

# THIAMINE TRANSPORTER TYPE 2 DEFICIENCY

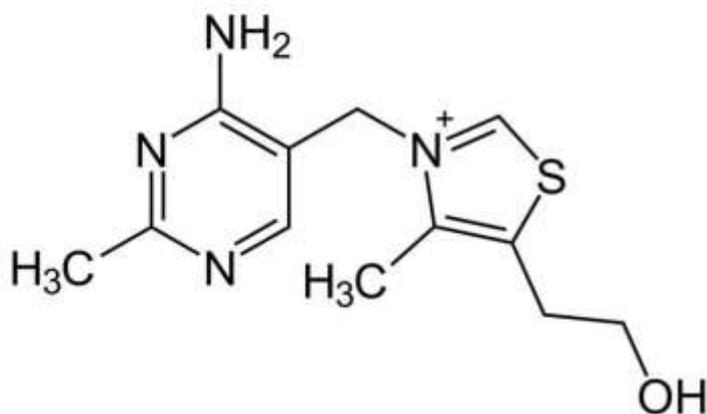
## WHAT IS THE THIAMINE TRANSPORTER TYPE 2 DEFICIENCY (hTHTR2)?

The **thiamine transporter type 2 deficiency (hTHTR2)** is a **inborn error of thiamine metabolism** caused by mutations in the **SLC19A3 gene** encoding it. Patients with this defect develop recurrent episodes of encephalopathy accompanied by other neurological manifestations.

## WHAT IS THIAMINE AND HOW IS IT METABOLIZED?

Thiamine is a water-soluble vitamin of the **B complex (vitamin B1)**, which is involved in the **mitochondrial functions** and is essential in the generation of cellular energy. Thiamine is also involved in cytosol reactions related to the production of ribose, an indispensable sugar for the synthesis of nucleic acids (DNA and RNA).

## Thiamine or vitamin B1



## Thiamine sources are cereals, fish, meat and milk

Among its phosphorylated derivatives, **thiamine pyrophosphate (TPP)** is involved in multiple cell reactions.

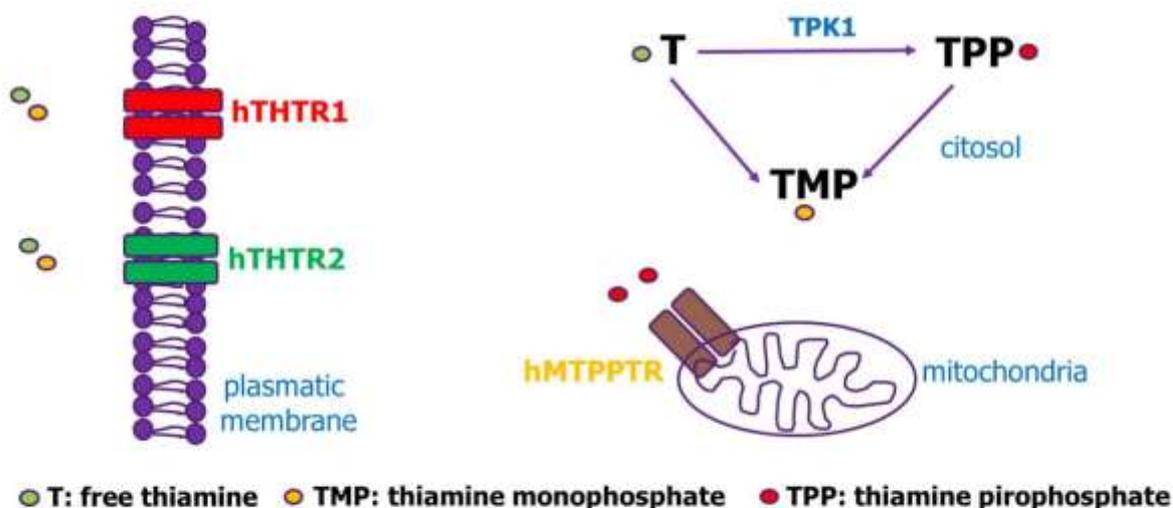
Free thiamine and thiamine monophosphate (TMP) are absorbed into the small intestine by two specific transporters: the **thiamine transporter type 1 (hTHTR1)** and the **thiamine transporter type 2 (hTHTR2)**, although other minor transporters may also be involved.

