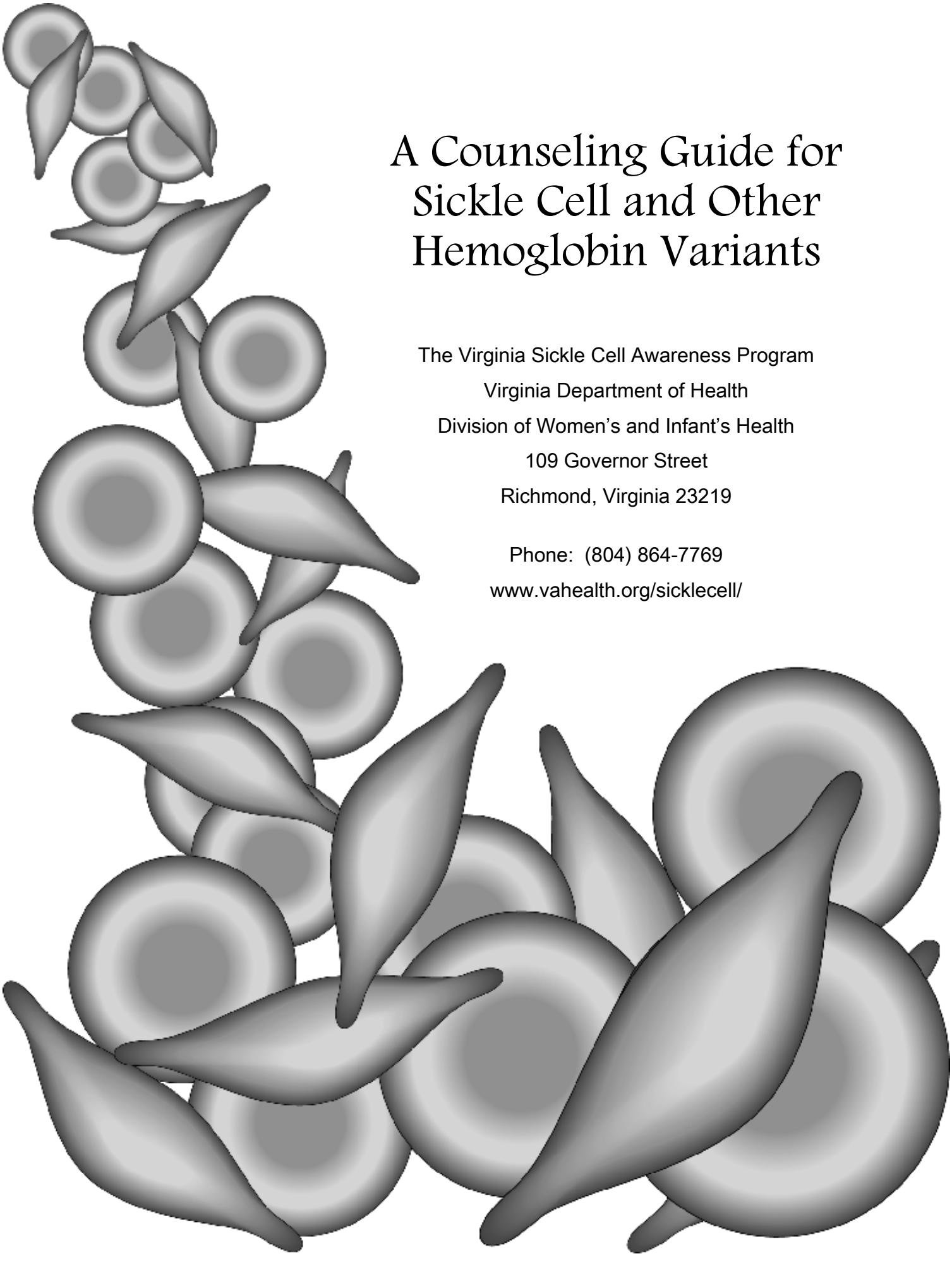
A Counseling Guide for Sickle Cell and Other Hemoglobin Variants

The Virginia Sickle Cell Awareness Program
Virginia Department of Health
Division of Women's and Infant's Health
109 Governor Street
Richmond, Virginia 23219

Phone: (804) 864-7769
www.vahealth.org/sicklecell/



Introduction

Hemoglobinopathies represent a major health problem in the United States. There are over 600 different types of hemoglobin identified in all races and populations of people. As the field of hemoglobinopathies continues to expand, so do the needs and interests of community health care providers. This manual is designed to serve as a resource for those counseling individuals with sickle cell disorders as well as those providing hemoglobinopathy screening, education, and genetic counseling to individuals identified with other hemoglobin variants.

Hemoglobin: Definition and Structure

Hemoglobin is a red protein pigment that is responsible for transporting oxygen from the lungs to tissues for energy. It also carries carbon dioxide from the tissues to the lungs for excretion. The hemoglobin molecule consists of two parts: a porphyrin group or heme, and the protein or globin portion. Globin is made up of four polypeptide chains attached to the porphyrin ring. In the normal subject these chains can be of four types: alpha, beta, delta and gamma. In normal and abnormal hemoglobins (with the exception of hemoglobin H and Bart' s), two sets of identical polypeptide chains make up the globin. The structure of the globin chain, like all proteins, is genetically controlled.

Normal Adult Hemoglobin

Normal adult hemoglobin consists primarily of hemoglobin A. Hemoglobin A is made up of 2 alpha chains and 2 beta chains. Beta chain synthesis begins early in fetal development. At the sixth week of gestation, hemoglobin A composes about 7% of the total hemoglobin; the percentages slowly increase throughout the pregnancy. At the thirtieth week there is a switch from gamma chain to beta chain production.

Fetal Hemoglobin

At birth babies have mostly fetal or F hemoglobin. Fetal hemoglobin falls to the normal level of less than 3 to 5% by the time the infant is 5-6 months of age. Most adults have less than 2% fetal hemoglobin. Fetal hemoglobin is made up of two alpha and two gamma chains.

Hemoglobin A2

Besides hemoglobin A and F, human red blood cells normally contain a third hemoglobin component, hemoglobin A_2. Two alpha and two delta chains make up hemoglobin A_2, which constitutes less than 3.5% of hemoglobin in a normal individual. A_2 is usually elevated in individuals with Beta Thalassemia trait.

Table 1: STRUCTURAL FORMULA FOR NORMAL HEMOGLOBIN

HEMOGLOBIN	STRUCTURAL FORMULA
A Major Adult Hemoglobin	2 Alpha Chains + 2 Beta Chains
F Fetal Hemoglobin	2 Alpha Chains + 2 Gamma Chains
A2 Minor Adult Hemoglobin	2 Alpha Chains + 2 Delta Chains

HEMOGLOBINOPATHIES

A hemoglobinopathy is a condition (disease or trait) caused by a defect in the genetic code for hemoglobin synthesis, there are over 600 known hemoglobin variants reported. These variants are characterized as either qualitative or quantitative. The vast majority of abnormal hemoglobin result from the mutation of a single polypeptide chain. The anomalies are transmissible, hereditary, autosomal traits. In the heterozygous subject (trait carrier), an abnormal gene is inherited from one parent and it directs the formation of abnormal hemoglobin. Theoretically, one part of the hemoglobin is abnormal and the other is normal, such as in sickle cell trait (A/S). In the homozygous subject, identical abnormal genes are inherited; one from each parent, and the majority of the hemoglobin is abnormal, such as in sickle cell anemia (S/S).

QUALITATIVE DEFECTS

Qualitative defects refer to structural variations that result in a change of the type of hemoglobin produced. 95% of the structural variants are caused by a single amino acid replacement. The amino acid replacement or substitution changes the quality, or characteristic of the hemoglobin. For example, hemoglobin S,C,E,D,G, and O, all contain a substitution of a different amino acid into the normal amino acid sequence of the beta globin chain. Each substitution changes the function of the hemoglobin molecule in a particular way. Thus each hemoglobin disease or trait has a different characteristic clinical picture.

QUANTITATIVE DEFECTS

Quantitative defects are characterized by a reduction or absence in the amount of normal alpha and/or beta globin chains produced. An example of a quantitative defect is beta thalassemia. When an individual has beta thalassemia trait, beta chains are being produced, but in a lesser

quantity. Because individuals with quantitative defects may still have hemoglobin A, hemoglobin electrophoresis alone cannot diagnose them.

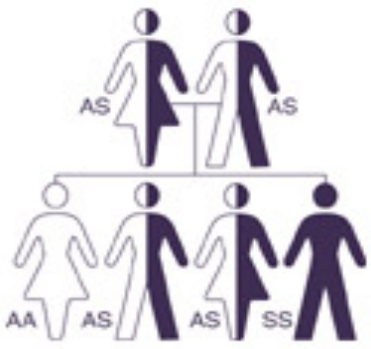
QUALITATIVE AND QUANTITATIVE HEMOGLOBIN TRAITS

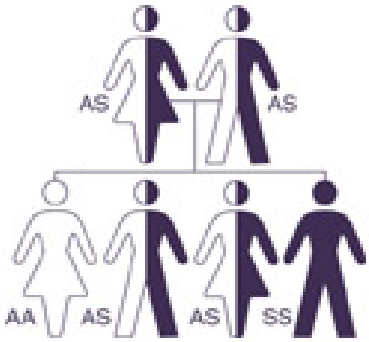
Hemoglobin traits occur when a person inherits one gene for the usual adult hemoglobin (A) and one gene for a hemoglobin variant. A large number of mutations have been observed, however only a few are of serious biological consequence. These are sickle hemoglobin (S), hemoglobin C and hemoglobin E.

In the following section we will more closely detail the more common qualitative and quantitative hemoglobin traits including: populations affected, frequency of occurrence, clinical symptoms, precautions, laboratory data and counseling guide.

INHERITANCE PATTERN

Genetic Transmission: Autosomal recessive





EDUCATIONAL GENETIC COUNSELING:

All clients who have been identified with a hemoglobin variant should be provided educational genetic counseling. This process involves the clear communication of the medical, psychological, social, and genetic factors related to the condition being discussed.

The burden is on the counselor to communicate the information needed by the counselee to make his or her own reproductive decisions in an open, non-judgmental environment.

GUIDELINES FOR COUNSELING

- Communicate a functional understanding of the particular hemoglobinopathy in question and the genetic mechanism by which it is produced.
- Correct any misconceptions that exist about the disease and its relationship to the carrier state.
- Present to couples “at-risk” for having a child with disease a thorough discussion of alternative reproductive options.
- Communicate effectively and clearly the facts of the situation to the counselee in a way that

can be clearly understood. Any new term that is introduced should be defined. Charts and audio-visuals and other visuals should be utilized.

