



■ COVER STORY

From The Endocrine Society's Research Affairs Committee
Co-edited by David A. Ehrmann, M.D., and Judith Turgeon, Ph.D.

NEW GENETIC THYROID DEFECT Identified

MCT8 Key to Thyroid Hormone Transport into Cells

Congenital hypothyroidism is the most common defect identified at birth. Its high incidence of 1 in 3,500 newborns and its devastating consequences if left untreated has prompted the institution of routine neonatal screening throughout the world. The identification of new syndromes of impaired sensitivity, availability, and metabolism of the thyroid hormone—with equally devastating effects but not detected by the routine screening based on high TSH and low T4—poses a new challenge to the health profession. One such challenging condition is the subject of this communication by three experts in the field.



Giving the molecular basis of thyroid hormone monocarboxylate transporter *MCT8* defects is Samuel Refetoff, M.D., Professor of Medicine, Pediatrics, the Committee on Genetics and Molecular Medicine and Director of the Endocrinology Laboratory at the University of Chicago Hospitals.



Presenting the clinical syndrome of thyroid hormone cell transport defect (THCTD) and when to suspect it, is Roy E. Weiss, M.D., Ph.D., Professor of Medicine and Molecular Medicine, Chief of Endocrinology, Diabetes and Metabolism and Director of the General Clinical Research Center at the University of Chicago.



Explaining the clinical manifestations and abnormal tests, is Alexandra M. Dumitrescu, M.D., Ph.D., Postdoctoral Scholar at the University of Chicago, Department of Medicine.

Summary of Perspectives

Monocarboxylate transporter 8, *MCT8* (also known as *SLC16A2* and *XPCT*) is a TH-specific transporter located on the X chromosome.

- *MCT8* gene defect should be suspected when psychomotor impairment (severe developmental delay, truncal hypotonia, and limb spasticity) is accompanied by high serum T_3 , low T_4 , and rT_3 concentrations.
- The neurological manifestations of this syndrome cannot be explained by the thyroid function tests and the observed phenotype is different from that of global thyroid hormone deficiency or excess.
- Treatment with physiological doses of L- T_4 has not corrected the phenotype in several patients. The efficacy of treatment during pregnancy, the use of higher L- T_4 doses, and of TH analogs should be tested.
- *Mct8* knockout mice replicate the characteristic thyroid phenotype. These mice have demonstrated tissue-specific TH excess and deprivation due to different tissue dependency on *Mct8* for cellular TH uptake.

Key Abbreviations

<i>MCT8</i>	monocarboxylate transporter 8 (gene)
TH	thyroid hormone
TR	thyroid hormone receptor
RTH	resistance to thyroid hormone
TSH	thyroid stimulating hormone
T_2	diiodothyronine
T_3	triiodothyronine
rT_3	reverse triiodothyronine
T_4	thyroxine
FT_4	free thyroxine
L- T_4	levothyroxine

From Samuel Refetoff, M.D.

The Thyroid Hormone Cell Transporter, *MCT8*: Its Gene, Structure, and Function

The monocarboxylate transporter 8 (*MCT8*) gene was first cloned during the physical characterization of the region in Xq13.2, known to contain the X-inactivation center.¹ It belongs to a family of genes officially named *SLC16*, the products of which catalyze proton-linked transport of monocarboxylates, such as lactate, pyruvate, and ketone bodies. The deduced products of the *MCT8* (*SLC16A2*) gene are proteins of 613 and 539 amino acids (translated from two in-frame start sites) containing 12 transmembrane domains with both amino and carboxyl termini located within the cell.² In 2003, Friesema et al.³ demonstrated that the rat homolog was a specific transporter of TH into cells. This and other TH transporters, together with iodothyronine deiodinases, regulate the level of active hormone at the cell level (Fig 1).

