Sickle cell disease is a clinical and hematologic phenotype caused by an assortment of genotypes **(Table 98-2)**. Sickle cell anemia, defined as homozygosity for the sickle hemoglobin mutation ($\alpha_2\beta^S_2$; glutamic acid [E] 7 valine [V] G*A*G-G*T*G), is the most common of these genotypes, followed by HbSC disease or compound heterozygosity for HbS and HbC ($\alpha_2\beta^C_2$; E 7 lysine [K] *G*AG-*A*AG) genes. Many different thalassemia mutations contribute to the HbS-β thalassemias. The compound heterozygous genotypes are less common than HbS homozygotes; as a rule, their symptoms develop later in life and are less severe. HbS has also been described with many other variant hemoglobins. Few of these genotypes, other than $HbSO^{Arab}$, HbSE, and $HbSD^{Punjab}$ are symptomatic.

TABLE 98-2 Common Sickle Hemoglobinopathies

GENOTYPE	CLINICAL ABNORMALITIES	HEMOGLOBIN LEVEL, g/L (g/dL)/MCV, fL	HEMOGLOBIN FRACTIONS (%)
Sickle cell trait (HbAS)	8% of African Americans; hematuria, papillary necrosis, hyposthenuria, increased incidence of chronic kidney disease; 2–4 times increased VTE risk; ? stroke; splenic infarction at altitude; rhabdomyolysis	Normal	HbA: 60–70 HbS: 30–40 Percent HbS dependent on presence or absence of α thalassemia
Sickle cell anemia (HbSS)	Vasoocclusion related: pain, acute chest syndrome, osteonecrosis, splenic infarction Hemolysis related: stroke, pulmonary and systemic vasculopathy, nephropathy, leg ulceration gallstones, priapism, leg ulcers	70–100 (7–10)/80–100	HbS: >75 HbF: 2–25 HbA_2: 3–4
HbS-β^0 thalassemia	Rate of complications similar to HbSS	80–100 (8–11)/60–85	HbS: >75 HbF: 2–15 HbA_2: 5–6
HbS-β^+ thalassemia	Rate of complications about half the rate of HbSS depending on percent HbA	100–140 (10–14)/70–80	HbS: 60–90 HbA: 5–40 HbF: 1–10 HbA_2: 5–6
Hemoglobin SC disease (HbSC)	Nearly asymptomatic to severe disease; about half the rate of complications as HbSS. Increased risk of retinopathy	100–140 (10–14)/70–100	HbS: 50 HbC: 50
HbSE	Resembles clinically HbS-β^+ thalassemia; symptoms delayed; often Asian/Indian ancestry	90–130 (9–13)/65–75	HbS: 65 HbE: 35 HbF: 1-5
HbSS-α thalassemia	Present in 30% of HbSS; phenocopies HbS-β^0 thalassemia; similar to HbSS but with fewer strokes and leg ulcers and less pulmonary vascular and renal disease	80–100 (8–11)/60–85	HbS: >75 HbF: 2–15 HbA_2: 4–5
HbS-HPFH	Most common genotype is due to large *HBB* deletions and is asymptomatic	110–140 (11–14)/70–80	HbS: 70 HbF: 20–30 HbA_2: 1–2

Note: Laboratory values are averages in untreated adults.

Abbreviation: VTE, venous thromboembolism.

■ ORIGIN, SPREAD, AND EPIDEMIOLOGY

HbS originated in Africa between 7000 and 22,000 years ago, reaching high frequencies because of the increased genetic fitness