Case Report

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Hoyeraal–Hreidarsson syndrome: a case report of dyskeratosis congenita with a novel PARN gene mutation

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Introduction and importance: Dyskeratosis congenita (DC) is a rare multisystem disorder primarily characterized by bone marrow failure due to telomere shortening. Typical clinical features include oral leukoplakia, skin hyperpigmentation, and nail dystrophy, along with an increased risk of malignancies. Hoyeraal–Hreidarsson syndrome (HH), a severe variant of DC, is associated with profound neurological and immunological complications, emphasizing the importance of early diagnosis and genetic evaluation to guide appropriate management.

Case presentation: The authors present a case of a 2-year-old girl diagnosed with Hoyeraal–Hreidarsson syndrome, linked to a newly discovered mutation in the poly (A)-specific ribonuclease (PARN) gene. The patient exhibited intrauterine growth retardation (IUGR), congenital cytomegalovirus (CMV) infection, immunodeficiency, microcephaly, and cerebellar hypoplasia. Whole-exome sequencing (WES) identified a novel mutation in the PARN gene.

Clinical discussion: Hoyeraal–Hreidarsson syndrome, a severe form of DC, manifests with multisystem involvement and is genetically heterogeneous. Early genetic testing through techniques such as WES can aid in diagnosing rare syndromes like HH and guide treatment strategies, including bone marrow transplantation.

Conclusion: This case underscores the importance of genetic evaluation in complex, rare syndromes like HH. Whole-exome sequencing plays a crucial role in identifying pathogenic mutations and tailoring management. The patient's prognosis is being closely monitored following bone marrow transplantation.

Keywords: bone marrow failure, dyskeratosis congenita, Hoyeraal–Hreidarsson syndrome, PARN gene, whole-exome sequencing

Introduction

Dyskeratosis congenita (DC) is a multisystem syndrome characterized by bone marrow failure resulting from impaired telomere maintenance. DC is associated with telomere biology disorders (TBDs)[1]. Dyskeratosis congenita is a genetic disorder with progressive multisystem involvement. Oral leukoplakia, hyperpigmentation, and nail dystrophy are typically seen in DC. Frequent complications include bone marrow failure, an increased risk of malignancy, and lung and liver diseases[2]. The Dyskerin Pseudouridine Synthase 1 (DKC1) gene, which encodes the dyskerin protein, has been found to be defective in individuals affected by the syndrome[3]. Telomere biology disorders (TBDs) result from germline mutations in telomere-related genes, leading to short telomeres. DC encompasses a spectrum of conditions, including Hoyeraal–Hreidarsson (HH) and Revesz syndromes[4]. Mutations in the poly (A)-specific ribonuclease (PARN) gene can also cause telomere diseases like DC[5]. In this case, we identified a novel mutation in the PARN gene using whole-exome sequencing (WES), contributing to the understanding of the genetic basis of DC.

HIGHLIGHTS

- Whole-exome sequencing identified a novel c.1200del (p.Leu401fs) mutation in the PARN gene, associated with dyskeratosis congenita and classified as highly pathogenic according to ACMG criteria.

Case report

A 2-year-old girl presented with persistent sores in the mouth and frequent infections. She had microcephaly, oral leukoplakia, and pes planus. Laboratory findings showed a white blood cell (WBC) count of 6×10^3/μl, hemoglobin (Hb) of 9.6 g/dl, red blood cell (RBC) count of 2.92×10^6/μl, and mean corpuscular volume (MCV) of 95.4 fl. The platelet count was ~12 000/mm^3, and a peripheral smear revealed single platelets. Bone marrow

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aspiration showed hypocellularity without atypical cells or blasts. Immunoglobulin levels were within normal ranges. Lymphocyte subgroup analysis revealed a CD4/CD8 ratio of 0.97%, considered low as it was less than 1. Immunodeficiency was ruled out based on further immunological evaluation. Cerebellar hypoplasia was detected on brain MRI (Fig. 1).

WES is a genetic analysis technique that focuses on sequencing all coding regions of the genome, which are known as exons. This method allows for the identification of mutations that may be responsible for genetic disorders. In our case, WES revealed a novel mutation in the poly (A)-specific ribonuclease (PARN) gene. The PARN gene is crucial for maintaining telomere length and function, and mutations in this gene can lead to disorders such as Dyskeratosis Congenita (DC). Understanding these genetic findings is essential, as they provide insights into the underlying mechanisms of the disease and can inform future therapeutic approaches.