Within the cell, free thiamine is converted to **thiamine pyrophosphate (TPP)** by the action of **thiamine pyrophosphokinase (TPK)**. TPP enters into the mitochondria by the **mitochondrial transporter hMTPPTR**. TPP is a cofactor of enzymes of great metabolic importance, in the cytosol, in the peroxisomes and in the mitochondria, many of them related to energy metabolism.

## WHAT IS THE THIAMINE TRANSPORTER TYPE 2 (hTHTR2) AND WHAT IS ITS FUNCTION?

The thiamine transporter type 2 belongs to the family of transmembrane proteins, whose function is to allow the entry of water-soluble substances, such as thiamine, into the cell.

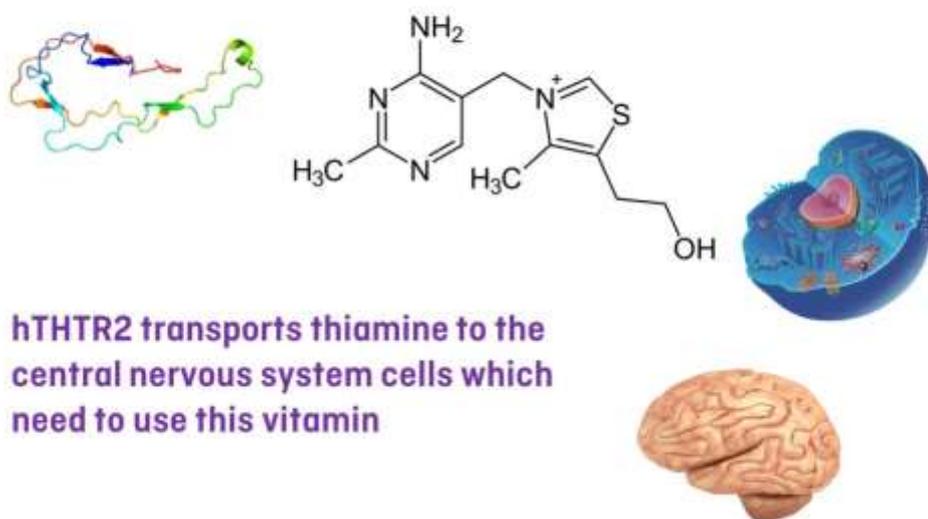
### Thiamine metabolism and transport



The hTHTR2 captures the thiamine, and introduces it into the cell through the membrane so that it can be used for cellular functions. This carrier is preferably located in tissues or organs which require thiamine for its activity. The hTHTR2 is found in the neuron membrane of the central nervous system (brain).

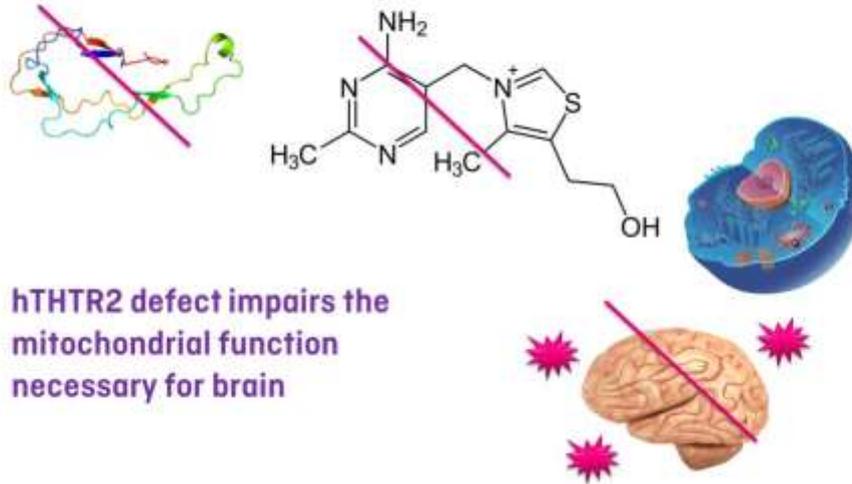
## WHAT DOES IT HAPPEN IN hTHTR2 DEFICIENCY?

