

# Transcobalamin II deficiency

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## Abstract

Transcobalamin II (TCII) deficiency is an autosomal recessive disease marked by defective intestinal absorption of vitamin B12. Homozygous TCII deficiency causes non-specific symptoms in one- and two-month-old infants (e.g. vomiting, poor growth) and infections due to an immune deficiency (hypogammaglobulinemia). The main symptom is megaloblastic anemia. Serum cobalamins, however, are normal, since the major circulating form, methyl vitamin B12, is bound to another transport protein (transcobalamin I). Specific treatment consists of massive *per os* or parenteral intake of vitamin B12. Symptoms disappear completely, except when the diagnosis is delayed and neurological signs have become permanent.

## Keywords

Transcobalamin II deficiency, cobalamin, vitamin B12, homocysteine, methyl malonic acid megaloblastic anemia.

## Definition

Transcobalamin II (TCII) deficiency is a very rare autosomal recessive disease. Megaloblastic anemia is the most specific sign of this disease. TCII is the primary transport for vitamin B12. The lack of vitamin B12 entry into the cells results in homocystinuria and methyl malonic aciduria.

## Prevalence

Hereditary human TCII deficiency is rare and no estimation has been published.

## Mechanism

TCII is a plasma protein that binds vitamin B12 (cobalamin; Cbl) and facilitates the cellular uptake of the vitamin by receptor-mediated endocytosis.

TCII, a non-glycosylated secretory protein of molecular mass 43 kDa, and its plasma membrane receptor (TCII-R), a heavily

glycosylated protein, are essential components of plasma vitamin B12 transport into all cells. Vitamin B12 passage from the intestine into the circulation is perhaps the most complex of all vitamin uptake mechanisms and involves no less than five separate vitamin B12 - binding molecules, receptors and transporters. Each molecule involved in uptake has a separate affinity and specificity for vitamin B12 as well as a separate cell receptor. Thus vitamin B 12 is initially bound by haptocorrin in the stomach, then by intrinsic factor in the small intestine. An intrinsic factor-receptor complex is then involved in uptake of the intrinsic factor-vitamin B12 complex by intestinal epithelial cells, with the subsequent proteolytic release of vitamin B12 and its binding to TCII. The TCII-Receptor then transports the TCII-vitamin B12 complex across the cell membrane. TCII can be synthesized in many

tissues and a mechanism exists in humans to rapidly synthesize and secrete enough apo-TC II.

### Clinical description

In autosomal recessive TCII deficiency, intracellular vitamin B12 deficiency occurs early, usually during the first few months of life, manifested by megaloblastic anemia that may be accompanied by neurological abnormalities and sometimes pancytopenia. Others common symptoms are: failure to thrive, vomiting, diarrhea, ulcers of mouth and infections. During childhood, patients may have recurrent bacterial and viral infections that are probably related to neutropenia and hypogammaglobulinemia. Impaired cognitive development and neurologic sequelae (epilepsy and gait disturbance) were observed in patients with TCII deficiency who had extended duration of illness, received inadequate cobalamin treatment, or were initially treated with folic acid instead of cobalamin

### Etiology

In the most common form of TCII deficiency, immunoreactive TCII is lacking in the plasma of patients. The other two forms result from the production of abnormal TCII which is either unable to bind vitamin B12 or is able to bind vitamin B12 but unable to assure its entry into cells. The molecular basis for the most common form of human TCII deficiency was recently identified: single nucleotide deletion or non-sense mutation. either causes a frameshift and introduces a premature termination codon.

TCII deficiency leads to disturbed function of the two cobalamin-requiring enzymes, methylmalonyl coenzyme A (CoA) mutase and methionine synthase, with deoxyadenosylcobalamin and methylcobalamin coenzymes, respectively. The TCII gene was isolated, it is composed of 9 exons and 8 introns spanning about 20kb, it is localised in 22q12-q13 chromosome

### Diagnostic methods

Defects in the early steps of intracellular transit of cobalamin-containing compounds result in methylmalonic aciduria (detected by gas chromatography-mass spectrometry) and homocystinuria (detected by ion-exchange chromatography with ninhydrin derivatization). The diagnosis of TCII deficiency is confirmed by the absence of radioimmunoassay-detectable TCII in the

most classic form or by the inability of cultured fibroblasts to synthesize TCII.

### Treatment

When given sufficiently early, treatment with parenteral vitamin B12 is highly effective on clinical and biological signs. It reverses the clinical and hematological manifestations of the disease.

### Prenatal diagnosis

No prenatal diagnosis is performed for this disease.

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