- Encourage the counselee to ask questions, express feelings.
- Invite family members or a potential spouse to participate in your program's education, and screening process, or make referral.
- Offer follow-up counseling session.
- Document session in a letter sent to the family and physician.

PREREQUISITE FOR COUNSELING: AN ACCURATE DIAGNOSIS

Counseling should not take place until accurate screening results are obtained from a competent laboratory, utilizing state of the art procedures (High Performance Liquid Chromatography, (HPLC), Cellulose Acetate Electrophoresis, Isoelectric Focusing (IEF), A2 and F quanitation).

SOLUBILITY TESTING should never be utilized as a primary screening tool.

A test result that only identifies if your client is positive or negative for sickle hemoglobin will not give you the information necessary to provide accurate educational genetic counseling regarding the reproductive risks of having a child with a serious hemoglobinopathy.

Sickle Hemoglobin

HEMOGLOBIN A/S
SICKLE CELL TRAIT

GENOTYPE: **AS** **Beta chain variant**	**Individuals have 38-42% S hemoglobin the rest is hemoglobin A. Each red cell contains a mixture of A and S. The amount of A in each cell is enough to prevent sickling under most physiological conditions.**
POPULATIONS AFFECTED	**African Americans: 8-10%** **Hispanic Americans: 2%** **Occurs frequently in Greeks, Italians, Saudi Arabians, East Indians and Middle Easterners**
CLINICAL SYMPTOMS	**Sickle cell trait is NOT associated with anemia.** **Sickle cell trait offers some protection against malaria.** **Occasional hematuria (blood in the urine) and hyposthenia (impaired renal concentrating ability) are associated with sickle trait.** **Splenic infarction has been reported to occur at altitudes greater than 7,000 feet** **Some studies suggest that individuals with sickle cell trait are at a greater risk for sudden death under extreme conditions such as those that might occur during basic training in the military. These conditions are: severe dehydration, malnutrition, physical overexertion and exhaustion. This risk though increased, is small.**
PRECAUTIONS	**Avoid hypoxic situations: deep sea diving, flying in unpressurized aircraft, strenuous physical activity over a prolonged period of time.**
LABORATORY DATA	**DO NOT USE SOLUBILITY TESTING AS A PRIMARY SCREENING METHOD.** **1. Cellulose Acetate Electrophoresis** **Result: Bands will be present in the A and S position** **2. Isoelectric Focusing (IEF)** **Result: Same as Cellulose Acetate** **3. Solubility: Positive (+)** **When the Solubility test is positive, no Citrate Agar Electrophoresis is necessary.** **4. A2 levels** **Normal range for sickle cell trait: 1.7 – 4.5 Mean: 2.9**

GENOTYPE: **AS** **Beta chain variant**	**Individuals have 38-42% S hemoglobin the rest is hemoglobin A. Each red cell contains a mixture of A and S. The amount of A in each cell is enough to prevent sickling under most physiological conditions.**
	(Isolab Inc.) **5. Red cell morphology usually normal**

COUNSELORS CHECK LIST FOR SICKLE CELL TRAIT

TEST RESULTS	COUNSELING POINTS TO BE MADE
AS Sickle Cell Trait	**Clinical indications:** • Person is a **healthy carrier**. • Person is **not sick**. • Sickle cell trait is **not** a disease. • Sickle cell trait will **not** cause you to be anemic. • There is a small amount of hemoglobin S, but not enough to change the shape of the red blood cell. • The red blood cells of a person with sickle cell trait remain round and flexible. **Explain circumstances which might trigger cells to sickle:** • High altitude in non-pressurized planes. • Other situations where one did not get sufficient oxygen • for a long period of time. • Prolonged strenuous aerobic exercise such as in basic training for the military. **Inheritance:** • It is inherited, you can **NOT** catch it. • It is passed directly from parent to child. • It does not “skip” generations. If you have it, that means one of your parents also has it. • It is not sex linked; meaning you may have gotten it from either your mother or your father. • Sickle cell trait will never change into sickle cell anemia. **Incidence:** • Sickle cell trait is not rare. • 1 in 8-10 individuals of African American ancestry is born with it. • It is also found in individuals of Italian, Greek, and East Indian ancestry. **Risks to offspring:** • One who has sickle cell trait may have a child with sickle cell disease if he or she mates with someone who also has the sickle trait or some other

	variant hemoglobin.
MATING	AS X AA AS X AS AS X SS AS X AC AS X A/Thal
PROBABLE OUTCOME	For future pregnancies, parents should be referred for genetic counseling and testing.

CLINICALLY SIGNIFICANT SICKLING DISORDERS

The three most common types of sickle cell disease are hemoglobin SS disease (also called sickle cell anemia), hemoglobin Sickle-C disease and Sickle Beta-Thalassemia. While some types of sickle cell disease are milder and cause fewer physical complications, every child is at risk for complications.

SICKLE CELL ANEMIA

GENOTYPE: S/S	**Hemoglobin S (90-100%)** **Hemoglobin F may be slightly elevated**
POPULATIONS AFFECTED	**Most common form of sickle cell disease identified in African Americans.**
CLINICAL SYMPTOMS	**Most severe form of sickle cell disease** **Clinical course variable** **Severe anemia** **Vaso-occlusion, pain episodes, organ damage** **Aplastic episode, splenic sequestration, increased risk for infection** **If HbF is greater than 10% there is a decreased risk of stroke** **See chart for other complications**
PRECAUTIONS	**Genetic counseling and screening to clarify risk for child born with sickle cell disease. Referral to High Risk OB Clinic for pregnancy.** **Hypoxia, dehydration**
LABORATORY DATA	**DO NOT USE SOLUBILITY TESTING AS A PRIMARY SCREENING METHOD.** **See Chart for screening results**

SICKLE HEMOGLOBIN C DISEASE

GENOTYPE: S/C	**Hemoglobin S and C present in near equal amounts, no HbA. Hemoglobin F may be slightly elevated**
POPULATIONS AFFECTED	**Second most common form of sickle cell disease identified in African Americans. Africans in Western and Northern Africa.**
CLINICAL SYMPTOMS	**Moderate to mild anemia Generally less severe than HbSS Fewer vaso-occlusive episodes Retinal thrombosis and necrosis of femoral head more common Spleen remains enlarged Susceptibility to infection increased**
PRECAUTIONS	**Genetic counseling and screening to clarify risk for child born with sickle cell disease. Referral to High Risk OB Clinic for pregnancy. Hypoxia, dehydration**
LABORATORY DATA	**DO NOT USE SOLUBILITY TESTING AS A PRIMARY SCREENING METHOD. See Chart for screening results**

SICKLE BETA^0 THALASSEMIA

GENOTYPE: S/F	**Hemoglobin S predominates with small amount of hemoglobin F** **See Chart**
POPULATIONS AFFECTED	**African Americans** **Mediterranean's**
CLINICAL SYMPTOMS	**Review Sickle Cell Complications** **Clinical course is variable** **Vaso-occlusive episodes may occur.** **S/Beta Thalassemia$^+$ having fewer complications than S/Beta Thalassemia^0 or sickle cell anemia (SS)** **Spleen remains enlarged but acute sequestration is rare** **Susceptibility to infection increased**
PRECAUTIONS	**Genetic counseling and screening to clarify risk for child born with sickle cell disease. Referral to High Risk OB Clinic for pregnancy.** **Hypoxia, dehydration**
LABORATORY DATA	**DO NOT USE SOLUBILITY TESTING AS A PRIMARY SCREENING METHOD.** **See Chart for screening results**

SICKLE BETA^{+} THALASSEMIA

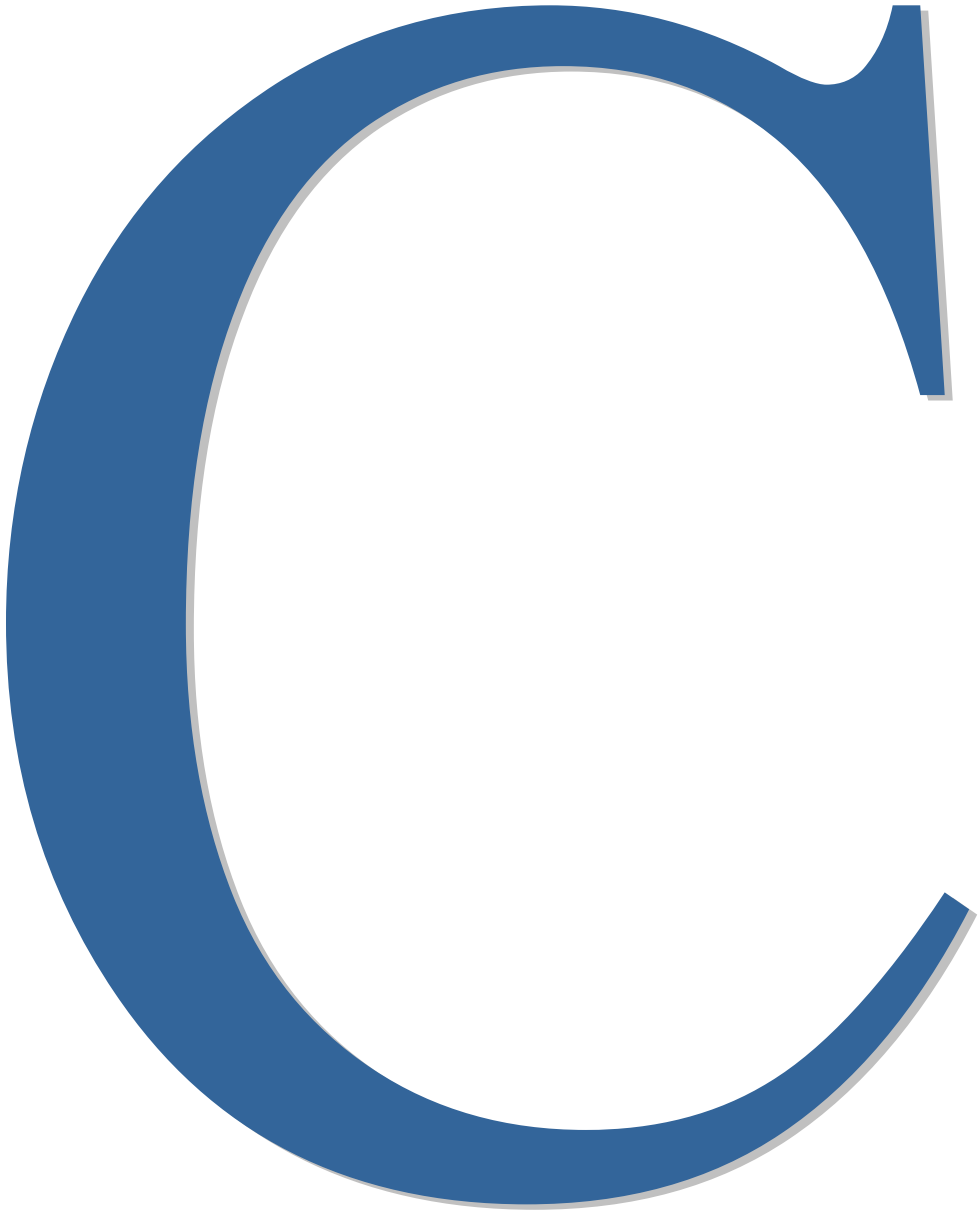
GENOTYPE: Doubly heterozygous SA, OR SAF	**Hemoglobin S predominates with small amount of hemoglobin A in Sickle Beta^{+} Thalassemia**
POPULATIONS AFFECTED	**Common sickling disorder among African Americans (1 in 1667 births) Greek, Turkish, Indian, Romanian and is the most common sickle disease in Mediterranean's**
CLINICAL SYMPTOMS	**Clinical course is variable:** **S/Beta Thalassemia^{+} (reduced beta chain production) having fewer complications than S/Beta Thalassemia^{0} (no beta chain production) or sickle cell anemia (SS).** **Spleen remains enlarged but acute sequestration is rare.** **Susceptibility to infection increased.** **See: CLINICAL COMPLICATIONS FOUND IN SICKLE CELL DISEASE**
PRECAUTIONS	**Genetic counseling and screening to clarify risk for child born with sickle cell disease. Referral to High Risk OB Clinic for pregnancy.** **Hypoxia, dehydration**
LABORATORY DATA	**DO NOT USE SOLUBILITY TESTING AS A PRIMARY SCREENING METHOD.** **Sickle Beta^{+} Thalassemia: Hemoglobin: 7-14 gm/dl, MCV:62-84** **Peripheral smear: Target cells, microcytosis, hypochromia**

