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# Hemolytic anemia with combinations of mutation SPTA1 c.6531-12C>T and SLC4A1 Pro868Leu

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## Introduction

When evaluating hemolytic anemia there are numerous causes and differentials to consider. This includes infection, drug-related, mechanical, hereditary and autoimmune. Obtaining a clear history on previous episodes of anemia can make hereditary causes more likely. The various types of hereditary hemolytic anemia include spherocytosis, elliptocytosis, stomatocytosis, and xerocytosis.<sup>3</sup> In the acute setting when there is hemodynamic instability, acute bleeding or acute thrombosis, urgent peripheral blood smear should be obtained to evaluate for thrombotic thrombocytopenic purpura or another primary thrombotic microangiopathy. When immune hemolysis is being considered, direct antiglobulin or Coombs should be tested. If positive, this is further differentiated between warm and cold agglutinins.

## Case Presentation

A 33-year-old male with no prior medical history presented to the hospital complaining of dizziness and lightheadedness upon standing associated with diaphoresis and near syncope. He also endorsed worsening exercise intolerance, dark colored urine, and night sweats. On evaluation, hemoglobin was noted to be 6.1, Ultrasound of the abdomen showed splenomegaly measuring 18 cm. Anemia work up revealed a low haptoglobin <30, reticulocytosis, hyperbilirubinemia and high LDH. Coombs test was negative. Peripheral smear showed elliptocytosis without fragmented red blood cells. These findings were consistent with non-immune hemolytic anemia. Pertinent negative studies include monoclonal protein, antinuclear antibody, rheumatoid factor, Epstein Barr Virus, Cytomegalovirus, human immunodeficiency virus, and Coombs antibody. Parovirus IgG was elevated. The patient was transfused packed red blood cells and hemoglobin improved to 9.7 prior to discharge from the hospital.

During outpatient follow-up his hemoglobin dropped to 7.9 requiring transfusion. He also underwent bone marrow biopsy that showed a hypercellular marrow and erythroid predominance, but with very mild dyserythropoiesis.

Continued work up on non-immune hemolytic anemia included hemoglobin electrophoresis, glucose-6-phosphate dehydrogenase, pyruvate kinase, and paroxysmal nocturnal hemoglobinuria all resulted negative.

With the diagnosis of elliptocytosis, he underwent splenectomy which showed reactive splenomegaly and red pulp expansion. Following splenectomy, his hemoglobin normalized.

Red blood cell membrane studies were also negative. Genetic testing revealed mutations of SPTA1 c.6531-12C>T and SLC4A1 Pro868Leu.

