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DEPT. OF HEALTH AND HUMAN SERVICES

## HEMOGLOBINOPATHIES

Most clinically significant hemoglobinopathies are inherited defects of the beta ( $\beta$ ) globin chain of adult hemoglobin. Red blood cells of newborns have a predominance of fetal hemoglobin which does not contain  $\beta$  globin. For this reason, clinical signs and symptoms of  $\beta$  globin abnormalities are usually not apparent at birth but become evident as adult hemoglobin replaces fetal hemoglobin.

Most of the hemoglobinopathies detected by newborn screening are the result of single amino acid substitutions in the  $\beta$  globin and are inherited as autosomal recessive disorders. Persons with two abnormal  $\beta$  globin genes (homozygotes or double heterozygotes) have "disease". Individuals with one abnormal  $\beta$  globin gene (heterozygotes) have "trait" and are carriers for "disease". That is, individuals can pass on "trait" or potential for "disease" to offspring.

Thalassemias are caused by the decreased synthesis of the globin chains. Infants with a thalassemia may be identified by newborn screening because Bart's hemoglobin (composed of four gamma chains) is readily detected. Beta thalassemia genes may interact with genes for  $\beta$  globin variants and produce serious hemoglobinopathies, but may not be detectable at birth.

The frequency of hemoglobinopathies varies among ethnic groups in the United States. Sickle hemoglobin is found in higher frequencies in descendants of people from Africa, Italy, Greece, Turkey, Arabia, and India. Hemoglobin C occurs predominantly among descendants of people from central and western Africa. Hemoglobin E is common in persons of Southeast Asian ancestry. Many thalassemia genes originated in west and central Africa, Italy, Greece, Asia, Africa, and the Pacific Islands.

### **Clinical Features:**

Sickle cell disease occurs in persons homozygous for the sickle gene (sickle cell anemia), in compound heterozygotes for sickle hemoglobin and hemoglobin C (hemoglobin SC disease), and in compound heterozygotes for sickle hemoglobin and beta thalassemia (sickle- $\beta$  thalassemia).

Infants with sickle cell disease may present with dactylitis, fever and sepsis, jaundice, anemia, or splenic sequestration (which may be life threatening in a small child) at any

time after a few months of age. Other symptoms may occur as the disease progresses, such as recurrent pain, acute chest syndrome, and stroke. These disorders vary in severity, and some clinical features are not present in all affected individuals.

In other hemoglobin diseases, clinical features are influenced by the type of hemoglobin variant. Homozygous hemoglobin C or hemoglobin E show only mild hemolytic anemia. Persons with thalassemias have varying degrees of microcytic hypochromic anemia, and the severe forms (E-Beta thalassemia) may have hemolysis and be transfusion dependent.

Most hemoglobin traits (heterozygotes) are associated with few or no clinical problems. Thus, the value of trait or carrier detection lies in the opportunity to educate families, to test other family members, and to provide genetic counseling.

**Laboratory Tests:**

Screening is performed by isoelectric focusing (IEF) of a hemolyte prepared from a dried blood spot. Hemoglobin "bands" are identified by the migration in the electrophoretic field. Positive screening results reflex to DNA for A, S, C and E alleles as well as 3 common  $\beta$ -thalassemia mutations. The confirmatory test is done on a new whole blood specimen by hemoglobin electrophoresis.

<b>*TEST RESULTS</b>	<b>LIKELY CAUSES</b>	<b>ACTIONS TO TAKE WHEN POSITIVE RESULT FOUND</b>
FA	Normal	None
FAS	Sickle cell trait  Sickle cell anemia after blood transfusion	Telephone and write submitter and newborn's physician to collect a repeat specimen for confirmatory tests  Telephone NNSP about results
FSA	S- $\beta$ thalassemia	
FAC	Hemoglobin C trait	
FAV	Possibilities include hemoglobin E, O, D, or G trait	
FAV	Possibilities include hemoglobin Barts which is indicative of $\beta$ thalassemia	
F only	Premature infant B thalassemia major	
AF Predominant A	Transfused infant Normal matured infant	
FV (no A)	Possibilities include homozygous hemoglobin E or hemoglobin E- $\beta$ thalassemia	
FS (no A)	Sickle cell anemia Sickle- $\beta$ thalassemia	

FSC (no A)	Sickle-hemoglobin C disease	
FC (no A)	Homozygous hemoglobin C	

\*Hemoglobins are reported in order of quantity (e.g., FAS = F>A>S).  
 F = fetal hemoglobin; A = adult hemoglobin S = sickle hemoglobin; V = unidentified variant; C = hemoglobin C

Barts hemoglobin is a fast migrating band that is present at birth in infants with a thalassemia and generally disappears by 4 months of age. Thus, infants with an unidentified fast band on the screening tests and with a normal confirmatory test should be suspected of having a thalassemia, especially if they have microcytosis and are of Asian, Mediterranean, or African ancestry. However, the absence of an unidentified fast band on the screening test does not exclude the possibility of a thalassemia.

**Confirmation and Treatment:**

Consultation with a pediatric hematologist should be made for confirmation and diagnosis (see ACT sheet for the particular hemoglobin pattern). Upon notification of a positive hemoglobinopathy screening result the physician should collect or cause to be collected 0.5 ml (purple top) EDTA whole blood and order a confirmatory hemoglobinopathy test (hemoglobin electrophoresis). It is important to obtain confirmation results and a diagnosis by 2 months of age for some clinically significant hemoglobinopathies (such as sickle cell disease) in order to initiate prophylactic treatment. Treatment for hemoglobin diseases is determined by the type and severity of the hemoglobin disorder. For some sickling disorders the specialist may recommend prophylactic penicillin when the screening results are known, prior to receiving confirmatory test results.

**Screening Practice Considerations:**

The laboratory tests should detect most abnormal hemoglobin subtypes, even if the specimen is collected before 24 hours of age, unless the infant has had an exchange transfusion. Blood transfusions may cause false negative results. ALWAYS OBTAIN A NEWBORN SCREENING SPECIMEN PRIOR TO A TRANSFUSION.

The primary purpose of hemoglobinopathy screening is the identification of infants with sickle cell diseases for whom early intervention has been shown to markedly reduce morbidity and mortality. The screening test is not diagnostic and confirmation of all abnormal results should be done.

The most commonly identified abnormal phenotype through newborn screening is FAS which is presumably positive for sickle trait. Parents of infants with sickle cell trait have a chance of having an infant with sickle cell disease if both parents carry the gene for sickle hemoglobin. Further testing of both parents combined with genetic counseling can apprise parents of their chances in future pregnancies of having children affected with clinically significant disease. The screening test that is done for hemoglobinopathies can not quantitate hemoglobins. There are some cases of results of FAS that on confirmation could be clinically significant FSA. Therefore it becomes even more important to confirm

every abnormal screening results. Every infant with a presumptive positive hemoglobinopathy screening result, must have confirmatory testing done in a timely manner.

Hemoglobinopathies are complex disorders, and practitioners are strongly encouraged to consult follow-up resources for more information concerning abnormal screening results and appropriate follow-up and treatment. Practitioners are encouraged to obtain a copy of "The Management of Sickle Cell Disease" National Institutes of Health, National Heart, Lung and Blood Institute, NIH publication No. 02-2117, June 2002. The internet site: <http://www.nhlbi.nih.gov/health/prof/blood/sickle/index.htm> has this information available for reading online.