

## **Carnitine Uptake Defect (Primary Carnitine Deficiency)**

[Primary carnitine deficiency](#) occurs when the protein OCTN2 is missing or contains errors that keep it from functioning normally. This protein, located within the cell membrane, transports a common molecule known as carnitine into cells. Carnitine is required to carry certain fats (long-chain fatty acids) into mitochondria, where the fats are used to produce energy. Fatty acids are a major source of energy for the heart and muscles ([213](#), [218](#)). During periods without food (fasting), fatty acids are also an important energy source for other tissues, especially the liver. OCTN2 not only transports carnitine into individual cells, but it also is essential for the whole body to take up carnitine and to maintain carnitine levels. In the gut, OCTN2 takes up carnitine from the diet, while in the kidney it also removes carnitine from the just filtered fluids, returning it to the blood. Without OCTN2, dietary carnitine cannot enter the blood and any carnitine made inside the body that enters the blood is lost through the kidney into urine, together resulting in a severe lack of circulating carnitine.

### **Signs and symptoms**

Symptoms of OCTN2 deficiency appear periodically whenever the body needs fat for energy. This usually happens when the patient is not eating (fasting) for a long period. Alternatively, they also may appear when more than the normal amount of energy is required, as when someone is sick or exercising intensely. Patients commonly show symptoms between the ages of three months and two years. Usually after a minor illness such as a stomach virus or an ear infection, infants become extremely sleepy and difficult to wake (lethargy), are irritable, refuse to eat, and have poor muscle tone. Clinically, they have low blood sugar (hypoglycemia) with low ketones (hypoketotic) and an enlarged poorly functioning heart (dilated cardiomyopathy) ([213](#), [218](#)). Their livers become damaged causing release of their liver enzymes into the blood. At later ages, they may have an enlarged heart (hypertrophic cardiomyopathy), progressive muscle weakness with fat deposits in muscle, accompanied by a mild increase in a muscle damage indicator (creatinine kinase). While much of this damage occurs because of inadequate energy for normal bodily functions, some results from the excessive accumulation of fats in cells. This disorder is sometimes mistaken for Reye syndrome, a severe disorder that may develop in children recovering from viral infections such as chicken pox or flu.

There are milder forms of OCTN2 deficiency. For example, several mothers without noticeable symptoms have been identified only during newborn screening of their infants (see below) ([219](#)). Occasionally, this disorder in the fetus can cause a dangerous form of fluid accumulation *in utero* called fetal hydrops ([220](#), [221](#)).

## Diagnosis

Newborn screening by tandem mass spectrometry of blood spots is the most common method for starting the diagnosis of primary carnitine transporter deficiency. Blood spots from these newborns have very low amounts of all carnitine containing molecules including free carnitine ([222](#)). There are other fatty acid disorders where carnitine levels can be low, but only this group has no dicarboxylic acids in their urine. The diagnosis can be complicated by the fact that during pregnancy the mother provides carnitine to the fetus. If the blood for the newborn screening is taken too soon, an affected infant may have enough left-over carnitine from the mother to pass the test (Longo, 2016). On the other hand, this same maternal situation has led to the diagnosis of several mothers with the defect, some who had undiagnosed symptoms and some without symptoms. For this reason, the carnitine status of the mother is an essential part of the diagnosis whenever low carnitine is found on newborn screening.

If necessary, the carnitine defect can be directly observed by testing for carnitine uptake by tissues such as cultured skin cells (fibroblasts) or white blood cells (lymphoblasts). Molecular testing of the OCTN2 gene (*SLC22A5*) is clinically available. Testing can also be performed on tissues or cultured cells (amniocytes) from a fetus, if a defect is suspected ([218](#), [225](#)).

## Genetics

The OCTN2 protein defective in primary carnitine transporter deficiency is coded for by the [SLC22A5](#) gene. Mistakes (mutations) in this gene can either make a low functioning protein or an unstable protein or no protein. More than 60 different mutations in the *SLC22A5* gene have been found ([222](#), [223](#)). Everyone has two copies of the *SLC22A* gene. Patients with carnitine transporter deficiency inherit one defective *SLC22A* gene from each parent (autosomal recessive inheritance).

Parents of these patients are carriers of the disease. With each pregnancy, the parents have a 25% risk (1 in 4) chance to have another child with the same *SLC22A* mutations. Siblings of the affected person should be tested for *SLC22A* defects, in case a diagnosis was missed. Primary carnitine deficiency is rare in the United States, occurring in approximately 1 in 100,000 newborns. In Japan, this disorder is more frequent and affects 1 in every 40,000 newborns.

## Treatment

Primary carnitine transporter deficiency is treated by giving large pharmaceutical quantities of L-carnitine to the patient. Their response is dramatic and life-saving. In emergency situations, it can be given intravenously, followed by larger oral doses for the rest of the patient's life ([218](#)). If the patient has progressed to symptomatic cardiomyopathy, treatment for the cardiac symptoms may be necessary until it has resolved. If the patient receiving these large L-carnitine doses develops a fishy odor, they can be given metronidazole orally to reduce this odor.