Genetic Carrier Screening

Test Indications

Carrier screening is a significant testing tool for inherited genetic conditions of prenatal care. The purpose of carrier screening is to identify couples at-risk for passing on genetic conditions to their offspring. Genetic Carrier Screening identifies pathogenic variant in one of these genes, or variants in genes associated with several high-risk diseases, can help health care providers and genetic counselors who wish to establish or confirm a diagnosis, predict the risk of having a child with a genetic disorder, or to guide patients' management decisions.

Considerations for Testing

A health care provider or genetic counselor may determine if an individual is at-risk to have offspring with a genetic disorder by obtaining a family health history. The Carrier screening test should be offered if:

- an individual has a genetic disorder.
- an individual has a child who has a genetic disease.
- an individual has a family history of a genetic disorder.
- an individual belongs to an ethnic group that has a high carrier rate of genetic disorders (e.g., Ashkenazi Jewish heritage).

Furthermore, The American College of Obstetricians and Gynecologists (ACOG) recommends that carrier screening for cystic fibrosis should be offered to all women who are considering pregnancy or are currently pregnant (2).

If a patient considering pregnancy is determined to be a carrier, testing is also recommended for their partner.

Genetics

The conditions listed in **Table 1** can be caused by inherited genetic variants. The variants are inherited in an autosomal recessive pattern in which a gene variant is a recessive gene located on one of the non-sex chromosomes (non-X and non-Y), or autosomes. One needs to inherit both copies of the pathogenic gene variant to be affected by the associated disorder. Autosomal recessive disorders are usually passed by two carriers, or individuals whose health is rarely affected but have one variant and one normal copy of the recessive gene. Two carriers have a 25% chance of having an affected child.

Clinical Characteristics

Cystic Fibrosis (CF) is the most common life-threatening autosomal recessive condition in the non-Hispanic, white population. It is a progressive, multisystem disease that primarily affects the pulmonary, pancreatic, and gastrointestinal systems by the buildup of a thick, sticky mucus that can clot the airways and block the intestine and ducts. The current median survival is approximately 37 years, with respiratory failure as the most common cause of death.

Cystic fibrosis is caused by pathogenic variants of the CF transmembrane regulator (CFTR) gene, which provides instructions for making a channel that transports negatively-charged chloride ions into and out of cells. Pathogenic variants of the CFTR gene disrupt the function of the chloride channels, preventing the regulation of chloride ions and water across cell membranes. As a result, cells that line the passageways of the lungs, pancreas, and other organs produce mucus that is unusually thick and sticky. Two copies of pathogenic variants of this gene cause CF.

Cystic fibrosis is a common genetic disease within the Caucasian population in the United States. The disease occurs in 1 in 2,500 to 3,500 white newborns. Cystic fibrosis is less common in other ethnic groups, affecting about 1 in 17,000 African Americans and 1 in 31,000 Asian Americans.

ACOG Recommendation:

- CF screening is important to be offered to women of reproductive age. It is becoming increasingly difficult to assign a single ethnicity to individuals.
- When one member of a couple is a carrier of CF, the other partner should be offered screening.

Spinal Muscular Atrophy (SMA) is an autosomal recessive neurodegenerative disease that results from the degeneration of spinal cord motor neurons leading to atrophy of skeletal muscle and overall weakness. Affected children have a deficiency in movement, possibly requiring wheelchair assistance. A frequent cause of death of patients with SMA is respiratory failure. There is no effective treatment for the disease.

The disorder is caused by a variation in the survival motor neuron gene (SMN1), which is responsible for the production of a protein essential to motor neurons. More than 98% of patients with SMA have an abnormality in both copies of the SMN1 gene, causing a deletion or other pathogenic variation.

The occurrence of SMA is approximately 1 in 10,000 live births and it is reported to be the leading genetic cause of infant death.

