

Genetics Fact Sheets 1, 2, 3, 4, 5 should accompany this Information Sheet.
Fact Sheets are available to download from www.genetics.edu.au

MAPLE SYRUP URINE DISEASE

Maple syrup urine disease (MSUD) is a rare inherited condition that is characterised by a distinctive sweet odour of the urine and sweat. It is a condition that, unless treated promptly and correctly, can be life threatening. Therapy must be started at the earliest possible age to achieve the best results. MSUD is manageable, but care and attention must be given to diet and to the treatment of even minor illnesses in an affected individual.

Symptoms of MSUD develop because the body is unable to break down (metabolise) three components of protein. These components are the amino acids called *leucine*, *isoleucine*, and *valine* and are known as the *branched chain amino acids* (BCAAs). A newborn with this condition will present with abnormally high concentrations of acidic by-products of the BCAAs in the blood and other tissues. This is known as metabolic acidosis and if left untreated, it may lead to seizures or coma, and may be life-threatening.

MSUD is classified in to four groups known as:

- Classic Maple Syrup Urine Disease
- Intermediate Maple Syrup Urine Disease
- Intermittent Maple Syrup Urine Disease
- Thiamine-Responsive Maple Syrup Urine Disease

MSUD varies in severity. The severity of the symptoms of MSUD is determined by how well the affected person can metabolise BCAAs.

Classical MSUD affects newborns within days after birth. Symptoms include the characteristic sweet odour of the urine, sweat, and earwax, but also may include poor feeding habits, vomiting, an irregular pattern of breathing, extreme lethargy, convulsive seizures, and/or coma. Most infants with this disease have episodes of abnormal muscle rigidity (hypertonia) alternating with periods of extreme floppiness (hypotonia). Developmental disability may be apparent in untreated infants who are a few months old.

Intermediate MSUD affects children just after the newborn period. These children usually develop a mild form of the disease during the course of another illness. Affected children usually have the characteristic smell to their urine, sweat and earwax, and have similar but milder symptoms than children with classical MSUD.

Intermittent MSUD occurs when previously healthy children with this disease are exposed to stress such as surgery or infections. Age of onset is usually delayed until 12 to 24 months of age. Symptoms include vomiting, the odour of maple syrup in the urine, sweat, and earwax, the inability to coordinate movement (ataxia), lethargy, and/or coma.

In Thiamine-Responsive MSUD affected children have mild or occasional symptoms that improve when thiamine is given in large doses.

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WHAT CAUSES MAPLE SYRUP URINE DISEASE?

MSUD occurs when an individual is born with a faulty pair of one of the “BCKADH complex” genes. There are at least three genes that provide the information to the cells to make the components for the BCKADH complex. The BCKADH complex is a molecule that assists in the breakdown of amino acids.

The BCKADH complex (*branched-chain alpha-ketoacid dehydrogenase*) usually breaks down the amino acids called leucine, isoleucine, and valine. When the genes are faulty, the BCKADH complex is faulty and the body cannot efficiently break down these amino acids. This results in accumulation of the amino acids and high levels of acid in the blood and other body tissues.

The three BCKADH complex genes usually associated with MSUD are called *BCKDHA*, *BCKDHB*, and *DBT*.

Genes, chromosomes and genetic conditions

Inside all the cells of our body, our genetic information is found on structures called *chromosomes*. There are usually 23 pairs of chromosomes, making a total of 46 chromosomes in each cell. One of each pair is passed on to us from our mother and the other from our father. 22 of these chromosome pairs are numbered. These numbered pairs are known as the *autosomal chromosomes*. The 23rd pair is made up of the *sex chromosomes* called X and Y. The different forms of MSUD are due to genes located on autosomal chromosomes.

We have many thousands of genes on our chromosomes that provide information for our body to grow, develop and remain healthy. The gene sends messages to the cell to make important chemical products such as proteins.

Genetics Fact Sheets 1, 2 and 3 provides more information on genes, chromosomes, and genetic conditions.

Everyone has variations (changes) in their genes, which is why we are all unique. Variations can either be harmless or at times, can cause a gene to be faulty. Variations that make a gene faulty are called *mutations*.

BCKDHA, *BCKDHB*, and *DBT* are three different genes that provide the instruction for different parts of the BCKADH complex. If any of the gene pairs are faulty, they are unable to provide the correct information to our cells. A faulty gene can either be passed down (*inherited*) from one or both parents or can occur as a new faulty gene during the making of an egg or sperm or at conception. Once a faulty gene is present in an individual, it can be passed on to future generations. This is referred to as *genetic inheritance*.

Inheritance

The pattern of inheritance of a faulty gene, and therefore the genetic condition it is related to, depends on (1) the whether the gene involved is located on an autosomal chromosome or a sex chromosome and (2) how much of the protein produced by the gene is needed by the cells to work normally.

