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The syndromes of reduced sensitivity to thyroid hormone

Alexandra M. Dumitrescu, MD PhD and

Department of Medicine, The University of Chicago, Chicago, Illinois, USA

Samuel Refetoff, MD

Departments of Medicine, Paediatrics and Genetics, The University of Chicago, Chicago, Illinois, USA

Abstract

Background—Six known steps are required for the circulating thyroid hormone (TH) to exert its action on target tissues. For three of these steps, human mutations and distinct phenotypes have been identified.

Scope of Review—The clinical, laboratory, genetic and molecular characteristics of these three defects of TH action are the subject of this review. The first defect, recognized 45 years ago, produces resistance to TH and carries the acronym, RTH. In the majority of cases it is caused by *TH receptor β* gene mutations. It has been found in over 3,000 individuals belonging to approximately 1,000 families. Two relatively novel syndromes presenting reduced sensitivity to TH involve membrane transport and metabolism of TH. One of them, caused by mutations in the TH cell-membrane transporter *MCT8*, produces severe psychomotor defects. It has been identified in more than 170 males from 90 families. A defect of the intracellular metabolism of TH in 10 individuals from 8 families is caused by mutations in the *SECISBP2* gene required for the synthesis of selenoproteins, including TH deiodinases.

Major Conclusions—Defects at different steps along the pathway leading to TH action at cellular level can manifest as reduced sensitivity to TH.

General Significance—Knowledge of the molecular mechanisms involved in TH action allows the recognition of the phenotypes caused by defects of TH action. Once previously known defects have been ruled out, new molecular defects could be sought, thus opening the avenue for novel insights in thyroid physiology.

Keywords

thyroid hormone; nuclear receptor; transmembrane transporter; selenoprotein; deiodinases; metabolism; MCT8; RTH; SBP2; inherited defects

Introduction

The concept of resistance to thyroid hormone (RTH) was born with the observation of apparent high thyroid hormone (TH) levels in three siblings that did not present symptoms

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Corresponding author: Samuel Refetoff, 5841 S. Maryland Ave MC3090, Univ of Chicago Medical Center, Chicago, IL 60637, srefetof@uchicago.edu, 773-702-6939.

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rezistenta la hh ty prin mutatii in receptorul beta a hh ty, rar prin defecte de receptor alpha
defecte de transport transmembranare defecte de metabolism ale hh ty

and findings of hormone excess, but rather hormone sufficiency and even deficiency [1, 2]. The identification of other cases supported the concept of RTH though proof had to await the cloning of the TH receptors (TRs) [3, 4]. In fact, 22 years later, a mutation in the *TRβ* gene (also known as *THRβ*) was found in a subject with RTH [5] closing the circle of hypothesis and proof.

More recently, TH cell membrane transport defects (THCMTD) [6, 7] and TH metabolism defects (THMD) [8] were described. This led to the broadening of the definition of reduced sensitivity to TH to encompass all defects that can interfere with the biological activity of a chemically intact hormone, secreted in normal amounts. The term reduced sensitivity to TH or RSTH, to denote reduced effectiveness of TH in the broader sense, was accepted at the 8th International Workshop on Resistance to Thyroid Hormone, which took place on the Azorean Island of San Miguel, October 2007 [9].

The long sought *TRA* gene (also known as *THRA*) defect was identified and reported only this year [10, 11], making this review particularly timely. We begin with a brief outline of thyroid physiology, including the regulation of hormone synthesis, secretion, transport, metabolism and action. The description of each syndrome in terms of clinical, genetic and biochemical aspects follow this. All reported cases and those not published by the authors have been reviewed and are included in this review. Mechanisms are discussed in light of animal models when available. Some clinical and diagnostic comparisons are provided as well as a combined section on treatment.

Brief outline of thyroid physiology

Supply of TH is insured by a feedback control mechanism involving the hypothalamus, pituitary, and thyroid gland (Fig. 1A). A decrease in the circulating TH concentration causes thyrotropin-releasing hormone (TRH) to be secreted into the portal system, reaching directly the anterior pituitary gland to stimulate the release of thyrotropin (TSH) into the systemic circulation. The latter stimulates the thyroid follicular cells to synthesize and secrete more hormone. TH excess, on the other hand, shuts down the system through the same pathway, until homeostasis is reinstated.

This centrally regulated system does not respond to changes in TH requirements in a particular organ or cell. Local requirements in TH are adjusted by additional mechanisms. One is the control of TH entry into the cell through active transmembrane transporters [12]. Another is the activation of the hormone precursor thyroxine (T_4) by removal of the outer ring iodine (5'-deiodination) to form 3,3',5-triiodothyronine (T_3) or, deactivate T_4 and T_3 by removal of the inner ring iodine (5-deiodination) to form 3,3',5'-triiodothyronine (reverse T_3 ; rT_3) and T_2 , respectively (Fig. 1B). Modulating the concentrations of deiodinases at the cell level, provides additional means for the local regulation of hormone supply [13].