Table 2: Physical Complications Caused by Sickling

ORGAN/TISSUE INVOLVED	PROBLEMS CAUSED
KIDNEY	• Inability to control urination • Hematuria (blood in the urine) • Unconcentrated urine • Frequent urination • Kidney disease
SPLEEN	• Spleen becomes non-functional by age 2 • Increased risk for serious infections • Splenic sequestration • Abdominal pain
LUNGS	• Pneumonia • Acute Chest Syndrome
BONES	• Infection • Aseptic necrosis
BRAIN	• Stroke • Headache
SKIN	• Slow healing leg ulcers
PENIS	• Priapism
EYES	• Sickle cell retinopathy
LIVER	• Enlarged liver

	• Cholelithiasis • Jaundice
• Not all these complications occur in every person with SCD. You need to know, however, that they **can** happen.	

Hemoglobin C



HEMOGLOBIN A/C
C TRAIT

GENOTYPE: **AC** **Beta chain variant**	**Individuals have 25-40% C hemoglobin the rest is hemoglobin A. Each red cell contains a mixture of Hb A and Hb C.**
POPULATIONS AFFECTED	**African Americans: 2-5%** **West Africans (Ghana): 20-25%**
CLINICAL SYMPTOMS	**No symptoms** **Hemoglobin C trait is NOT associated with anemia.**
PRECAUTIONS	**Genetic counseling to clarify risk for child born with homozygous CC Anemia or Sickle C Anemia.**
LABORATORY DATA	**DO NOT USE SOLUBILITY TESTING AS A PRIMARY SCREENING METHOD.** **1. Cellulose Acetate Electrophoresis** **Result: Bands will be present in the A and C position** **2. Isoelectric Focusing (IEF)** **Result: Same as Cellulose Acetate** **3. Solubility : Negative (-)** **4. Citrate Agar Electrophoresis is necessary.** **Result: Two bands present in the A and C position.** **Blood count normal** **Moderate target cells on blood smear in the range 10-30%.**

COUNSELORS CHECK LIST FOR HEMOGLOBIN C TRAIT

TEST RESULTS	COUNSELING POINTS TO BE MADE
AC	**Clinical Indications:** • Person is a **healthy carrier**. • Person is **not sick**. • C trait is **not** a disease. • There is a small amount of hemoglobin C, but not enough to change the shape of the red blood cell. • Some times persons have red blood cells that resemble a bulls-eye, we call those target cells. They do not cause problems. **Inheritance:** • It is inherited, you can **NOT** catch it. • It is passed directly from parent to child. • It does not "skip" generations, if you have it that means one of your parents also has it. • It is not "sex-linked" meaning you may have gotten it from either your mother or your father. **Incidence:** • Hemoglobin C is not rare • 1 in 50 or 2% of individuals of African American ancestry is born with it. **Risks to offspring:** • One who has C trait may have a child with sickle cell disease if he or she mates with someone who has the sickle trait or some other variant hemoglobin. • One with C trait may have a child with homozygous C Disease if he or she mates with someone who also has the C trait.
MATING	AC X AA AC X AS AC X AC AC X A/Thal
PROBABLE OUTCOME	For future pregnancies, parents should be referred for genetic counseling and testing.

HEMOGLOBIN CC ANEMIA

GENOTYPE: **CC** **Beta chain variant**	**Only C hemoglobin present.** **For proper confirmation of this genotype. Both parents would have A/C Trait.**
POPULATIONS AFFECTED	**1 in 10,000: African Americans** **Africans from Western and Northern Africa**
CLINICAL SYMPTOMS	**Anemia mild** **Jaundice intermittent** **Splenomegaly** **Decreased red cell plasticity** **Occasional episodes of joint and abdominal pain** **Aplastic events and gallstones may occur** **No specific therapy is available or required for patients with Hemoglobin C Disease. Anemia may become more severe following infections, but the overall prognosis is considered to be excellent.**
PRECAUTIONS	**Genetic counseling to clarify risk for child born with hemoglobin C Disease, C/Beta Thalassemia or Sickle C Disease.**
LABORATORY DATA	**DO NOT USE SOLUBILITY TESTING AS A PRIMARY SCREENING METHOD.** **1. Cellulose Acetate Electrophoresis** **Result: One band will be present in the C position.** **C moves in the same position as hemoglobin A2, E, and O at an alkaline pH. These hemoglobins are readily distinguished from hemoglobin C by acid agar gel electrophoresis.** **2. Isoelectric Focusing (IEF)** **Result: Same as Cellulose Acetate** **3. Solubility: Negative (-)** **4. Citrate Agar Electrophoresis** **Result: One band in the C position.** **Hemoglobin: 8-10 g/dl.** **Normal indices** **Marked increase in the number of target cells.** **Hemoglobin C crystals, microspherocytes, osmotic fragility may be decreased.**

HEMOGLOBIN C/BETA THALASSEMIA

GENOTYPE: **CF or CA** **Double heterozygous** **Gamma chain variant** **Beta chain variant**	**Individuals are double heterozygotes for hemoglobin C and Beta Thalassemia.** **C/Beta Thalassemia^{+} = 65-80% Hb C and 20-30% Hb A, and increased Hb F.** **C/Beta Thalassemia^{0} = No A with increased F and C.**
POPULATIONS AFFECTED	**African Americans** **Rare in Italians, Turks, Algerians**
CLINICAL SYMPTOMS	**C/Beta Thalassemia^{+} = Mild anemia, low MCV value, and target cells.** **C/Beta Thalassemia^{0} = Moderately severe anemia, splenomegaly, and possible bone changes.** **May be misdiagnosed a family study is essential for proper confirmation of this genotype. One parent would have A/C the other Beta Thalassemia trait. A elevated A2 would be present in the parent with thalassemia gene.**
PRECAUTIONS	**Genetic counseling to clarify risk for child born with possible Hemoglobin C Disease, C/Beta Thalassemia, or Sickle C Disease.**
LABORATORY DATA	**DO NOT USE SOLUBILITY TESTING AS A PRIMARY SCREENING METHOD.** **1. Cellulose Acetate Electrophoresis** **Result: Bands will be present in the C and A position (C/Beta^{+}) or in the C position with a faint band in the F position (C/Beta^{0}).** **Note: C moves in the same position as hemoglobin A2, E, and O at an alkaline pH. These hemoglobins are readily distinguished from hemoglobin C by acid agar gel electrophoresis.** **2. Isoelectric Focusing (IEF)** **Result: Same as Cellulose Acetate** **3. Solubility: Negative (-)** **4. Citrate Agar Electrophoresis** **C predominates with faint band of A or F.** **Blood smear yields microcytosis, hypochromia, microspherocytosis, target cells, reticulocytosis.** **Blood indices: decreased**

HEMOGLOBIN C TRAIT WITH HEREDITARY PERSISTENCE OF FETAL HEMOGLOBIN

GENOTYPE: **CF or C/HPFH** **Double heterozygous state Gamma chain variant** **Beta chain variant**	**(See Hereditary Persistence of Fetal Hemoglobin)** **Individuals have 20 to 30% F and 70 to 80% hemoglobin C.**
POPULATIONS AFFECTED	**African Americans**
CLINICAL SYMPTOMS	**Usually asymptomatic** **No anemia** **May be misdiagnosed as C/Thalassemia, a family study is essential for proper confirmation of this genotype. One parent would have A/C the other A/F with normal A2 value.**
PRECAUTIONS	**Genetic counseling to clarify risk for child born with hemoglobin FC and identified as possible Hemoglobin C Disease or C/Beta Thalassemia on newborn screen. When one parent is identified with A/F and the other A/C, there is a 25% chance the newborn screen will read FC.** **A child born with this pattern would have hemoglobin C trait with hereditary persistence of fetal hemoglobin. This is not associated with disease.**
LABORATORY DATA	**DO NOT USE SOLUBILITY TESTING AS A PRIMARY SCREENING METHOD.** **1. Cellulose Acetate Electrophoresis** **Result: Bands will be present in the C and F position** **2. Isoelectric Focusing (IEF)** **Result: Same as Cellulose Acetate** **3. Solubility: Negative (-)** **4. Citrate Agar Electrophoresis** **Result: Hemoglobin C predominates.** **5. Homogeneous distribution of hemoglobin F in the red cell when observed by Kleihauer-Betke stain.** **Normal blood indices.** **Normal blood count** **Blood smear: moderate target cells**

