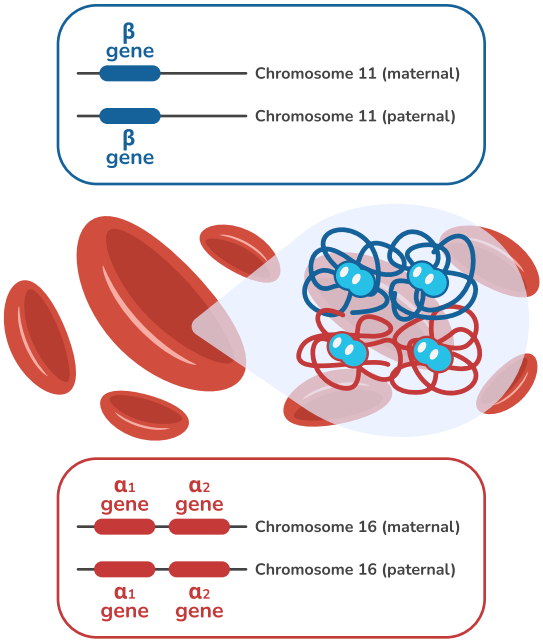
A Provider's Guide to Hemoglobinopathies

What causes hemoglobinopathies?

- Adult hemoglobin is composed of four protein subunits, most often two **α-chains** and two **β-chains**. Mutations in the genes that code for these chains affect hemoglobin production and can alter the number and/or shape of red blood cells.
- There are two copies of the β-globin gene, one inherited from each parent. Point mutations in both of these genes can cause sickle cell disease and β-thalassemia.
- There are four copies of the α-globin gene, two inherited from each parent (αα/αα). Deletions of these gene copies can cause α-thalassemia.



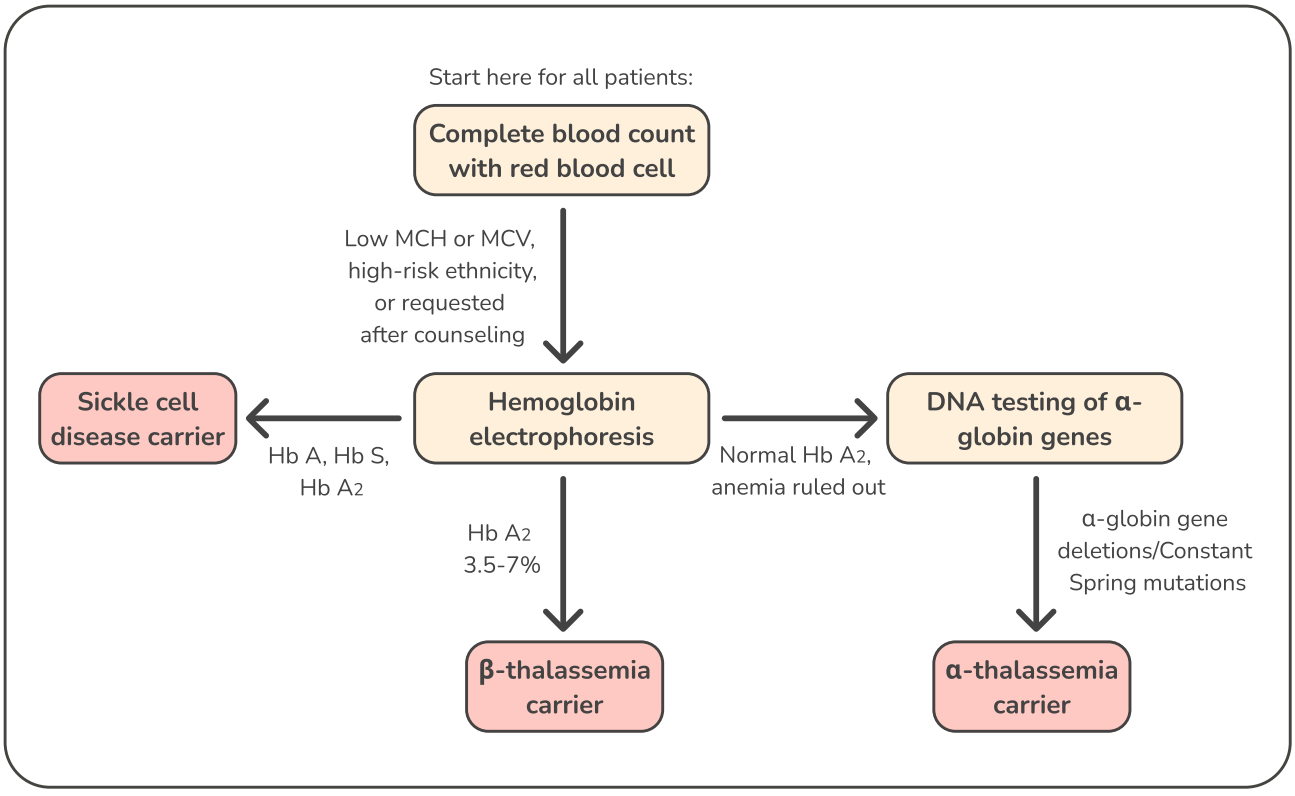
What are the different types of hemoglobinopathies?