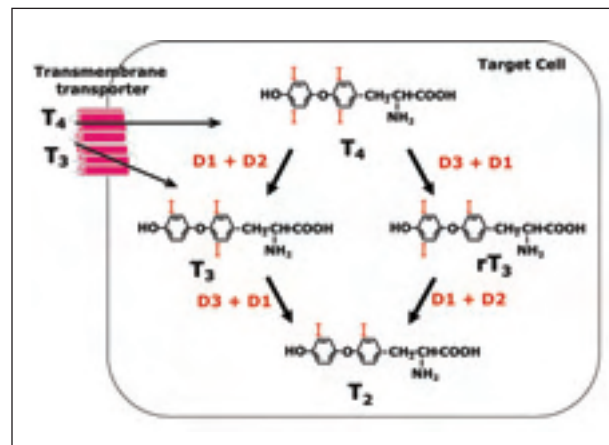


Figure 1. Regulation of intracellular TH bioactivity. After active cellular uptake of TH through transmembrane transporters, the precursor, 3,3',5,5'-tetraiodothyronine (thyroxine, T_4), is converted into the active 3,3',5-triiodothyronine (T_3) hormone or inactive 3,3',5'-triiodothyronine metabolite (reverse T_3 , rT_3). Deiodinases 1 (D1) and 2 (D2) are the principal enzymes that catalyze 5'-deiodination, converting T_4 to T_3 and rT_3 to 3,3'-diiodothyronine (T_2), whereas deiodinase 3 (D3), and to a lesser extent D1, catalyze 5-deiodination, converting T_4 to rT_3 and T_3 to T_2 .

Identification of *MCT8* Gene Defects

A form of mental retardation associated with motor abnormalities was described in 1944⁴ and subsequently named the Allan-Herndon-Dudley (A-H-D) syndrome. This condition was further mapped to a locus on chromosome X: Xq13-q21⁵ and Xq12-q13.⁶ In 2004, two laboratories identified, independently, mutations in the *MCT8* gene in 7 unrelated families, in which males presented with high serum T_3 , and low T_4 and rT_3 concentrations, together with psychomotor abnormalities reminiscent of the A-H-D syndrome.^{7, 8} The following year, families previously identified as suffering from the A-H-D syndrome, including the family first reported in 1944, were found to harbor mutations in the *MCT8* gene and had high serum T_3 levels.⁹

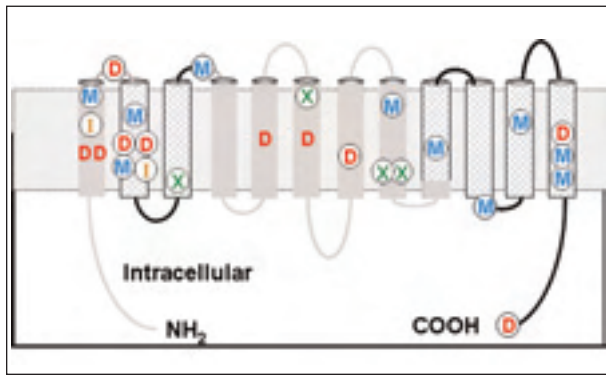


Figure 2. *MCT8* gene mutations in 26 families. Their type and location are presented graphically (M, missense; X, nonsense; I, insertion; D, deletion).

We now know of 26 families with *MCT8* gene mutations^{10, 11} (and personal observations). The mutations are distributed throughout the coding region of the gene (Fig. 2). Single amino acid substitutions causing missense mutations were found in 10 families and in 4 they resulted in nonsense mutations. Single amino acid deletions or insertions were each reported in 2 families. One or two nucleotide deletions or insertions produced 2 stop codons, and in one case a 64-amino-acid extension of the carboxyl terminus of the *MCT8* molecule. Deletions of 10 nucleotides or more were reported in 4 families, and in 1, an intronic mutation affected the splice site. It is of note that the mutations F229 Δ and S448X each occurred in 2 unrelated families.

The identification of 26 families with *MCT8* defects in fewer than 3 years indicates that this syndrome is more common than initially suspected. From a population genetics point of view, the spontaneous *MCT8* mutations were maintained in the population because carrier females are asymptomatic, thus preventing negative selection to take place.

Correlation of Genotype with Phenotype

Given the variability in disease severity, we searched for correlations between phenotypes and genotypes. A comparison of the clinical picture in families with identical mutations would have helped determine if such correlations existed. Unfortunately, detailed clinical information is not available in more than one family with each mutation. However, early deaths were reported in two families with a truncated *MCT8* molecule (S448X); two affected males died at ages 13 and 39 years in one, and at 20, 22, and 30 years in the other. Early death was also reported in subjects harboring the P537L, 404 frameshift 416X, F229 Δ , S194F, and 612 frameshift with 64-amino-acid carboxyl-terminal extension mutations. Aspiration pneumonia caused death in 4 of 14. The ability to predict outcome by genotype would help in patient care and genetic counseling.

Functional analysis of cellular T_3 uptake in 12 different mutations¹⁰ revealed no activity in 4, 2 missense (Leu471Pro and Leu512Pro), and 2 nonsense (Arg245X and Ser448X). In three mutations, del Phe229, ins Ile189, and Ala224Val, uptake was from 2.4% to 5%. In the remaining five, T_3 uptake ranged from 8.6% to 33%, compared to 100% for the

wild-type *MCT8*; all five were missense mutations (S194F, V235M, R271H, L434W, and L598P).

