# Rare *MPIG6B* Gene Mutation in an Indian Male with Anemia and Thrombocytopenia

## Anemi ve Trombositopenili Hintli Bir Erkekte Nadir *MPIG6B* Gen Mutasyonu

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**To the Editor,**

A 21-year-old male initially presented in the hematology clinic with generalized weakness. On examination, no physical abnormalities were seen. He was the offspring of a third-degree consanguineous marriage. Laboratory evaluations showed white blood cell count of $13x10^9$/L, absolute neutrophil count of $8.6x10^9$/L, hemoglobin of 7.8 g/dL, mean corpuscular volume of 87 fL, and platelet count of $20x10^9$/L. Upon peripheral blood smear examination, red blood cells showed anisopoikilocytosis, teardrop cells, spherocytes, stomatocytes, microcytes, and macrocytes with giant platelets (Figure 1). On further evaluation, the results of direct and indirect Coombs tests, ANA, and anti-dsDNA tests were negative. We followed a diagnostic algorithm to rule out autoimmune cytopenia [1]. Vitamin D, vitamin B12, and folate levels were normal. A bone marrow examination was performed, which showed trilineage hematopoiesis and adequate megakaryocytes, with focal grade 1 fibrosis. Chromosomal fragility testing and the myelodysplastic panel were negative. A whole-exome sequence showed a homozygous loss-of-function mutation in *MPIG6B*: c.132G>A (p.Trp44Ter). This gene was confirmed by Sanger sequencing (Figure 2). This gene with the c.132G>A mutation is absent in the clinical variant database. The present case thus revealed a novel mutation. In silico analysis identified the variant as pathogenic. The present case is in the process of being registered in the clinical variant database.

The *MPIG6B* gene, also known as *G6B* or *C6orf25*, is located in the class III region of the major histocompatibility complex and expressed on platelets, and it is required for red blood cell and platelet differentiation [2]. This gene encodes a cell surface receptor of the immunoglobulin superfamily that further activates inhibitory signaling pathways by triggering Shp1 and Shp2 via immunoreceptor tyrosine-based inhibitory motifs in its cytoplasmic domain [3,4]. In G6b-B knockout mice, low platelet counts, giant platelets, and platelet dysfunction were observed. The uncoupling of G6b-B from Shp1 and Shp2 leads to severe thrombocytopenia with reduced platelet production, giant megakaryocytes, and myelofibrosis [5]. In the present case, the patient had persistent anemia, thrombocytopenia, and mild splenomegaly. The whole blood counts of the mother and father were normal. We could not do a functional genetic study of the mother and father due to financial constraints. The patient maintained a platelet count of $25x10^9$/L to $30x10^9$/L with occasional mucosal bleeding. He received steroids, but there was a poor response. He responded well to romiplostim at 250 µg/week, with a platelet count of more than $40x10^9$/L. The

