**TABLE 129-3 INHERITED DISEASES OF THE RED CELL MEMBRANE-CYTOSKELETON COMPLEX**

| Gene | Chromosomal Location | Protein Produced | Disease(s) with Certain Mutations (Inheritance) | Comments |
|---|---|---|---|---|
| *SPTA1* | 1q22-q23 | α-Spectrin | HS (recessive) | Rare |
| | | | HE (dominant) | Mutations of this gene account for about 65% of HE. More severe forms may be due to coexistence of an otherwise silent mutant allele. |
| *SPTB* | 14q23-q24.1 | β-Spectrin | HS (dominant) | Rare |
| | | | HE (dominant) | Mutations of this gene account for about 30% of HE, including some severe forms. |
| *ANK1* | 8p11.2 | Ankyrin | HS (dominant) | May account for majority of HS. |
| *SLC4A1* | 17q21 | Band 3; also known as AE (anion exchanger) or AE1 | HS (dominant) | Mutations of this gene may account for about 25% of HS. |
| | | | Southeast Asia ovalocytosis (dominant) | Polymorphic mutation (deletion of 9 amino acids); clinically asymptomatic; protective against *Plasmodium falciparum*. |
| | | | Stomatocytosis | Certain specific missense mutations shift protein function from anion exchanger to cation conductance. |
| *EPB41* | 1p33-p34.2 | Band 4.1 | HE (dominant) | Mutations of this gene account for about 5% of HE, mostly with prominent morphology but no hemolysis in heterozygotes; severe hemolysis in homozygotes. |
| *EPB42* | 15q15-q21 | Band 4.2 | HS (recessive) | Mutations of this gene account for about 3% of HS. |
| *RHAG* | 6p21.1-p11 | Rhesus antigen | Chronic nonspherocytic hemolytic anemia (recessive) | Very rare; associated with total loss of all Rh antigens. |
| | | | | A specific mutation causes overhydrated stomatocytosis. |
| *PIEZO1* | 16q23-q24 | PIEZO1 | Dehydrated hereditary stomatocytosis (dominant) | Also known as xerocytosis with pseudohyperkalemia. Patients may present with perinatal edema. PIEZO1 is a mechanosensitive cation channel. |

***Abbreviations:*** HE, hereditary elliptocytosis; HS, hereditary spherocytosis.

***HEREDITARY ELLIPTOCYTOSIS (HE)*** HE is at least as heterogeneous as HS, both from the genetic point of view (Table 129-3, Fig. 129-3) and from the clinical point of view. Again, it is the shape of the red cells (Fig. 129-4*B*) that gives the name to the condition, but there is no direct correlation between the elliptocytic morphology and clinical severity. In fact, some mild or even asymptomatic cases may have nearly 100% elliptocytes, whereas in severe cases, all kinds of bizarre poikilocytes can predominate. Clinical features and recommended management are similar to those outlined above for HS. Although the spleen may not have the specific role it has in HS, in severe cases, splenectomy may be beneficial. The prevalence of HE causing clinical disease is similar to that of HS. However, an in-frame deletion of nine amino acids in the *SLC4A1* gene encoding band 3, causing the so-called *Southeast Asia ovalocytosis*, has a frequency of up to 7% in certain populations, presumably as a result of malaria selection; it is asymptomatic in heterozygotes and probably lethal in homozygotes.

**Disorders of Cation Transport** These rare conditions with autosomal dominant inheritance are characterized by increased intracellular sodium in red cells, with concomitant loss of potassium; indeed, they are sometimes discovered through the incidental finding, in a blood test, of a high serum $K^+$ (*pseudohyperkalemia*). In patients from some families, the cation transport disturbance is associated with gain of water; as a result, the red cells are overhydrated (low MCHC), and on a blood smear, the normally round-shaped central pallor is replaced by a linear-shaped central pallor, which has earned this disorder the name *stomatocyto*sis (Fig. 129-3). In patients from other families, instead, the red cells are dehydrated (high MCHC), and their consequent rigidity has earned this disorder the name *xerocytosis*. One would surmise that in these disorders the primary defect may be in a cation transporter; indeed, xerocytosis results from mutations in *PIEZO1*. In other patients with stomatocytosis, mutations are found in other genes also related to solute transport (Table 129-3), including *SLC4A1* (encoding band 3), the Rhesus gene *RHAG*, and the glucose transporter gene *SLC2A1* responsible for a special form called cryohydrocytosis. Hemolysis can vary from relatively mild to quite severe. From the practical point of view, it is important to know that in stomatocytosis, splenectomy is strongly contraindicated because it has been followed in a significant proportion of cases by severe thromboembolic complications.

**Enzyme Abnormalities** When there is an important defect in the membrane or in the cytoskeleton, hemolysis is a direct consequence of the fact that the very structure of the red cell is abnormal. Instead, when one of the enzymes is defective, the consequences will depend on the precise role of that enzyme in the metabolic machinery of the red cell, which, in first approximation, has two important functions: (1) to provide energy in the form of ATP and (2) to prevent oxidative damage to hemoglobin and to other proteins by providing sufficient reductive potential; the key molecule for this is NADPH.

***ABNORMALITIES OF THE GLYCOLYTIC PATHWAY*** Because red cells, in the course of their differentiation, have sacrificed not only their nucleus and their ribosomes, but also their mitochondria, they rely exclusively on the anaerobic portion of the glycolytic pathway for producing energy in the form of ATP. Most of the ATP is required by the red cell for cation transport against a concentration gradient across the membrane. If this fails, due to a defect of any of the enzymes of the glycolytic pathway (Table 129-4), the result will be hemolytic disease.

***Pyruvate kinase deficiency*** Abnormalities of the glycolytic pathway are all inherited and all rare. Among them, deficiency of pyruvate kinase (PK) is the least rare, with an estimated prevalence in most populations of the order of 1:10,000. However, very recently, a polymorphic PK mutation (E277K) was found in some African populations, with heterozygote frequencies of 1–7%, suggesting that this may be another malaria-related polymorphism. The clinical picture of homozygous (or compound biallelic) PK deficiency is that of an HA that often presents in the newborn with neonatal jaundice; the jaundice persists, and it is usually associated with a very high reticulocytosis. The anemia is of variable severity; sometimes it is so severe as to require regular blood transfusion treatment, whereas sometimes it is mild, bordering on a nearly compensated hemolytic disorder. As a result, the diagnosis may be delayed, and in some cases, it is made, for instance, in a young woman during her first pregnancy, when the anemia may get worse. The delay in diagnosis may be also helped by the fact that the anemia is remarkably well tolerated, because the metabolic block at the last step in glycolysis causes an increase in bisphosphoglycerate (or DPG; Fig. 129-1), a major effector of the hemoglobin-oxygen dissociation curve; thus, the oxygen delivery to the tissues is enhanced, a remarkable compensatory feat.