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Genetic Carrier Screening: Historical Perspective and Overview

GENETIC CARRIER SCREENING AND counseling is an important part of preconception and prenatal care.[1] As genetic testing technology rapidly evolves, clinicians often face questions regarding the most appropriate testing methods to use for their patients. In addition, prospective mothers often have questions about whether to undergo particular screening tests or procedures. This article, the first of a 3-part series, reviews the purpose of genetic carrier screening and summarizes current preconception and prenatal screening guidelines.

Inheritance of Autosomal Recessive Disorders

Genetic conditions are inherited in one of several patterns.[2] In autosomal recessive disorders, both copies of a gene must carry a variant for the patient to be affected with a condition.[2] Heterozygous carriers have 1 copy of the variant gene, do not show symptoms of the condition, and may be unaware of their carrier status.[1,2] If 2 reproductive partners are both heterozygous carriers, each offspring has a 1 in 4 risk of inheriting the variant in both gene copies, 1 from each parent.[1,2] This child will be homozygous for the mutation and will be affected by the condition.

Purpose of Carrier Screening

Carrier screening allows individuals without a known personal or family history of recessive disorders to learn about potential risks that may affect their offspring.[3] If screening reveals carrier status in both reproductive partners, they can receive information about the disease's natural history and management, as well as available reproductive options.[1] In this way, couples can make autonomous choices.[3]

If a patient is a carrier for a genetic condition, the reproductive partner should also be tested. Results acquired from the test can lead to more accurate information regarding potential reproductive outcomes.[4] Genetic counseling should be available for couples in which both partners have been identified as carriers of a genetic disorder.[4] Reproductive options to reduce the risk of an affected offspring should be discussed.[4] In addition, if an individual is found to be a carrier for a genetic disease, the individual should be encouraged to inform his or her relatives because these relatives are also at risk of carrying the same genetic variant.[4]

Carrier screening and counseling performed before pregnancy allows couples the opportunity to consider the most reproductive options.[4] The range of reproductive possibilities include the choice to not attempt conception, use of reproductive technologies such as donor gametes and preimplantation genetic diagnosis, and other family building options such as adoption.[1,4] When genetic screening is performed during pregnancy, knowledge of carrier status allows patients to consider pregnancy management options, including early prenatal diagnosis, pregnancy termination, or planning for the birth of an affected offspring.[1]

Conventional Genetic Screening

Traditionally, carrier screening is performed in select patients based on:

- Family and personal history of known or suspected genetic disorders[1]
- Ethnicity, some of which are considered to be high risk for specific autosomal recessive disorders[1]
- History of children born with congenital anomalies[1]

Genetic counseling should accompany carrier screening.[1] In addition to the nature of the disorders being tested, individuals should be provided with information about the limitations of the screening tests.[1] Because some genetic screening tests do not screen for all possible mutations associated with the disorder, residual risks exist despite a negative test result.[1] In some ethnic groups, specific mutations responsible for the disease may be incompletely understood, and conventional genetic screening may not detect these mutations.[4,5]

Guideline-Recommended Carrier Screening

Cystic Fibrosis

Cystic fibrosis is an autosomal recessive disease affecting the airways, pancreas, intestines, and in males, the vas deferens.[4] It is caused by genetic mutations in the cystic fibrosis transmembrane regulator (*CFTR*) gene.[4]

Carrier frequencies of cystic fibrosis vary by ethnic origin, with non-Hispanic whites having an especially high carrier frequency.[4] Cystic fibrosis is also most common in this ethnic group (incidence of 1 in 2500).[4]

Guideline-Based Carrier Screening

According to guidelines from the American College of Obstetrics and Gynecology (ACOG) and the National Society of Genetic Counselors (NSGC), cystic fibrosis carrier screening should be offered to all women of reproductive age (women considering pregnancy and all pregnant women) regardless of ethnicity, ancestry, and personal or family history for cystic fibrosis.[4,6] If a woman is found to be a carrier for cystic fibrosis, her reproductive partner should also be tested.[4,6]

There are currently more than 2000 mutations identified for cystic fibrosis.[7] For genetic screening, the American College of Medical Genetics and Genomics (ACMG) recommended a panel that contained 23 of the most common mutations present in patients with cystic fibrosis.[5] Because this panel does not identify all known mutations, the sensitivity of the screening test differs among ethnic groups.[4,8] In individuals with Asian ancestry, the sensitivity is less than 50%, as compared to 94% in individuals of Ashkenazi Jewish ancestry (**Table 1**).[4,8] As such, a negative cystic fibrosis screening result does not entirely eliminate the possibility of being a carrier, and there is a residual risk of being a carrier and having an affected offspring.[4] Because extended mutation panels and full *CFTR* gene sequencing are commercially available, sensitivity for carrier detection may increase.[4]