## Clinical Images

Figure 1. Spherocytes<sup>4</sup>

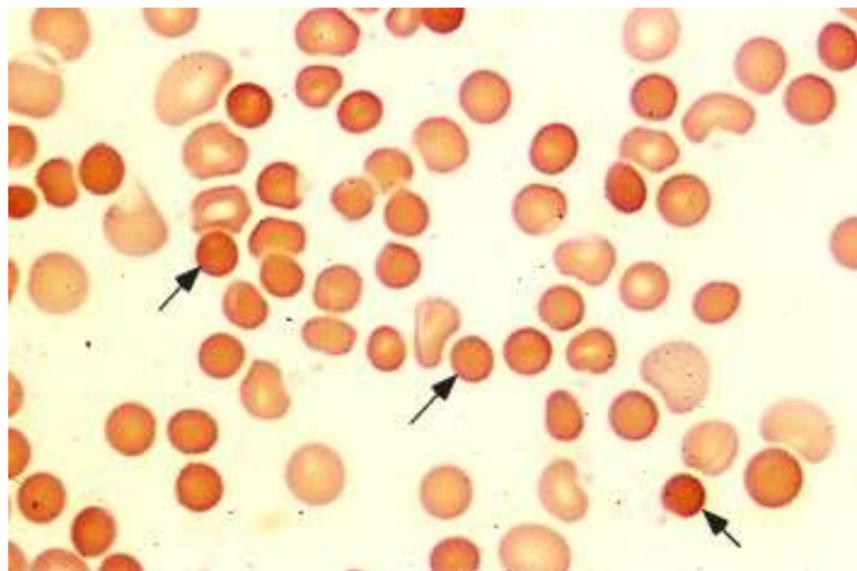
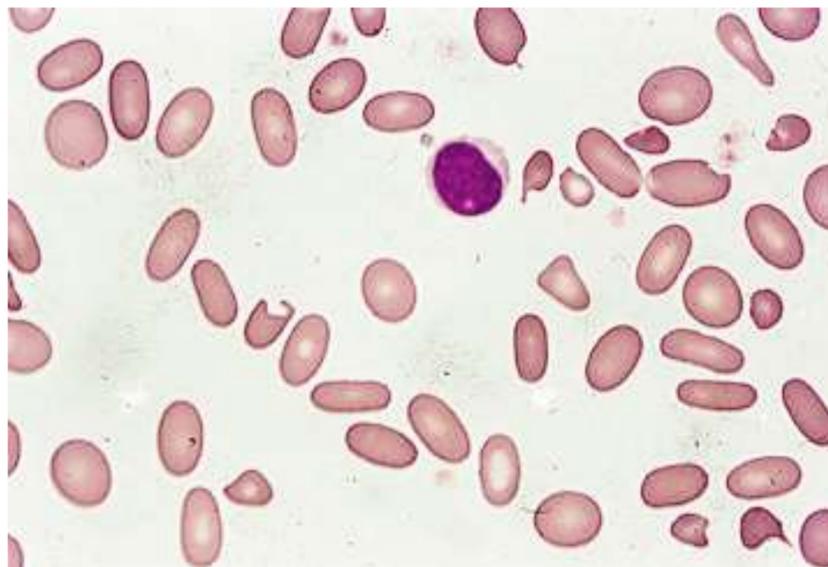


Figure 2. Elliptical red cells in hereditary elliptocytosis<sup>5</sup>



## Impact

Mutation of SPTA1 c.6531-12C>T encodes for the protein spectrin and can cause a worse phenotype of hemolytic anemia in patients with elliptocytosis or poikilocytosis. SLC4A1 Pro868Leu is seen in acanthocytosis and encodes for band 3, a protein on the red blood cell membrane involved in ion exchange. These mutations have not been reported together before but we cannot rule out that even though they are not pathogenic standing alone, that they could cause hemolysis when found together.

## Discussion

Of the various types of non-immune hemolytic anemias, aberrations in spectrin has been shown to be associated with various membrane defects ranging from spherocytosis to poikilocytosis<sup>1</sup>.

Mutations in the anion exchanger SLC4A1 Pro868Leu has been shown to result in disturbances that can disrupt membrane ion equilibrium leading to acanthocytosis. Like this channel, SLC4AE, is involved in ion exchange and connects to other proteins that compose the cytoskeleton of red blood cells, stabilizing the structure<sup>1</sup>. A mutation of this channel would lead to disturbance in the red cell membrane leading to abnormalities such as acanthocytosis.

Mutation of SPTA1 c.6531-12C>T has been associated with a worse phenotype of hemolytic anemia in patient's red cell membrane abnormalities. Many mutations in the *SPTA1* gene affect the interaction sites of the alpha and beta spectrin molecules, leading to elliptocytosis<sup>2</sup>. Conversely, mutation at other sites can lead to pyropoikilocytosis and spherocytosis. The *SPTA1* homozygous mutation showed signs of disruption at the cellular level whereas the heterozygous parents were absent of abnormalities clinically<sup>2</sup>.

There are no cited cases of these two simultaneous mutations. Together these two heterozygous mutations in the same individual could lead an observable phenotype. This information can provide a proposed hypothesis for future research involving red cell membrane disorders. Furthermore, this information can be applied to future studies studying novel mutations and the impact on red cell membrane stability.

## References

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