Finally, the abundance and the type of TRs, through which TH action is mediated, determine the nature and degree of hormonal response. TH action takes place in the nucleus with lesser direct effect in the cytosol [14]. The genomic effect of TRs has been most extensively studied [15, 16] (Fig. 1C). TRs are transcription factors that, together with co-regulators, bind to specific areas of DNA on genes whose expression they regulate.

From the foregoing it is obvious that proper TH action requires 1) the availability of an authentic TH, 2) its correct transport across cell membrane, 3) intracellular metabolism and hormone activation, 4) cytosolic and nuclear processing, 5) association with receptors and 6) interaction with co-regulators or other post receptor effects required for the expression of the TH effects.

How Thyroid Hormone Deficiency and Excess Coexist

TH deficiency and excess produce typical symptoms and signs reflecting the effects of global shortage and excess of the hormone, respectively, on all body tissues. A departure to this rule was recognized with the identification of the RTH syndrome. Usually caused by mutations in the *TR β* gene, subjects have high TH levels without TSH suppression. This paradox is observed clinically and in biochemical tests some of which suggest TH deficiency and others sufficiency or excess, depending on the level of *TR β* gene expression in various tissues [17]. The syndrome of TH cell membrane transport defect (THCMTD) presents a similar paradox, as subjects have high serum T₃ concentration but the uptake of TH is not uniform in all tissues and cell types [18].

Resistance to thyroid hormone (RTH)

Intracellular TH action

An optimal amount of intracellular TH, in its active form T₃, is required for the expression of TH action. Rapid, non-genomic action, involving ion channels, oxidative phosphorylation and second messengers, is exerted at the level of the plasma membrane and cytoplasm [14]. The principal and best studied, the genomic effect of TH requires T₃ translocation into the nucleus where it interacts with TRs to activate or repress transcription of target genes. Specific sequences (TH response elements or TREs), at or near the promoter region of these genes, allow binding of TRs to DNA. In the absence of T₃, TRs interact with other molecules, most notably the coregulator retinoid X receptor, and corepressors. The latter produce a silencing effect on genes positively regulated by TH. T₃ binding induces conformational changes in the TR molecule, triggering a chain of events that include, release of the corepressors, recruitment of coactivators and a large number of other proteins, some with histone acetylation activity. In genes positively controlled by TH, this results in the loosening of the nucleosome structure making the DNA more accessible to transcription factors that mediate binding of RNA polymerase II and general transcription initiation factors [19] (Fig. 2).

rezistenta la hh ty - clinic
T4, T3 crescute
TSH nesupresat
fara semne de hiperty sau
alternanta de semne de
hypo si hyper tiroidism
gusa

Cloning of the TR genes in 1986 provided an explanation for a syndrome recognized two decades earlier as refractoriness to TH. Most subjects with RTH were subsequently found to have mutations in the *TR β* gene. While the clinical presentation is variable, the cardinal features are (a) high serum FT₄ and usually also T₃ concentration, (b) non-suppressed (normal or high) serum TSH, (c) absence of the usual symptoms and signs of thyrotoxicosis, and (d) commonly a goiter [17].

Variants: clinical and genetic

genetic
majoritar mutatii receptor beta de hh ty
nou descris mutatii de receptor alpha
15% - cauza necunoscuta, fara mutatii receptor alpha sau beta si fara mозаicism
autozomal dominant,
f:b=3:1; aparent afectare de cofactor, dar nu e identificat
incă care

Before *TR β* gene mutations were recognized, RTH was subdivided on clinical basis into generalized, isolated pituitary and peripheral tissues resistance [20]. Although based on symptoms and signs this sub classification appeared to have a clinical usefulness, it has no logical etiologic grounds since the former two are encountered in individuals with identical *TR β* gene mutations and show no distinctive laboratory differences [21]. The latter clinical subtype of only peripheral tissue resistance was reported in a single patient [22] and represents the development of tolerance to the ingestion of excess TH.

The term nonTR-RTH refers to a subgroup of individuals with the cardinal features of RTH but no mutations in the *TR β* gene. It occurs in 15% of families with RTH. In several of these families mutations in both *TR β* and *TR α* genes have been excluded by cosegregation analysis, thus ruling out mosaicism [23].

