fragmented and hybridized with CentoXome™ (CENTOGENE, Rostock, Germany). Libraries were generated with Illumina-compatible adapters and sequenced on the Illumina platform (Illumina, Inc., San Diego, CA, United States). Sequenced readings were aligned to the hg19 version of



DOI: 10.12998/wjcc.v10.i33.12440 Copyright ©The Author(s) 2022.

Figure 1 Clinical findings in the patient. A: Dystrophic fingernails; B: Dystrophic toenails; C: White patches on the tongue representing leukoplakia; D: Upper trunk showing reticulate skin pigmentation.



DOI: 10.12998/wjcc.v10.i33.12440 Copyright ©The Author(s) 2022.

Figure 2 Histopathological study. A and B: Skin biopsy images showing dyskeratocytes. The arrows point to these abnormal cells.

the human genome (Genome Reference Consortium GRCh37) using validated software (Rostock, Germany). All variants reported in the *Human Gene Mutation Database* (HGMD®), ClinVar, and CentoMD, as well as those in which the frequency of the least common allele was less than 1% in the Single Nucleotide Polymorphism database (dbSNP) and the Genome Aggregation Database (gnomAD) were considered. After analysis, a novel mutation, Chr14(GRCh37):g.24709832del NM_001099274.1:c.854delp.(Val285Alafs*32), was identified in exon 6 of the *TINF2* gene. This mutation was verified by Sanger sequencing. Bidirectional sequencing and comparison to the coding sequence of *TINF2* was performed (Figure 3). The reference sequence was NM_001099274.1.

Telomere analysis

To assess telomere length, genomic DNA was extracted from peripheral blood leukocytes using the Flexigene DNA kit (QIAGEN, Hilden, Germany) and qPCR was performed using the Absolute Human Telomere Length and Mitochondrial DNA Copy Number Dual Quantification qPCR kit (ScienCell Research Laboratories, San Diego, CA, United States) on a CFX96 Touch Real-Time PCR Detection System (Bio-Rad, Hercules, CA, United States) according to the supplier's recommendations. The