There are two copies of the three MSUD genes in each cell and both copies of the gene normally send a message to the cells to produce part of the BCKADH complex. In a person with MSUD, *both copies* of the particular BCKADH complex gene are faulty and they have no working copy of the gene. So the amount of protein produced is either very reduced or even absent. This means that there may not be enough of the

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protein for the cells and certain processes in the body will not work as efficiently as they should. MSUD is described as being “recessive” as a person has to have both gene copies faulty to develop symptoms.

Therefore MSUD is inherited in an **autosomal recessive** manner.

For a person to have both their MSUD genes faulty, they will have inherited the faulty gene copies from both their mother and father. Usually, both the mother and father each have one working copy of the gene and one faulty copy in their cells. That means that the amount of protein they produce is reduced, but they will not have MSUD. They are *genetic carriers* of MSUD. Genetic carriers are not affected by the condition but can pass on the faulty gene copy to their children.

When both parents are genetic carriers of MSUD there is a 1 in 4 chance (25%) in every pregnancy that they will each pass on to their child their faulty MSUD gene copy. There is however 2 in 4 chances (50%) in every pregnancy that the child will be an unaffected genetic carrier (just like the parents) and a 1 in 4 chance (25%) that they will not pass on the faulty gene copy at all.

Genetics Fact Sheet 8 provides more information on autosomal recessive inheritance.

WHO IS AFFECTED BY MAPLE SYRUP URINE DISEASE?

MSUD is a very rare condition that affects males and females in equal numbers. In the classical form of the disease, the symptoms begin during the first week of life.

One study found that in the USA, MSUD occurs in approximately 1 per 185,000 newborns.

HOW IS MAPLE SYRUP URINE DISEASE DIAGNOSED AND TREATED?

Diagnosis

Newborn screening in NSW include a test for maple syrup urine disease along with other inherited metabolic diseases that require immediate treatment and dietary management. Newborn screening is a heel prick blood test offered in the first few days after a baby is born.

The diagnosis of MSUD can be suspected because of the characteristic odour found in the urine and sweat. It may be confirmed by specialised laboratory tests which show abnormally high levels of leucine, isoleucine, and valine (branch chain amino acids) in the blood. Isoleucine may also be present in increased amounts in the fluid that surrounds the brain and spinal cord (cerebrospinal fluid). The early diagnosis and treatment of MSUD (i.e., at 3 days old versus 10 days old) may lead to less severe symptoms.

Treatment

The treatment of MSUD should begin as soon as possible after birth. Treatment is usually managed by doctors and nurses who specialise in metabolic conditions. Infants with MSUD must be placed on a diet free of foods that are broken down into branched chain amino acids. Therefore, the diets are protein restricted. Calorie supplementation is also recommended and may include semi-synthetic dietary supplementation. Children with this condition must stay on a strict diet that restricts the intake of branched chain amino acids for life.

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Infection and illness can worsen the symptoms of MCAD. Special care in hospital may be required to restore the balance of proteins in the body during ill health.

In rare cases of Thiamine-Responsive MSUD, newborns are treated with large doses of thiamine. The symptoms may respond in part to this treatment and occasionally resolve completely.

Pregnant women affected with MSUD will need special care to manage her own diet but not risk causing harm to the baby.

Genetic Testing Options

Genetic testing is available for this condition. It may be carried out on individuals, on an unborn baby (prenatal testing) or on an embryo (pre-implantation genetic diagnosis - PGD). For the most useful and accurate information, contact a genetic counselling service. A genetic counsellor will talk to you about testing, discuss your specific options and answer any questions.

Genetics Fact Sheet 3, 17 and 18 provides more information on genetic counselling, prenatal diagnosis, and PGD.

MORE INFORMATION AND SUPPORT

If you would like to discuss support options and possible contact with other affected individuals or families, please contact:

Association of Genetic Support of Australasia (AGSA)

Telephone: (02) 9211 1462
E-mail: info@agsa-geneticsupport.org.au
Web: www.agsa-geneticsupport.org.au

Additional information and support may be available from the following sources:

Maple Syrup Urine Disease Family Support Group (USA)

Web: www.msud-support.org

For more information about genes, inheritance patterns, genetic testing and genetic services discussed in this information sheet please contact:

Centre for Genetics Education (CGE)

Telephone: (02) 9462 9599
E-mail: contact@genetics.edu.au
Web: www.genetics.edu.au

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This document is based on information obtained from the following sources:
National Organization for Rare Disorders (NORD) - www.rarediseases.org
Online Mendelian Inheritance in Man - www.ncbi.nlm.nih.gov/omim
GENE TESTS (Gene Reviews) – www.genereviews.org

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