fact sheet

MCAD Deficiency

Medium-chain acyl-CoA dehydrogenase

HuGE Net

Human Genome Epidemiology Network

Author: Sophia Wang, PhD Published May, 2000

MCAD Gene

The gene for medium-chain acyl-CoA dehydrogenase (MCAD) is located at chromosome 1p31. MCAD is an enzyme responsible for the metabolism of medium chain fatty acids.

Gene Variants

Twenty-six MCAD gene variants have been reported. One of these gene variants, the K304E MCAD mutation, accounts for the majority of MCAD mutations identified to date. MCAD is an autosomal recessive disorder; therefore, individuals who are homozygous or compound heterozygous for an MCAD mutation may have abnormal protein product and subsequent inefficient enzymatic activity to metabolize medium-chain fatty acids. MCAD deficiency is therefore an inherited error of fatty acid metabolism.

Prevalence of K304E

K304E is reportedly found in 90% of all retrospectively identified MCAD deficient patients' alleles; 81% of all MCAD deficient patients are homozygous, and 18% of MCAD deficient patients are compound heterozygous for K304E. Caucasians of Northern European descent exhibit the highest frequency of MCAD deficient genotypes. The carrier frequency of K304E among this group is estimated to be 1:40-100 and the homozygote frequency is 1:6,500-20,000.

Clinical manifestation of MCAD Deficiency

In general, MCAD-deficient patients are at risk for a combination of the following outcomes: hypoglycemia, vomiting, lethargy, encephalopathy, respiratory arrest, hepatomegaly, seizures, apnea, cardiac arrest, coma, and sudden death. Long-term outcomes may include developmental and behavioral disability, chronic muscle weakness, failure to thrive, cerebral palsy, and attention deficit disorder (ADD). However, differences in clinical disease specific to allelic variants (e.g., genotypic-phenotypic correlations) have not been documented.

The penetrance of MCAD genotypes is also unknown; there appears to be a number of asymptomatic MCAD- deficient individuals and some uncertainty as to who will manifest symptoms and who will remain asymptomatic.

A precipitating factor is needed for clinical symptoms to present. It is often in times of metabolic stress induced by fasting or infection, when the demands on fatty acid oxidation are particularly high, that an MCAD-deficient patient may present with symptoms. Factors that may contribute to presentation and/or increased severity of clinical outcomes include prolonged fasting, infections or recent immunization, age, and family history of Sudden Infant Death Syndrome (SIDS) or MCAD deficiency.

K304E and SIDS

A recent review of the literature evaluating the relationship between the main MCAD allelic variant, K304E, with sudden infant death syndrome (SIDS), defined as the sudden and unexplained death of an infant in the first year of life, indicates that while people homozygous for K304E may have an increased risk for SIDS, the K304E MCAD allelic variant accounts for less than 0.1% of SIDS' cases in the U.S., Europe, and Australia. The study did not find that infants heterozygous for K304E were at an increased risk for SIDS.

Laboratory tests for detecting MCAD mutations

MCAD mutations can be identified through DNA-based tests using polymerase chain reaction (PCR) and therefore can be detected in newborns by DNA analysis from newborn blood spots. When identification of the K304E is used for diagnostic purposes, detection of homozygosity confirms diagnosis of MCAD deficiency; those heterozygote for K304E will need confirmation of a second MCAD allelic variant. Since 81% of MCAD-deficient individuals are homozygous for K304E and 18% are heterozygous for K304E, approximately 1% of MCAD-deficient patients will remain undetected if diagnosis is based on K304E DNA analysis. Mass screening for MCAD deficiency, however, is generally conducted with the detection of abnormal metabolites in urine or blood by tandem mass spectrometry (MS/MS). Typically, MS/MS is used as an initial screening modality followed by confirmation of MCAD deficiency with urine organic acid profile or DNA mutation analysis.

Current status of testing for MCAD

Testing for MCAD deficiency is currently conducted on the basis of the detecting abnormal metabolites (via tandem mass spectrometry) in newborns. North Carolina and Massachusetts currently test for MCAD deficiency as part of their newborn screening programs. California will soon offer optional testing for MCAD deficiency, and Wisconsin will begin conducting testing for MCAD deficiency on a pilot basis. In addition, Neo Gen Screening (Pittsburgh, PA, 15220) offers voluntary MCAD-deficiency testing to newborns born at birthing centers in the Northeast; 75% of Pennsylvania's newborns receive this test in addition to the testing provided by the Pennsylvania State Screening Program. From a recent TMS survey, there are currently eleven states with tandem MS/MS in use, either by private or state laboratories. At least seven of these states test for MCAD deficiency, either on a pilot, voluntary, or mandatory basis. In Europe, the Institute of Child Health in London is planning a population-based pilot study of MS/MS screening on newborns, which includes screening for MCAD deficiency. Identification of MCAD mutations is offered by laboratories but is more typically used to confirm diagnoses.

Web sites

National Organization for Rare Disorders, Inc.
http://www.stepstn.com/nord/rdb_sum/585.htm

Fatty Acid Oxidation Disorder Network
http://www.cinternet.net/FOD/mcad3.html
http://www.cinternet.net/FOD/mcad2.html

UC San Diego MCAD presentation
http://chem-faculty.ucsd.edu/harvey/MCAD/index.html

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