GSC Biological and Pharmaceutical Sciences

eISSN: 2581-3250 CODEN (USA): GBPSC2

Cross Ref DOI: 10.30574/gscbps

Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

Check for updates

Relationship between MCT8 gene and thyroid disorder

Hayam Aziz Mohammed *

Department of Biology, College of Education for Pure Science (Ibn Al-Haytham), Baghdad University, Baghdad, Iraq.

GSC Biological and Pharmaceutical Sciences, 2026, 34(02), 118-124

Publication history: Received on 29 December 2025; revised on 07 February 2026; accepted on 10 February 2026

Article DOI: https://doi.org/10.30574/gscbps.2026.34.2.0048

Abstract

Thyroid hormone metabolism, intracellular activity, and transmembrane transport are processes facilitated by specific transport proteins. Over the past 20 years, several thyroid hormone transporters have been discovered, such as monocarboxylate transporter 8 (MCT8). MCT8 is a 12-domain transmembrane protein that crosses the cell membrane and transports monocarboxylates. The MCT8 gene (encoded by SLC16A2) is located on chromosome Xq13.2. This transporter (MCT8) is essential for the uptake of thyroid hormone (T3) in neurons and also plays a crucial role in optimal neuronal development. MCT8 supplies neurons with T3 and is found in the choroid plexus and neuronal cell membranes. The hypothalamus has been identified as an important site for integrating thyroid hormone feedback and gene control, and several pathogenic mutations in the MCT8 transporter are associated with it. These mutations include large-scale deletions involving one or more missing exons, frameshift mutations, deletions or insertions of a single amino acid, and alterations in a single amino acid. Some have also been observed in multiple unrelated cases. Several of these mutations have been functionally evaluated in cell lines that permanently or temporarily overexpress MCT8, resulting in complete loss of MCT8 function.

Keywords: Transport Monocarboxylate; Thyroid Hormone; Genetic Mutations

1. Introduction

Thyroid hormone is a critical regulator of physiological processes essential for growth, differentiation, and functional maintenance of multiple organs, particularly the brain, cardiovascular system, liver, and skeletal muscle [1]. Cellular metabolism and oxygen are modulated. energy homeostasis, protein synthesis, and consumption, all of which are essential for regular growth as well as systemic function [2]. Triiodothyronine (T3), the form that is biologically active, acts through nuclear thyroid hormone receptors, which are transcription factors that depend on ligands. regulating target cell gene expression [3]. Thyroid hormones are mostly found as thyroxine (T4). and triiodothyronine (T3), which are both produced by thyroid follicular cells under the control of TSH, or thyroid-stimulating hormone [4]. T4 is secreted in greater quantities, but it primarily serves as a prohormone converted intracellularly to the active T3 by iodothyronine deiodinases, allowing regulation of thyroid hormone action in tissue [5]. Therefore, one important factor influencing hormone bioactivity is intracellular T3 concentration. Because thyroid hormones are lipophilic, it was once believed that they would passively diffuse across membranes. However, increasing data indicate that specialized transporters are primarily responsible for cellular uptake [6]. The SLC16A2 gene encodes the high-affinity, T3-specific transporter MCT8. MCT8 plays a crucial role in neurodevelopment and metabolic regulation, as evidenced by its high expression in neurologically important tissues like the brain and liver [7]. Thyroid hormones can also cross membranes with the aid of other transporters. Solute carriers that are limited to specific tissues and substrates include organic anion-transporting polypeptides (OATPs), particularly OATP1C1, which facilitates T4's entry into the brain. [8]. Thyroid hormones can be metabolized and bind nuclear receptors in intracellular compartments where their physiological effects are determined thanks to the coordinated action of these transporters [9].

