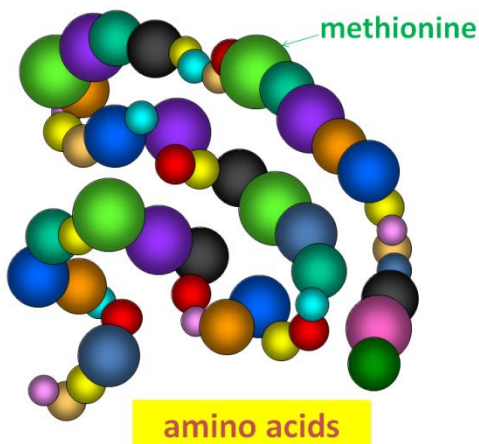


# METHIONINE ADENOSYL-TRANSFERASE (MAT) DEFICIENCY

## WHAT IS MAT DEFICIENCY?

Is an **inborn error of methionine metabolism** due to the enzyme **methionine adenosyl transferase (MAT)** deficiency, which causes an accumulation of methionine in blood (**hypermethioninemia**) and in urine.

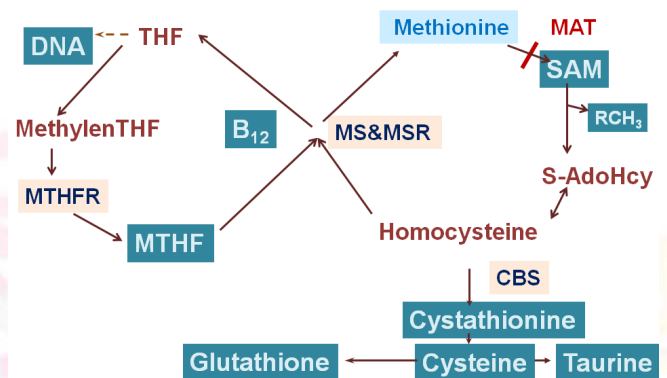
## WHAT IS METHIONINE?



Methionine is an **amino acid**, single molecule that is part of **proteins** (long chains of amino acids). Methionine is formed by the degradation of dietary proteins.

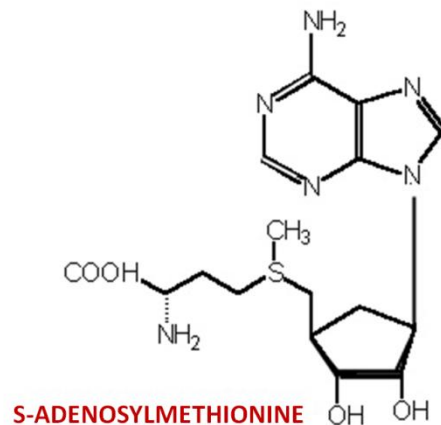
Methionine is a sulfur amino acid (containing sulfur) that is essential in human nutrition. It has its own metabolic pathway by which is capable of forming other biologically important compounds: S-adenosyl-methionine (SAM), other amino acids (cysteine, cystathionine and taurine), and antioxidants (glutathione).

## Methionine metabolism



## WHAT IS S-ADENOSYL METHIONINE (SAM)?

SAM is synthesized in the first step of methionine degradation by the action of the enzyme methionine adenosyl transferase (MAT). SAM is a major donor of methyl groups that are necessary to synthesize essential compounds for the organism, such as phospholipids, phosphatidylcholine and sphingomyelin. Furthermore, SAM is essential to regulate sulfur amino acid metabolism and thus vitamin B12 and folate metabolism.



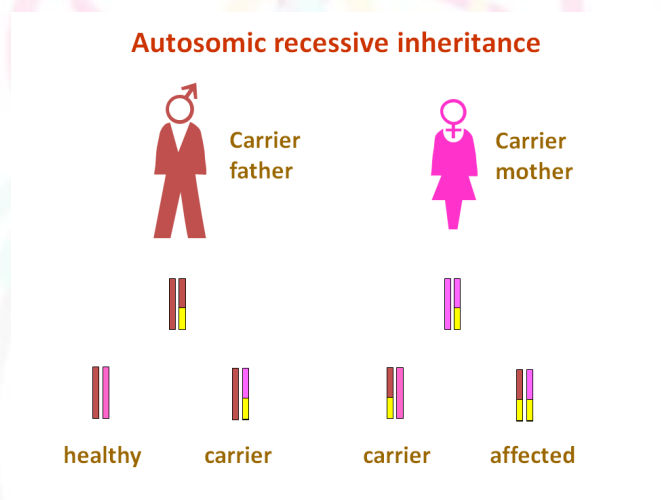
The correct synthesis of SAM is so important that its catalyzing enzyme MAT is found in all organisms. There are three known forms of MAT (**MAT I, II, and III**), which are encoded by two genes **MAT1A** (encoding MAT I and MAT III) and **MAT2A** (encoding MAT II), but only MAT I and especially MAT III are expressed in human liver (MAT II only expresses in fetal liver.)

