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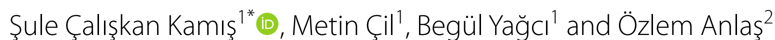

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A novel nonsense *RPS26* mutation in a patient with Diamond–Blackfan anemia: a case report

Şule Çalışkan Kamış[1*], Metin Çil[1], Begül Yağcı[1] and Özlem Anlaş[2]

Abstract

Background Diamond–Blackfan anemia is a rare congenital disorder characterized by erythroid hypoplasia and is associated with mutations in ribosomal protein genes. This case report describes a novel variant in the *RPS26* gene, which, to our knowledge, has not been previously documented. Reporting this case adds to the understanding of Diamond–Blackfan anemia's genetic diversity and phenotypic manifestations.

Case presentation A 16-month-old Turkish girl presented with pallor and macrocytosis. There was no familial history of anemia. Hemoglobin electrophoresis showed hemoglobin F at 10.8%, hemoglobin A2 at 1.7%, and hemoglobin A at 87.5% (normal range 0–2%). Peripheral smear demonstrated macrocytosis and reticulocytopenia. Bone marrow examination revealed marked erythroid hypoplasia and dyserythropoiesis. Targeted next-generation sequencing, which included genes such as *RPL11, RPL15, RPL26, RPL35A, RPL5, RPS10, RPS17, RPS19, RPS24, RPS26, RPS28, RPS29, RPS7*, and *TSR2*, identified a heterozygous c.221G>T (p.C74F) variant in the *RPS26* gene. This variant is reported here for the first time.

Conclusions The identification of the c.221G>T (p.C74F) variant in *RPS26* provides new insights into the genetic underpinnings of Diamond–Blackfan anemia. This finding underscores the importance of genetic testing in diagnosing Diamond–Blackfan anemia and highlights the potential for new mutations to contribute to the clinical presentation of the disease. Further research into *RPS26* mutations may enhance the understanding of Diamond–Blackfan anemia's pathogenesis and lead to improved diagnostic and therapeutic strategies.

Keywords Diamond–Blackfan anemia, *RPS26*, Ribosomopathy, Case reports

Introduction

Diamond–Blackfan anemia (DBA) is a rarely diagnosed congenital erythroid hypoplasia [1]. Ribosomal dysfunction is commonly seen in DBA; consequently, patients often present with hypoplastic anemia and congenital anomalies [2]. Characteristically, macrocytic anemia and reticulocytopenia are detected in DBA. Moreover, the risk of malignancy is increased in these patients. Hematological complications are detected by 1 year of age in 90% of affected individuals [3]. The malignancies to which patients with DBA are predisposed include acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and osteogenic sarcoma [4]. Patients with DBA often have

*Correspondence:
Şule Çalışkan Kamış
sulecaliskan87@yahoo.com
[1] Department of Pediatric Hematology and Oncology, Adana Faculty of Medicine, Adana City Education and Research Hospital, University of Health Sciences, Adana, Turkey
[2] Department of Medical Genetics, Adana Faculty of Medicine, Adana City Education and Research Hospital, University of Health Sciences, Adana, Turkey

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elevated erythrocyte adenosine deaminase (eADA) and hemoglobin F levels [5]. The condition is mostly inherited in an autosomal dominant manner, though 55–60% of cases occur sporadically [6]. The incidence of DBA is estimated at 1–4 per 500,000 per year [7]. DBA is categorized as a ribosomopathy [8] and is characterized by mutations in either the ribosomal protein large (*RPL*) or ribosomal protein small (*RPS*) subunit genes [9]. Mutations have been identified in nine of the ribosomal genes: *RPS19, RPL5, RPS26, RPL11, RPL35A, RPS10, RPS24, RPS26, RPS28, RPS29, RPS7, and RPS17* [10]. *RPS26* is an essential component of mRNA processing. The detection of mutations in the *RPS26* gene affects the small subunit of the ribosome, which can lead to significant clinical manifestations. Currently, 30 variants reported to cause DBA are known [11, 12]. Here, we present a patient with DBA according to the genetic test results. Notably, this is the first report of the c.221G>T (p.C74F) variant in the *RPS26* gene.