* Corresponding author: Hayam Aziz Mohammed

Genetic abnormalities in the thyroid hormone transporter have important clinical implications. SLC16A2 mutations cause Allan-Herndon-Dudley syndrome (AHDS), an X-linked neurodevelopmental disorder characterized by severe cognitive and motor impairment, hypotonia, and abnormal thyroid hormone profiles due to defective neuronal uptake [10]. These abnormalities are replicated in animal models such as Mct8 and Mct8/Oatp1c1 knockout mice, which show poor thyroid hormone delivery to the brain and related neurological dysfunction [11]. For some deficiencies, triac and other thyroid hormone analogs showed promise as substitute treatments. We now have a better understanding of thyroid hormone transport pathways thanks to recent structural biology research. The structure of human MCT8 in relation to T3 and its ligands was determined using cryoelectron microscopy, which revealed characteristics that affect substrate recognition, transporter selectivity, and conformational dynamics during hormone translocation [12, 13]. These findings open up new possibilities for specialized therapeutic approaches and help to clarify pathways. Lastly, intracellular metabolism, transporter-mediated cellular uptake, and receptor interaction are some of the crucial processes that control thyroid hormone bioactivity [14].

A comprehensive understanding of MCT8 and related transporters is therefore essential for elucidating normal thyroid physiology and the pathogenesis of thyroid hormone–related neurological and metabolic disorders [15].

2. Pathophysiology of Thyroid Disease

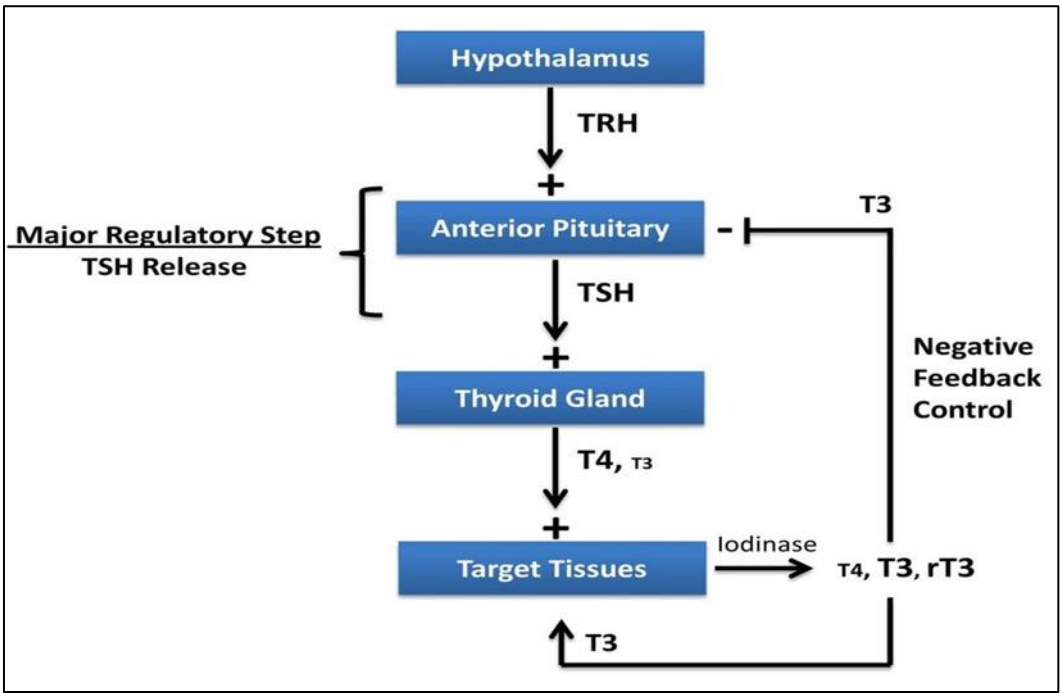

Figure 1 Regulation of thyroid hormone synthesis and secretion (hypothalamus - pituitary gland) [21]