## WHAT HAPPENS IN MAT DEFICIENCY?

When there is an error in metabolism, one reaction may not occur as effectively as expected, and the previous compounds accumulate, while those that should be synthesized are deficient. In MAT deficiency, methionine cannot effectively transform to SAM because MAT enzyme fails to work properly. This causes an accumulation of methionine in blood (**hypermethioninemia**) and especially, a **defective synthesis of SAM** and SAM derivatives.

## WHY DOES MAT DEFICIENCY OCCUR?

Each one of the metabolic reactions that will produce the compounds, which make up our body is genetically determined (encoded). We all inherit from our parents the right or altered information that determines all the metabolic reactions. If we inherit from our parents a misinformation or partially altered information, this specific reaction will function improperly and can lead to an **inborn error of methionine metabolism**.

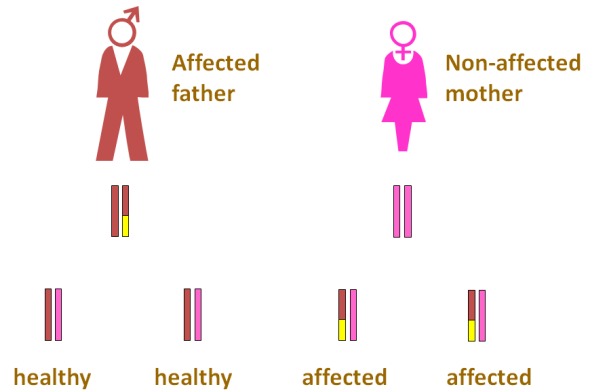


Deficient MAT I/III activity occurs due to mutations (stable and hereditary changes) in **MAT1A** gene. It is a genetic disorder with **autosomal recessive or dominant inheritance**. In the first case, the parents are carriers of mutations in this gene but they do not suffer the effects

of the enzyme deficiency. If both parents transmit the mutation to their baby, he/she will suffer a genetic MAT deficiency.

In the second case, a single parent is carrier of a mutation, which if transmitted to the son/ daughter, will cause **hypermethioninemia**.

## Autosomal dominant inheritance



## WHAT HAPPENS WHEN A CHILD IS BORN WITH MAT DEFICIENCY?

The child presents with **hypermethioninemia**, which will be higher or lower depending on the mutation/s causing MAT deficiency.

If the enzymatic block is important because of two severe mutations that alter the MAT protein structure, hypermethioninemia will be important (600-2000  $\mu\text{mol/L}$ ), and the child may show an unpleasant **breath and body odour** (cabbage smell because of the presence of dimethylsulfide).

When hypermethioninemia is due to a single mutation in **MAT1A**, plasma methionine shows much lower values (45-400 $\mu\text{mol/L}$ ) and no breath or body odour is perceived.

Although **most cases show no clinical features (are asymptomatic)**, some patients are described with severe MAT deficiency associated to neurological troubles [tremor, movement disorders (dystonia, dysmetria), language problems, myelination disorders (formation of the cerebral white matter, ie the myelin sheath covering nerve fibers) and some intellectual dyscapacity].

## HOW IS DIAGNOSED MAT DEFICIENCY?

Hypermethioninemia due to MAT deficiency began to be often diagnosed due to expanded newborn screening for classic homocystinuria detection (another much more serious metabolic disease, which also presents with hypermethioninemia, plus hyperhomocysteinemia). Previously only few cases have been described in the literature, due to its generally asymptomatic presentation. The finding of a newborn with hypermethioninemia requires differential diagnosis with classical homocystinuria, tyrosinemia type I and other rare genetic disorders. Since MAT activity is only expressed in liver, liver biopsy is not acceptable to examine a commonly asymptomatic condition, therefore mutations of **MAT1A gene**, which encodes MAT I / III, are usually analysed.

MAT deficiency is a usually **asymptomatic genetic disorder**, but clinical and biochemical monitoring of detected cases seems important to evaluate the suitability of a potential SAM supplementation or some degree of protein restriction.

### Translation

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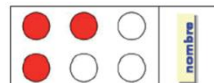


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### Diagnosis of hypermethioninemia

#### Newborn screening

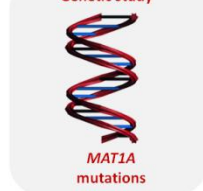


#### Biochemical study



↑ methionine    ↑ methionine  
↓ homocysteine    ↓ homocysteine  
↓ tyrosine    ↓ succinylacetone

#### Genetic study



MAT1A  
mutations

## A CHILD WITH MAT DEFICIENCY SHOULD BE TREATED?

Since most cases are asymptomatic, **MAT deficiency requires no treatment**. Only some specific cases with two severe mutations and significant hypermethioninemia associated to neurological features justify a methionine restriction in the diet (ie a low protein diet). Moreover, the adverse effects of MAT deficiency appear to be due to SAM deficiency rather than to hypermethioninemia, so that methionine restriction in diet could aggravate the defect of SAM. Therefore it has been suggested the possibility of supplementation with SAM, which has been performed in some patients, although the effectiveness of such treatment has not yet been verified.