Prenatal Carrier Screening for Genetic Conditions
Deborah A. Driscoll, Harish M. Sehdev and Dominic A. Marchiano

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Objectives  After completing this article, readers should be able to:

1. Discuss the benefits and limitations of carrier screening.
2. Describe the recommendations for screening for hemoglobinopathies.
3. List the genetic disorders for which carrier screening is available for individuals of Ashkenazi Jewish ancestry.
4. Describe the recommendations for cystic fibrosis carrier screening.

Introduction

Carrier screening for hemoglobinopathies, Tay-Sachs and Canavan diseases, and more recently, cystic fibrosis has been incorporated into routine obstetric care. These genetic disorders are autosomal recessive, and when both members of a couple are carriers, there is a 25% risk of having an affected child in each pregnancy. Although many states routinely screen newborns for sickle cell disease and cystic fibrosis, recognition that a couple is at increased risk for having a child with one of these disorders permits a wider array of options, including antenatal diagnosis and termination of an affected fetus. In some cases, identification of an affected fetus allows a couple, their obstetrician, neonatologist, pediatrician, and pediatric specialists to prepare for the birth of an affected fetus. Screening completed prior to conception provides couples with additional reproductive options to consider, including donor gametes, preimplantation genetic diagnosis, and adoption if they choose to reduce their risk of having an affected child.

As a result of the Human Genome Project and advances in technology, DNA-based tests can be used for carrier screening and prenatal diagnosis for many inherited conditions. In addition to screening for sickle cell disease, thalassemia, and Tay-Sachs disease, carrier screening now is available for cystic fibrosis, Canavan disease, and other disorders that are more common in individuals of Ashkenazi Jewish ancestry. Carrier screening recommendations for these genetic conditions are based on a person’s ethnicity. However, the importance of family history cannot be underestimated. The family history is used to determine whether an individual or couple is at increased risk for any other genetic condition, congenital malformation, or mental retardation. Genetic counseling is recommended to assess the risk and make recommendations for screening and monitoring the pregnancy of individuals who have a positive family history. Genetic testing is available for a vast number of disorders, such as hemophilia, spinal muscular atrophy, and Duchenne muscular dystrophy. Geneticists and genetic counselors often use online resources such as www.genetests.org to identify clinical and research laboratories that offer carrier testing or prenatal diagnostic testing for a specific condition. Screening for other genetic disorders such as fragile X mental retardation in the absence of a family history remains controversial, but it may be only a matter of time before additional carrier tests are available to the general population.

Carrier Screening for Hemoglobinopathies

Traditionally, certain ethnic groups are considered at increased risk for specific hemoglobinopathies (Table 1). Groups not believed to be at increased risk include northern Europeans, Japanese, Koreans, and native North America populations (Eskimo, American Indian, Alaskan native, and native Hawaiian).

*Division of Reproductive Genetics.
†Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Pennsylvania Hospital, University of Pennsylvania Health System, Philadelphia, PA.
Indians, and Mexican Indians). Unfortunately, in the United States, we often do not have the luxury of a homogeneous population on which to model individual risk. Therefore, each person’s risk of hemoglobinopathy must be individualized.

Sickle cell anemia is the most common beta-globin chain defect encountered in the United States. One in 12 African-Americans is a carrier of sickle cell trait; approximately 1 in 144 matings are at risk for producing affected offspring. One in 708 children born to African-American couples is affected by sickle cell anemia. Sickle cell syndromes are caused by a mutation in the gene for beta-globin that changes the sixth amino acid from glutamine to valine. A couple who are both carriers may elect to have prenatal testing to determine whether the fetus is homozygous (affected) for this mutation using DNA obtained from either chorionic villus at 10 to 12 weeks’ gestation or amniocytes after 15 weeks’ gestation.

The American College of Obstetricians and Gynecologists (ACOG) recommends that hemoglobin electrophoresis be used to screen individuals at risk for specific hemoglobinopathies, including sickle cell anemia. Sickle cell syndromes are caused by a mutation in the gene for beta-globin that changes the sixth amino acid from glutamine to valine. A couple who are both carriers may elect to have prenatal testing to determine whether the fetus is homozygous (affected) for this mutation using DNA obtained from either chorionic villus at 10 to 12 weeks’ gestation or amniocytes after 15 weeks’ gestation.