A complete analysis of the CFTR gene is not recommended for routine practice but is reserved for specific situations when carrier screening using the standard 23-mutation panel yields negative results.[4] These include patients with a family history of cystic fibrosis, but the family test results are not available; and neonates with a positive newborn screening test result, but a negative genetic screening result.[4]

Importantly, newborn screening does not replace preconception or prenatal carrier screening.[4] Newborn screening programs identify affected newborns but do not provide any information about the parents' carrier status.[4] Therefore, although cystic fibrosis screening is part of newborn screening panels in all 50 states, it is important that cystic fibrosis carrier screening continue to be offered to women considering pregnancy and those who are pregnant.[4]

Spinal Muscular Atrophy

Spinal muscular atrophy is a disorder characterized by spinal cord motor neuron degeneration, leading to skeletal muscle atrophy and muscle weakness.[4] It is an autosomal

TABLE 1. Cystic Fibrosis Carrier Risk by Ethnic Origins[4,8]

Ethnicity	Detection Rate[a]	Carrier Frequency of a *CFTR* Mutation (Individual risk of being a carrier before testing)	Residual Risk (Individual risk of being a carrier after a negative screening test result)
African American	64.46%	1/61.4	1/171
Ashkenazi Jewish	94.04%	1/23.8	1/384
Asian American	48.93%	1/93.7	1/183
Hispanic white	71.72%	1/58.2	1/203
Non-Hispanic white	88.29%	1/25.0	1/206

CFTR indicates cystic fibrosis transmembrane regulator.
[a]Based on the use of a 23-mutation panel, as currently recommended by guidelines.
Adapted from ACMG Standard and Guidelines for Clinical Genetics Laboratories; and ACOG Committee on Genetics Committee Opinion No. 691, *Obstet Gynecol*. 2017;129(3):e41-e55.

recessive disease caused by a mutation in the survival motor neuron gene (*SMN1*).[4] *SMN1* is responsible for the production of a protein critical to motor neuron function.[4]

Approximately every 1 in 6000 to 10,000 births is affected with spinal muscular atrophy.[4] Carrier frequencies vary among different ethnicities,[9] with the risk lowest in Hispanics (**Table 2**).[4] Spinal muscular atrophy is the most common cause for genetic infant death.[4] Nusinersen (Spinraza), approved in March 2018, is currently the only drug available for the treatment of spinal muscular atrophy.

Guideline-Based Carrier Screening

Current recommendations from both ACOG and ACMG state that carrier screening for spinal muscular atrophy be offered to all women who are contemplating pregnancy or are currently pregnant.[4,10]

Carrier screening measures *SMN1* copy number.[4] About 3% to 4% of the population have 2 *SMN1* gene copies on the same chromosome and no copies on the other chromosome, and will not be identified as carriers.[4] These individuals are known as silent carriers and run the risk of passing on the chromosome with the missing *SMN1* allele to future offspring.[4] The missing *SMN1* allele is more common in African Americans. In this group, the carrier detection rate is only 71%.[4,9] Hence, patients should be counseled about screening detection rates and residual risks.[4]

Hemoglobinopathies

The hemoglobin molecule is made up of 4 polypeptide chains, each with a heme molecule attached.[4] The 4 chains are[4]:

- Two α-chains, and;
- Either:
  - Two β-chains (hemoglobin A)[4], or
  - Two γ-chains (hemoglobin F)[4], or
  - Two δ-chains (hemoglobin A2).[4]

Sickle Cell Disease

In sickle cell disease, a single nucleotide substitution in the β-globin gene results in an abnormal hemoglobin S instead of the normal hemoglobin A.[4] Heterozygous hemoglobin S carriers are asymptomatic and are considered to have sickle cell trait.[4] An individual who is homozygous for hemoglobin S (hemoglobin SS) has sickle cell disease.[4]

In addition to hemoglobin S, hemoglobin C is another abnormal form of hemoglobin.[4] In hemoglobin C, a single nucleotide substitution in the β-globin gene occurs. A patient with the hemoglobin genotype SC may have significant vaso-occlusive episodes and hemolytic anemia like individuals with hemoglobin SS, and is also considered to have sickle cell disease.[4]