A hormone gland involved in human growth, development, and metabolism is the thyroid. The butterfly-shaped thyroid gland (glandular thyroidal) is located at the front of the neck, beneath the protrusion of the Adam's apple (thyroid cartilage). Its two side lobes are joined at the front by an isthmus and surround the trachea. In 16 Thyroglobulin (TG) and enzymes like thyroid peroxidase (TPO), which are in charge of organification, oxidation, and coupling reactions, are found in the colloid that fills the central lumen of each lobe, which is composed of follicles made of follicular and parafollicular cells [16]]17].The thyroid hormones triiodothyronine (T3) and thyroxine (T4), which affect baseline metabolic processes and increase oxygen consumption in almost all body tissues, are produced by the gland and released into the bloodstream [18]. Additionally, thyroid hormones affect neural development, dentition, bone development, linear growth, and brain function, including intelligence and memory [19]. Thyroid-stimulating hormone (TSH), which is secreted by the anterior pituitary gland, controls hormone synthesis. The hypothalamus produces thyrotropin-releasing hormone (TRH) [20]. Thyrotropin cells secrete the hypothalamic peptide thyrotropin-releasing hormone (TRH), which controls pituitary stimulating hormone (TSH), which controls the production of thyroid hormone through G protein-coupled TSH receptors on follicular cells (Figure 1) [21]. TSH attaches to and activates the thyroid gland by a well-known mechanism. The enzyme denylate cyclase, which is found in the plasma membrane, is activated when TSH binds to a particular membrane receptor on the surface of the thyroid epithelial cell. This activation raises intracellular levels of cyclic adenosine monophosphate (cAMP), which in turn stimulates additional intracellular

signaling events that result in the synthesis and secretion of thyroid hormone through negative feedback [22]. TSH secretion and sensitivity to TSH decline as T3 levels rise. T4 and T3 are generated and released after circulating iodide is absorbed at the basolateral membrane [23].

3. Thyroid hormone transporter families

The transport of thyroid hormones across cell membranes, whether into the cell (absorption) or into the extracellular environment (exocytosis), or through a combination of both mechanisms, depends primarily on a specialized system of membrane transporters. Available evidence suggests that end thyroxine (ETH) can cross the cell membrane via approximately sixteen different thyroid hormone transporters [24]. These transporters belong to five distinct protein families, most notably monocarboxylate transporters (SLC16, also known as MCTs), L-type amino acid transporters (LATs), and organic anion transporters, including the OATP, SLC10, and SLC17 families [25]. It is important to note that the ability of some of these proteins to function as thyroid hormone transporters requires specific cellular conditions, such as ionic gradients or binding to cofactors, which directly impacts the kinetics of cellular transport in both absorption and excretion [26].Such transport behavior is commonly observed in secondary active transport systems that exploit pre-existing ionic gradients, most notably those established by sodium (Na^+) or hydrogen ions (H^+)[27]. Through functional coupling to these ions, the transporters enhance the passage of thyroid hormones across the plasma membrane in accordance with electrochemical driving forces [28]. Monocarboxylate transporters (MCTs) are integral membrane proteins composed of several membrane-crossing regions, which are most commonly organized into twelve transmembrane helices [29]. Rather than serving a single function, these transporters participate in the controlled influx and efflux of a diverse group of substrates across the cell membrane. This group includes monocarboxylates and selected aromatic amino acids, such as lactate, pyruvate, ketone bodies, and carnitine. Through this activity, MCTs contribute directly to the regulation of intracellular metabolic balance [30][31].