Alpha-thalassemia is more complex. There are four loci or two pairs of genes for alpha-globin, and most cases result from large deletions of one or more of the alpha-globin genes. A deletion of only one of these loci produces no clinical or laboratory evidence of a hemoglobinopathy. Deletions of two loci result in alpha-thalassemia trait, three in hemoglobin H disease, and deletions of all four loci result in hemoglobin Bart. Because the fetus relies on hemoglobin F, which is comprised of alpha and gamma chains, markedly abnormal or decreased alpha-chain production results in abnormal fetal hemoglobin and fetal anemia. Patients who have hemoglobin H disease are transfusion-dependent, and hemoglobin Bart causes lethal nonimmune hydrops fetalis in utero. Therefore, it is critical to identify couples at risk.

Alpha-thalassemia trait is suspected in the presence of a low mean corpuscular volume and normal findings on hemoglobin electrophoresis. Iron deficiency must be excluded as a cause of microcytosis. It is helpful to exclude iron-deficiency anemia as a cause of microcytosis, but the diagnosis of iron deficiency does not eliminate genetic screening.

### Table 1. Carrier Rates for Sickle Cell Disease and Thalassemias

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Sickle Cell</th>
<th>Beta-thalassemia</th>
<th>Alpha-thalassemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>African-American</td>
<td>1/12</td>
<td>1/75</td>
<td>1/30</td>
</tr>
<tr>
<td>West African</td>
<td>1/12</td>
<td>1/50</td>
<td>1/30</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>1/30 to 50</td>
<td>1/20 to 30</td>
<td>1/30 to 50 trans</td>
</tr>
<tr>
<td>Caribbean (non-hispanic)</td>
<td>1/12</td>
<td>1/50 to 75</td>
<td>1/30</td>
</tr>
<tr>
<td>Caribbean (hispanic)</td>
<td>1/30</td>
<td>1/75</td>
<td>Variable</td>
</tr>
<tr>
<td>Latin American (hispanic)</td>
<td>1/30 to 200</td>
<td>1/30 to 50</td>
<td>Variable</td>
</tr>
<tr>
<td>Southeast Asian</td>
<td>Rare</td>
<td>1/30</td>
<td>&gt;1/20 cis</td>
</tr>
<tr>
<td>South Asian</td>
<td>1/50 to 100</td>
<td>1/30 to 50</td>
<td>Variable</td>
</tr>
<tr>
<td>Other Asian</td>
<td>Rare</td>
<td>1/50</td>
<td>1/20</td>
</tr>
<tr>
<td>Middle Eastern</td>
<td>1/50 to 100</td>
<td>1/50</td>
<td>Variable</td>
</tr>
</tbody>
</table>
the possibility of hemoglobinopathy because these conditions may coexist. Further characterization by a molecular diagnostic laboratory is required to identify the gene deletions in suspected carriers of alpha-thalassemia and to determine if they exist in cis (on the same chromosome) or trans (on different chromosomes). Individuals of Southeastern Asian or Mediterranean ancestry are more likely to have cis deletions that can result in severe fetal anemia leading to fetal hydrops. African descendants are at risk for trans deletions, and at-risk couples may produce infants affected only by alpha-thalassemia trait, making prenatal diagnosis less desired.

Prenatal carrier screening also can identify the couple at risk for having offspring affected with other hemoglobinopathies, although these tend to be milder. Sickle-thalassemia serves as an example of the importance of proper prenatal screening. Hemoglobin solubility testing will not identify a mother who is affected by a mild form of beta-thalassemia. Therefore, her partner will not be asked to undergo carrier testing. If he happens to be a carrier of the sickle cell trait, the fetus is at risk for sickle-thalassemia, and prenatal testing is feasible. Hemoglobin C disease is seen classically in North African populations, rarely in African-Americans, and can cause a mild hemolytic anemia. The combination of hemoglobin C trait with sickle cell trait can result in hemoglobin SC disease. Although this condition is milder than sickle cell disease, it is associated with rare vaso-occlusive crises and hematuria. Prenatal testing for the specific gene mutation that causes hemoglobin C is possible, but in most cases, the parents can be reassured and a sample of cord blood can be obtained at the time of delivery to assess the infant’s hemoglobin.