### Thiamine transporter: hTHTR2

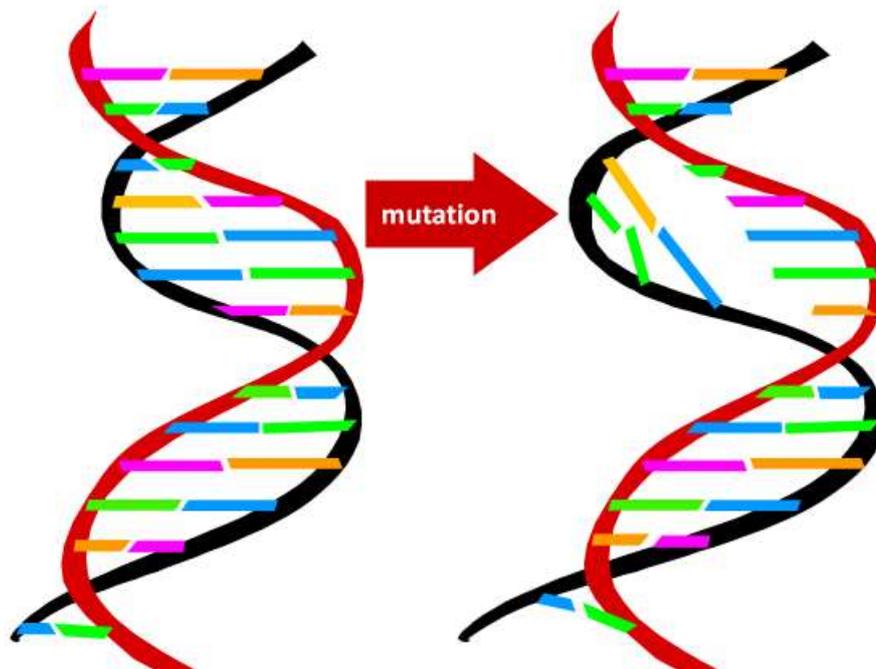


When the thiamine transporter type 2 does not work correctly different diseases occur with some common features, probably due to the alteration of mitochondrial energy production necessary for the different neurological functions. It is a genetic deficiency, although the symptoms may not present at birth.