Case report

A 16-month-old Turkish girl presented with pallor. The family history was unremarkable. Physical examination did not reveal hepatosplenomegaly. Laboratory tests indicated hemoglobin (Hb) at 5.2 g/dL (normal range 10.8–14.6 g/dL), red blood cell (RBC) count of 1.41×10^6/microliter (reference range 3.97–5.01×10^6/microliter), and reticulocyte count of 1.43% (reference 2–6%). Mean corpuscular volume (MCV) was found to be 115.5 fL (normal range 71.3–82.6 fL). White blood cell (WBC) and platelet counts were within normal limits. Bone marrow examination revealed marked erythroid hypoplasia and dyserythropoiesis, while the granulocyte and megakaryocyte lineages appeared normal. Testing for blood serum antibodies, including cytomegalovirus immunoglobulin (Ig)M, parvovirus B19, herpes simplex virus IgM, and toxoplasma virus IgM, yielded negative results. No hemolysis was detected, as indicated by the lactate dehydrogenase (LDH) level of 327 U/L, total bilirubin of 0.45 mg/dL, direct bilirubin of 0.09 mg/dL, and a negative direct Coombs test. Hemoglobin electrophoresis revealed HbF at 10.8%, Hb A2 at 1.7%, and HbA at 87.5% (normal range 0–2%). No thymoma was identified on X-ray and tomography. The patient had no history of drug use and was subsequently diagnosed with DBA. Steroid treatment was initiated, and the patient exhibited a positive response. The patient's genomic DNA was studied using next-generation sequencing (NGS) on the MiSeq platform (Illumina). The test screened the *RPL11, RPL15, RPL26, RPL35A, RPL5, RPS10, RPS17, RPS19, RPS24, RPS26, RPS28, RPS29, RPS7,* and *TSR2* genes for point mutations and small genomic deletions or insertions with over 99% sensitivity. The variants were analyzed with Sequencing Analysis Viewer (SAV) Software from Illumina and The Integrative Genomics Viewer (IGV) based on pathogenicity scores, *in silico* prediction tools, and genotype–phenotype correlation. After NGS analysis, a heterozygous c.221G>T (p.C74F) variant was detected in the *RPS26* gene (Fig. 1). This mutation was confirmed as a *de novo* mutation by NGS, indicating that neither of the patient's parents were carriers of the mutation. This variant has been interpreted as "pathogenic" according to the American College of Medical Genetics and Genomics (ACMG)'s variant guidelines. We report a *de novo* variant in our patient, summarizing that this heterozygous variant in *RPS26* is highly likely to contribute to DBA in this case.

Discussion

Diamond–Blackfan anemia is caused by defective ribosome biogenesis due to heterozygous pathogenic variants in ribosomal protein (RP) genes. A decreased number of functional ribosomes leads to the activation of pro-apoptotic pathways and reduced translation of genes essential for erythropoiesis [13]. In DBA, mutations in the *RPS26* gene are found in 5.3–11.6% of cases [11]. Mutations affecting the RPs of both small (*RPS24, RPS17, RPS19, RPS10, RPS26, RPS7*) and large (*RPL35A, RPL5, RPL11, RPL26*) ribosomal subunits have been identified in patients with DBA [14]. Chae *et al.* reported heterozygous mutations in *RPS19, RPS26*, and *RPS17* in seven patients with DBA [15]. *GATA1, TSR2,* and *RPS26* mutations may also be observed in DBA [16]. In the study conducted by Wan *et al.*, a correlation was noted between *RPL11* or *RPS26* mutations and the risk of short stature in patients with DBA [17]. Gripp *et al.* identified pathogenic *RPS26* mutations in two of six families in their study [18] . In our case, NGS was performed, revealing a heterozygous variant in the *RPS26* gene (c.221G>T), which results in the amino acid change p.C74F. Sanger sequencing confirmed that neither of the patient's parents were carriers of this mutation. This represents a *de novo* variant in a family with no previous history of the disease. Therefore, we conclude that this heterozygous variant in *RPS26* likely contributes to the DBA phenotype in this patient.