Available clinical, chemical, and in vitro information does not clearly correlate with the degree of T_3 transport impairment by mutant *MCT8* molecules nor with the serum T_3 levels. This is probably due to the important role played by underlying perturbations in iodothyronine metabolism involved in T_3 production, as demonstrated in *Mct8* knockout mice.¹² Furthermore, no clinical consequence other than early death appears to correlate significantly with the degree of functional or structural disruption of the *MCT8* molecule. Genetic factors, variability in tissue *MCT8* expression, and other iodothyronine cell membrane transporters could be the basis for this lack of phenotype/genotype correlation. However, the possibility that *MCT8* is involved in the transport of other ligands has not been excluded.

From Roy E. Weiss, M.D., Ph. D.

How Can Thyroid Hormone Deficiency and Excess Coexist?

TH deprivation and excess are associated with typical symptoms and signs reflecting the effects of global hormonal changes, on all body tissues. A deviation from this rule was recognized with the identification of the syndrome of RTH. In such cases, usually caused by heterozygous mutations in the *TR β* gene, the phenotype is that of high levels of total and free T_4 and T_3 concentrations in the presence of non-suppressed TSH. This paradox extends to clinical and biochemical observations suggesting TH deficiency, sufficiency, and excess, depending on the level of *TR β* gene expression in various tissues. For example, the hypothalamus and pituitary, dependent on *TR β* , manifest relative hormone deprivation, whereas the heart, dependent on *TR α* , exhibits signs of hormone excess in the form of tachycardia.¹ Recently, two new syndromes manifesting a similar paradox have been identified.^{2, 3} One affecting the *MCT8* gene,² located on the X-chromosome and encoding a protein that transports TH across the cell membrane, is the subject of this communication. Typical thyroid function abnormalities in the three syndromes of reduced sensitivity to TH are shown in the table on page 19.

How Did Our Patients Present?

In 2002, we were consulted regarding two boys ages 3 and 8 years, from different families, who presented with severe psychomotor retardation. Evaluation of thyroid function revealed low serum T_4 concentrations and minimally elevated TSH levels. To our surprise, serum T_3 concentrations clearly exceeded the upper normal limit and reverse T_3 (rT_3), the inactive metabolite of T_4 , was below normal. Treatment with L- T_4 produced no clinical response. Although this suggested a defect in TH metabolism, the genes for the three iodothyronine deiodinases involved in the conversion of T_4 to T_3 and

Comparison of thyroid test abnormalities in syndromes of reduced sensitivity to TH

Syndrome	Gene	FT ₄	FT ₃	rT ₃	TSH	Goiter	Other
THCTD	<i>MCT8</i>	↓	↑↑	↓	NL, ↑	-	Severe psychomotor impairment
RTH	<i>TRβ</i>	↑↑	↑	↑↑	NL, ↑	+	Tachycardia, occasional growth problems, ADD
THMD	<i>SBP2</i>	↑	↓	↑↑	NL, ↑	-	Growth delay

THCTD, TH cell transport defect; THMD, TH metabolism defect; NL, normal; FT₃, free triiodothyronine; rT₃, reverse T₃; ADD, attention deficit disorder.

rT₃ and deiodination of T₃ and rT₃ to T₂, were normal. However, we found mutations in the newly identified X-linked TH transporter, *MCT8* (monocarboxylate transporter 8),⁴ suspected because a defect in a TH transmembrane transporter could account for the observed thyroid function tests.

The Global Clinical Picture

Within a year, more than 100 individuals from 11 additional families with similar thyroid test abnormalities and severe psychomotor retardation, in males only, were found to have *MCT8* gene defects.^{5, 6} Review of these families indicates that parents were not consanguineous and gestation and delivery were normal. Infants were normal in length, weight, and head circumference. Early signs of a defect were hypotonia and feeding difficulties within the first few weeks of life. With advancing age, weight gain lagged and microcephaly became apparent, although linear growth proceeded normally. Whereas truncal hypotonia persisted, progressive development of limb rigidity led to spastic quadriplegia, often with joint contractures. In these cases, muscle mass is diminished with generalized muscle weakness, often with myopathic facies, but characteristic poor head control, originally described as "limber neck."⁷ Purposeless movements in the form of choreoathetosis and characteristic paroxysms of kinesigenic dyskinesias are common. The latter are typically triggered by somatosensory stimuli such as changing of clothes or lifting the child. Attacks consist of body extension, opening the mouth, and limb stretching or flexing that last less than minutes.⁸ In addition to these nonepileptic events, true seizures can also occur. Reflexes are usually brisk, clonus is often present, but nystagmus and extension plantar responses are less common. Most affected children are never able to sit by themselves or walk; those who do so lose the ability with time, indicating progressive deterioration.

