

### What is maple syrup urine disease?

Maple syrup urine disease (MSUD) is an inherited metabolic disease. When untreated, the classic form of MSUD is characterized by life threatening complications in the newborn period, including poor feeding, vomiting, lethargy, developmental delay, and a distinctive sweet odor in the urine. Individuals with MSUD have abnormalities in an enzyme complex that is responsible for breaking down the amino acids leucine, isoleucine, and valine. The symptoms of MSUD are due to the toxic build-up of these amino acids and their metabolites in the body, especially affecting the nervous system. MSUD is also known as branched-chain ketoaciduria and BCKD deficiency, and it is also known by its subtypes: MSUD types 1A, 1B, and 2.<sup>1</sup>

### What are the symptoms of maple syrup urine disease and what treatment is available?

MSUD can vary in age of onset and severity. Classic MSUD is the severe and most common form of the disease. Symptoms are evident soon after birth and may include:<sup>1</sup>

- A distinctive sweet, maple syrup odor of the ear wax and urine
- Distinctive movements and abnormal muscle contractions known as “bicycling” and “fencing”
- Poor feeding
- Lethargy (lack of energy)
- Irritability
- Difficulty breathing
- Brain swelling

If untreated, symptoms worsen and coma and death may occur within the first two weeks of life.<sup>1</sup>

Less severe forms of MSUD may occur in infancy, childhood, or periodically throughout life. Symptoms may be similar to the classic form and include feeding problems, poor growth, developmental delays, risk of brain swelling, and psychological problems. Episodes of decompensation (severe symptoms requiring intensive care) may occur after illness, infections, or fever.<sup>1</sup>

There is no cure for any form of MSUD, but available treatments for MSUD include a low-protein diet and nutritional supplements throughout life. Treatment can result in dramatic improvement of disease; however, individuals with MSUD remain at an increased risk for episodes of decompensation. Liver transplantation is sometimes considered for individuals with classic MSUD.<sup>1</sup>

MSUD is included on newborn screening panels in all 50 states.<sup>2</sup>

### How is maple syrup urine disease inherited?

MSUD is an autosomal recessive disease caused by mutations in three genes. Mutations in the *BCKDHA* (MSUD type 1A) or *BCKDHB* (MSUD type 1B) genes account for approximately 80% of all cases of MSUD. Mutations in the *DBT* (MSUD type 2) gene are responsible for the remaining cases.<sup>1</sup>

An individual who has one mutation in any of these genes is a carrier and is not expected to have related health problems. An individual who inherits two mutations in the same gene, one from each parent, is expected to be affected with MSUD. For example, a child with two *BCKDHA* mutations is expected to have MSUD, and a child with one *BCKDHA* mutation and one *BCKDHB* mutation is a carrier.

If both members of a couple are carriers of mutations in the same gene, the risk for an affected child is 25% in each pregnancy; therefore, it is especially important that the reproductive partner of a carrier be offered testing.

### Who is at risk for maple syrup urine disease types 1A and 1B?

MSUD can occur in individuals of all races and ethnicities. MSUD type 1A is more common in Old Order Mennonites of southeastern Pennsylvania and derivative settlements. In that population, there is a carrier frequency of 1 in 13.<sup>3</sup> MSUD type 1B is more common in individuals of Ashkenazi (Eastern European) Jewish ancestry with a carrier frequency of 1 in 97.<sup>1,4</sup>

Having a relative who is a carrier or who is affected can increase an individual's risk of being a carrier. Consultation with a genetics health professional may be helpful in determining carrier risk and appropriate testing.

### What does a positive test result mean?

If a gene mutation is identified, an individual should speak to a physician or genetics health professional about the implications of the result and appropriate testing for the reproductive partner and at-risk family members.

### What does a negative test result mean?

A negative result reduces, but does not eliminate, the possibility that an individual carries a gene mutation. The likelihood of being a carrier is also influenced by family history, medical symptoms, and other relevant test results.

### Where can I get more information?

MSUD family support group: <http://www.msud-support.org/>

Screening, Technology and Research in Genetics:  
<http://www.newbornscreening.info/Parents/aminoacid disorders/MSUD.html>

### References

1. Strauss KA *et al.* Maple syrup urine disease. *GeneReviews* Available at <http://www.ncbi.nlm.nih.gov/books/NBK1319/>. Accessed February 28, 2012.
2. National Newborn Screening Status Report. November 2, 2014. Available at: <http://genes-r-us.uthscsa.edu/sites/genes-r-us/files/nbsdorders.pdf>. Accessed January 6, 2016.
3. Puffenberger EG. Genetic heritage of the Old Order Mennonites of Southeastern Pennsylvania. *Am J Med Genet Part C (Semin. Med. Genet.)* 2003; 121C:18-31.
4. Scott, SA *et al.* Experience with Carrier Screening and Prenatal Diagnosis for 16 Ashkenazi Jewish Genetic Diseases *Hum Mut.* 2010; 31:1240-1250.