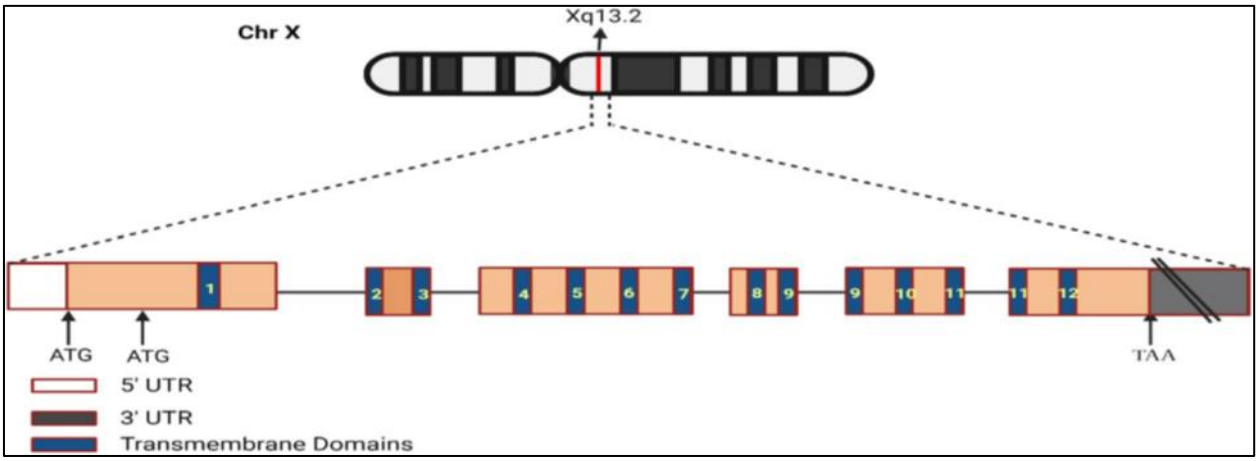

Figure 2 MCT8/SLC16 genome arrangement The A2. An illustration of the MCT8 gene at location Xq13.2 on the X chromosome. ATG stands for transcription start site, and TAA for transcription stop Sitting In [32]

4. The physiological function of the thyroid hormone receptor MCT8

The thyroid hormone transporter MCT8 has a unique role as almost all tissues, such as basal metabolism, tissue control, and regeneration, depend on thyroid hormones, especially the active hormones T4 and T3 [33]. While plasma membrane transporter proteins enable the uptake and flow of T4 and T3, the enzyme deiodinase 3 (DIO1-3) either activates or deactivates thyroid hormones and influences the T3 concentration within the target thyroid cells [34, 35]. Only around 0.1% of the total amount of circulating thyroid hormone, or T4, can enter the cells in the unbound phase by a transporter-mediated process (Figure 3A) [36].

Because it supplies neurons with T3 and controls its levels in brain tissues, MCT8, which is found in the choroid plexus and neuronal cell membranes, is crucial to the development of the nervous system [37]. As a result, the brain's only source of T3 is the creation of endogenous T3 levels, which neurons can access via a number of membrane transporters [1]. This involves a number of mechanisms, including astrocytes' uptake of T4 and deiodinase 2's (D2) conversion of T4 to T3. The astrocytes then produce T3, which is then carried to the neurons via the nuclear receptor, where D3 will continue to degrade T3 (Figure 3B) [23][38].

A number of destructive alterations in the MCT8 transporter cause changes in T3 levels and neurological problems in the hypothalamus, which is a vital site for processing feedback from thyroid hormones and regulating genes [39]. Myelination is a critical phase in brain development in which thyroid hormones play a key role. Individuals with an inactive mutation in the MCT8 gene, which can affect how thyroid hormone works on oligodendrocytes, have been shown in studies to experience delays in the myelination process [40].

It leads to impaired production of oligodendrocytes and also an increased ratio of small to large axons, both of which are associated with MCT8 Allan-Herndon-Dudley syndrome, which is linked to the X chromosome and caused by non-functional mutations in the SLC16A2 gene, first documented in 1944. Patients with this disease suffer from significant motor-neuro impairment with central hypotonia, as well as spasms, lack of coordination, global developmental delay, severe intellectual disability, basic communication abilities, and speech impairment. [41].

In various studies conducted, researchers reported individuals with similar clinical weakness and changes in serum thyroid hormone concentrations, such as increased T3 and decreased T4 and T3, along with normal or slightly elevated TSH values. Mutations in the gene encoding MCT8 were found as a result of these hormonal abnormalities, which suggested a malfunction in thyroid hormone metabolism. [42].