- **Sickle Cell Disease (SCD)**: SCD is caused by point mutations in both copies of the β-globin gene that cause red blood cells to become sickled. Clinical features may include hemolytic anemia, painful vasoocclusive crises, organ damage, functional asplenia, increased frequency and severity of infections, and acute chest syndrome.
- **β-Thalassemia**: β-Thalassemia is caused by mutations in both copies of the β-globin gene that cause deficient or absent β-chain production, depending on the specific mutation. Clinical features range depending on severity from mild anemia to extramedullary erythropoiesis and developmental delay.
- **α-Thalassemia**: Hemoglobin H disease is caused by a deletion of three α-globin gene copies (α-/--), and hemoglobin Bart disease is caused by a deletion of all four α-globin gene copies (--/--). Carriers of two α-gene deletions may have mild microcytic anemia and their children may be at-risk of having more severe forms of thalassemias. Depending on severity, clinical features range from hemolytic anemia and variable organ/bone effects to hydrops fetalis.
- **Combined Hemoglobinopathies**: Inheriting two different abnormal hemoglobin genes can cause a combined hemoglobinopathy, such as hemoglobin SC disease and hemoglobin S/β-thalassemia. Clinical features depend on the specific cause.

Who should receive carrier screening?

The American College of Obstetricians and Gynecologists recommends the following (ACOG 2017; reaffirmed 2023):

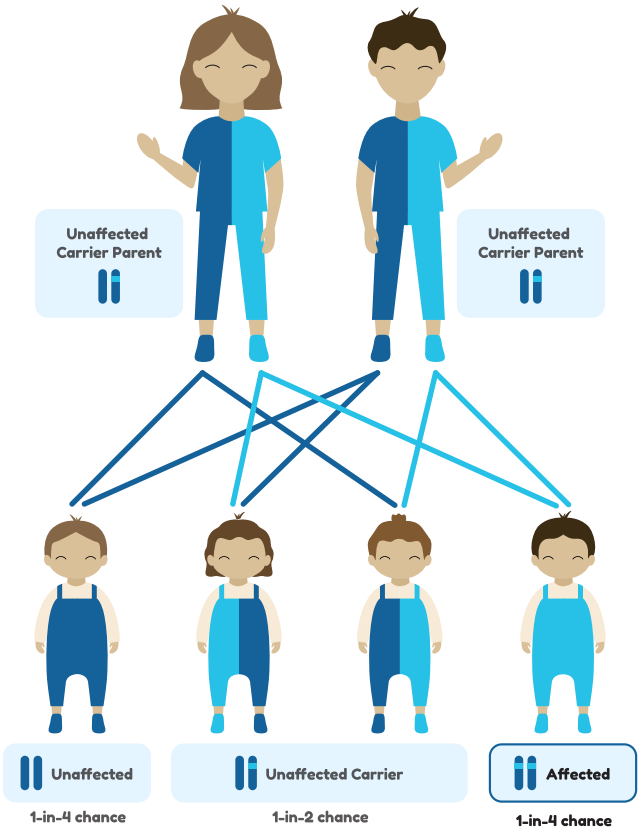
- Information about carrier screening should be provided to every pregnant person and person planning to become pregnant. A patient may request or decline carrier screening regardless of ethnicity and family history.
- A complete blood count with red blood cell should be performed in all people who are currently pregnant or planning to become pregnant.
- A hemoglobin electrophoresis should be performed if the red blood cell counts indicate a low mean corpuscular hemoglobin or mean corpuscular volume, or if there is a suspicion of hemoglobinopathy based on ethnicity (i.e., African, Mediterranean, Middle Eastern, Southeast Asian, or West Indian descent).
- Hemoglobin electrophoresis cannot identify α-thalassemia trait. Therefore, if the mean corpuscular volume is below normal, iron deficiency anemia has been excluded, and the hemoglobin electrophoresis is not consistent with β-thalassemia, then DNA-based testing should be used to detect α-globin gene deletions.