WES analysis showed a previously unreported mutation in the PARN gene. In the analysis of the patient's data, highly pathogenic changes were detected in the PARN gene (NM_002582.4) c.272A > G (p.Tyr91Cys) (Heterozygous)/ c.1200del (p.Leu401fs) (Heterozygous). The detected changes were confirmed by further study with the next-generation sequencing (NGS). The patient's parents were found to be carriers. Mother c.272A > G (p.Tyr91Cys) heterozygous carrier, father c.1200del (p.Leu401fs) heterozygous carrier. The c.272A > G (p.Tyr91Cys) change detected in the PARN gene in the analyzes was a previously reported change in the ClinVar database (ClinVar ID: 542669). According to the American College of Medical Genetics and Genomics (ACMG) criteria, this change was evaluated as "highly pathogenic". The detected c.1200del (p.Leu401fs) change is a genetic change (novel variant) that has not been reported before in the literature, but this change was also evaluated as "highly pathogenic" according to ACMG criteria.

At the check-up on 14 August 2024, the patient's age was 4 years, 8 months, and 22 days. The patient's weight was 13 kg (SDS: –2.34, Percentile: 0.96, Weight Age: 2.45), height was 98 cm (measured in a standing position) (SDS: –2.07, Percentile: 1.92, Height Age: 3.36), and BMI was 13.54 kg/m² (SDS: –1.55, Percentile: 6.06). The patient's vital signs were within the normal range for her age. The patient is enrolled in the donor screening program for a bone marrow transplant, but no related donor has been found. The search for an unrelated donor is ongoing.

Methods

This work has been reported in accordance with the SCARE 2023 criteria[6].

Discussion

Dyskeratosis congenita (DC) is a rare disease, with an incidence of ~1 in 1 000 000. The classic and initial presentation of DC is typically characterized by mucocutaneous symptoms such as abnormal skin pigmentation, nail dystrophy, and leukoplakia[7]. PARN gene mutations cause DC by affecting the stability of non-coding RNAs, which leads to impaired telomere maintenance[8]. Burris *et al.*[9] reported that while most mutations involved in the pathogenesis of DC are found in genes critical for hTR assembly (DKC1) or telomerase RNA stability (TERC), mutations in the PARN gene are associated with a more severe form of DC known as Hoyeraal–Hreidarsson (HH) syndrome.

Approximately 70% of patients with DC have been found to carry mutations in known DC-associated genes, including DKC1,

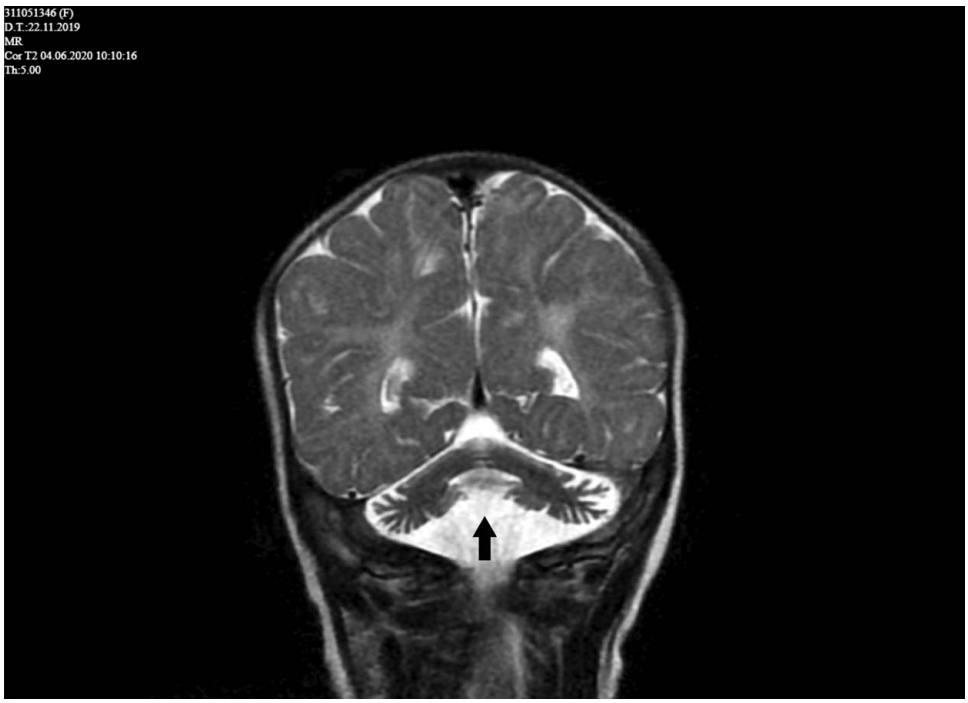

Figure 1. MRI of the patient's brain, demonstrating cerebellar vermis hypoplasia.

