GENETICS

Carrier testing for Ashkenazi Jewish disorders in the prenatal setting: navigating the genetic maze

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Exciting developments in the fields of genetics and genomics have facilitated the identification of the etiological basis of many Mendelian disorders. Several of the methods used in gene discovery have focused initially on homogeneous populations, including the Ashkenazi Jewish population. The founder effect is well recognized in this community, in which historical events and cultural behaviors have resulted in a limited number of mutations underlying genetic disorders with substantial health impact. New technologies have made it possible to rapidly expand the test panels, changing testing paradigms, and thereby creating challenges for the physician in deciphering the appropriate approach to genetic screening in this population. The goal of this review is to help primary obstetric health care providers navigate through this quickly moving field so as to better counsel and support their patients of Ashkenazi Jewish heritage.

Key words: Ashkenazi Jewish, genetic screening, genomic medicine, preconception care, prenatal testing

Recently published data from the 1000 Genomes Project suggest that everyone carries approximately 50-100 variants previously implicated in inherited disorders.[1] For recessive conditions, individuals who have 1 normal allele and a disease causing mutation in the other allele are considered carriers but will not develop the condition, whereas children of carrier couples will have a 1 in 4 risk of being affected with the disease.

Carrier screening ideally seeks to identify, preferably at the preconception stage, individuals who are carriers of such genetic conditions. This allows carrier couples to anticipate pregnancies that may be at increased risk for genetic disorders and choose among several reproductive strategies or alternatively prepare for the birth of an affected child.

Although it is still not possible to screen for all known conditions in all populations with a universal testing system, targeted screening approaches have become integrated into clinical care. One of the most successful targeted programs has led to the almost complete eradication of Tay-Sachs disease (TSD) from the Ashkenazi Jewish (AJ) population.[2] The results of the TSD program, initiated in the 1970s, illustrate the public health perspective that informs most successful population wide screening programs.

The first and most important criterion for the selection of TSD as an appropriate condition for prenatal or preconception screening was the high incidence of the disorder, approximately 1:3600 TSD cases in AJ newborns. Also specific for this condition was the early availability of a robust and cheap biochemical enzyme assay that could identify almost all carriers and also be used for prenatal diagnosis.

The success of the TSD carrier screening program included the fact that it was community driven to a large extent. For example, the Dor Yeshorim program addressed the needs and concerns of a very traditional Orthodox Jewish community with regard to prohibitions against termination of pregnancy as well as potential stigma and labeling of carriers. Jews of other less restrictive denominations likewise partnered with the medical community further contributing to a culturally sensitive and successful model. Since the initiation of the TSD programs, other carrier screening programs have been adopted and endorsed by the American College of Obstetricians and Gynecologists (ACOG), including screening for hemoglobinopathies in high-risk populations as well as pan-ethnic testing for cystic fibrosis (CF).[3]

Characteristics of the AJ population that underlie the feasibility of expanded genetic carrier screening programs

In populations of defined ancestries, specific variants are found in a higher proportion than in individuals of diverse ancestries. There are several reasons for this phenomenon, usually related to well-known mechanisms of population genetics. The European AJ population, originating from the Middle East, underwent migrations and contractions leading to a bottleneck effect in which only a relatively small number of variants were transmitted to the descendants during subsequent population expansions. A mutation that was present in

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TABLE 1
Disorders for which screening is recommended by the ACOG and/or ACMG

Disease name (abbreviation)	Disease incidence[a]	Carrier frequency[a]	Detectability[a]	Disease characteristics
Cystic fibrosis[b]	1:2500-1:3000	1 per 29	97%	Progressive, multisystem disease that primarily affects the pulmonary, pancreatic, and gastrointestinal systems but does not affect intelligence. The current median survival is approximately 37 years, with respiratory failure as the most common cause of death. Approximately 15% of individuals with CF have a mild form of the disease with a median survival of 56 years. More than 95% of males with CF have primary infertility with obstructive azoospermia secondary to congenital bilateral absence of the vas deferens. It is caused by mutations in the CF transmembrane regulator (*CFTR*) gene, located on chromosome 7.
Tay-Sachs disease[b]	1:3000	1 per 30	98% by enzyme test, 94% by DNA-based test	Severe, progressive disorder of the central nervous system, leading to death within the first few years of life. Infants with TSD appear normal at birth but by age 5-6 months develop poor muscle tone, have delayed development, have loss of developmental milestones, and develop mental retardation. Children with TSD lose their eyesight at age 12-18 months. This condition usually is fatal by age 6 years. TSD is caused by a deficiency of the hexosaminidase A enzyme. No effective treatment currently is available.
Familial dysautonomia[b]	1:3600	1 per 32	99%	Neurological disorder characterized by abnormal suck and feeding difficulties, episodic vomiting, abnormal sweating, pain and temperature insensitivity, labile blood pressure levels, absent tearing, and scoliosis. There currently is no cure for familial dysautonomia, but some treatments that can improve the length and quality of a patient's life are available.
Canavan disease[b]	1:6400	1 per 40	98%	Disorder of the central nervous system characterized by developmental delay, hypotonia, large head, seizures, blindness, and gastrointestinal reflux. Most children die within the first several years of life. Canavan disease is caused by a deficiency of the aspartoacylase enzyme. No treatment currently is available.
Gaucher disease type I	1:900	1 per 15	95%	Genetic disorder that mainly affects the spleen, liver, and bones; it occasionally affects the lungs, kidneys, and brain. It may develop at any age. Some individuals are chronically ill, some are moderately affected, and others are so mildly affected that they may not know that they have Gaucher disease. The most common symptom is chronic fatigue caused by anemia. Patients may experience easy bruising, nosebleeds, bleeding gums, and prolonged and heavy bleeding with their menses and after childbirth. Other symptoms include an enlarged liver and spleen, osteoporosis, and bone and joint pain. Gaucher disease is caused by the deficiency of the β-glucosidase enzyme. Treatment is available through enzyme therapy, which results in a vastly improved quality of life.

Ferreira. Carrier testing for the Ashkenazi Jewish population. Am J Obstet Gynecol 2014. *(continued)*

one of these few individuals (a founder) in the original population was thereby transmitted to a resulting relatively genetically homogeneous population of descendants in which there was minimal interpopulation cross-mating. The result is a significant proportion of recessive diseases caused by a relatively small number of mutations.