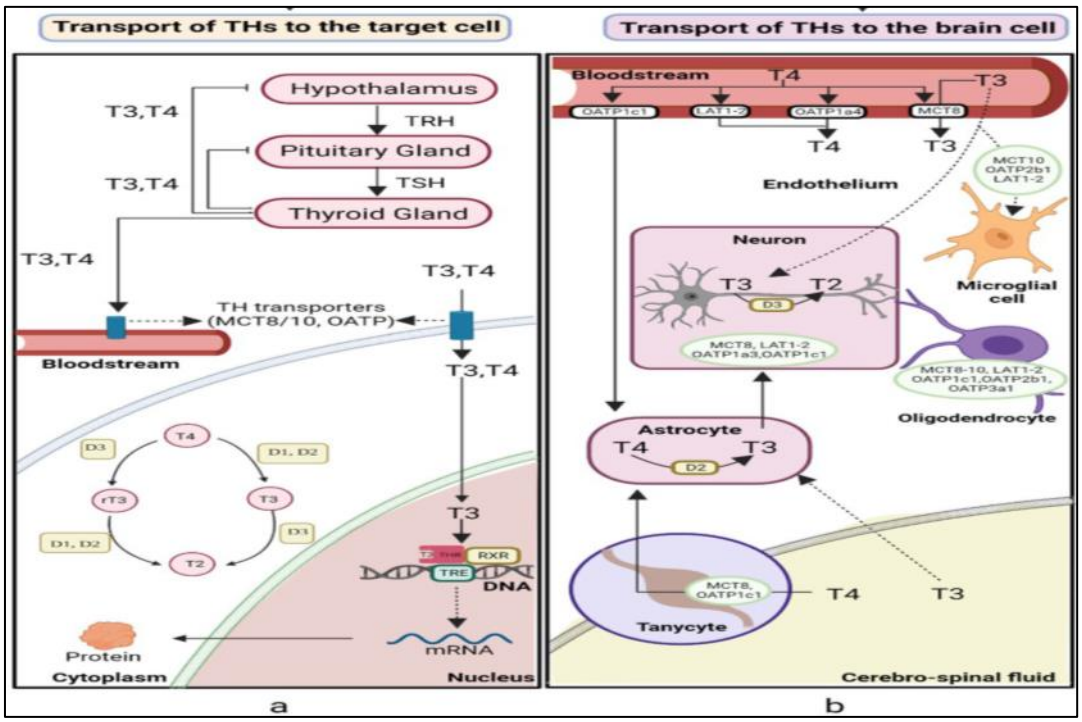

Figure 3 (a) MCT8's function in blood TH transportation and its impact on the target cell. (b) The MCT8 transporter's function in TH absorption in brain cells [43]

5. Genetic mutations in Monocarboxylate transporter) MCTs8)

Genetic Alterations in SLC16A2 With a diversity of underlying genomic mutations, Allan-Herndon-Dudley syndrome has been identified in at least 320 overstated people from 132 families [44]. These mutations include frameshifts deletions or insertions of a single amino acid, massive deletions that result in the loss of one or more exons, and on its own amino acid changes, some of which have been found in multiple unrelated cases. While a portion of these mutations have demonstrated notable residual function, several of these mutations have been functionally assessed in cell lines that either temporarily or permanently overexpress MCT8 and have resulted in total loss of MCT8 function [45]. These functional studies have identified about three distinct pathogenic pathways. The transporter's mobility is changed by the first class of mutations, but its expression levels at the cell membrane are unaffected. These mutations can eliminate MCT8-mediated thyroid hormone transport entirely (class 1b) or partially (class 1a). Mutations that disrupt protein stability and/or transit to the cell membrane make up the second type. Different cell types may exhibit varying levels of residual activity of these mutant transporters. The first two categories primarily include heterozygous mutations and single amino acid insertions or deletions. Large deletions, early stop mutations, and primarily frame shift mutations that totally deactivate the MCT8 protein irrespective of the test model comprise the third class of mutations. MCT8 has been

identified as the primary thyroid hormone transporter in dermal fibroblasts, additionally to these in vitro overexpression investigations.