First reported in 1996 [24], nonTR-RTH it is clinically and biochemically undistinguishable from RTH with *TR β* gene mutations. In families with more than one affected subject, the inheritance is autosomal dominant. It is 3-fold more frequent in women. The *TR β* gene transcripts are of normal size and abundance. While the genetic defect remains unknown, cultured fibroblasts from such individuals are resistant to the in-vitro effect of TH. The finding of an aberrant interaction of nuclear extracts of fibroblasts from such an individual with the wild-type (WT) *TR β* suggests that the defect involves an aberrant cofactor. However, cosegregation analysis, and direct screening for mutations by DNA sequencing of several families with nonTR-RTH excluded the involvement of coactivators (SRC-1/NCoA-1; and NCoA-3/SRC-3/AIB1/RAC-3), two corepressors (NCoR and SMRT) and two coregulators (RXR γ and TRIP1) as well as the cell-transporter LST-1 (OATP1B1) [23].

RTH due to a *TR α* gene mutation

mutatii rec alpha de hh
ty
prezent mai ales in mm,
oase, inima, creier, tub
digestiv. 2 cazuri
descrie.
megacolon cu
contipatie, omphalocel
macroglosie, eruptie
dentara intarziata
inchidere tarzie a
fontanelelor,
macrocefalie
hipotonie
retard psihomotor

paraclinic: T4 scazut, T₃
mare, rT₃ scazut,
asemanator cu MCT8

The long sought mutation in the *TR α* gene was identified this year by exomic sequencing of DNA obtained from a 6 year-old girl with chronic constipation noted upon weaning at 7 months of age, with growth and developmental delay [10]. The nonsense mutation identified produces a truncated *TR α 1* (E403X) that lacks the C-terminal α -helix. Findings suggestive of TH deficiency involved organs expressing predominantly *TR α* , including bones, gastrointestinal tract, heart, striated muscle and central nervous system. Indeed, X-rays showed patent cranial sutures with wormian bones, delayed dentition, femoral epiphyseal dysgenesis and retarded bone age. In addition, diminished colonic motility with megacolon, slow heart rate, reduced muscle strength were suggestive of hypothyroidism, as was her placid affect, slow monotonous speech and cognitive impairment. Recently, another family with *TR α* gene mutation was reported [11]. In the first three years of life the proposita had macroglossia, omphalocele, congenital hip dislocation, delayed bone age, delayed closure of skull sutures, delayed tooth eruption, delayed motor development, and macrocephaly. In both reports, thyroid function tests were distinct from those found in classical RTH with or without *TR β* gene mutations. They had some similarity to those in mice with *TR α* gene mutations, low serum T₄, high T₃, and very low rT₃. In addition they are somewhat reminiscent of MCT8 defects (see the THCMTD section below), presumably due to alterations in iodothyronine metabolism.

Clinical features and course of the disorder

clinic mutatii de receptor
beta
3000 cazuri, aD (1
familie ar)

tahicardie (=semn de
hiper)
hiperactivitate
intarziere in dezvoltarea
neuromotorie si dificultat
de invatare, (= semn
de hipo)
gusa, care se
nodularizeaza cu timpul
si recidiveaza postop.
pe termen lung, de
obicei normali dar cu
modificarii hh
caracteristice, ocazional
un anumit grad de retard
mental si deficit de
inaltime persista.

Characteristic of the RTH syndrome is the sparseness of specific clinical manifestations. When present, they are variable from one patient to another [17, 21]. Common features that bring subjects to medical attention are goiter, hyperactive behavior, learning disabilities, developmental delay and sinus tachycardia. The finding of elevated serum free T₄ (FT₄) concentration in association with nonsuppressed TSH usually trigger further studies that lead to the diagnosis.

With the exception of some rare subjects, particularly those homozygous for *TR β* mutations [25, 26], the majority maintain a near normal metabolic state at the expense of high TH levels. The degree of compensation for the hyposensitivity to TH is variable among individuals as well as among different tissues, and results in the coexistence of clinical and laboratory evidence for TH deficiency and excess. Thus, delayed growth and bone maturation, learning disabilities, which are compatible with hypothyroidism, can be present along with hyperactivity and tachycardia, suggestive of thyrotoxicosis. Typical symptoms of hypothyroidism are common in individuals who received treatment to normalize their serum TH levels.

Goiter is the most common finding, reported in 66–95% of cases. Enlargement is usually diffuse with gross asymmetry. Nodularity often occurs in recurrent goiters after surgery.

Sinus tachycardia is very common and together with goiter could lead to the erroneous diagnosis of autoimmune thyrotoxicosis.

About one-half of subjects with RTH have learning disability but mental retardation (IQ <60) was found only in 3% of cases [17]. Attention deficit hyperactivity disorder is also present in half of the children with RTH [27]. However, RTH in children with attention deficit disorder is extremely rare [28, 29]. Recurrent ear infections are very common in childhood but hearing impairment of variable degree has been reported in 10 to 20% of cases [30]. Various somatic malformations have been reported, mostly coincidental.