Cognitive impairment is severe. Individuals never develop speech or, at most, acquire the ability to emit garbled sounds. Their behavior is otherwise normal, and they appear to respond with a social smile.

Although brain MRI is often normal, atrophy of the cerebrum, thalamus, and basal ganglia have been reported, probably reflecting dysmyelination.^{9, 10}

Female carriers do not manifest any of these psychomotor abnormalities. However, intellectual delay and frank mental retardation have been described.^{2, 11}

Thyroid Test Abnormalities

Most characteristic, if not pathognomonic, are the high serum T₃ and low rT₃ concentrations. Although T₄ is reduced in most cases and is usually the first thyroid abnormality identified during neonatal screening, T₄ is normal in some individuals.¹² TSH levels are normal or slightly elevated, rarely above 6 mU/L. Interestingly, heterozygous female carriers have serum TH concentrations intermediate between affected males and unaffected family members (Fig. 3), yet they lack the typical psychomotor abnormalities always found in affected males.

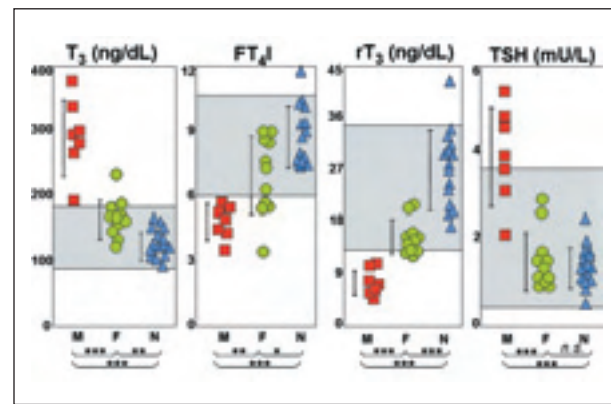


Figure 3. Thyroid function tests from 6 families studied at the University of Chicago: 7 affected males (M), 11 carrier females (F), and 15 unaffected family members (N). (**P* < .05; ***P* < .01; ****P* < .001). Shaded area depicts the normal range for the corresponding test. Bars represent 2 SDs.

From Alexandra Dumitrescu, M.D., Ph.D.

Mechanisms for Targeted Delivery of Thyroid Hormone

Constancy of TH level is ensured by a feedback control mechanism. A decrease in the circulating TH concentration produces a hypothalamus-mediated stimulation of TSH secretion from the pituitary thyrotrophs, which stimulate the thyroid to synthesize and secrete more hormone. In contrast, TH excess shuts the system down using the same pathway. This centrally regulated system does not consider changes in TH demand in a particular organ or cell. Local TH requirements are regulated by additional processes such as the control of TH entry into the cell through active transmembrane transporters¹ and activation of the hormone precursor T₄ by removal of the outer ring iodine (5'-deiodination) to form T₃ or inactivation of

T_4 and T_3 by inner ring 5'-deiodination to form rT_3 and T_2 , respectively. The activating deiodinases are D1 and D2, whereas the inactivating enzyme is D3. Their presence in changing concentrations in various cell types allows an additional level of local hormone supply regulation.² Finally, the presence and abundance of TRs, through which TH action is mediated, determine the type and degree of hormonal response.³

The Working Model

From this it is evident that the local (tissue) TH effects may not be proportional to the circulating hormone level. This served as the basis for rationalizing the unusual clinical and biochemical manifestations observed in TH transport abnormalities due to *MCT8* gene defects. However, support for this paradigm could not be provided by human data. A putative selective T_3 deficiency did not result in the classical cretinism typical of TH deprivation. Nor could the postulated T_3 excess in muscle, presumably causing muscle atrophy, be supported by the high levels of lactic acid found in one case,⁴ but not in others⁵ (and personal observation). Mice lacking functional Mct8 (Mct8 knockout or KO) were thus created to help understand the underlying MCT8 deficiency mechanism.⁶

Mct8-Deficient Mice Recapitulate the Thyroid Phenotype of Humans

Mct8KO mice replicate the characteristic thyroid phenotype observed in humans, high serum T_3 and low T_4 and rT_3 compared to wild-type male littermates.⁶ Thus they provide a good model for the study of the pathophysiology underlying the thyroid phenotype.