Hemoglobin E

HEMOGLOBIN A/E
E TRAIT

GENOTYPE: **AE** **Beta chain variant**	**Individuals have 20-40% E hemoglobin the rest is hemoglobin A. Each red cell contains a mixture of A and E.**
POPULATIONS AFFECTED	**South East Asians 30-40% in those from the Khmer region of Thailand and Cambodia.** **Occasionally African Americans.** **North Americans of European Ancestry: 1:70,000**
CLINICAL SYMPTOMS	**No symptoms** **Hemoglobin E trait is NOT associated with anemia.** **Clinically and hematologically normal.**
PRECAUTIONS	**Genetic counseling to clarify risk for child born with homozygous EE Disease, S/E Disease or Hemoglobin E/Thalassemia**
LABORATORY DATA	**DO NOT USE SOLUBILITY TESTING AS A PRIMARY SCREENING METHOD.** **1. Cellulose Acetate Electrophoresis** **Result: Bands will be present in the A and C position Hemoglobin E migrates with Hb C and A2 therefore, hemoglobin A2 quanitation cannot be run by column chromatography.** **2. Isoelectric Focusing (IEF)** **Result: Band of Hb in the A position however there is a slight separation between the E and the C allowing one to differentiate between the two.** **3. Solubility: Negative (-)** **4. Citrate Agar Electrophoresis is necessary.** **Result: Bands present in the A and E position.** **May show elevated red cell count.** **Occasional target cells on blood smear.** **Slight hypochromia and mild microcytosis.** **Red cell survival normal.**

COUNSELORS CHECK LIST FOR HEMOGLOBIN E TRAIT

TEST RESULTS	COUNSELING POINTS TO BE MADE
AE	**Clinical Indications:** • Person is a **healthy carrier** of one gene for hemoglobin E • Person is **not sick**. • Hemoglobin E trait does not cause any medical problems • Hemoglobin E trait does not require any special medical care **Inheritance:** • It is inherited, you can **NOT** catch it. • It is passed directly from parent to child. • If your child has hemoglobin E trait, this means at least one parent also has hemoglobin E. **Incidence:** • Hemoglobin E is not rare • It is the third most prevalent hemoglobin type identified in the world • 30-40% of people with south east Asian ancestry have this hemoglobin type **Risks to offspring:** • When both parents have hemoglobin E trait there is a 25% chance with each pregnancy that they may have a child with EE Anemia. These children have normal hemoglobin levels and no significant clinical problems • If one parent has beta thalassemia trait there is a 25% chance that the newborn could have e/Beta thalassemia. A hematologist should follow these children.
MATING One parent with A/E and the other with significant variants	AE X AA 50% chance of having a child with E Trait – no clinical problems AE X AE 25% chance of having a child with EE Anemia - little or no clinical problems AE X AS 25% chance of having a child with Sickle/E Disease – mild sickle cell disease AE X Beta Thalassemia May have severe clinical complications
PROBABLE OUTCOME	For future pregnancies, parents should be referred for genetic counseling and testing. Hemoglobin electrophoresis and a quantitative A2 should be ordered on the parent who does not have hemoglobin E.

HEMOGLOBIN E/Beta^{+} Thalassemia

GENOTYPE: **E/A or E/A/F** **Beta chain variant**	**Individuals have 40% E hemoglobin 1-30% A, with a significant increase in Hb F (30-50%)**
POPULATIONS AFFECTED	**South East Asians 30-40% in those from the Khmer region of Thailand and Cambodia.** **Occasionally African Americans.** **North Americans of European Ancestry: 1:70,000**
CLINICAL SYMPTOMS	**Moderate anemia.** **Microcytosis, splenomegaly, jaundice**
PRECAUTIONS	**Genetic counseling to clarify risk for child born with homozygous EE Disease, S/E Disease or Hemoglobin E/Thalassemia** **Family studies are necessary.**
LABORATORY DATA	**DO NOT USE SOLUBILITY TESTING AS A PRIMARY SCREENING METHOD.** **1. Cellulose Acetate Electrophoresis** **Result: Bands will be present in the A,C and F position Hemoglobin E migrates with Hb C and A2. Hemoglobin A2 quanitation cannot be run by column chromatography.** **2. Isoelectric Focusing (IEF)** **Result: Band of Hb in the A position however there is a slight separation between the E and the C allowing one to differentiate between the two.** **3. Solubility: Negative (-)** **4. Citrate Agar Electrophoresis is necessary.** **Slight hypochromia and mild microcytosis. Family studies necessary to confirm**

HEMOGLOBIN E/Beta^0 Thalassemia

GENOTYPE: **E/A or E/A/F** **Beta chain variant**	**Individuals have E hemoglobin with a significant increase in Hb F (30-60%) and no hemoglobin A**
POPULATIONS AFFECTED	**South East Asians 30-40% in those from the Khmer region of Thailand and Cambodia.** **Occasionally African Americans.** **North Americans of European Ancestry: 1:70,000**
CLINICAL SYMPTOMS	**Severe disease with severe anemia** **Microcytosis, splenomegaly, jaundice, expansion of marrow space. Treatment is similar to homozygous beta thalassemia.**
PRECAUTIONS	**Genetic counseling** **Family studies are necessary to confirm diagnosis.**
LABORATORY DATA	**DO NOT USE SOLUBILITY TESTING AS A PRIMARY SCREENING METHOD.** **1. Cellulose Acetate Electrophoresis** **Result: Bands will be present in the C and F position** **Hemoglobin E migrates with Hb C and A2. Hemoglobin A2 quanitation cannot be run by column chromatography.** **2. Isoelectric Focusing (IEF)** **Result: Band of Hb in the E and F position** **3. Solubility: Negative (-)** **4. Citrate Agar Electrophoresis is necessary.**

Hemoglobin E Disease

GENOTYPE: **E/E** **Beta chain variant**	**Individuals have 90-98% E hemoglobin. There may be a slight increase in Hb F. 1-30% A, with a significant increase in Hb F (30-50%)**
POPULATIONS AFFECTED	**South East Asians 30-40% in those from the Khmer region of Thailand and Cambodia.** **Occasionally African Americans.** **North Americans of European Ancestry: 1:70,000**
CLINICAL SYMPTOMS	**Clinically well, with rare to moderate anemia, microcytosis.** **Rare splenomegaly**
PRECAUTIONS	**Genetic counseling** **Family studies are necessary.**
LABORATORY DATA	**DO NOT USE SOLUBILITY TESTING AS A PRIMARY SCREENING METHOD.** **1. Cellulose Acetate Electrophoresis** **Result: Band will be present in the C position.** **Hemoglobin A2 quanitation cannot be run by column chromatography.** **2. Isoelectric Focusing (IEF)** **Result: Band of Hb in the A2 position** **3. Solubility: Negative (-)** **4. Citrate Agar Electrophoresis is necessary.**

Hemoglobin

HPFH
HEREDITARY PERSISTENCE OF FETAL HEMOGLOBIN

GENOTYPE: **AF or A/HPFH** **Gamma chain variant**	**Fetal hemoglobin (F) is the predominant hemoglobin at birth. After birth the proportion of F usually diminishes and converts to adult hemoglobin. In HPFH the concentration of hemoglobin F remains increased throughout life.** **Individuals have 15 to 35% F hemoglobin the rest is hemoglobin Each red cell contains a mixture of A and C.**
POPULATIONS AFFECTED	**African Americans** **Jamaicans** **Greeks** **British**
CLINICAL SYMPTOMS	**No symptoms** **Hemoglobin F is NOT associated with anemia.**
PRECAUTIONS	**Genetic counseling to clarify risk for child born with hemoglobin SF and identified as sickle cell disease on newborn screen.** **(See Sickle Cell Trait with HPFH)**
LABORATORY DATA	**DO NOT USE SOLUBILITY TESTING AS A PRIMARY SCREENING METHOD.** **1. Cellulose Acetate Electrophoresis** **Result: Bands will be present in the A and F position** **2. Isoelectric Focusing (IEF)** **Result: Same as Cellulose Acetate** **3. Solubility : Will be negative (-)** **4. Citrate Agar Electrophoresis** **Result: Hemoglobin F predominates.** **5. Staining Method: Kleihauer-Betke Stain** **6. A2 results within normal range.**

GENOTYPE: AF or A/HPFH Gamma chain variant	**Fetal hemoglobin (F) is the predominant hemoglobin at birth. After birth the proportion of F usually diminishes and converts to adult hemoglobin. In HPFH the concentration of hemoglobin F remains increased throughout life.** **Individuals have 15 to 35% F hemoglobin the rest is hemoglobin** **Each red cell contains a mixture of A and C.**
	Alkali-resistant **Normal blood indices.** **Intracellular to pancellular distribution of hemoglobin F in the red cell.**

Hemoglobin F is the major hemoglobin of the fetus and the newborn. Usually by 6 months of age HbF is 1% of total hemoglobin, however it can be as high as 5% for 12-24 months of age. Only trace (<0.5%) is found in adults. Synthesis of HbF increases in about 25% of women during pregnancy. Most significant during the 4th month of pregnancy. The increase is usually less than 5%. An increase in HbF levels can be seen in Hereditary Persistence of Fetal Hemoglobin (HPFH) and with the juvenile form of chronic myeloid leukemia (30 to 90% HbF). Increases are also seen with Aplastic Anemia (Fanconi type caused by benzene poisoning). Will see 5-15% HbF with this disorder. An increase of HbF is also seen with Beta Thalassemia and Delta-beta thalassemia (homozygote is 100% F). Use alkali denaturation (Singer and Betke methods) or HbF RID to quantitate HbF.

Hemoglobin

Variant Hemoglobins

Variant “V” is not a hemoglobin type

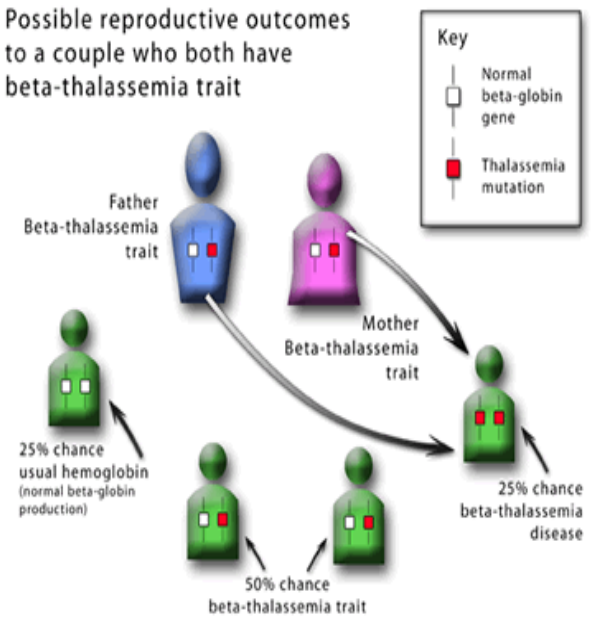
Hemoglobin identification

Using high performance liquid chromatography (HPLC), most screening laboratories have the ability to identify only 10 to 15 of the most common hemoglobin variants.