Committee Opinion No. 691: Carrier Screening for Genetic Conditions. Obstet Gynecol. 2017 Mar (Reaffirmed 2023); 129(3):e41-e55. doi: 10.1097/AOG.0000000000001952. PMID: 28225426.

What are next steps if my patient is a carrier?

- If your patient is found to be a carrier of a hemoglobinopathy, then their reproductive partner should be offered hemoglobinopathy carrier screening to inform their chance of a having an affected child.
- If their partner is not a carrier: The chance of having an affected child is very low.
- If their partner is a carrier (including of a different hemlogobinopathy):
  - Each pregnancy may have a 1-in-4 or 25% chance of being affected. In the case of α-thalassemia trait, the risk to children depends on the number of α-globin gene deletions and whether the deletions are in cis or in trans.
  - Genetic counseling should be offered to review hemoglobinopathy inheritance, natural history, treatment, prenatal genetic testing, and reproductive options.



How do I refer my patient to a genetic counselor?

- A genetic counselor can meet with your patient to discuss hemoglobinopathies, carrier screening, prenatal diagnostic testing, and more.
- To refer your patient to a certified and licensed genetic counselor through Genetic Support Foundation, fill out our Genetic Counseling Referral Fax Form and fax this form along with the relevant medical records and insurance information to 844-813-3892.
- For more information:

geneticsupportfoundation.org/clinics-and-providers

(844) 743-6384

(844) 813-3892

Hemoglobinopathy Carrier Screening Cheat Sheet

Condition	Genetic Basis	Carrier Test
Sickle Cell Disease (SCD)	**Carriers (sickle cell trait)**: Point mutation in one β-globin gene that affects hemoglobin structure (Hb AS). **SCD**: Point mutations in both copies of the β-globin gene that affect hemoglobin structure (Hb SS).	**Hb electrophoresis**: Hb A, Hb S, Hb A_2
β-Thalassemia	**Carriers (β-thalassemia minor)**: Point mutation in one β-globin gene that affects the amount of β-chain produced. **B+-thalassemia intermedia**: Point mutations in both copies of the β-globin gene causing mildly decreased β-globin production (Hb F 20-40%). **β+-thalassemia major**: Point mutations in both copies of the β-globin gene causing moderately to severely decreased β-globin production (Hb F 70-90%). **B0-thalassemia major**: Point mutations in both copies of the β-globin gene causing absent β-globin production (Hb F 98%).	**Blood count**: Low MCH & MCV **Hb electrophoresis**: Hb A_2 3.5-7%
α-Thalassemia	**Carriers (α-thalassemia trait, α-thalassemia minor)**: Two α-globin gene deletions (α-/α- or *αα/--) or Constant Spring point mutations. **Hemoglobin H disease**: Three α-globin gene deletions (α-/--). **Hemoglobin Barts disease**: Four α-globin gene deletions (--/--). *Cis deletion carriers are more common in SEA ancestry and have an increased risk of having children with α-thalassemia major.	**Blood count**: Low MCV **Hb electrophoresis**: Normal **Genetic testing**: α-globin gene deletions or CS mutations