## Thiamine transporter defect: hTHTR2



### WHY DOES A hTHTR2 DEFICIENCY HAPPEN?

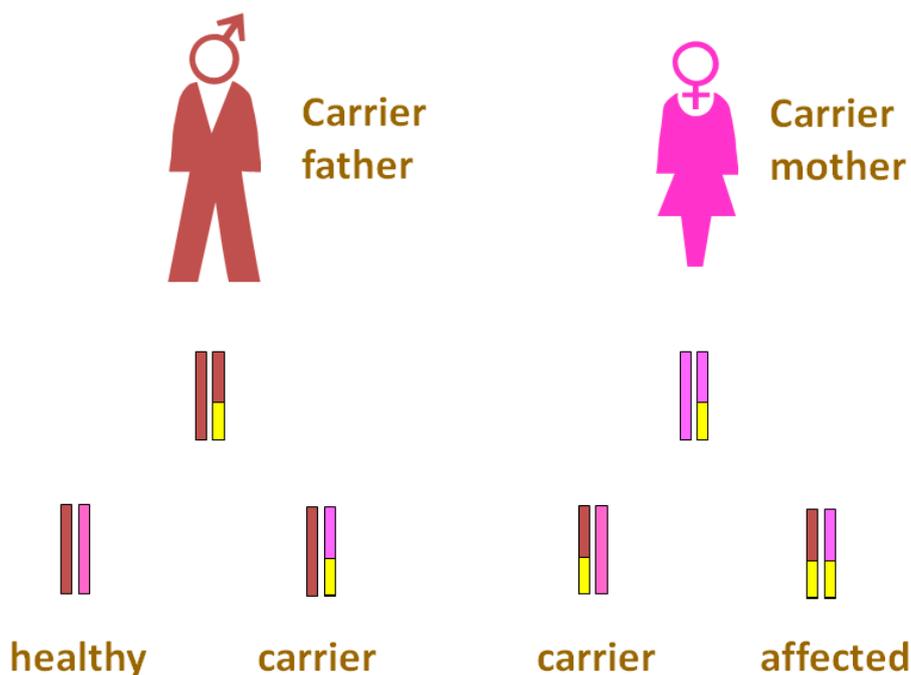


Each of the metabolic reactions that are going to generate the compounds that form our body is genetically determined (codified). We all inherit from our parents the correct or altered information that determines metabolic reactions. If we inherit a total or partially altered information, that metabolic step will not function correctly and this may lead to an **inborn metabolic error**.

Deficiency of thiamine transporter-2 is caused by **mutations** (stable and inheritable changes) in the **SLC19A3** gene encoding the **hTHTR2** protein.

The hTHTR2 deficiency is a genetic disease of autosomal recessive inheritance, which means that parents are usually carriers of a mutation in the gene without presenting symptoms. If both parents transmit the mutation to the baby, he/she will present a **deficiency of the thiamine transporter 2**, with consequent clinical manifestations.

## Autosomal recessive inheritance



## CLINICAL PRESENTATION OF THE DEFECT OF TIAMINE TRANSPORTER TYPE 2

Children initially have a normal psychomotor development (symptoms appear before the age 12 years in 80% of cases), until they develop **acute and recurrent episodes of encephalopathy**, often triggered by fever, trauma or vaccination. Encephalopathy may be associated with dystonia, dysarthria, external ophthalmoplegia, seizures, etc ... along with lesions in different areas of the brain.

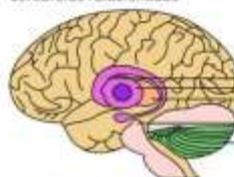
In general, four different clinical forms have been described:

- 1. Basal ganglia disease with biotin response (BBGD):** This disease develops in episodes or outbreaks. Patients are asymptomatic until, at a variable age in infancy, they present with **encephalopathy** (lethargy, stupor, ...) movement disorders, difficulties in speech or loss of speech, difficulties in swallowing, epileptic seizures ... These symptoms respond characteristically to treatment with **biotin and thiamine** at high doses, hence the name given to this form of the disease.
- 2. Leigh-like encephalopathy:** Acute encephalopathy with bilateral striatal necrosis. This form has an early and serious presentation that can be greatly improved with early thiamine treatment. Infants present with irritability, increased muscle tone, vomiting and a detectable neuronal lesion on magnetic resonance imaging, associated with metabolic acidosis, hyperlactacidemia and increased excretion of some metabolites such as alpha-ketoglutarate.
- 3. Wernicke-like encephalopathy:** It occurs more frequently in adult patients presenting with double vision (due to an alteration of the ocular motor nerves), ataxia (instability of the gait) and confusion.

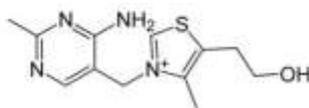
4. **Infantile spasms:** Very severe epilepsy during the first months of life that associates with a very important delay in the child development.