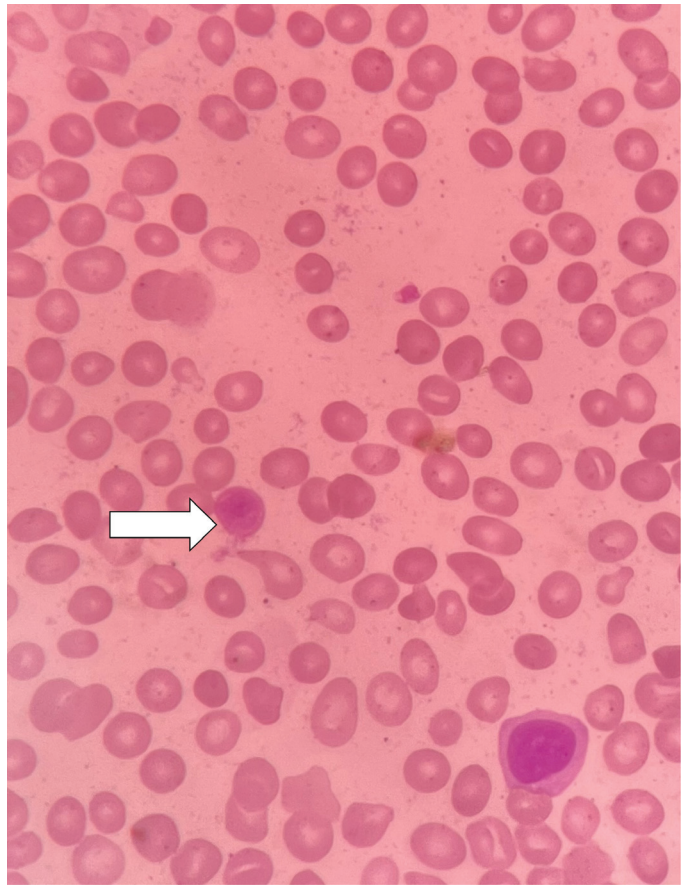

**Figure 1.** Peripheral blood smear showing anisopoikilocytosis, teardrop cells, spherocytes, stomatocytes, microcytes, and macrocytes with giant platelets (arrow).

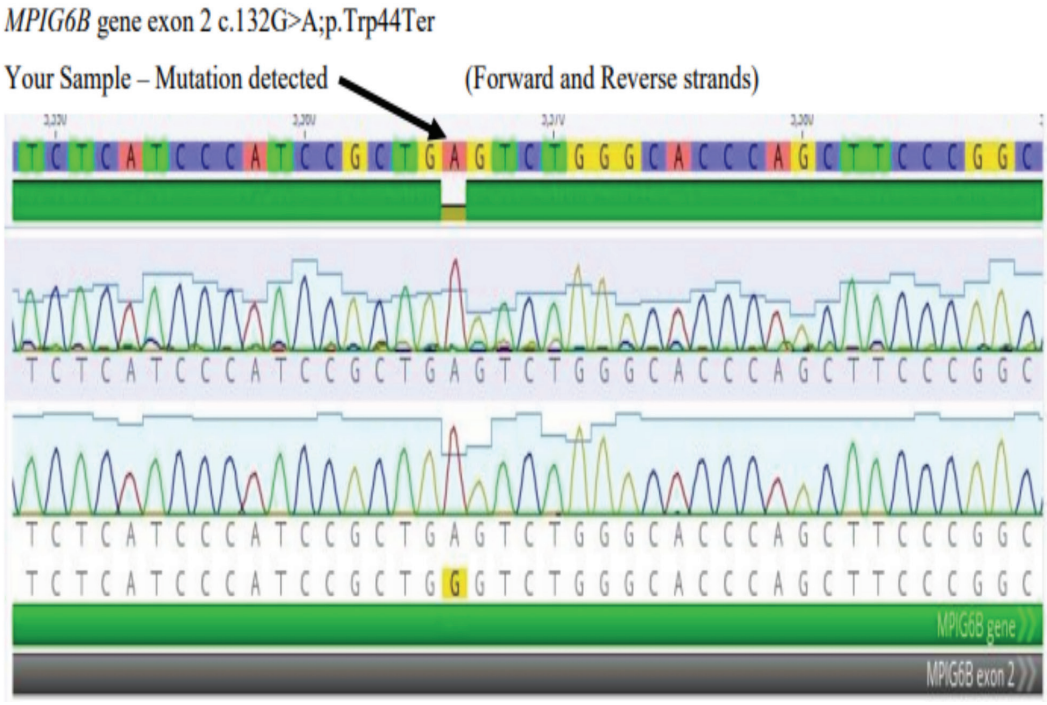


**Figure 2.** Sanger sequencing confirming the *MPIG6B* gene.

anemia in this case was related to the *MPIG6B* gene mutation and it did not improve with romiplostim. The patient received intermittent blood transfusions for anemia. His follow-up remains satisfactory.

A summary of all case reports published to date is shown in Table 1 [6,7,8,9,10]. The probable mechanism leading to myelofibrosis in cases of mutated *G6B* is dysplastic megakaryocytes. These dysplastic cells secrete cytokines such as transforming growth factor-β, causing myelofibrosis [5]. Another mechanism is the autoimmune process causing persistent inflammation that leads to myelofibrosis in the bone marrow [5]. Mutated *G6B* is expressed in CD4+ T-cells and might cause immune dysregulation [5]. As previous case reports revealed, inflammation is more common in the bone marrow with potential roles of inflammation or immune dysregulation in the development of myelofibrosis. High degrees of consanguinity and birth order are risk factors for the manifestation of such rare genetic disorders. If a patient presents with anemia and thrombocytopenia with giant platelets, the physician should consider the differential diagnosis of such rare inherited conditions.