Hemoglobin type A with Variant “V” is not a type of hemoglobin, it is a collective term used to group those rare hemoglobin types that our screening test could not identify.
Most variants cause no medical problems or complications. However, if the client is currently pregnant, or planning a family, you may want to have her partner tested. If the partner has sickle cell trait, they may be at risk for having a child with a serious hemoglobinopathy.
Mutations are constantly being defined.

Quantitative Hemoglobin Variants

Thalassemia



THALASSEMIA: The Quantitative Hemoglobin Variants

Thalassemia is a genetic blood disorder. People with thalassemia disease are not able to make enough hemoglobin, which causes severe anemia. Hemoglobin is found in red blood cells and carries oxygen to all parts of the body. When there is not enough hemoglobin in the red blood

cells, oxygen cannot get to all parts of the body. Organs then become starved for oxygen and are unable to function properly.

Two main divisions exist in the classification of thalassemia, the major and minor forms. Thalassemia major represents the homozygous or disease state where no chains are being produced. For example, beta thalassemia major (Cooley' s Anemia) indicates no beta chains are being produced, while beta thalassemia minor represents the heterozygous or trait form that indicates decreased production by one gene and normal production by the other gene.

In this section we will examine the clinical and laboratory manifestations of the more common thalassemic syndromes.

CLASSIFICATION OF BETA SYNDROMES

TYPE	TRAIT (Minor)	HOMOZYGOUS (Major)
Beta^{+} Thalassemia	Hemoglobin A2: increased	Hemoglobin F Hemoglobin A: 10-50%
Beta^{0} Thalassemia	Hemoglobin A2: increased	Hemoglobin F + HbA2 No hemoglobin A
Delta Beta Thalassemia	Hemoglobin A2: normal or slightly reduced hemoglobin F: 5-10%	No hemoglobin A or A2 hemoglobin F: 100%
Delta Beta Lepore	10-15% Lepore Hemoglobin F: 2-10%	No hemoglobin A or A2 HbF and Lepore present

BETA THALASSEMIA MINOR (TRAIT)

GENOTYPE: **A/BETA THAL** **Beta chain deletion**	**One gene for production of the usual amount of beta chains with the correct structure, and one gene for a decreased amount of beta chain production.** **Individuals have 89-95% hemoglobin A with elevated hemoglobin A2 between 3.5-8.0%. The normal range for A2 is between 1.7 and 3.4%. Hemoglobin F may be present in the ranges of 1.5-5%.**
POPULATIONS AFFECTED	**Individuals of Mediterranean ancestry: 5%** **Asians: 5%** **Bengalese (India): 4%** **African Americans: 2%**
CLINICAL	**Mild anemia and pallor** **Slight splenomegaly in some carriers**

GENOTYPE: A/BETA THAL **Beta chain deletion**	**One gene for production of the usual amount of beta chains with the correct structure, and one gene for a decreased amount of beta chain production.** **Individuals have 89-95% hemoglobin A with elevated hemoglobin A2 between 3.5-8.0%. The normal range for A2 is between 1.7 and 3.4%. Hemoglobin F may be present in the ranges of 1.5-5%.**
SYMPTOMS	**Growth and development normal** **Carrier may appear to have an iron deficiency anemia for which iron therapy is not effective.**
PRECAUTIONS	**Genetic counseling and families studies to clarify risk for child born with Sickle Beta thalassemia or Beta Thalassemia Major.** **Possible iron overload if carrier is prescribed medicinal levels of iron.**
LABORATORY DATA	**DO NOT USE SOLUBILITY TESTING AS A PRIMARY SCREENING METHOD.** **Beta Thalassemia trait can not detected on cord blood electrophoresis or high pressure liquid chromatography. It can not be diagnosed in the newborn because it is impossible to quantitate the percent of Hemoglobin A2 which is necessary to make the diagnosis.** **In order to diagnosis Beta Thalassemia it is essential the lab is provided with the clients Mean Corpuscular Volume (MCV). The client should be at a minimum of l2 months of age.** **1. Cellulose Acetate Electrophoresis** **Result: Band of Hb in the A position and a small amount in the F position.** **2. Isoelectric Focusing (IEF)** **Result: Same as Cellulose Acetate** **3. Solubility: Negative (-)** **4. Citrate Agar Electrophoresis (acid)** **Result: Band present in the A and F position.** **5. Blood smear: Hypochromic/microcytic RBC's, target cells, ovalocytes, schitocytes, basophilic stippling, polychromasia, erythrocytosis.** **6. Blood indices:** **Microcytosis (MCV < 80 in adults)** **Hypochromia (MCH < 26)** **Hemoglobin (1-2 gm below normal for age)** **7. A2 Quantitation is elevated (>3.5)** **8. Studies to detect iron deficiency are normal.** **9. A family study is highly recommended.**

Normal hemoglobin concentrations are considered to fall within the following range:

- Hemoglobin A = 95%
- A_2 = 1.7-3.4% an elevated A_2 would be greater than 3.5%. (Note the exception of A_2 levels in sickle cell trait, see Table 2) Also note with quanitation of Hb A_2 by Micronchromatography, elevated levels of this hemoglobin (usually between 4.0% to 8.0%) generally indicate beta thalassemia trait

- F = <1%

CBC (complete blood count) should be performed and reviewed. The mean erythrocyte corpuscular volume (MCV) is used as the first criterion of the screening protocol for thalassemia. Patients with microcytosis should be offered further testing to determine thalassemia carrier status.

A low MCV is defined as:

- less than 80 for adults
- less than 76 in children ages 4 to 7 years
- less than 74 in children ages 18 months to 4 years
- less than 70 in children ages 6 months to 18 months

The A_2 elevation associated with beta thalassemia trait may be suspected from careful inspection of the electrophoresis strip, but must be confirmed quantitatively.

- Electrophoresis on cellulose acetate medium at alkaline ph is a useful screening procedure for separating hemoglobin variants that are interacting with thalassemia and the hemoglobin of the thalassemia syndromes such as HbS. H, Barts, Constant Spring and Lepore.
- Specimens that give results in the borderline or indeterminate range when quantitated by densitometry will usually give results that are clearly either normal or elevated when studied by chromatography.

Quantitation of Hb A_2 by Micronchromatography

Very small amounts of Hb A_2 (normally up to 3.5%) are found in normal adults. Elevated levels of this hemoglobin, between 4.0% to 8.0%, generally indicate beta thalassemia trait.

Quantitation of Hb F

There are numerous situations in which the quanitation of Hb F is beneficial to further categorize certain thalassemia conditions. Significantly elevated Hb F levels are seen in homozygous B^0 and B^+ thalassemia. Moderate or slight elevation in Hb F generally is seen in thalassemia minor conditions and the heterocellular forms of HPFH.

Quanitation of A2 by Microcolumn

Utilization of DEAE cellulose to separate A_2 from other hemoglobin. A_2 levels between 3.5 and 10% are indicative of beta thalassemia minor.

Interferences

- The hemoglobin variants C and E will co-elute on the micro-columns with Hb A_2.
- Any sample with indicated A_2 levels greater than 10% should be checked by other assays such as electrophoresis to confirm the identity of abnormal hemoglobin (such as C or E).
- Iron deficiency can depress Hb A_2 levels in beta thalassemia carriers.

COUNSELORS CHECK LIST FOR BETA THALASSEMIA TRAIT

TEST RESULTS	COUNSELING POINTS TO BE MADE

A/A with A2 Or A/A with elevated F Thalassemia Trait	**Clinical Indications:** • Person is a **healthy carrier**. • Person is **not sick**. • Beta thalassemia trait is **not** a disease. • This trait can cause you to have small, pale red blood cells. • This condition looks like an iron deficiency anemia. • No amount of iron supplementation will correct it. You should not take medicinal iron because your body will store it, causing other medical complications **Inheritance:** • It is inherited, you can **NOT** catch it. • It is passed directly from parent to child. • It does not "skip" generations, if you have it that means one of your parents also has it. • It is not "sex-linked" meaning you may have gotten it from either your mother or your father. **Incidence:** • Beta thalassemia trait is not rare • It has a worldwide distribution and is one of the most common hemoglobin variants identified. **Risks to offspring:** ➢ One who has Beta thalassemia trait may have a child with sickle cell disease if he or she mates with someone who has the sickle trait. ➢ If both partners have Beta thalassemia trait they are at risk for having a child with Beta thalassemia Major, a very serious blood disease.
MATING	A/Thal x AA, A/ Thal x AS, A/Thal x A/Thal
PROBABLE OUTCOME	For future pregnancies, parents should be referred for genetic counseling and testing.

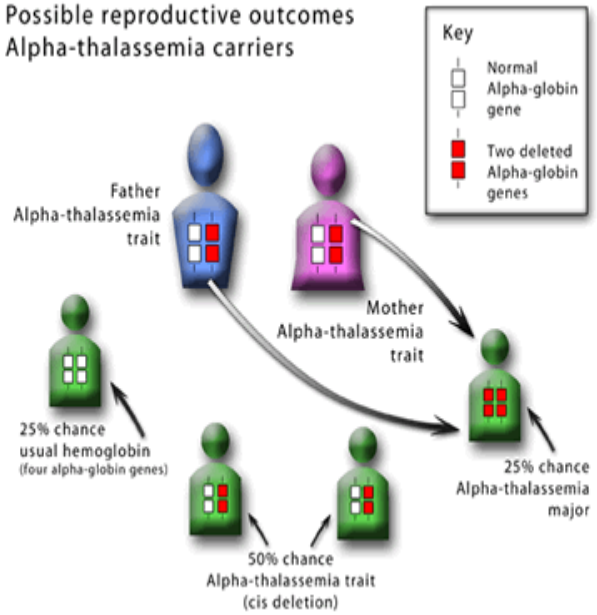
BETA THALASSEMIA MAJOR
COOLEYS ANEMIA

GENOTYPE: BETA THAL **Beta chain deletion**	**Inherited defect in beta chain synthesis, resulting in practically no production of hemoglobin A with an increase in available alpha chains.** **Individuals have 98-100% hemoglobin F with elevated hemoglobin A2.**
POPULATIONS AFFECTED	**Individuals of Mediterranean ancestry** **Asians** **African Americans**
CLINICAL SYMPTOMS	**Jaundice, splenomegaly, bone malformations, pallor, weakness, failure to thrive, growth retardation, increased risk for infection, and shortened lifespan.** **Severe anemia, client is transfusion and chelation therapy dependent.** **Without treatment, death my result by age 4.** **Generally less severe in the African American population than in the Mediterranean or Asian population.**
PRECAUTIONS	**The lifespan of individuals with Beta Thalassemia has been greatly increased due to chelation therapy, which rids the body of excess iron produced by chronic transfusions.**
LABORATORY DATA	**DO NOT USE SOLUBILITY TESTING AS A PRIMARY SCREENING METHOD.** **1. Cellulose Acetate Electrophoresis** **Result: Band of Hb in the F position and a small amount of A2** **When concentration of F is high, HbA2 is absent or normal.** **When HbF is only moderately increased HbA2 range will be 5-9%** **2. Isoelectric Focusing (IEF)** **Result: Same as Cellulose Acetate** **3. Solubility: Will be negative (-)** **4. Citrate Agar Electrophoresis** **Result: Band present in the F position.** **5. Blood smear: Hypochromic/microcytic RBC's, fragmented RBC's target cells, Howel-Jolly bodies, normoblasts, poikilocytosis, schitocytes, polychromasia.** **6. Blood indices: Low with MCV < 75** **Hemoglobin: 5.0 gm/100 with transfusions** **7. A family study is highly recommended.**