Obstetricians generally follow the ACOG guidelines for screening patients considered at risk for hemoglobinopathies. When a woman and her partner are identified as carriers, they are offered genetic counseling and prenatal testing. Many couples at risk for having a child who has sickle cell disease decline testing. Instead, they have the infant tested after delivery. Molecular testing for thalassemia has become more widely available and acceptable.

Carrier Screening for Genetic Diseases in the Ashkenazi Jewish

Couples of Ashkenazi Jewish descent, whose ancestors originated from Eastern Europe, are at increased risk for having children with several devastating genetic disorders, even if they have no family history of such diseases. The classic example is Tay-Sachs disease. As a result of carrier screening programs established in the 1970s, the incidence of Tay-Sachs disease in the North American Ashkenazi Jewish population has decreased by more than 90%. Initially, carrier screening for Tay-Sachs disease was based solely on the measurement of hexosaminidase A (the enzyme deficient in the disease) in serum or leukocytes. Now, molecular testing for common mutations in the alpha-subunit of hexosaminidase A is possible. As genes have been identified for other inherited conditions more prevalent in Ashkenazi Jews, carrier tests have been developed. These tests are relatively cost-effective and very sensitive (detection rates of 94% to 99%) because each of the disorders results from one to five common mutations. In 1998, ACOG recommended that obstetricians begin to offer molecular carrier screening for Canavan disease, a lethal progressive disorder of the central nervous system. Today, couples of Ashkenazi Jewish ancestry have a wide range of carrier tests from which to choose (Table 2). When both partners are carriers, genetic counseling is provided, and prenatal diagnosis is available for each of these disorders.

Carrier testing is voluntary, and many laboratories require informed consent. Genetic counseling is available to help patients select carrier tests based on disease severity, treatment options, frequency and carrier rates, detection rates, and reproductive choices. For most of these disorders, the disease frequency, carrier rate, and mutations in non-Jewish populations is not known. Therefore, the member of the couple who is Jewish is offered screening. If the high-risk partner is a carrier, the non-Jewish partner can be screened, but the couples are counseled about the limitations of the screening test. Tay-Sachs disease is an exception. Some non-Ashkenazi Jewish populations (French Canadian and Cajun) have an increased carrier frequency, and hexosaminidase A serum or leukocyte screening is recommended.

Cystic Fibrosis Carrier Screening

Cystic fibrosis (CF) is a common autosomal recessive disorder among Caucasians. Approximately two thirds of individuals who have CF are diagnosed prior to 1 year of age. Typical manifestations include progressive pulmonary disease, recurrent bronchial and sinus infections, malabsorption, pancreatic insufficiency, nasal polyps, and congenital bilateral absence of the vas deferens in males. In 2001, ACOG and the American College of Medical Genetics (ACMG) issued clinical and laboratory guidelines for preconception and prenatal carrier screening for CF. The goal of CF carrier screening is to identify couples at risk for having offspring with classic CF. Carrier screening for CF no longer is recommended only for individuals who have a family history, partners of individ-
uals who have CF, and males who have bilateral congenital absence of the vas deferens. The guidelines recommend that CF carrier screening be offered to Caucasians of European or Ashkenazi Jewish decent and be available to any patient planning a pregnancy or seeking prenatal care. The distinction is based on the frequency of CF, carrier rate, and the test detection rate in different populations (Table 3).

CF carrier screening is very complex. The laboratory guidelines recommend use of a standard panethnic panel of 25 common mutations for carrier screening. More than 800 mutations have been identified in CF patients thus far, but most of these are rare, and it is not cost-effective or feasible to use an extended mutation panel or sequencing as a screening test. The ability to detect a mutation using this panel depends on an individual’s ethnic background. The highest test sensitivity is for Caucasians. Hence, it is important for patients to understand that a negative test result only reduces their risk of being a carrier and the likelihood of having an affected child. Testing is available to couples, but in many cases begins with the mother during her first prenatal visit. If a patient is found to be a carrier, her partner should be tested. Occasionally, CF carrier screening identifies an asymptomatic or mildly affected individual. These individuals are referred to a CF clinic or pulmonologist.