Because of this, multiple groups have employed these cells as an ex vivo model of MCT8 deficiency [46] [47]. Although the genotype-phenotype relationship is still unknown, both methods may offer a helpful method for predicting the degree of neurocognitive impairment [48].

6. Conclusion

The translocation of thyroid hormones across cell membranes is an essential stage in controlling thyroid function and physiological functions. MCT8 is the primary specialized protein facilitating this translocation, unlike other transporters which can handle it to varying degrees. Mutations in the gene encoding this transporter have been shown to cause serious X-linked neurodevelopmental disorders, associated with marked impairments in thyroid hormone secretion and metabolism. There are three major classes of disease-causing mutations in the MCT8 gene, each characterized by a distinct molecular mechanism. In most cases, class I mutations do not significantly affect the level of MCT8 protein expressed at the cell membrane, indicating that membrane targeting is largely preserved. In contrast, class II mutations primarily impair transporter function by reducing protein stability or disrupting its intracellular trafficking. These molecular alterations result either in decreased levels of MCT8 at the plasma membrane or in an increased rate of protein turnover at the membrane surface. Pathogenic mutations affecting the MCT8 gene can be classified into three main categories, differing in the molecular mechanisms governing their functional effects. In most cases, mutations in the first category do not show a significant change in the levels of MCT8 protein located on the cell membrane, indicating that the protein's translocation process remains largely intact. In contrast, mutations in the second category are associated with impaired transporter function, primarily affecting protein stability or its intracellular transport pathways, which negatively impacts its functional efficiency.

References

[1] Freund MET, van der Most F, Visser WE. Diagnosis and therapy in MCT8 deficiency: ongoing challenges. J Clin Res Pediatr Endocrinol. 2024;16(1):1–3. doi: 10.4274/jcrpe.galenos.2024.2024-1-23.

[2] Salas-Lucia F, et al. Impaired thyroid hormone transport in MCT8-deficient human cerebral organoids underlies neurodevelopmental defects. JCI Insight. 2024;9(7):e174645. doi: 10.1172/jci.insight.174645.

[3] Tan J, et al. Structural insights into thyroid hormone transporter MCT8 revealed by cryo-EM. Nat Commun. 2025; 16:813. doi:10.1038/s41467-025-58131-8.

[4] Groeneweg S, et al. Mapping variants in thyroid hormone transporter MCT8 to disease severity by genomic and functional integration. Nat Commun. 2025; 16:642. doi:10.1038/s41467-025-56628-w.

[5] Gavryutina I, Fordjour L, Chin VL. Genetics of thyroid disorders. Endocrines. 2022;3(2):198–213. doi:10.3390/endocrines3020018.

[6] Felmlee MA, Jones RS, Rodriguez-Cruz V, Morris ME. Monocarboxylate transporters (SLC16): function, regulation, and role in health and disease. Pharmacol Rev. 2020;72(2):466–485. doi:10.1124/pr.119.018762.

[7] Giannocco G, Kizys MM, Maciel RM, de Souza JS. Thyroid hormone action in the central nervous system. Semin Cell Dev Biol. 2021; 114:47–56. doi: 10.1016/j.semcdb.2020.12.003.

[8] Bianco AC, Dumitrescu AM, Gereben B, et al. Paradigms of dynamic control of thyroid hormone signaling. Endocr Rev. 2019; 40:1000–1047.

[9] Prezioso G, Giannini C, Chiarelli F. Effect of thyroid hormones on neurons and neurodevelopment. Horm Res Paediatr. 2018; 90:73–81. Groeneweg S, et al. MCT8 deficiency in females with skewed X-inactivation. J Clin Endocrinol Metab. 2025.

