LETTERS TO THE EDITOR
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Unmasking Congenital Methemoglobinemia: Novel CYB5R Mutation Discovered in an Adult with Symptomatic Polycythemia

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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 commonest 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 years old male presented to clinic with complaints of headache, fatigue and exertional dyspnea for the last 5 months. He denied any history of recent drug intake or any toxic substance exposure. Physical examination revealed cyanosis of lips and nail beds with an oxygen saturation of 74% by pulse oximetry on room air. Laboratory investigations demonstrated polycythemia with hemoglobin levels of 21 g/dL, hematocrit of 63%.(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 a metHb level of 52.5% (through spectrophotometry principle), confirming the diagnosis of methemoglobinemia. Clinical exome sequencing (CES) revealed a novel homozygous missense mutation in the exon 5 of 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 and a repeat ABG showing a metHb level of 15.1%.

The CYB5R gene encodes cytochrome b5 reductase, an enzyme essential for the reduction of metHb to functional hemoglobin. Mutations in the CYB5R gene leads to accumulation of methemoglobin and subsequent tissue hypoxia. Persistent tissue hypoxia leads to stimulation of erythropoiesis resulting in polycythemia. There are 2 types of CYB5R deficiency. In type I, the deficiency of the enzyme affects only the RBCs and causes isolated methemoglobinemia. The patients are usually asymptomatic apart from cosmetic issues. Type II deficiency affects all the tissues and is associated with intellectual disability, developmental delay and other neurological abnormalities with reduction of life span[1]. Thus, our patient fits into the type 1 variant, who stayed asymptomatic for many years and It's possible that he might have experienced an additional, unidentified insult that led to the additional accumulation of higher methemoglobin levels, ultimately becoming symptomatic. Nakata et al, reported a similar case, who was diagnosed at 79 years of age [3].

Till now, around 80 pathogenic variants have been described in the CYB5R gene. The CYB5R defect is endemic in some communities in the US and Russia [2]. The novel mutation identified in our case (p.Gly144Val) results in 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 at the same coding region was reported in a case causing disease phenotype [3].

Management primarily focuses on reducing metHb levels and alleviating symptoms of tissue hypoxia. Phlebotomy is not recommended. Treatment options include intravenous methylene blue for acute symptomatic patients. High dose ascorbic acid can be used in ambulatory cases and at instances where methylene blue is contraindicated like G6PD deficiency [4]. The mechanism involves reduction of ferric iron (Fe^{3+}) in methemoglobin to ferrous iron (Fe^{2+}). The dose typically ranges from 500 mg to 1g 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 formation of sodium oxalate nephrolithiasis [6].

References

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Table 1: Laboratory results at presentation.

Laboratory test	**Result (Baseline)**	**Reference range**
pH	7.402	7.35 -7.45
PaO2	85 mmHg	83 -108 mmHg
PCO2	35 mmHg	32 -48 mmHg
SaO2	96.4%	94 -98%
MetHb	52.5%	0 -1.5%
WBC	7.2 $\times 10^3$/uL	4 -11$\times 10^3$/uL
Hb	21 g/dL	12 -15 g/dL
Hct	63 %	36 -46%
MCV	89 fL	82 -100 fL
PLT	170 $\times 10^3$/uL	150 -400$\times 10^3$/uL

pH: potential of hydrogen (blood acidity); PaO_2: partial pressure of oxygen; PCO_2: partial ,pressure of oxygen dioxide, SaO2: saturation of oxygen in blood; WBC: white blood cell count; Hb: hemoglobin; Hct: hematocrit; MCV: mean cell volume; PLT: platelets count

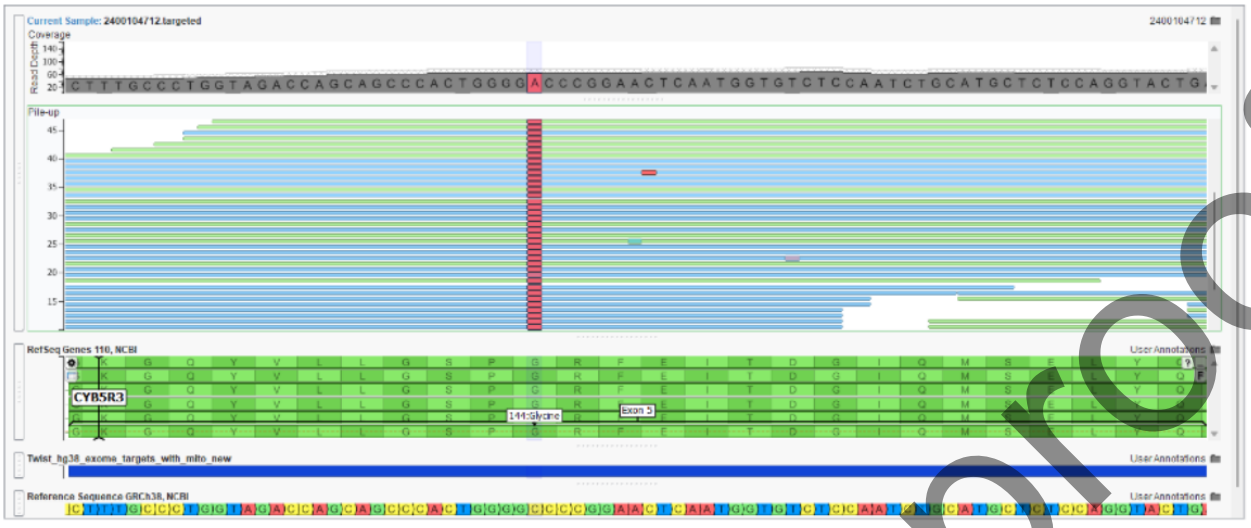

Figure 1. Clinical Exome Sequencing on the Illumina Novaseq 6000 NGS(Next Generation Sequencing) Platform shows Homozygous variant in Exon 5 of gene CYB5R3 (chr22: g.42628184C>A). A missense variant “G” to “T” detected at nucleotide position 431 leading to change in amino acid sequences from Glycine to Valine at codon 144.