The exact pathophysiology of this disease is not known; hence, more studies are needed to understand the disease pathology and potential therapeutic targets. In our case, an increase in platelet count was seen with romiplostim. As of now, only hematopoietic stem cell transplantation is a feasible treatment modality for progressive disease.

**Keywords:** Anemia, Thrombocytopenia, Splenomegaly

**Anahtar Sözcükler:** Anemi, Trombositopeni, Splenomegali

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### Ethics

**Informed Consent:** Obtained.

### Authorship Contributions

Concept: A.A.K., S.G.R.; Design: A.A.K., S.G.R.; Writing: A.C., A.J., S.A.G.

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**Table 1. Summary of cases of homozygous pathogenic mutations in *MPIG6B*.**

| Features | Present case | Batis et al. [6] | Melhem et al. [7] | Hofmann et al. [8] | Saliba et al. [9] | Chen et al. [10] |
|---|---|---|---|---|---|---|
| No. of patients | 1 | 2, unrelated | 4, siblings | 9 (4 unrelated families) | 1 | 1 |
| Sex (M/F) | 1/0 | 0/2 | 3/1 | 6/3 | 0/1 | 1/0 |
| Patient's origin | Indian | Arab | Arab | Arab | European | Chinese |
| Age/median age | 21 | 4/10 | 41.5 (30-48) | 1 (0.1-7) | 11.8 (at 26 years) | 10 months |
| Clinical characteristics | Anemia, thrombocytopenia, splenomegaly | Epistaxis, splenomegaly in 1 patient | Bruising and splenomegaly in two patients | Mild bleeding<br>Unaffected (n=1) | Easy bruising and development of Evans Syndrome after five years | Petechiae, splenomegaly |
| Peripheral blood smear | Giant platelets<br>RBC: Anisopoikilocytosis, teardrop cells, spherocytes, stomatocytes, microcytes, and macrocytes | Giant platelets RBC: Anisopoikilocytosis, teardrop cells, schistocytes, elliptocytosis, and spherocytes | RBC: Anisopoikilocytosis and teardrop cells | Large platelets<br>RBC: Microcytosis, anisopoikilocytosis, schistocytes, and target cells | Giant platelets<br>RBC: Teardrop cells | Giant platelets<br>RBC: Anisopoikilocytosis, teardrop cells |
| Bone marrow | Trilineage hematopoiesis and adequate megakaryocytes<br>Focal grade 1 fibrosis | Hypercellular infiltration by atypical lymphoid cells and subsequently marrow showing fibrosis in the older child | Hypercellular increased megakaryocytes, and moderate to severe reticulin | Atypical megakaryocytes, reticulin fibrosis | Hypercellular Adequate megakaryocytes, mild grade 1 fibrosis at 26 years, and grade 2 fibrosis at the age of 41 years | Hypercellular marrow, mild focal myelofibrosis Increased lymphocyte infiltration |
| Homozygous *MPIG6B* mutation | NM_138272.3:<br>C.132G>A;<br>P.Trp44Ter<br>Exon2, nonsense, homozygous | c.523C>T(p.Arg175Ter(n=1)<br>C.149dup(p.Ala52GlyfsX128) (n=1) | C.324C>A(p.Cys108Ter | c.61_61+dup(n=1)<br>c.149dup(p.Ala52GlyfsX128) (n=2)<br>C469G>A(p.Gly157Arg) (n=2) | C469G>A(P.Gly157Arg) | c.392delC(p.P134Lfs*10) |
| Hemoglobin, g/dL, range | 7-8 | 7-8 | 6-10 | 5.1-12.1 | 11.8 | 7-9 |
| Platelets, µ/L, Range | 20000-25000 | 10000-42000 | 10000-42000 | 10000-468 | 57000 | 4000-1100 |
| Treatment | No response to steroids, intermittent platelet transfusion Response to romiplostim. | Platelet and blood transfusions occasionally<br>Splenectomy for one patient with transient improvement in platelets; for the other patient, improvement in hemoglobin and platelets after steroid use | Occasional platelet transfusions, no response to steroids | Regular platelet transfusions and occasional blood transfusions<br>Stem cell transplant for three patients | Transient improvement in platelet count after splenectomy | Occasional blood support |
| Outcome | Alive | Alive | Alive | One patient died of a stem cell transplant complication; the others are alive | Alive | Alive. |

RBC: Red blood cells

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