## Clinical features of the hTHTR2 defect

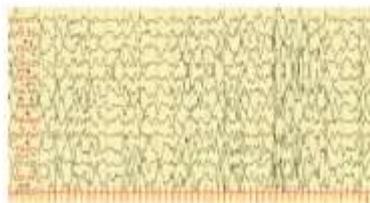
Ganglios basales y estructuras cerebrales relacionadas



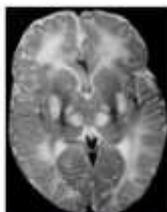
**Biotin-responsive basal ganglia disease**



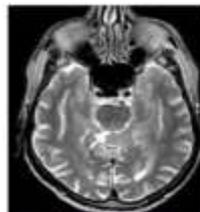
↓ **thiamine**



**Infantile spasms**



**Leigh syndrome**



**Wernike encefalopatya**

In each of these four forms the brain magnetic resonance shows characteristic alterations and this may help to suspect the diagnosis.

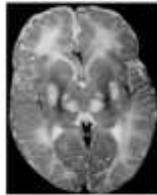
### DIAGNOSIS OF hTHTR2 DEFICIENCY

Symptoms and brain MRI may lead to suspicion of the diagnosis.

Patients with hTHTR2 defect show **normal thiamine concentrations** in plasma, but **free thiamine is reduced in cerebrospinal fluid (CSF)**, so this parameter may be a **biomarker** of this deficiency if there is clinical suspicion. Some patients show an increase in nonspecific biomarkers of mitochondrial dysfunction, such as increased lactate, alpha-ketoglutarate or alpha-alanine in biological fluids (blood, urine and CSF).

The diagnosis of confirmation of hTHTR2 deficiency is made by **the mutational study** of the **SLC19A3 gene**.

## Diagnosis of hTHTR2 defect



Clinical suspicion?

### Biochemical study



↓ lactate  
↓ amino acids



↓ alpha-ketoglutarate?



↓ thiamine

### Genetic study



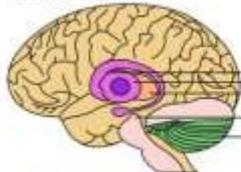
Mutacions  
in *SLC19A3* gene

## TREATMENT OF hTHTR2 DEFICIENCY

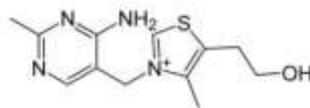
Daily treatment with high doses of thiamine and biotin results in different responses in the different clinical settings that have been associated with hTHTR2 deficiency.

## Treatment of the hTHTR2 defect

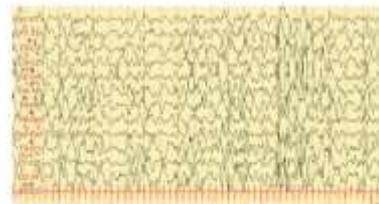
Ganglios basales y estructuras cerebrales relacionadas



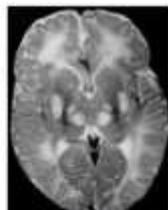
Biotin-responsive basal ganglia disease



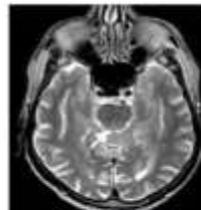
↓ thiamine + biotin



Infantile spasms



Leigh syndrome



Wernicke encefalopatya

In the **BBGD form**, the start of treatment with high doses of biotin and thiamine greatly improves the symptomatology and prevents relapses, so it should not be interrupted.

In **Leigh-like encephalopathy**, treatment with thiamine may improve symptomatology and normalize metabolic abnormalities.

In **Wernicke-type encephalopathy**, response to thiamine has also been observed in high doses, especially for the control of epileptic seizures.

Finally, in the form with **infantile spasms**, the response to these vitamins doesn't greatly improve the prognosis. (In any case, it must be considered that the cases of these last two diseases that have been described to date are very scarce).

In general, a **symptomatic treatment**, such as the use of antiepileptic drugs for epilepsy, may also be associated. Certain factors such as early presentation of the disease (<6 months of age), involvement of certain areas of the central nervous system in brain MRI and some mutations have been associated with poor prognosis of the disease.

### WHAT CAN YOU DO TO PREVENT THE HTHTR2 DEFICIENCY?

**Genetic counseling** can be performed in families where a patient with a disease associated with the hTHTR2 deficiency has previously presented.

