Turk J Hematol 2024;41:281-282

Unmasking Congenital Methemoglobinemia: A Novel *CYB5R* Mutation Discovered in an Adult with Symptomatic Polycythemia

Doğuştan Methemoglobinemiyi Açığa Çıkarmak: Semptomatik Polisitemisi Olan Bir Yetişkinde Keşfedilen Yeni Bir *CYB5R* Mutasyonu

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To the Editor,

Methemoglobinemia is characterized by the presence of elevated levels of methemoglobin (metHb), a form of hemoglobin with reduced oxygen-carrying capacity. The most common cause of congenital methemoglobinemia is cytochrome b5 reductase (CYB5R) enzyme deficiency [1]. The clinical presentation of congenital methemoglobinemia varies widely, ranging from asymptomatic cases to severe tissue hypoxia and cyanosis [2].

A 29-year-old male patient presented to our clinic with complaints of headache, fatigue, and exertional dyspnea for the last 5 months. He denied any recent history of drug intake or exposure to toxic substances. Physical examination revealed cyanosis of the lips and nail beds with oxygen saturation of 74% by room-air pulse oximetry. Laboratory investigations demonstrated polycythemia with hemoglobin of 21 g/dL and hematocrit of 63%. Further findings are summarized in Table 1. Echocardiography did not suggest any evidence of structural heart disease. Arterial blood gas (ABG) analysis revealed oxygen saturation of 96.4% and metHb of 52.5% based on spectrophotometry, confirming the diagnosis of methemoglobinemia. Clinical exome sequencing revealed a novel homozygous missense mutation in exon 5 of the *CYB5R* gene, NM_000398.7:c.431G>T [p.Gly144Val], resulting in substitution of glycine to valine at codon 144 (Figure 1). Ascorbic acid was administered as treatment, leading to symptomatic improvement. Subsequent ABG analysis revealed a metHb level of 15.1%.

Table 1. Laboratory results at presentation.

Laboratory test	Result (baseline)	Reference range
pH	7.402	7.35-7.45
PaO_2	85 mmHg	83-108 mmHg
PCO_2	35 mmHg	32-48 mmHg
SaO_2	96.4%	94%-98%
MetHb	52.5%	0%-1.5%
WBC	$7.2x10^3$/µL	$4-11x10^3$/µL
Hb	21 g/dL	12-15 g/dL
Hct	63%	36%-46%
MCV	89 fL	82-100 fL
PLT	$170x10^3$/µL	$150-400x10^3$/µL

PaO_2: Partial pressure of oxygen; PCO_2: partial pressure of oxygen dioxide; SaO_2: saturation of oxygen in blood; MetHb: methemoglobin; WBC: white blood cell count; Hb: hemoglobin; Hct: hematocrit; MCV: mean cell volume; PLT: platelet count.

The *CYB5R* gene encodes cytochrome b5 reductase, an enzyme essential for the reduction of metHb to functional hemoglobin. Mutations in the *CYB5R* gene lead to the accumulation of metHb and subsequent tissue hypoxia. Persistent tissue hypoxia leads to stimulation of erythropoiesis, resulting in polycythemia. There are two types of CYB5R enzyme deficiency. In type I, the deficiency of the enzyme affects only red blood cells and causes isolated methemoglobinemia. These patients are usually asymptomatic beyond cosmetic issues. Type II deficiency affects all tissues and is associated with intellectual disability, developmental delay, and other neurological abnormalities with reduction of the life span [1]. Thus, our patient can be said to have the type 1 variant, as he remained asymptomatic for many years and it is possible that he might have experienced an additional unidentified event that led to the additional accumulation of higher metHb levels, ultimately becoming symptomatic. Nakata et al. [3] reported a similar case of a patient who was diagnosed at 79 years of age.

To date, approximately 80 pathogenic variants have been described in the *CYB5R* gene. *CYB5R* mutation is endemic in some communities in the United States and Russia [2]. The novel mutation identified in our case (p.Gly144Val) results in an amino acid substitution, Arg58Gln, which was predicted to be "probably damaging" by PolyPhen2 software and "deleterious" by SIFT software. This mutation was not reported previously. However, a nucleotide substitution in the same coding region was previously reported, causing a disease phenotype [3].