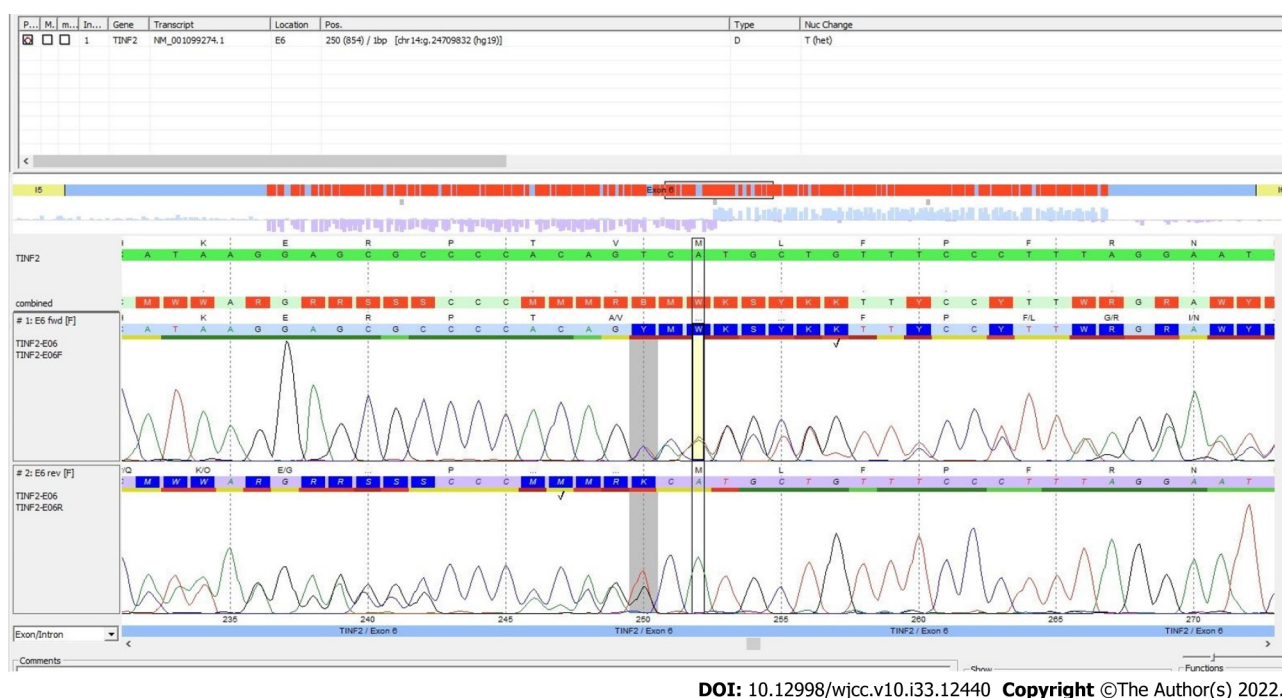


Figure 3 Sequencing study. Plot showing the identification of the mutation in the *TINF2* gene (deletion of the T in the position 250; shaded area). Courtesy of Centogene AG, Rostock, Germany.

analysis showed an absolute telomere length of 2.80 ± 0.09 kb.

FINAL DIAGNOSIS

Based on clinical features and molecular analysis, the patient was diagnosed with dyskeratosis congenita.

TREATMENT

Prednisone (1 mg/kg/d) is administered as therapy for 21 d, whenever platelet count drops by nearly $30000/\text{mm}^3$.

OUTCOME AND FOLLOW-UP

Hopefully, the patient has had a favorable evolution, as she has not developed aplastic anemia or bone marrow failure, although she is currently off medication.

DISCUSSION

Dyskeratosis congenita is caused more than 99% of the time by a germline mutation in one of the parents[9], as was the case of our patient, who presented with the typical triad of this disease: Dystrophy in fingernails and toenails, leukokeratosis plaques on the tongue, and reticulate skin pigmentation. Mutations in the *TINF2* gene (which encodes the TIN2 protein, a component of the shelterin telomere protection complex)[2] represent the second most common cause of dyskeratosis congenita, accounting for approximately 12% of the cases, only after mutations in the *DKC1* gene (approximately 25%)[1]. It is well known that patients with a mutation in the *TINF2* gene have a more severe course and a higher risk of developing aplastic anemia before the age of 10 years[6]. To date, there are more than 200 punctual variations in the *TINF2* gene recorded in the ClinVar database. Most of them result in missense mutations, eight in nonsense, and almost twenty are frameshift mutations (Table 2), although some are associated with Revesz syndrome, a more severe variant of dyskeratosis congenita. Most pathogenic mutations occur in exon 6, principally between codons 280 and 288[10]. The

Table 2 Frameshift mutations in *TINF2* causing dyskeratosis congenita[10]

| Location (GRCh37) | Mutation | Protein change |
|-------------------------|--|----------------|
| Chr14:24709067 | NM_001099274.3(TINF2):c.1292del (p.Pro431fs) | P431fs |
| Chr14:24709132 | NM_001099274.3(TINF2):c.1227del (p.Leu410fs) | L410fs |
| Chr14:24709288-24709289 | NM_001099274.3(TINF2):c.1202dup (p.Asn401fs) | N401fs |
| Chr14:24709507-24709508 | NM_001099274.3(TINF2):c.1090dup (p.Leu364fs) | L364fs |
| Chr14:24709627-24709628 | NM_001099274.3(TINF2):c.1058dup (p.Glu354fs) | E354fs |
| Chr14:24709676 | NM_001099274.3(TINF2):c.1010del (p.Gly337fs) | G337fs |
| Chr14:24709794 | NM_001099274.3(TINF2):c.892del (p.Gln298fs) | Q298fs |
| Chr14:24709836-24709837 | NM_001099274.3(TINF2):c.849dup (p.Thr284fs) | T284fs |
| Chr14:24709860 | NM_001099274.3(TINF2):c.826del (p.Arg276fs) | R276fs |
| Chr14:24710080 | NM_001099274.3(TINF2):c.606del (p.Glu202fs) | E202fs |
| Chr14:24710937-24710938 | NM_001099274.3(TINF2):c.342_343del (p.Phe114fs) | F114fs |
| Chr14:24711135-24711136 | NM_001099274.3(TINF2):c.257_258del (p.His86fs) | H86fs |
| Chr14:24711394-24711395 | NM_001099274.3(TINF2):c.144_145insTT (p.Val49fs) | V49fs |

mutation detected in this patient was a deletion of a nucleotide (frameshift), which also occurred in exon 6, codon 285, and caused an amino acid change at position 285 and a stop codon 31 amino acids later.