## Genetic counseling



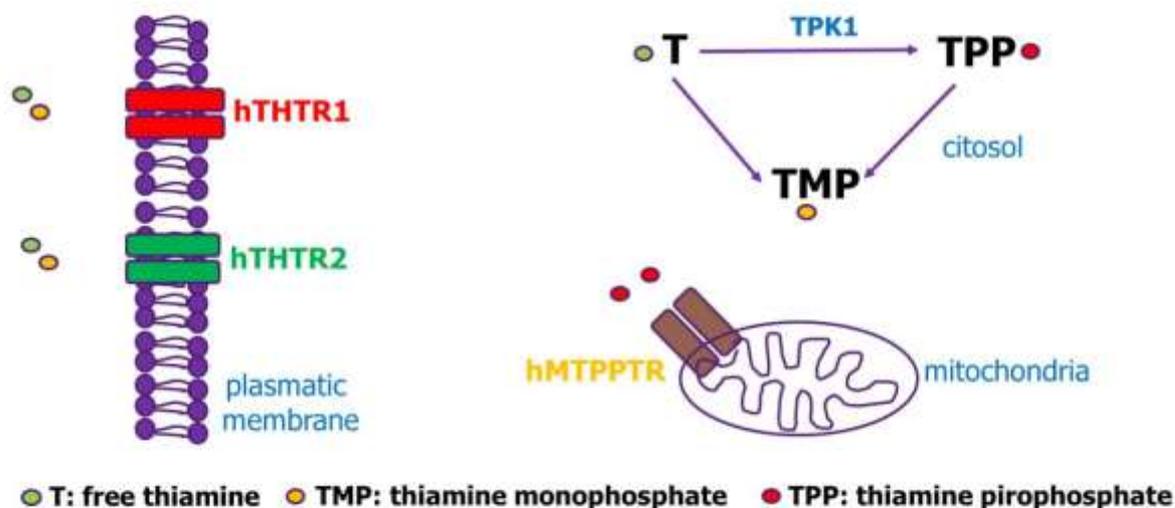
**Prenatal diagnosis** is possible by the genetic study of the fetus, if the mutation that caused the disease is known.

### OTHER DEFECTS IN THE TRANSPORT AND METABOLISM OF THIAMINE

Three defects have been described in **transport involved genes** (*SLC19A2*, *SLC19A3* and *SLC25A19*) and one involved in the **metabolism of thiamine** (*TPK1*).

Clinical phenotypes caused by mutations in these genes are as follows:

## Thiamine metabolism and transport defects



1) **hTHTR1 transporter deficiency**, caused by mutations in the **SLC19A2** gene, associated with a triad of thiamine-responsive megaloblastic anemia, non-autoimmune diabetes mellitus, and early-onset sensorineural deafness. These symptoms may not occur simultaneously, making the diagnosis difficult. Supplementation with thiamine results in improved symptoms, control of anemia and glycaemia, but does not prevent hearing loss.

2) **Deficiency of the transporter hTHTR2**, caused by mutations in the **SLC19A3** gene, already treated extensively in the previous sections, since it is the most frequent defect (about 116 patients described).

3) **Deficiency of the enzyme thiamine pyrophosphokinase (TPK)**, caused by mutations in the **TPK1** gene, associated with **Leigh syndrome**. The clinical picture of these children is more severe than the defect of the previously commented transporters. Some patients respond to thiamine supplementation and the ketogenic diet.

4) **Deficiency of the mitochondrial thiamine pyrophosphate transporter (hMTPPTR)**, caused by mutations in the **SLC25A19** gene, associated with Amish type microcephaly or bilateral striatal necrosis with progressive polyneuropathy. The clinical form of striatal necrosis responds to thiamine supplementation.

The **thiamine transport and metabolism defects** are neurometabolic diseases which untreated can have serious consequences. However, early diagnosis and treatment greatly improves the prognosis and quality of life of the affected children.



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