Tissue-Specific Thyroid Hormone Excess and Deficiency

Studies of Mct8-deficient mice⁶ have provided much-needed insight into the mechanisms responsible for the thyroid phenotype.⁷ Measurements of tissue T_3 content have demonstrated that the high circulating T_3 levels are differentially available to tissues, depending on redundancy in TH transmembrane transporters. Tissues, such as the liver,¹ which express transporters other than Mct8, proportionally reflect the circulating T_3 levels and are "thyrotoxic" in Mct8-deficient mice (Fig. 4A). The baseline hepatic thyrotoxicosis in *Mct8KO* mice results in increased D1 enzymatic activity (Fig. 4B), decreased serum cholesterol levels, and increased serum alkaline phosphatase levels (Fig. 4C). In contrast, tissues with limited redundancy in cellular TH transporters, such as the brain,¹ have decreased T_3 content in *Mct8KO* mice (Fig. 4D). As a consequence, local D2 enzymatic activity is increased (Fig. 4E), as its role is to maintain local levels of T_3 through posttranslational up-regulation by TH deficiency.²

Our findings of coexistent T_3 excess and deficiency in *Mct8KO* mouse tissues can explain, in part, the mechanisms

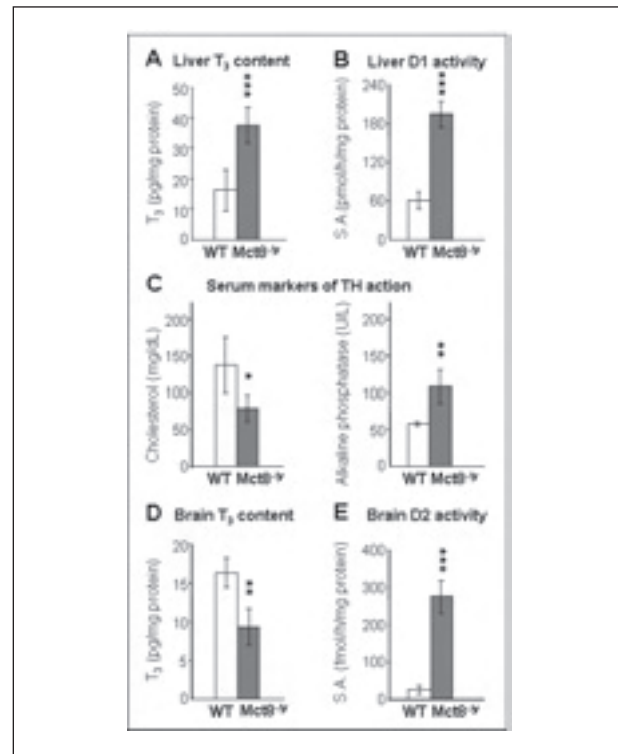


Figure 4. Consequences of Mct8 deficiency: (A) Liver T_3 content; (B) Liver deiodinase 1 enzymatic activity; (C) Serum cholesterol and alkaline phosphatase levels; (D) Brain T_3 content; (E) Brain deiodinase 2 enzymatic activity. Bars represent mean \pm SD. (WT, male wild-type mice; *Mct8*^{-/-}, male *Mct8* knockout mice; S.A., specific activity; * $P < .05$, ** $P < .01$, *** $P < .001$).⁶

responsible for the thyroid tests pattern observed in Mct8 deficiency.⁶ The increased D1 and D2 activities, stimulated by opposite states of intracellular TH availability, have an additive consumptive effect on T_4 and result in increased T_3 generation. The impaired T_3 uptake in the brain makes circulating T_3 less available to deiodination by D3. The increased liver D1 enzymatic activity also stimulates rT_3 metabolism. These tissue-specific differences in intracellular TH content and consequent changes in TH metabolism are likely responsible for the unusual clinical presentation of this defect compared to global TH deficiency.

Potential Perspective on Treatment and Prevention

Prenatal testing and genetic counseling of carrier females from families with known *MCT8* gene mutations can prevent transmission of this defect to male offspring.

Finding treatment options for patients with *MCT8* gene mutations is challenging. Detection of low T_4 or elevated TSH by neonatal screening has prompted L- T_4 treatment in several patients, but physiological doses did not improve the outcome because the cellular TH uptake is impaired in MCT8-dependent tissues. Administration of T_4 during pregnancy and the efficacy of several TH analogs to bypass the molecular defect using alternative transporters are avenues with therapeutic potential currently tested in Mct8-deficient mice. ■

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