Sickle cell disease is most commonly found in African Americans, presenting in about 1 in 350 individuals. (One in 10 African Americans has the sickle cell trait.) Other populations, such as Greek and Italian, also present with high frequencies of hemoglobin S.[4]

Red blood cells in individuals with sickle cell disease change their shape to resemble sickles, leading to hemolysis, anemia, increased viscosity, and a decrease in oxygenation. When sickling occurs in small blood vessels, the blood supply is obstructed from vital organs (vaso-occlusive crisis).[4]

TABLE 2. Spinal Muscular Atrophy Carrier Risk by Ethnicity[4]

Ethnicity	Detection Rate	Carrier Frequency of an *SMN1* Mutation
African American	71%	1/66
Ashkenazi Jewish	90%	1/41
Asian American	93%	1/53
Hispanic white	91%	1/117
Non-Hispanic white	95%	1/35

*SMN*1 indicates survival motor neuron gene.
Adapted from ACOG Committee on Genetics Committee Opinion No. 691, *Obstet Gynecol.* 2017;129(3):e41-e55.

The Thalassemias

Alpha-Thalassemia

α-thalassemia results when 2 or more copies of the 4 α-globin genes are deleted.[4] Individuals with a deletion of 2 α-globin genes have α-thalassemia trait (α-thalassemia minor) and mild microcytic anemia.[4] Individuals with a deletion of 3 or 4 copies of the α-globin gene have α-thalassemia major.[4] Deletion of 3 α-globin genes can be associated with mild or moderate hemolytic anemia.[4] Deletion of 4 copies of the α-globin gene (absence of α-globin) leads to intrauterine death, hydrops fetalis, and preeclampsia.[4]

Beta-Thalassemia

Beta-thalassemia is caused by variants in the β-globin gene, leading to deficient or absent β-chain production and absence of hemoglobin A.[4] Beta-thalassemia variants are found in high frequencies in persons of Asian, Mediterranean, Middle Eastern, West Indian, and Hispanic descent.[4] Individuals with β-thalassemia minor are heterozygous for the variant. Individuals with β-thalassemia major (Colley's anemia) or thalassemia intermedia are homozygous for the variant.[4] Patients with β-thalassemia major have severe anemia, delayed sexual development, and poor growth.[4] Patients usually succumb to the disease by age 10 unless periodic blood transfusions are initiated early.[4] In thalassemia intermedia, a variable amount of hemoglobin A is produced.[4] An individual can inherit a β-thalassemia mutation from one parent and a hemoglobin S mutation from the other parent, resulting in hemoglobin S/β-thalassemia.[4]

Guideline-Based Carrier Screening

ACOG suggests obtaining a complete blood count with red blood cell indices in all pregnant women to assess for the risk of hemoglobinopathy.[4] Hemoglobin electrophoresis should be performed in cases of low mean corpuscular volume or low mean corpuscular hemoglobin.[4] Hemoglobin electrophoresis should be performed routinely in patients of high-risk ethnic groups (African, Mediterranean, Middle Eastern, Southeast Asian, or West Indian ancestry), ideally before pregnancy.[4] In some cases, DNA analysis may be needed to assess for the presence of α-globin gene deletions. This can occur when mean corpuscular volume is low, or if results of hemoglobin electrophoresis are not consistent with the β-thalassemia trait; iron deficiency anemia must also be excluded.[4]

Fragile X Syndrome

The most commonly inherited cause of intellectual disability is fragile X syndrome.[4] Impairment ranges from learning disabilities to severe cognitive and behavioral disabilities.[4] Study results suggest that autism spectrum disorder occurs in 21% of individuals with fragile X syndrome, particularly males.[11]

The syndrome is transmitted through the X chromosome.[4] It is characterized by expansion of a repeated trinucleotide, cytosine-guanine-guanine, that leads to abnormal transcription of the fragile X mental retardation 1 gene (*FMR1*).[4] The number of triplet cytosine-guanine-guanine repeats varies among individuals and is used to classify individuals into 4 groups: unaffected, intermediate, premutation, and full mutation.[4]