[10] Valcárcel-Hernández V, et al. Deficient thyroid hormone transport to the brain impairs axonal caliber and oligodendroglial development. Neurobiol Dis. 2022; 162:105567. doi: 10.1016/j.nbd.2022.105567.

[11] Gothié JD, Vancamp P, Demeneix B, Remaud S. Thyroid hormone regulation of neural stem cell fate. Acta Physiol. 2020;228: e13316. doi:10.1111/apha.13316.

[12] Thomas J, Sairoz J, Jose A, et al. Role and clinical significance of monocarboxylate transporter 8 during pregnancy. Reprod Sci. 2023;30(6):1758–1769. doi:10.1007/s43032-022-01162-z.

[13] Dubinski I, et al. MCT8 deficiency in infancy: opportunities for early diagnosis and screening. Newborn Screening. 2025;11(3):66.

[14] Novara F, et al. Clinical and molecular characteristics of SLC16A2 mutations in Allan–Herndon–Dudley syndrome. Hum Mutat. 2017;38:260–264.

[15] Capri Y, Friesema EC, Kersseboom S, et al. Relevance of cellular models for functional characterization of MCT8 mutations. Hum Mutat. 2013;34(7):1018–1025.

[16] Visser WE, et al. Novel pathogenic mechanisms suggested by ex vivo analysis of MCT8 mutations. Hum Mutat. 2009;30(1):29–38.

[17] Groeneweg S, et al. Chemical chaperones improve thyroid hormone transport by MCT8 mutants. Endocrinology. 2018;159(3):1290–1302.

[18] Braun D, Schweizer U. Efficient activation of pathogenic MCT8 mutations by pharmacological chaperones. Endocrinology. 2015;156(12):4720–4730.

[19] Mullur R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. Physiol Rev. 2014; 94:355–382.

[20] Silva JF, Ocarino NM, Serakides R. Thyroid hormones and female reproduction. Biol Reprod. 2018; 99:907–921.

[21] Wirth EK, Schweizer U, Köhrle J. Transport of thyroid hormone in the brain. Front Endocrinol (Lausanne). 2014; 5:98.

[22] Strømme P, et al. Mutated thyroid hormone transporter OATP1C1 associates with neurodegeneration. Thyroid. 2018;28(11):1406–1415.

[23] Mayerl S, et al. Transporters MCT8 and OATP1C1 maintain brain thyroid hormone homeostasis. J Clin Invest. 2014; 124:1987–1999.

[24] Braun D, et al. Developmental and cell-specific expression of thyroid hormone transporters in the brain. Glia. 2011; 59:463–471.

[25] Bernal J, Guadano-Ferraz A, Morte B. Thyroid hormone transporters: functions and clinical implications in brain development and disease. Front Endocrinol (Lausanne). 2021; 12:656125. doi:10.3389/fendo.2021.656125.

[26] Brent GA. Mechanisms of thyroid hormone action. J Clin Invest.2012;122:3035–3043.

[27] Uter JC, et al. Polymorphisms in MCT8, MCT10 and DIO2 contribute to cognitive variability. Exp Clin Endocrinol Diabetes. 2020; 128:573–581.

[28] Sperling MA, et al. Disorders of the thyroid in the newborn and infant. Pediatric Endocrinology. Elsevier; 2014.

[29] Armstrong M, Asuka E, Fingeret A. Physiology, thyroid function. StatPearls Publishing. 2021.

[30] Pirahanchi Y, Tariq MA, Jialal I. Physiology, thyroid. StatPearls Publishing. 2021.

[31] Dietrich JW, et al. TSH and thyrotropic agonists in thyroid homeostasis. J Thyroid Res. 2012; 2012:351864.

[32] Dumitrescu AM, et al. A novel syndrome combining thyroid and neurological abnormalities associated with MCT8 mutations. Am J Hum Genet. 2004; 74:168–175.