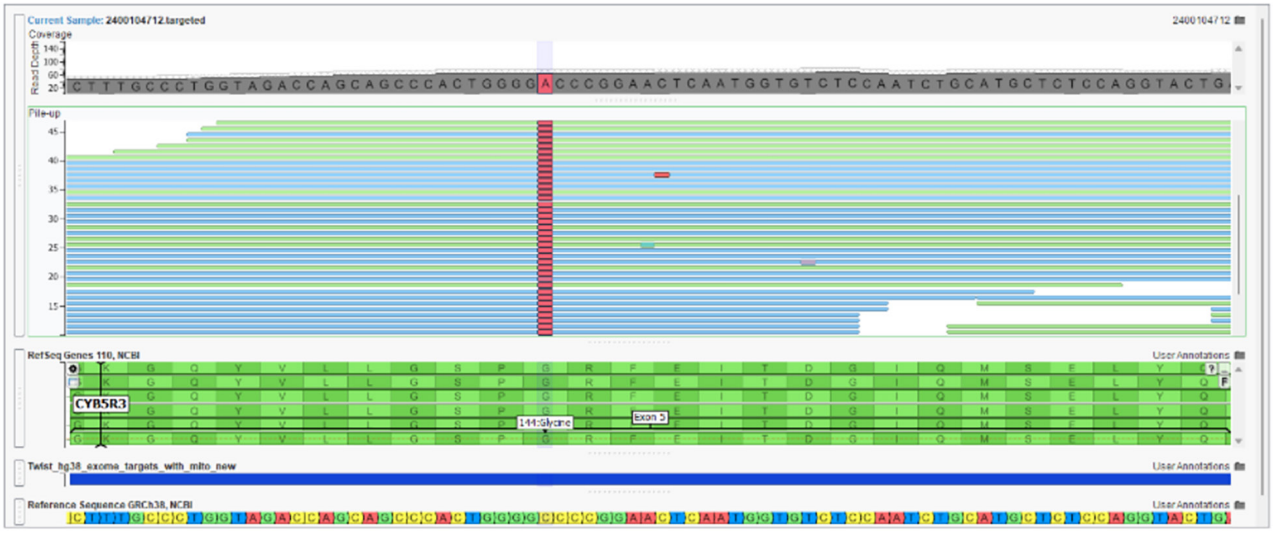

Figure 1. Clinical exome sequencing on the NovaSeq 6000 NGS Platform (Illumina, San Diego, CA, USA) shows a homozygous variant in exon 5 of *CYB5R* (chr22: g.42628184C>A). A missense variant of G to T was detected at nucleotide position 431, leading to a change in amino acid sequences from glycine to valine at codon 144.

Management of these cases primarily focuses on reducing metHb levels and alleviating symptoms of tissue hypoxia. Phlebotomy is not recommended. Treatment options include intravenous methylene blue for acutely symptomatic patients. High-dose ascorbic acid can be used for ambulatory patients and cases in which methylene blue is contraindicated, such as cases of G6PD deficiency [4]. The relevant mechanism involves reduction of ferric iron (Fe^{3+}) in metHb to ferrous iron (Fe^{2+}). The dose typically ranges from 500 mg to 1 g three to four times daily [5]. As our patient was ambulatory without any acute history, he was given ascorbic acid. The choice of medication and dosing regimen should be tailored to the patient. Chronic administration may lead to sodium oxalate nephrolithiasis [6].

Keywords: Congenital methemoglobinemia, *CYB5R*, Polycythemia, Saturation gap

Anahtar Sözcükler: Doğuştan methemoglobinemi, *CYB5R*, Polisitemi, Satürasyon farkı

Ethics

Informed Consent: Obtained from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.R.N., P.G., S.T., J.D., P.K., M.A.; Concept: A.R.N., P.G., S.T., J.D., P.K., M.A.; Design: A.R.N., P.G., S.T., J.D., P.K., M.A.; Data Collection or Processing: A.R.N., P.G., S.T.; Analysis or Interpretation: J.D., P.K., M.A.; Literature Search: A.R.N., J.D., P.K., M.A.; Writing: A.R.N., P.G., S.T., J.D., P.K., M.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Received/Geliş tarihi: June 23, 2024
Accepted/Kabul tarihi: August 9, 2024
DOI: 10.4274/tjh.galenos.2024.2024.0232