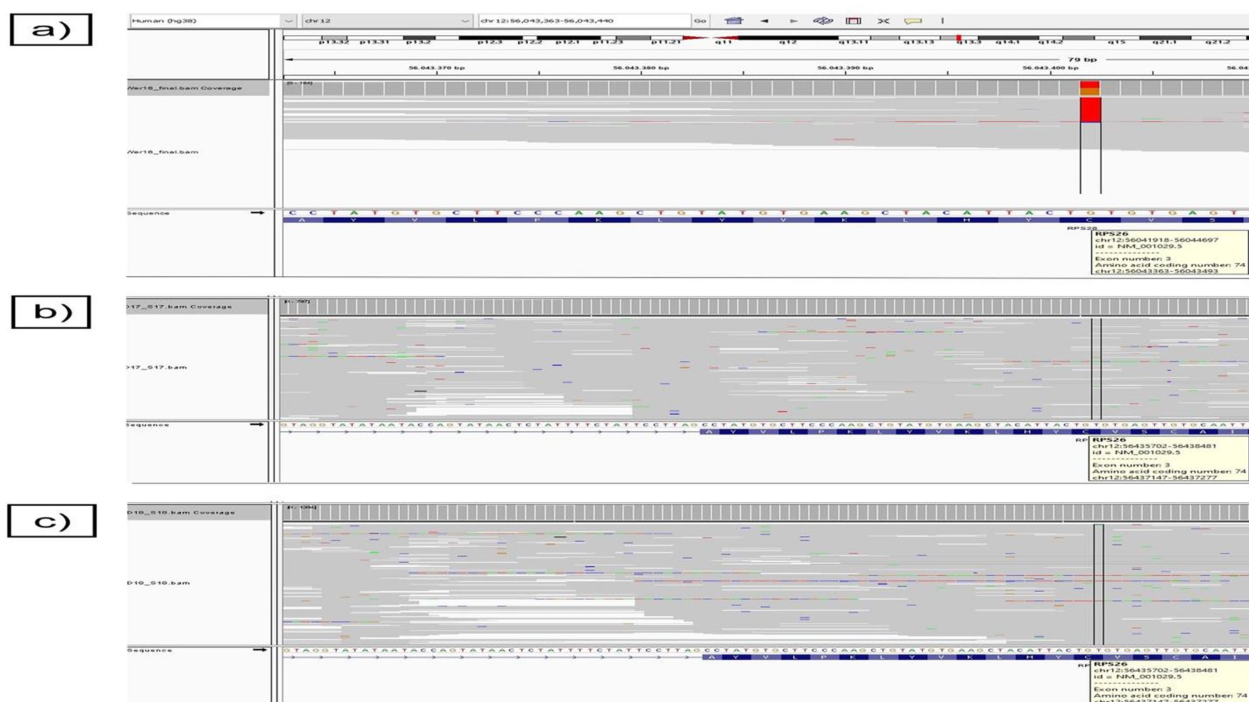

Fig. 1 **a** The mutation analysis revealed a heterozygous amino acid chance at codon 74 in the patient (c.221G>T; p.Cys74Pfe). **b**, **c** No mutation was detected in the parents

Conclusion

Mutations in the *RPS26* gene may be responsible for the DBA phenotype in this case. The hematological outcomes and congenital anomalies observed are likely a result of abnormal ribosome biogenesis stemming from the associated mutation.

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Author contributions
ŞÇK carried out the conception, writing, data collection, and/or processing. MÇ carried out the revision and editing, conception, and design. BY carried out the supervision, design, analysis, and/or interpretation. ÖA contributed to the revision and editing, data collection, and data analysis.

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

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the ethical standards set by the relevant ethics committee. Written informed consent was obtained from the patient's guardian for participation in the study.

Consent for publication
Written informed consent was obtained from the patient's guardian for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

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