[33] Wang Y, Wang T, Montero-Pedrazuela A, Guadaño-Ferraz A, Rausell E.

[34] Thyroid hormone transporters MCT8 and OATP1C1 are expressed in pyramidal neurons and interneurons in the adult motor cortex of human and macaque brain. Int J Mol Sci. 2023;24(4):3207. doi:10.3390/ijms24043207.Wang Y, Wang T, Montero-Pedrazuela A, Prensa L, Guadaño-Ferraz A, Rausell E.

[35] Thyroid hormone transporters MCT8 and OATP1C1 are expressed in projection neurons and interneurons of basal ganglia and motor thalamus in adult human and macaque brains. Int J Mol Sci. 2023;24(11):9643. doi:10.3390/ijms24119643.

[36] Bauer A, Auble H, Clark M, et al.Unmet patient needs in monocarboxylate transporter 8 (MCT8) deficiency. Orphanet J Rare Dis. 2024; 19:112. doi:10.1186/s13023-024-03012-9.

[37] Wagenaars F, van Herwaarden AE, Friesema ECH, et al.Screening for endocrine disrupting chemicals inhibiting MCT8-facilitated thyroid hormone transport using a modified non-radioactive assay. Toxicol In Vitro. 2023; 96:105770. doi: 10.1016/j.tiv.2023.105770.

[38] Remerand G, et al. MCT8 deficiency in females: clinical, genetic and functional data. J Clin Endocrinol Metab. 2025;110(1): e145–e156. doi:10.1210/clinem/dgaf311.

[39] Kersseboom S, et al.Structural insights into brain thyroid hormone transport via MCT8 and OATP1C1. Cell. 2025;188(20):5576–5588.e17. doi: 10.1016/j.cell.2025.06.032.

[40] Salas-Lucia F, et al.Impaired T3 uptake and action in MCT8-deficient cerebral organoids underlie Allan-Herndon-Dudley syndrome. JCI Insight. 2024;9(7): e174645. doi: 10.1172/jci.insight.174645.

[41] Groeneweg S, Peeters RP, Visser WE, Visser TJ.Thyroid hormone transporters in endocrine and neurological disease. Nat Rev Endocrinol. 2022; 18:177–190. doi:10.1038/s41574-021-00576-3.

[42] Graffunder A, Bresser ABJ, Anthofer L, et al.Spatiotemporal expression of the thyroid hormone transporter MCT8 during cortical neurogenesis in human cerebral organoids. Endocrine Abstracts. 2022;84:PS1-04-35.

[43] Hagestedt A, et al.Emerging roles of thyroid hormone transporters in neurodevelopmental and neurodegenerative disorders. Neuropharmacology. 2023; 210:109000. doi: 10.1016/j.neuropharm.2022.109000.

[44] Lee HJ, Smith TL, Nguyen QT, et al.Genotype–phenotype spectrum of SLC16A2 mutations causing X-linked intellectual disability. Mol Genet Genomic Med. 2024;12(4):e2156. doi:10.1002/mgg3.2156.

[45] Zhou Y, et al.Functional impact of structural variants in MCT8 on thyroid hormone transport efficiency. Hum Mol Genet. 2024;33(12):1512–1525. doi:10.1093/hmg/ddae042

[46] Fernandez A, Bernal J.Role of thyroid hormone transporters in human brain development. Front Neurosci. 2022; 16:947319. doi:10.3389/fnins.2022.947319.

[47] Petrovic S, et al.Single-cell transcriptomic insights into thyroid hormone transporter regulation during neural circuit formation. Nat Neurosci. 2023;26(8):1125–1136. doi:10.1038/s41593-023-01345-7.

[48] Gupta R, et al.Identification of small-molecule modulators of MCT8 transport activity through high-throughput screening. J Pharmacol Exp Ther. 2023;386(3):123–136. doi:10.1124/jpet.123.001245.