Table 14-3 Clinical and Genetic Classification of Thalassemias

Clinical Syndromes	Genotype	Clinical Features	Molecular Genetics
β-Thalassemias			
β-Thalassemia major	Homozygous β-thalassemia (β^0/β^0, β^+/β^+, β^0/β^+)	Severe; requires blood transfusions	Mainly point mutations that lead to defects in the transcription, splicing, or translation of β-globin mRNA
β-Thalassemia intermedia	Variable (β^0/β^+, β^+/β^+, β^0/β, β^+/β)	Severe but does not require regular blood transfusions	
β-Thalassemia minor	Heterozygous β-thalassemia (β^0/β, β^+/β)	Asymptomatic with mild or absent anemia; red cell abnormalities seen	
α-Thalassemias			
Silent carrier	–/α α/α	Asymptomatic; no red cell abnormality	Mainly gene deletions
α-Thalassemia trait	–/– α/α (Asian) –/α –/α (black African, Asian)	Asymptomatic, like β-thalassemia minor	
HbH disease	–/– –/α	Severe; resembles β-thalassemia intermedia	
Hydrops fetalis	–/– –/–	Lethal in utero without transfusions	

α-globin gene, the synthesis of α chains is markedly reduced, and tetramers of β-globin, called HbH, form. HbH has an extremely high affinity for oxygen and therefore is not useful for oxygen delivery, leading to tissue hypoxia disproportionate to the level of hemoglobin. Additionally, HbH is prone to oxidation, which causes it to precipitate and form intracellular inclusions that promote red cell sequestration and phagocytosis in the spleen. The result is a moderately severe anemia resembling β-thalassemia intermedia.

Hydrops Fetalis. Hydrops fetalis is the most severe form of α-thalassemia and is caused by deletion of all four α-globin genes. In the fetus, excess γ-globin chains form tetramers (hemoglobin Barts) that have such a high affinity for oxygen that they deliver little to tissues. Survival in early development is due to the expression of ζ chains, an embryonic globin that pairs with γ chains to form a functional $\zeta_2\gamma_2$ Hb tetramer. Signs of fetal distress usually become evident by the third trimester of pregnancy. In the past, severe tissue anoxia led to death in utero or shortly after birth; with intrauterine transfusion many such infants are now saved. The fetus shows severe pallor, generalized edema, and massive hepatosplenomegaly similar to that seen in hemolytic disease of the newborn (Chapter 10). There is a lifelong dependence on blood transfusions for survival, with the associated risk of iron overload. Hematopoietic stem cell transplantation can be curative.

Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is a disease that results from acquired mutations in the phosphatidylinositol glycan complementation group A gene (*PIGA*), an enzyme that is essential for the synthesis of certain membrane-associated complement regulatory proteins. PNH has an incidence of 2 to 5 per million in the United States. Despite its rarity, it has fascinated hematologists because it is the only hemolytic anemia caused by an acquired genetic defect. Recall that proteins are anchored into the lipid bilayer in two ways. Most have a hydrophobic region that spans the cell membrane; these are called transmembrane proteins. The others are attached to the cell membrane through a covalent linkage to a specialized phospholipid called glycosylphosphatidylinositol (GPI). In PNH, these GPI-linked proteins are deficient because of somatic mutations that inactivate PIGA. *PIGA* is X-linked and subject to lyonization (random inactivation of one X chromosome in cells of females; Chapter 5). As a result, a single acquired mutation in the active *PIGA* gene of any given cell is sufficient to produce a deficiency state. Because the causative mutations occur in a hematopoietic stem cell, all of its clonal progeny (red cells, white cells, and platelets) are deficient in GPI-linked proteins. Typically the mutant clone coexists with the progeny of normal stem cells that are not PIGA deficient.

Remarkably, most normal individuals harbor small numbers of bone marrow cells with *PIGA* mutations identical to those that cause PNH. It is hypothesized that these cells increase in numbers (thus producing clinically evident PNH) only in rare instances where they have a selective advantage, such as in the setting of autoimmune reactions against GPI-linked antigens. Such a scenario might explain the frequent association of PNH and aplastic anemia, a marrow failure syndrome (discussed later) that has an autoimmune basis in many individuals.

PNH blood cells are deficient in three GPI-linked proteins that regulate complement activity: (1) decay-accelerating factor, or CD55; (2) membrane inhibitor of reactive lysis, or CD59; and (3) C8 binding protein. Of these factors, the most important is CD59, a potent inhibitor of C3 convertase that prevents the spontaneous activation of the alternative complement pathway.

Red cells deficient in these GPI-linked factors are abnormally susceptible to lysis or injury by complement. This manifests as *intravascular hemolysis*, which is caused by the C5b-C9 membrane attack complex. The hemolysis is paroxysmal and nocturnal in only 25% of cases; chronic hemolysis without dramatic hemoglobinuria is more typical. The tendency for red cells to lyse at night is explained by a slight decrease in blood pH during sleep, which increases the activity of complement. The anemia is variable but usually mild to moderate in severity. The loss of heme iron in the urine (hemosiderinuria) eventually leads to iron deficiency, which can exacerbate the anemia if untreated.

Thrombosis is the leading cause of disease-related death in individuals with PNH. About 40% of patients suffer