While telomere shortening is a molecular feature of dyskeratosis congenita[5], this is dramatic in patients with *TINF2* mutations[11], as their telomere lengths are significantly shorter than those of patients with *DKC1* mutations[6]. Our case showed an absolute telomere length of 2.80 ± 0.09 kb, which is considered very short relative to the patient's age. As a reference, a study performed on healthy young women aged 18 to 30 years showed an absolute telomere length of 4.59 ± 0.24 kb[12]. *TINF2* is important for telomere protection, and *TINF2* deficiency increases the risk of telomeric DNA damage and consequent telomere shortening[13-15]. Short telomeres are known to cause premature aging and increase the risk of developing cancer[16]. Accordingly, patients with dyskeratosis congenita have a higher risk of developing bone marrow failure, acute leukemia, myelodysplastic syndrome, and squamous cell carcinoma of the head and neck[3]. However, despite her extremely short telomere length, our patient has had a favorable evolution, as she has not developed aplastic anemia or bone marrow failure, although she is currently off medication.

CONCLUSION

Since patients with mutations in the *TINF2* gene have a more severe course and a higher risk of developing aplastic anemia[6], it is important to detect patients with such mutations to follow them more frequently, mainly through blood cytometry, and, if necessary, to provide some treatment, as has been done in this patient. In the meantime, she and her parents are hoping for an orphan or experimental drug that will impede the progression of the disease.

The strength of this case report is that it was approached with a clinical, genetic, and pathological focus. The main limitation is that it is a single case.

ACKNOWLEDGEMENTS

We thank the proband and her parents for their collaboration and support for the publication of this case. We also thank the biomedicine and genomic biotechnology students, Liliana Itzel Patrón Baro (fellowship PROF-API-UAS-2022, Pro_A3_031) and Lucero García Hernández, respectively, for the technical and samples collection support. Special thanks to Centogene AG, Germany for its support for the whole-exome sequencing analysis.

FOOTNOTES

Author contributions: Picos-Cárdenas VJ conceptualization, data collection, and manuscript preparation; Beltrán-

Ontiveros SA, Contreras-Gutiérrez JA, Arámbula-Meraz E, and Angulo-Rojo C performed clinical examination and data analysis; Cruz-Ramos JA telomere study and critical review; Guadrón-Llanos AM, Leal-León EA, Cedano-Prieto DM collection of samples and interpretation of molecular studies; Meza-Espinoza JP supervision, drafting, reviewing, and editing. All the authors approved the final version of the manuscript.

Informed consent statement: Written consent was obtained from the patient's parents for the publication of this case and the accompanying images.

Conflict-of-interest statement: All the authors indicated no conflicts of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016). The manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Mexico

ORCID number: Verónica Judith Picos-Cárdenas 0000-0002-4320-9619; Saúl Armando Beltrán-Ontiveros 0000-0002-8411-0957; José Alfonso Cruz-Ramos 0000-0002-5791-612X; José Alfredo Contreras-Gutiérrez 0000-0003-3774-1278; Eliakym Arámbula-Meraz 0000-0003-1026-7430; Carla Angulo-Rojo 0000-0002-5097-2444; Alma Marlene Guadrón-Llanos 0000-0003-4782-6398; Emir Adolfo Leal-León 0000-0001-9927-5917; Dora María Cedano-Prieto 0000-0002-4204-2175; Juan Pablo Meza-Espinoza 0000-0003-2621-7649.