Individuals may have tremor or ataxia if they are premutation carriers (55-200 repeats), but not fragile X syndrome.[4] Females with a premutation may have *FMR1*-related premature ovarian insufficiency.[4] A male with a full mutation (more than 200 repeats) is considered to be affected with fragile X syndrome.[4] A female with a full mutation may have variable expression.[4] During spermatogenesis in the male, repeats very rarely expand.[4] Hence, only an affected male can pass on the full mutation to his female offspring.[4] Because the number of maternal triplet repeats increases the likelihood of expansion into a full mutation, repeats may expand during oogenesis in the female, resulting in an affected child.[4]

In the United States, carrier frequency (premutation and full mutation) of fragile X is 1 in 257 women with no family history of intellectual disability and 1 in 86 in individuals with a family history.[12]

Guideline-Based Carrier Screening

The ACOG and ACMG recommend fragile X premutation carrier screening in pregnant women and women considering pregnancy if they have a family history of intellectual disability or fragile X-related disorders, unexplained ovarian insufficiency, or an elevated follicle-stimulating hormone prior to 40 years of age.[4,13] The NSGC supports ACMG and ACOG guidelines on patient selection for *FMR1* mutation testing.[14] Genetic counseling should be provided to individuals with intermediate, premutation, or full mutation.[4]

Tay-Sachs Disease

Tay-Sachs disease is a progressive neurodegenerative autosomal recessive disease.[4] Deficiencies in hexosaminidase A enzyme can cause an accumulation of GM2 gangliosides in individuals with Tay-Sachs disease.[4] Accumulation of GM2 gangliosides in the central nervous system causes early childhood death in the affected individual.[4] The carrier rate for Tay-Sachs disease is 1 in 30 in individuals of Ashkenazi Jewish (Eastern or Central European) descent, whereas the carrier rate is 1 in 300 in non-Jewish individuals.[4] Individuals of Cajun and French-Canadian descent also have a carrier frequency (about 1 in 50).[4]

Guideline-Based Carrier Screening

ACOG recommends that screening for carrier status should be offered to preconception or prenatal women if either partner is of Ashkenazi Jewish, French Canadian, or Cajun descent, or if there is a family history of Tay-Sachs disease.[4] If the woman's partner is from one of these high-risk groups, he should be offered screening.[4] If one partner is a carrier, screening should be offered to the other partner.[4]

Carrier screening should be performed by measuring hexosaminidase enzymatic activity in leukocytes or serum, or by using mutation analysis.[4] Regardless of ethnicity, 98% of carriers are detected during enzyme testing. False positives are suspected in women talking oral contraceptives and women who are pregnant. Tests should be taken using leukocytes to avoid false-positive results. Although limited due to rare mutations, high-risk ethnic groups can use molecular testing.[4]

Summary

This article provides an overview and current guidelines of genetic carrier screening. Carrier screening describes genetic testing of an individual who may have a variant allele associated with a genetic disorder but does not have any overt phenotype for the disorder.[4] The primary purpose of carrier screening in individuals without a known family history of recessive disorders is to inform their risk of having offspring affected by a genetic condition.[3] If an individual is confirmed to be a carrier of a genetic condition, the reproductive partner should be tested as well to more accurately inform potential reproductive outcomes. Genetic counseling should be offered to partners that are both carriers of a genetic disorder.[4] In addition, if an individual is found to be

a carrier for a genetic condition, he or she should be encouraged to inform his or her relatives, because these relatives are also at risk of carrying the same genetic variant.[4]

Carrier screening and counseling should ideally be performed before pregnancy because this allows couples to be informed about their reproductive risk and the opportunity to consider the most complete range of reproductive options.[4] When genetic screening is performed during pregnancy, knowledge of carrier status allows patients to consider pregnancy management options, including early prenatal diagnosis, pregnancy termination, or planning for the birth and expectant management of an affected offspring.[4]

ACOG provides recommendations for carrier screening of the more common genetic diseases including cystic fibrosis, spinal muscular atrophy, hemoglobinopathies (including sickle cell disease, α- and β-thalassemias), fragile X syndrome, and Tay-Sachs disease.[4] ACOG recommends that carrier screening for cystic fibrosis and spinal muscular atrophy should be offered to all women considering pregnancy and all pregnant women, regardless of ethnicity, personal, or family history.[4] In addition, a complete blood count together with red blood cell indices should be performed in all pregnant women and ideally to all women before pregnancy, to assess the risk of anemia as well as hemoglobinopathies.[4] For other genetic diseases, ACOG recommends an ethnic group- and personal/family history-based approach.[4]

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