ACOG Recommendations:

Genetic counseling and SMA carrier screening should be offered to the following patients or couples:

- Those with a family history SMA or SMA-like disease
- Those who request SMA carrier screening and

Table 1. MDL's Genetic Carrier Screening Detected Diseases, Target Genes and Frequencies. Carrier Frequency- The chance of an individual with no symptoms having a disease-causing variant. Detection Rate- The percentage of carriers calculated to be detected by the Genetic Carrier Screening test. Residual Risk- The chance of being a carrier even if an individual is found negative for the disease-causing variants tested.

Disease	Gene	Population	Carrier Frequency	Detection Rate	Residual Risk
♦*Cystic Fibrosis	CFTR	Caucasian	1 in 25	94%	1 in 417
		Asian	1 in 94	65%	1 in 269
		Ashkenazi	1 in 24	97%	1 in 800
♦* Spinal Muscular Atrophy	SMN1	Ashkenazi	1 in 41	94%	1 in 683
		European Caucasian	1 in 354	95%	1 in 700
		Asian	1 in 53	93%	1 in 757
		Hispanic	1 in 117	95%	1 in 2,340

♦ Available for order as an individual test.

have completed genetic counseling that included discussion of the sensitivity, specificity, and limitations of screening.

Test Methodology

Genomic DNA is extracted from a blood or ***OneSwab***® sample. High-throughput Next Generation Sequencing is performed to examine over 1,300 DNA variants. Some pathogenic variants are more severe than others. These variant regions are sequenced to high coverage and the sequences are compared to standards and references of normal variation. All the reported variants are confirmed by the "gold standard" Sanger sequencing. In addition, some of the variants in the panel may be partially subjected to Sanger sequencing to ensure adequate sequencing.

SMA methodology: The MDL Spinal Muscular Atrophy test uses Multiplex Ligation-dependent Probe Amplification (MLPA) technique. The principle of MLPA is based on the amplification of up to 60 probes, each of which detecting a specific DNA sequence of approximately 60 nucleotides in length. After denaturation of the sample DNA, a mixture of MLPA probes is added to the sample. Each MLPA probe consists of two oligonucleotides that must hybridize to immediately adjacent target sequences in order to be ligated into a single probe. Each probe in an MLPA probe mix has a unique amplicon length, typically ranging between 130-500 nucleotides. During the subsequent PCR reaction, all ligated probes are amplified simultaneously using the same PCR primer pair. One PCR primer is fluorescently labelled, enabling the amplification products to be visualized during fragment separation. The relative height of each individual probe peak, as compared to the relative probe peak height in various reference DNA samples, reflects the relative copy number of the corresponding target sequence in the sample. Five probes used in the MDL Spinal Muscular Atrophy test detect SMN1 exon 7, SMN1 exon 8, SMN2 Exon 7 and two probes that detect the rare allele of two polymorphisms that may be present in the SMN1 gene. More than 95% of SMA patients show homozygous deletion of at least exon 7 of the SMN1 gene. The great majority of SMA carriers can be identified by the presence of only a single SMN1 exon 7 copy.

Variant Classification System: The MDL variant classification system is based on the 5-tier system recommendations for the interpretation of sequence variants proposed by the American College of Medical Genetics and Genomics (ACMG) and complies with the standards and guidelines for the interpretation of sequence variants by ACMG and the Association for Molecular Pathology (AMP). To classify each variant, MDL assigns weight to each piece of available evidence, including literature review, reputable database reports, population frequencies, and computational evidence and prediction.

Any detected variants that are a recognized cause of the disease (Pathogenic) will be reported. In addition, variants that have not previously been established as a recognized cause of disease may be identified. In these cases, only variants classified as "likely" pathogenic are reported. Benign variants, likely benign variants and variants of uncertain significance, and variants not directly associated with the intended disease phenotype are not reported.

MDL variant results are reported using numbering and nomenclature recommended by the Human Genome Variation Society (HGVS http://hgvs.org). All results are reported in reference to Human Genome 19, Human Build 37.

- **Turnaround Time**14 to 21 days

Specimen Requirements

- Whole Blood (Yellow top tube-ACD A)
- ***OneSwab***®

References

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