S-Editor: Liu JH

L-Editor: A

P-Editor: Liu JH

REFERENCES

- Dokal I, Vulliamy T, Mason P, Bessler M. Clinical utility gene card for: Dyskeratosis congenita - update 2015. *Eur J Hum Genet* 2015; **23** [PMID: 25182133 DOI: 10.1038/ejhg.2014.170]
- Savage SA, Giri N, Baerlocher GM, Orr N, Lansdorp PM, Alter BP. TINF2, a component of the shelterin telomere protection complex, is mutated in dyskeratosis congenita. *Am J Hum Genet* 2008; **82**: 501-509 [PMID: 18252230 DOI: 10.1016/j.ajhg.2007.10.004]
- Savage SA, Niewisch MR. Dyskeratosis Congenita and Related Telomere Biology Disorders. 2009 Nov 12. In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993 [PMID: 20301779]
- Wang P, Xu Z. Pulmonary fibrosis in dyskeratosis congenita: a case report with a PRISMA-compliant systematic review. *BMC Pulm Med* 2021; **21**: 279 [PMID: 34479523 DOI: 10.1186/s12890-021-01645-w]
- Nelson ND, Bertuch AA. Dyskeratosis congenita as a disorder of telomere maintenance. *Mutat Res* 2012; **730**: 43-51 [PMID: 21745483 DOI: 10.1016/j.mrfmmm.2011.06.008]
- Walne AJ, Vulliamy T, Beswick R, Kirwan M, Dokal I. TINF2 mutations result in very short telomeres: analysis of a large cohort of patients with dyskeratosis congenita and related bone marrow failure syndromes. *Blood* 2008; **112**: 3594-3600 [PMID: 18669893 DOI: 10.1182/blood-2008-05-153445]
- Dyskeratosis congenita, autosomal dominant 1 in: Online Mendelian Inheritance in Man. Available from: <https://omim.org/entry/127550>
- Barbaro PM, Ziegler DS, Reddel RR. The wide-ranging clinical implications of the short telomere syndromes. *Intern Med J* 2016; **46**: 393-403 [PMID: 26247919 DOI: 10.1111/imj.12868]
- AlSabbagh MM. Dyskeratosis congenita: a literature review. *J Dtsch Dermatol Ges* 2020; **18**: 943-967 [PMID: 32930426 DOI: 10.1111/ddg.14268]
- TINF2 gene in: ClinVar. Available from: <https://www.ncbi.nlm.nih.gov/clinvar/?term=TINF2%5Bgene%5D&redir=gene>
- Frescas D, de Lange T. A TIN2 dyskeratosis congenita mutation causes telomerase-independent telomere shortening in mice. *Genes Dev* 2014; **28**: 153-166 [PMID: 24449270 DOI: 10.1101/gad.233395.113]
- Hagman M, Frisrup B, Michelin R, Krustup P, Asghar M. Football and team handball training postpone cellular aging in women. *Sci Rep* 2021; **11**: 11733 [PMID: 34083635 DOI: 10.1038/s41598-021-91255-7]
- Kim SH, Beausejour C, Davalos AR, Kaminker P, Heo SJ, Campisi J. TIN2 mediates functions of TRF2 at human telomeres. *J Biol Chem* 2004; **279**: 43799-43804 [PMID: 15292264 DOI: 10.1074/jbc.M408650200]
- Lansdorp PM. Telomeres, aging, and cancer: the big picture. *Blood* 2022; **139**: 813-821 [PMID: 35142846 DOI: 10.1182/blood.2021014299]
- Sasa GS, Ribes-Zamora A, Nelson ND, Bertuch AA. Three novel truncating TINF2 mutations causing severe dyskeratosis congenita in early childhood. *Clin Genet* 2012; **81**: 470-478 [PMID: 21477109 DOI: 10.1111/j.1399-0004.2011.01658.x]
- Takai KK, Kibe T, Donigian JR, Frescas D, de Lange T. Telomere protection by TPP1/POT1 requires tethering to TIN2. *Mol Cell* 2011; **44**: 647-659 [PMID: 22099311 DOI: 10.1016/j.molcel.2011.08.043]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