ALPHA THALASSEMIA

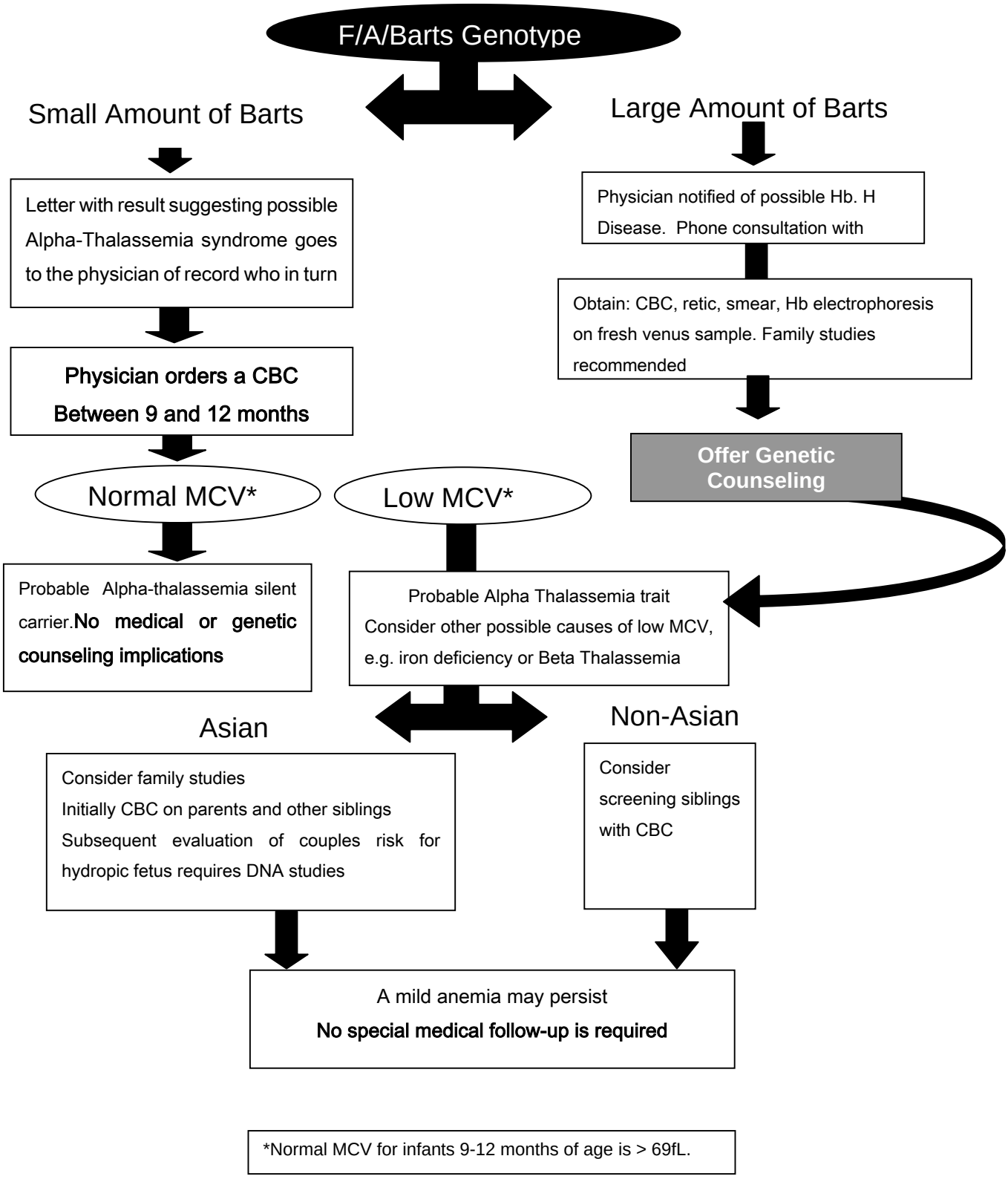
Alpha thalassemia syndromes are caused by genetic deletions of the alpha genes. Progressive decrease in alpha chain synthesis results in more severe anemia and symptoms as more alpha

genes are deleted. Alpha thalassemia is commonly found in people of Asian origin. Countries in which it is especially frequent are: China, the Philippines, Malaysia, Thailand, Cambodia, Laos, Vietnam, Burma, and India. Certain forms of alpha thalassemia are also present in people of African ancestry, including African American. There are four classifications of alpha thalassemia, the type an individual has depends upon their inheritance pattern for alpha globin chain production.



In the newborn, alpha thalassemia is picked up through the presence of hemoglobin Barts on the newborn screen. The percentage of hemoglobin Barts in the cord blood sample may indicate the number of alpha genes that have been lost. If the percentage of hemoglobin Barts is small (less than 5 %), the infant most likely has lost one gene and will be a normal carrier for alpha thalassemia minor. Hemoglobin Barts between 5 to 10% indicates the presence of alpha thalassemia minor with loss of two alpha genes. If the hemoglobin Barts is greater than 10% (usually 15-20%), a more severe form of alpha thalassemia may be present and further testing is indicated. Individuals with alpha thalassemia minor (hemoglobin Barts 5 to 10%) will have a very mild anemia with microcytosis (small red blood cells) and no other clinical problems. This anemia is, however, frequently confused with iron deficiency anemia. Parents of infants with hemoglobin Barts should be told their child has alpha thalassemia minor and this disorder will have no effect on the child' s health. They should be told it is inherited so others in the family may have a similar disorder. They should be instructed to tell health professionals that alpha thalassemia runs in their family to prevent unnecessary tests or treatment with iron. If alpha thalassemia minor is detected in Oriental or Mediterranean infants, family studies should be initiated to detect the presence of more serious forms of alpha thalassemia. Infants with greater than 10% Barts hemoglobin should be referred to tertiary care centers for further evaluation.

Followup Procedure for Barts in the Newborn


F/A/Barts Genotype
Small Amount of Barts
Large Amount of Barts
Letter with result suggesting possible Alpha-Thalassemia syndrome goes to the physician of record who in turn
Physician orders a CBC Between 9 and 12 months
Physician notified of possible Hb. H Disease. Phone consultation with
Obtain: CBC, retic, smear, Hb electrophoresis on fresh venus sample. Family studies recommended
Offer Genetic Counseling
Normal MCV*
Low MCV*
Probable Alpha-thalassemia silent carrier.No medical or genetic counseling implications
Probable Alpha Thalassemia trait
Consider other possible causes of low MCV, e.g. iron deficiency or Beta Thalassemia
Asian
Non-Asian
Consider family studies
Initially CBC on parents and other siblings
Subsequent evaluation of couples risk for hydropic fetus requires DNA studies
Consider screening siblings with CBC
A mild anemia may persist
No special medical follow-up is required
*Normal MCV for infants 9-12 months of age is > 69fL.

CLASSIFICATION OF ALPHA SYNDROMES

GENE DELETION	CLASSIFICATION Complications	TESTING METHOD
Single gene deletion Remaining three genes compensate almost completely.	Silent Carrier Clinically and hematologically normal	Traces of Hb Barts at birth that disappear. Diagnosed by enumeration of the alpha genes by recombinant DNA technology. This is both technically difficult and expensive.
Deletion of two alpha genes	Alpha Thalassemia Trait Mild anemia with small red cells. No evidence of iron deficiency A2 levels are normal	Traces of Hb Barts at birth that disappear at 3-4 months of age
Deletion of three alpha genes	Hemoglobin H Disease Moderately severe microcytic hemolytic anemia resembling mild Cooley's anemia. (See section on Hemoglobin H Disease)	5-20% Hemoglobin H
Deletion of four alpha genes	Fetal Hydrops Syndrome Severe hemolytic anemia beginning in utero. Affected infants develop heart failure, often stillborn between 34 and 40 weeks or dies within the first hours of birth. Pregnant women carrying an infant with Fetal Hydrops Syndrome have a high rate of severe toxemia of pregnancy and postpartum bleeding.	Hemoglobin Barts with small amounts of Hemoglobin H and Portland. No hemoglobin A or F The parents have a thalassemic blood picture with low MCV and MCH and normal hemoglobin electrophoresis.

HEMOGLOBIN H DISEASE

GENOTYPE: **3 alpha chain deletions**	**Inherited defect in alpha chain synthesis.** **Hemoglobin H ranges from 5-30%** **Hemoglobin A present for the balance.**
POPULATIONS AFFECTED	**South East Asians** **Greeks**
CLINICAL SYMPTOMS	**Clinical findings are variable, some patients being almost as severely affected as Cooley's Anemia, while many have a milder course.** **Chronic transfusions may be indicated, but unlikely.** **Lifelong anemia, splenomegaly, gallstones, increased risk for infections, jaundice, increased hemolysis and leg ulcers.**
PRECAUTIONS	**Lifespan usually not greatly affected.** **Pregnancy may worsen the anemia and increase complications.** **Genetic counseling and families studies to clarify risk for child born with Fetal Hydrops Syndrome.**
LABORATORY DATA	**DO NOT USE SOLUBILITY TESTING AS A PRIMARY SCREENING METHOD.** **1. Cellulose Acetate Electrophoresis** **Result: Band of Hb in the A and H position** **Fast moving hemoglobin, almost migrates off the plate.** **2. Isoelectric Focusing (IEF)** **Result: Same as Cellulose Acetate** **Will see Barts present: 25% at birth, less in adults** **3. Solubility: Negative (-)** **4. Citrate Agar Electrophoresis (acid)** **Result: Migrates with A** **5. Blood smear: Hypochromia, microcytosis, target cells, and anisopoikilocytosis.** **6. Brilliant cresyl blue (BCB) stain for inclusion bodies** **BCB prep: Positive** **6. Blood indices: Decreased - Hemoglobin: 8-10 gm** **7. A family study is highly recommended.**

NEWBORN SCREENING

The code of Virginia Section 31.1-65 mandates that all infants born in the Commonwealth shall be tested for sickle cell disease and other hemoglobinopathies. In doing so harmless traits will also be identified. We must be prepared to help parents understand the significance of these traits.