When both partners are carriers, counseling by a geneticist, genetic counselor, or specialist who has expertise in CF is recommended. Prenatal diagnostic testing is available when both partners are identified as CF carriers. Testing for the specific mutations can be performed on chorionic villi or amniocytes. Although prenatal testing is accurate, it is not always possible to predict severity, in particular, the severity of the pulmonary disease. Some mutations are associated with a variable and milder phenotype; others with pancreatic sufficiency. Data available in the literature and from the CF Consortium often are used to provide couples with up-to-date information on the clinical phenotype associated with their specific mutations. Some couples elect to have testing for information only; others choose not to continue the pregnancy.

Pregnancies that involve an affected fetus and in those at risk for CF who decline prenatal testing should be evaluated by ultrasonography in the third trimester for signs of meconium ileus. Approximately 15% of affected infants have meconium ileus at birth. The viscid meco-

<table>
<thead>
<tr>
<th>Disease</th>
<th>Carrier Rate</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tay-Sachs</td>
<td>1/30</td>
<td>Severe, lethal, progressive central nervous system (CNS) disorder, poor muscle tone, developmental delay, mental retardation (MR), deafness, blindness</td>
</tr>
<tr>
<td>Canavan</td>
<td>1/40</td>
<td>Lethal CNS disorder, developmental delay, hypotonia, seizures, blindness</td>
</tr>
<tr>
<td>Gaucher</td>
<td>1/15</td>
<td>Variable onset and severity, chronic fatigue, anemia, easy bruising, nosebleeds, bleeding gums, hepatosplenomegaly, bone and joint pain</td>
</tr>
<tr>
<td>Familial dysautonomia</td>
<td>1/32</td>
<td>Abnormal suck, feeding difficulties, vomiting, pain and temperature insensitivity, labile blood pressure, absent tearing, scoliosis</td>
</tr>
<tr>
<td>Niemann-Pick (Type A)</td>
<td>1/89</td>
<td>Severe neurodegenerative disorder similar to Tay-Sachs</td>
</tr>
<tr>
<td>Fanconi anemia (Group C)</td>
<td>1/90</td>
<td>Pancytopenia; limb, cardiac, renal, and CNS anomalies; some with MR; increased risk for leukemia</td>
</tr>
<tr>
<td>Bloom syndrome</td>
<td>1/100</td>
<td>Prenatal and postnatal growth retardation, predisposition to malignancies, abnormal pigmentation, facial telangiectasias, some with learning difficulties and MR</td>
</tr>
<tr>
<td>Mucolipidosis IV</td>
<td>1/127</td>
<td>Growth and psychomotor retardation, corneal clouding, retinal degeneration, strabismus, most at level of 1 to 2 years of age</td>
</tr>
</tbody>
</table>

Table 3. Cystic Fibrosis Carrier Rate and Mutation Detection Rate

<table>
<thead>
<tr>
<th>Ethnic/racial Group</th>
<th>Carrier Rate</th>
<th>Mutation Detection Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashkenazi Jewish</td>
<td>1/29</td>
<td>97%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>1/29</td>
<td>80%</td>
</tr>
<tr>
<td>Hispanic American</td>
<td>1/46</td>
<td>57%</td>
</tr>
<tr>
<td>African American</td>
<td>1/65</td>
<td>69%</td>
</tr>
<tr>
<td>Asian American</td>
<td>1/90</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* Based on American College of Medical Genetics-recommended panel of mutations.
† Assumes no family history of cystic fibrosis.
mium collects in the distal ileum and can result in obstruction, with subsequent dilatation of the proximal bowel and possible rupture. When meconium ileus is suspected, referral to a pediatric surgeon and delivery at a tertiary care medical center are recommended. When a carrier couple declines prenatal testing, mutation testing on a sample of cord blood obtained at the time of delivery and a postnatal sweat chloride test are recommended to establish whether the infant is affected. Whether identified pre- or postnatally, the infant who has CF is referred to a CF specialist. Siblings and other relatives of CF carriers are at risk of being carriers. Individuals identified as carriers are urged to notify their relatives of the risk and the availability of screening programs. When both parents are identified as CF carriers, sweat chloride testing, DNA testing, or both are recommended for their existing children.