TERC, TERT, TINF2, NHP2, NOP10, ACD, CTC1, NAF1, PARN, POT1, RTEL1, STN1, and WRAP53[10,11]. Hoyeraal–Hreidarsson syndrome is an early-onset form of DC characterized by features such as intrauterine growth retardation (IUGR), immunodeficiency, cerebellar hypoplasia, abnormal skin pigmentation, nail dysplasia, and oral leukoplakia[12]. If MRI imaging reveals cerebellar hypoplasia and delayed myelination in a patient diagnosed with DC, the possibility of Hoyeraal–Hreidarsson syndrome should be considered[13,14].

In our case, in addition to the typical findings of DC, the patient also presented with cerebellar hypoplasia, oral leukoplakia, immune deficiency, and IUGR, which are suggestive of Hoyeraal–Hreidarsson syndrome. Mutations in the PARN gene have been linked to autosomal recessive forms of HH syndrome.

Conclusion

In conclusion, it has been established that PARN deadenylation function is important in telomere biology. Irrespective of the precise mechanism(s), PARN mutations link the basic deadenylation pathway to telomeropathies such as DC.

Ethical approval

This case report was conducted in accordance with ethical standards. As it is a case report, ethics approval was not required. However, informed consent for publication was obtained from the patient's family.

Consent

Family consent form was received.

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No funding was received.

Author contribution

Ş.Ç.K.: conception, writing, data collection and/or processing. M.Ç.: data collection, design, analysis. B.Y.: supervision, design, analysis and/or interpretation.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

Not applicable.

Data availability statement

Data and materials will be made available upon reasonable request and with the author's approval.

References

[1] Savage SA, Bertuch AA. The genetics and clinical manifestations of telomere biology disorders. Genet Med 2010;12:753–64.
[2] Gitto L, Stoppacher R, Richardson TE, *et al*. [Article Partial Retraction] Dyskeratosis congenita. Autopsy Case Rep 2020;10:e2020203.
[3] Kirwan M, Dokal I. Dyskeratosis congenita, stem cells and telomeres. Biochim Biophys Acta (BBA)-Mol Basis Dis 2009;1792:371–9.
[4] Niewisch MR, Savage SA. An update on the biology and management of dyskeratosis congenita and related telomere biology disorders. Expert Rev Hematol 2019;12:1037–52.
[5] Tummala H, Walne A, Collopy L, *et al*. Poly (A)-specific ribonuclease deficiency impacts telomere biology and causes dyskeratosis congenita. J Clin Invest 2015;125:2151–60.
[6] Sohrabi C, Mathew G, Maria N, *et al*. The SCARE 2023 guideline: updating consensus Surgical CAse REport (SCARE) guidelines. Int J Surg 2023;109:1136–40.
[7] Dokal I. Dyskeratosis congenita. Stiehm's Immune Deficienc 2014;1:267–80.
[8] Shukla S, Bjerke GA, Muhlrad D, *et al*. The RNase PARN controls the levels of specific miRNAs that contribute to p53 regulation. Mol Cell 2019;73:1204–16.
[9] Burris AM, Ballew BJ, Kentosh JB, *et al*. Hoyeraal-Hreidarsson syndrome due to PARN mutations: fourteen years of follow-up. Pediatr Neurol 2016;56:62–8.
[10] Khincha PP, Savage SA. Genomic characterization of the inherited bone marrow failure syndromes. In *Seminars in hematology* 2013;50:333–47.
[11] Wegman-Ostrosky T, Savage SA. The genomics of inherited bone marrow failure: from mechanism to the clinic. Br J Haematol 2017;177:526–42.
[12] Moon DH, Segal M, Boyraz B, *et al*. Poly (A)-specific ribonuclease (PARN) mediates 3′-end maturation of the telomerase RNA component. Nat Genet 2015;47:1482–8.
[13] Zhang MJ, Cao YX, Wu HY, *et al*. Brain imaging features of children with Hoyeraal-Hreidarsson syndrome.. Brain Behav 2021;11:e02079.
[14] Dhanraj S, Gunja SMR, Deveau AP, *et al*. Bone marrow failure and developmental delay caused by mutations in poly (A)-specific ribonuclease (PARN). J Med Genet 2015;52:738–48.