A WORD ABOUT TRAITS

It is important to remember that while the objective of newborn screening is to identify the high-risk child with a serious hemoglobinopathy, in doing so, we will identify newborns with harmless traits. It is just as important to inform these parents of their newborn' s carrier status and provide them with educational genetic counseling and family studies to identify if this couple is " at-risk" for having children with sickle cell disease. This enables parents to make informed decisions for subsequent pregnancies. In counseling the parent of the newborn identified with trait, the provider should:

- Clarify the difference between the trait and disease
- Stress the benign nature of the trait
- Help the parent understand the concept of "at-risk" status
- Offer testing and counseling to other family members
- Send such samples to VASCAP for free testing
- Understand the possibility for disclosure of non-paternity

Table 3: COMMON NEWBORN HEMOGLOBIN TYPES

RESULT	DIAGNOSIS	CLINICAL SUGGESTIONS
FA	Fetal and normal (A)	Physician notify family of results
FSC	Sickle Hemoglobin C Disease	Repeat sample; confirm test results, provide counseling, offer or refer for family studies, refer to comprehensive sickle center or hematologist.
FS FSA	Probable Sickle Cell Anemia Probable Sickle Beta^{+} Thalassemia	Repeat sample; confirm test results, provide counseling, offer or refer for family studies to identify Sickle Beta^{0} $^{or +}$ Thalassemia or S/HPFH; refer to comprehensive sickle center or hematologist if Sickle Beta$^{0 \text{ or } +}$ Thalassemia is confirmed by family study. (See information on S/HPFH)
FC	Hemoglobin C Disease or C/Beta Thalassemia	Repeat sample; confirm test results, provide counseling, offer or refer for family studies to identify C/Thalassemia or C/HPFH; refer to hematologist if C/Thalassemia is detected.
FE	Hemoglobin E Disease	Repeat sample; confirm test results, provide counseling, offer or refer for family studies including electrophoresis, CBC, and iron profile; refer for counseling if one

		parent has Beta-thal trait. Repeat at 6 months and one year to exclude E/Beta Thalassemia; if E/Thal or EE refer to hematologist.
FAE	**E Trait**	**Counseling and family studies to rule out possibility of risk for E/Beta Thalassemia. (See above)**
FAS **FAC**	**Sickle Cell Trait** **C Trait**	**Counseling and family studies to identify risks for future pregnancys.**
FA/Barts	**Possible Alpha Thalassemia**	**Counseling and family studies (see section on Alpha Thalassemias)**
FA Variant	**Unidentified variant**	**Repeat electrophoresis on baby, counseling and family studies.**

Patient Education Fact Sheets

Fast Facts About. . .

Sickle Hemoglobin

Hemoglobin is a protein responsible for carrying oxygen and giving blood its red color. Worldwide, there are hundreds of different hemoglobin types.

Sickle Hemoglobin is the most common hemoglobin typed identified in African Americans (1in 10). It has also been identified in people from South and Central America, Saudi Arabia, Egypt, and the Mediterranean countries of Italy and Greece.

Sickle Cell Trait: A/S

A **gene** is a unit of inheritance that is passed from parent to child. People who have inherited a gene for normal adult hemoglobin A, and one gene for sickle hemoglobin S, are said to have the sickle cell trait (A/S). Their red blood cells contain a small amount of sickle hemoglobin, but not enough to change the shape of the cell.

The Healthy Carrier

Sickle cell trait is not a disease and will never change into sickle cell anemia.

Trait carriers should however, take precautions in **high altitudes** (above 10,000 feet). It is also important to guard against **dehydration** (loss of body fluid) and extreme fatigue during strenuous physical activity over a prolonged period, such as during basic training for the military.

Sickle Cell Anemia: S/S

When both partners have sickle cell trait, there is a one in four, or 25% chance with each pregnancy that they may have a child with **Sickle Cell Anemia.**

How does sickle cell anemia affect a child?

These children may have many different complications, however the most common are:

- Severe anemia
- Increased risk for life threatening bacterial infections.
- Periodic episodes of severe pain
- Tissue, organ, and bone damage

Children with sickle cell anemia should be followed by a hematologist and started on penicillin to help combat infections. Early identification, along with proper care, good nutrition, immunizations, early treatment of infections, and prophylactic administration of penicillin greatly improves the outlook for individuals living with sickle cell disease.

Are you at risk for having a child with sickle cell disease?

Ask your health care provider about testing for you and your partner. The test is called HEMOGLOBIN ELECTROPHORESIS.

Datos Concretos Sobre . . .

La Anemia de Célula Falciforme

Hemoglobina es una proteina que se encuentra en los glóbulos rojos de la sangre - a ella se debe el color rojo de ésta-, y cuya función es el transporte de oxígeno desde los pulmones a todos los tejidos del organismo. Mundialmente hay cientos de tipos distintos de hemoglobina.

Hemoglobina Falciforme es el tipo más común de hemoglobina identificada en los Americanos Africanos (1de cada 10). También ha sido identificada en personas de Centroamérica, Sudamérica, Arabia Saudita, Egipto y de paises mediterráneos como Italia y Grecia.

Rasgo de la Célula Falciforme (A/S)

Al igual que el color de los ojos o la forma de la nariz, el tipo de hemoglobina también es hereditario.

Un **gen** es una unidad hereditaria que pasa de padres a hijos. Las personas que han heredado un gen de la hemoglobina normal de adulto " A" y un gen de la hemoglobina Falciforme " S" , se dice que presentan el Rasgo de de la Célula Falciforme (A/S). Estas personas tienen una cantidad pequeña de hemoglobina falciforme y por tanto sus glóbulos rojos no se deforman.

El Portador Sano

El ' Rasgo de la Célula Falciforme' no es una enfermedad y nunca podrá cambiar a ser Anemia Falciforme. Sin embargo, los portadores de este rasgo deberán tomar precauciones en **altitudes altas** (por encima de los 10,000 pies). También es importante que estén prevenidos contra una **deshidratación** (pérdida de fluido corporal) y una fatiga extrema durante una actividad física estrenuosa sobre un período de tiempo prolongado, tal como ocurre en el entrenamiento básico militar.

Anemia de Célula Falciforme (S/S)

Cuando ambos padres presentan el Rasgo de la Célula Falciforme, existe una probabilidad del 25% en cada embarazo (o uno de cada cuatro) de que el hijo(a) tenga anemia de célula falciforme.

¿Cómo afecta al niño(a) la Anemia de Célula Falciforme?

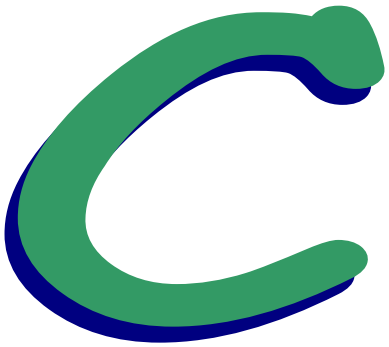
Estos niños pueden tener complicaciones distintas pero las más comunes son:

- Anemia severa (insuficiencia de glóbulos rojos) que puede resultar en un retraso en el crecimiento y en el desarrollo físico
- Riesgo mayor de contraer infecciones bacterianas graves.
- Episodios periódicos o crisis de dolor agudo
- Tejidos, órganos y huesos dañados.

Los niños que padecen anemia falciforme deben ser atentidos por un hematólogo o especialista en sangre y ser tratados con penicilina para combatir posibles infecciones. Tanto el diagnóstico temprano, como los cuidados adecuados, una nutrición buena, las vacunaciones, el tratamiento temprano de infecciones y la administración profiláctica de penicilina, todo ésto contribuye a una gran mejora de las perspectivas para aquellas personas que viven con la enfermedad de anemia de célula falciforme.

¿Corre usted el riesgo de tener un hijo(a) con la enfermedad anemia de célula falciforme?

La mejor prevención es el conocimiento. Pregunten a su médico si es conveniente que le hagan a ustedes la prueba de diagnóstico llamada ELECTROFORESIS DE HEMOGLOBINA.



Fast Facts About . . .

Hemoglobin C

Hemoglobin is a protein responsible for carrying oxygen and giving blood its red color. Worldwide, there are hundreds of different hemoglobin types.

Hemoglobin C

Hemoglobin C very common in people from West Africa. In the United States, about 1 in 40 African Americans is born with hemoglobin C, making it the second most common hemoglobin type identified in this population.

Hemoglobin C Trait: A/C

Like many of our physical characteristics, our hemoglobin type is inherited. A gene is a unit of inheritance that is passed from parent to child. People who have inherited one gene for normal adult hemoglobin (A) and one gene for hemoglobin C are said to have the C trait.

The Healthy Carrier

- Hemoglobin C- trait is not a disease.
- It will not develop into a disease later in life.
- People with C trait have no symptoms and no anemia.
- They do not need special medical care.
- Under the microscope, some red blood cells will look like targets or a "Bulls Eye" but most will have the usual round shape.

Hemoglobin C Disease: C/C

There is medical treatment required for people with Hemoglobin C Disease.

When both partners have hemoglobin C-trait, there is a 25% chance with each pregnancy that they may have a child born with only hemoglobin C. Children with this disorder may experience:

- Mild anemia which could become more severe following an infection
- Occasional episodes of joint and abdominal pain
- Enlarged spleen and gallstones

Sickle Hemoglobin C Disease: S/C

When one partner has hemoglobin C- trait and the other has the sickle cell trait, there is a 25% chance with each pregnancy that they may have a child born with Sickle Hemoglobin C Disease. These children should be followed by a hematologist and started on penicillin to help combat infections. They have a mild anemia and may also have periodic episodes of pain.

Do you know your hemoglobin type?

Ask your health care provider about testing for you and your partner.

Fast Facts About . . . Hemoglobin Barts and Alpha Thalassemia

Hemoglobin is a protein responsible for carrying oxygen and giving blood its red color. Worldwide, there are hundreds of different hemoglobin types. Each hemoglobin molecule contains two pairs of globin chains, one is called alpha and the other is called beta.

Alpha Thalassemia is caused by a decrease in the number of alpha globin chains being produced. There are at least four forms of alpha thalassemia. If your baby has been identified with Hemoglobin Barts

at birth, this means he/she is probably a health carrier. More serious forms of Alpha Thalassemia will be tracked through the Newborn Screening Follow-up Program at the Virginia Department of Health.