Screening for Other Genetic Disorders
The need for additional carrier screening usually is determined by a genetic counselor or geneticist based on a couple’s family history and prior pregnancy history. When a family history suggests that a woman or her partner may be at increased risk of being carriers or of having a child who has an inherited condition, the first step is to determine if the gene for that disorder and mutations have been identified. If the gene is known, the optimal strategy is to test the affected relative. Testing for disorders that result from one or more common mutations can be used for both diagnostic and carrier testing if the diagnosis in the affected relative is correct. For example, a carrier test has been developed for spinal muscular atrophy, a common autosomal recessive disorder caused by a deletion in exon 7 of the SMN gene. This is a highly accurate carrier test because most cases are caused by this deletion. In contrast, many disorders are caused by numerous unique mutations, and DNA sequencing is required to identify the disease-causing mutation. Once a mutation is confirmed in the affected individual, it is possible to test relatives at risk for carrier status. For some inherited disorders, DNA sequencing can be used as a carrier screen, but it is expensive and less reliable than testing the affected person. Many laboratories accept buccal swabs or blood samples for testing. Testing also is possible on postmortem tissue samples and paraffin blocks.

In some cases, a carrier screening test is requested when a particular diagnosis is suspected based on ultrasonographic findings in the pregnancy. The antenatal evaluation of a fetus that has a congenital malformation typically includes a thorough ultrasonographic examination and fetal echocardiography to look for associated anomalies as well as a fetal karyotype. Single-gene disorders often are considered in the differential diagnosis but until recently were not amenable to prenatal testing. Now that the molecular basis of many of these disorders has been elucidated, either carrier screening of the parents or diagnostic testing of the pregnancy is possible when a particular diagnosis is suspected. For example, carrier screening for Fanconi anemia should be considered as part of the evaluation of a fetus that has absent radius, particularly if the couple are of Ashkenazi Jewish ancestry. Other manifestations that may be apparent on ultrasonography include renal anomalies and cardiac and central nervous system defects. In the Ashkenazi Jewish population, the carrier frequency is 1 in 90, and one mutation has been identified in approximately 99% of affected individuals. In some instances, testing the parents to determine their carrier status can help establish or exclude a diagnosis in the fetus that has an anomaly.

Lastly, carrier testing may be performed on request because of heightened anxiety and concern. It is not uncommon for patients to request a test based on a personal experience or recent newspaper article or television show. In these instances, it is important for them to understand their individual risk of being a carrier and having an affected child as well as the risks, benefits, and limitations of testing. Pre- and posttest counseling is very important. For most rare disorders, this is not a cost-conscious approach, but the availability of high-throughput molecular technology testing is making it more affordable. Although it has become feasible to perform these tests, our ability to predict outcome and future risks associated with carrier status sometimes is limited. In many cases, longitudinal studies of carriers are needed to define the risks and benefits of testing better.

An excellent example is the controversy surrounding population-based screening for fragile X mental retardation syndrome. Patients often inquire about testing for mental retardation. The cause of mental retardation is heterogeneous, and in the setting of a positive family history, a number of tests may be recommended, including chromosome analysis, telomere studies, and fragile X carrier screening. Some clinicians and laboratories offer carrier screening for fragile X syndrome to patients regardless of the family history. This has not been endorsed by professional organizations. The ACMG currently recommends screening of individuals who have a positive family history of mental retardation or fragile X syndrome and individuals who have mental retardation, developmental delay, or autism, especially if they have
behavioral or physical characteristics of fragile X syndrome. Fragile X syndrome, a common cause of mental retardation predominantly involving but not limited to males, is caused by a full mutation of a trinucleotide (CGG)-repeat (>200 repeats) in the FMR1 gene on the X chromosome. Carriers have a premutation (55 to 200 repeats) that can expand to a full mutation during female meiosis. The estimated carrier frequency of the premutation is 1 in 259 females and 1 in 813 males. Although DNA-based carrier testing and prenatal diagnostic testing to determine the repeat number is very accurate and relatively inexpensive to perform, legitimate concerns remain about offering carrier screening to the general population. Does the carrier rate justify the expense? Can we counsel patients adequately about the complex inheritance pattern and possible outcomes? Do we know enough about the implications for a carrier’s health? At present, important issues need to be resolved before fragile X carrier screening can be offered in obstetric practices.

Suggested Reading

NeoReviews Quiz

8. As a result of advances in genetic technology, carrier screening and prenatal diagnosis is possible during obstetric care for many inherited diseases. The prevalence of such diseases varies, depending on the ethnicity of the patients. Of the following, the ethnic group most at risk for inherited beta-thalassemia is:

A. African-American.
B. Mexican Indian.
C. Native North American.
D. Northern European.
E. Southeast Asian.
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