The Silent Carrier: One gene deletion

In the silent carrier, only three out of the four genes that regulate the production of alpha globin chains are passed from the parent to the child. A very small amount of " Barts" hemoglobin is identified at birth, however it soon disappears. **The child has no anemia and will require no medical treatment.**

Alpha Thalassemia Trait: Two gene deletion

Only two genes are inherited for the production of alpha globin chains. A small amount of Barts hemoglobin is identified at birth, however it soon disappears. A mild anemia may be present. Parents who have been told that their newborn had Barts hemoglobin at birth should tell their health care provider. This information could prevent unnecessary testing or treatment with iron. **No medical treatment for alpha thalassemia is necessary, even for the child with a two gene deletion.**

Hemoglobin H Disease: Three gene deletion

Only one gene for the production of alpha chain production has been inherited. A large amount of Barts hemoglobin (>20) is usually identified at birth. Referral to a doctor who specialized in disorders of the blood (hematologist) is recommended. Complications might include; severe, lifelong anemia, jaundice, enlarged spleen and gallstones. This complication is most common in people of Southeast Asian ancestry.

Fetal Hydrops Syndrome: Four gene deletion

No genes for the production of alpha chains have been inherited. The fetus is stillborn or dies within the first few hours of birth. This condition is seen almost exclusively in people from Southeast Asia.

Newborn Screening

Alpha thalassemia can be detected in the newborn through the presence of hemoglobin Barts at birth. Diagnosis through DNA analysis in the adult is both technically difficult and expensive. If your newborn has been identified with hemoglobin Barts, this means that you and your partner may be healthy carriers. If you are planning to have more children, you may wish to speak to a genetic counselor about alpha thalassemia.

Fast Facts About . . . Beta Thalassemia

Hemoglobin is a protein responsible for carrying oxygen and giving blood its red color. Worldwide, there are hundreds of different hemoglobin types. The kind of hemoglobin you have depends upon your genetic inheritance. **Genes** are units of inheritance passed on from your parents. These messengers determine characteristics such as skin, eye, and hair color. They also determine hemoglobin type.

Thalassemia **is the medical term for one kind of inherited anemia.**

Thalassemia Minor or Thalassemia Trait are terms are used interchangeably to describe people who have inherited one gene for normal adult hemoglobin " A" and one gene for the limited production of beta chains. People born with beta thalassemia trait are healthy. Physicians often mistakenly diagnose iron deficiency in people with beta thalassemia trait because their red blood cells are often small and pale in color. However, taking iron supplements cannot cure this inherited anemia. As a matter of fact, individuals with thalassemia trait should be careful not to over supplement their diets with medicinal iron.

Precautions

When both partners carry the beta thalassemia trait, there is a 25% chance with each pregnancy that they may have a child with a serious blood disease called Cooleys Anemia. Untreated, Cooleys Anemia can result in heart failure from severe anemia, enlargement of the liver and spleen, and changes in the bones.

Sickle Beta Thalassemia

When one partner has beta thalassemia and the other has the sickle cell trait, there is a one in four, or 25% chance with each pregnancy that they may have a child with **Sickle Beta Thalassemia.** These children may have many different complications, however the most common are:

- Severe anemia (low blood) that can result in delayed physical growth and development
- Increased risk for life threatening bacterial infections.
- Periodic episodes of severe pain
- Tissue, organ, and bone damage

Do you know your hemoglobin type?

Ask your health care provider about testing for you and your partner. The test is called **Hemoglobin Electrophoresis.** An **A_2 Quanitation** is needed to identify possible Beta thalassemia.

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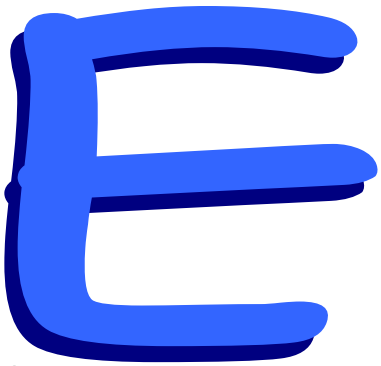
Hemoglobin E



Hemoglobin is a protein responsible for carrying oxygen and giving blood its red color. Worldwide, there are hundreds of different hemoglobin types. The kind of hemoglobin you have depends upon your genetic inheritance.

Hemoglobin E is found most often in people from Thailand, Cambodia, Bengal, Vietnam, Laos, Malaysia, the Philippines and Southern China. In some parts of the world, hemoglobin E is the most common hemoglobin

type seen.

Hemoglobin E-Trait: A/E

People who have inherited one gene for normal adult hemoglobin (A) and one gene for hemoglobin E are said to have, hemoglobin E Trait.

The Healthy Carrier

- Hemoglobin E trait is not a disease
- It will not develop into a disease later in life
- It causes no health problems
- It requires no special medical care

HEMOGLOBIN E Anemia: E/E

When both partners have hemoglobin E Trait, there is a 25% chance with each pregnancy that they may have a child born with only hemoglobin E.

- These children may have a normal hemoglobin level or they may be slightly anemic
- There are no significant clinical problems

HEMOGLOBIN E Beta Thalassemia: E/Beta Thal

When one partner has hemoglobin E trait and the other carries the trait for Beta Thalassemia, there is a 25% chance with each pregnancy, their newborn could have E/Beta Thalassemia. These children should be followed by a hematologist . Untreated, E/Beta Thalassemia can cause the following complications:

- Severe anemia that may require blood transfusions
- Enlargement of the heart, liver, and spleen
- Poor growth
- Progressive bone changes

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Adult Variant Hemoglobins

Hemoglobin is a protein responsible for carrying oxygen and giving blood its red color. Worldwide, there are hundreds of different hemoglobin types. The type of hemoglobin you have depends on your genetic

inheritance. Genes are chemical messengers passed on from your parents. These messengers determine characteristics such as eye color, skin color, and hemoglobin type.

The healthy carrier

Most people are born with two genes for the production of normal adult hemoglobin, called hemoglobin (A). It is not uncommon for someone to inherit one gene for normal hemoglobin (A) from one of their parents, and one gene for different or " variant" hemoglobin from the other. Common hemoglobin variants include sickle cell trait (A/S) and hemoglobin C trait (A/C).

Hemoglobin identification

Hemoglobin variants are identified in all races and ethnic groups. Using high performance liquid chromatography (HPLC), most screening laboratories have the ability to identify only 10 to 15 of the most common hemoglobin variants.

Hemoglobin type A with Variant: A/V Trait

Variant "V" is not a type of hemoglobin, it is a collective term used to group those rare hemoglobin types that our screening test could not identify. If your test result reads, A/V, this means you have inherited one gene for normal hemoglobin (A) production from one of your parents and an unidentified variant from the other. Most variants cause no medical problems or complications. However, if you are currently pregnant, or planning a family, you may want to have your partner tested. When both parents have a hemoglobin variant, they may be at risk for having a child with a serious disorder of the blood.

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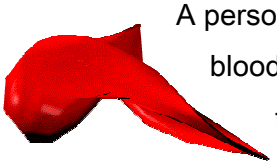
Sickle Cell Disease

Sickle cell disease is a group of inherited red blood cell disorders that affect both the shape and function of the red blood cell. Regular red blood cells are round like doughnuts, they move through the small blood vessels in the body to deliver oxygen.



A person born with sickle cell disease has no regular red blood cells. When their red blood cells give off oxygen, they become twisted, hard, and sticky. As they pass through the blood vessels, they break up and stick together, blocking the flow of blood and oxygen and causing other serious complications.

What are the complications?

Complications include:

- Episodes of extreme pain
- Strokes
- Increased infections
- Leg ulcers
- Bone damage
- Yellow eyes or jaundice
- Early gallstones
- Lung blockage
- Kidney damage and loss of body water in urine
- Painful erections in men (priapism)
- Blood blockage in the spleen or liver (sequestration)
- Eye damage
- Low red blood cell counts (anemia)
- Delayed growth

Are there different types of sickle cell disease?

There are three common types of sickle cell disease in the United States.

- Hemoglobin S/S or Sickle Cell Anemia
- Hemoglobin S/C or Sickle C disease
- Hemoglobin Sickle Beta-Thalassemia

Prevention and Care

While some types of sickle cell disease are milder than others, ***every person living with sickle cell disease should be under the care of a medical team that understands this complex disorder.*** There is currently no universal cure for sickle cell disease; however, there are safe and effective treatments for the serious complications. Patients and families should watch for the following conditions that need an urgent medical evaluation:

- Fever that is greater than 101.5 ^{0}
- Chest pain
- Shortness of breath
- Increasing tiredness
- Abdominal swelling
- Unusual headache
- Any sudden weakness or loss of feeling in the arm or leg
- Pain that will not go away with home treatment
- Priapism (painful erection that will not go down)
- Sudden vision change

Guidelines for Keeping the Sickle Cell Patient Healthy

- Take the vitamin folic acid (folate) daily to help make new red cells
- Take penicillin every day until age six to prevent serious infection
- Drink water daily (8-10 glasses for adults) to keep red blood cells from sticking together
- Avoid staying in places where the temperature is too hot or too cold
- Avoid swimming in unheated pools or in water that is below 80 degrees
- Avoid over exertion and stress
- Avoid the use of excessive alcohol
- Do not smoke and avoid second hand smoke
- Get plenty of rest
- Get regular check-ups from health care providers who understand sickle cell

How do you get sickle cell disease?

You are born with it. Like the color of your eyes, or the shape of your nose, your hemoglobin type is passed to you from your parents through messengers called genes. If you inherit only

one sickle gene, you have **sickle cell trait**. If you inherit two sickle cell genes you have **sickle cell disease**.

What is sickle cell trait?

A person born with sickle cell trait has inherited one gene for sickle hemoglobin from one parent and one gene for regular adult hemoglobin from the other. They have a small amount of sickle hemoglobin in their red blood cells, but not enough to cause problems. One in ten African Americans is born with sickle cell trait and may not even know it. Sickle cell trait will never change into sickle cell anemia; however, when both parents have sickle cell trait they may have a child with sickle cell disease.

Is sickle cell found only in African Americans?

Sickle cell disease is the most common genetic disease identified in African Americans; however, it is also found in people from South and Central America, Italy, Greece, Turkey, Saudi Arabia and East India.

How can I be tested?

Your doctor or health care provider can do a simple blood test called the ***hemoglobin electrophoresis***. This test will tell if you are a carrier of the sickle cell trait or any other hemoglobin variant.

For more information about sickle cell disorders contact

The Virginia Sickle Cell Awareness Program
Virginia Department of Health
(804) 864-7769