The course of the condition is also variable. Most individual achieve normal stature and development, and lead a normal life at the expense of high TH levels and a slight thyroid gland enlargement. In others, low stature and intellectual impairment persist. Symptoms of hyperactivity tend to improve with age. Goiter usually recurs after surgery. As a consequence, some of the RTH subjects have been submitted to repeat thyroidectomies or treatments with radioiodide.

Genetics

Inheritance and incidence—Neonatal screening programs based on blood TSH determination rarely identify RTH. However, a limited survey of newborn for high blood T₄ found 1 case per 40,000 live births [31, 32]. Known cases surpass 3,000 with wide geographic distribution and reported in Whites, Blacks, Asians and Amerindians. In the majority of families, the syndrome is transmitted in an autosomal dominant fashion and occurs with equal frequency in both sexes. In one family with complete deletion of the TR β gene, inheritance was recessive [33].

2 receptoriprincipali
alpha - izoforma 1 (
izoforma 2 e inactiva
pt ca nu poate lega hh
ty)
beta - izoforma 1 si 2

la rec beta - peste
170 mutatii diferite.
purtatorii de o mutatie
si o gena normala au
rez la hh ty, purtatorii
de o deletie si o gena
normala sunt normali

homozigotii fara
receptor beta au
anomalii hormonale,
surditate si color
blindness.
homozigotii pt mutatii
de receptor beta au
hipoty nervos si osos
sever (receptorul
mutsnt interfara si cu
receptorul normal
alpha in procesul de
dimerizare)

TR genes and mutations—The TR β and TR α are members of the nuclear receptor family. They have structural and sequence similarities and are encoded by genes located on chromosomes 17 and 3, respectively. Alternative splicing and promoter usage produce 2 major TR α (α .1, α .2) and 2 major TR β (β .1, β .2) isoforms [14]. Most important are the three isoforms that bind TH (TR α .1, TR β .1 and TR β .2). The absence of the ligand-binding domain (LBD) precludes TH binding to TR α .2, but does not prevent binding to TREs through its DNA-binding domain (DBD). Although it does not function as a proper TR, [34] it appears to have a weak antagonistic effect [35]. The significance of the other TR isoforms in humans remains unknown [36]. The level of expression and relative product distribution of the two TR genes vary among tissues and at different stages of development. TR β and TR α are to a certain degree interchangeable [36, 37]. However, the compensatory effects observed in the absence of one of the receptors are not complete and some TH effects are TR isoform specific.

TR β gene mutations are located in the functionally relevant domain of the LBD and its adjacent hinge region. They are mostly contained within three clusters rich in CpG "hot spots" [38–40] (Fig. 3). The mutant (mut) TR β molecules have either reduced affinity for T₃ [39, 41], or abnormal interaction with one of the cofactors involved in TH action [40, 42].

Mutations have been now identified in 459 families, 432 of which have single nucleotide substitutions, resulting in one amino acid replacement and in 11 truncated molecules. Twenty other families have nucleotide deletions, insertions or duplications, some producing frameshifts that create nonsense proteins. From the 171 different mutations identified, some are shared by more than one family. Proof that they developed independently has been obtained [38]. TR β R338W, caused by a C to T replacement in a CpG has been identified in 33 unrelated families. Mutations have also produced different amino acids in the same

codon. Seven such different substitutions were identified in codon 453 (P453T,S,A,N,Y,H,L).

In contrast to the androgen receptor gene [43], belonging to the same receptor family, not a single TR β gene mutation has been reported in non-coding regions or reported to produce abnormal splice variants. Sequencing of cDNA is important in subjects with clinically proven RTH in whom no mutations could be found in genomic DNA. Somatic TR β gene mutations have been identified in two TSH-producing pituitary adenomas [44, 45].

T4, fT4 crescut (putin sau de cateva ori peste normal)
T3, fT3, rT3 crescut
TSH nesuppesat cu raspuns
normal/exagerat la TRH.
raport normal T3:T4
anticorpi antitiroidieni pot fi prezenti, chiar mai frecvent decat in pop generala.

RIC crescut, fara spalare la adm de perclorat

test prin administrarea de T3
50 mcg 3 zile --> 100 mcg 3 zile--> 200 mcg 3 zile (divizat in 3 prize).
crestere mica de SHBG si feritina,
supresie inadecvata de TSH, colesterol si creatinkinaza

Laboratory findings—A high serum FT₄ concentration and nonsuppressed TSH are required to raise the suspicion of RTH. Usually they are accompanied by high serum T₃ and rT₃ levels. Serum T₄ and T₃ can be just above to several fold the upper limit of normal, but, contrary to autoimmune thyrotoxicosis, can maintain a near normal T₃:T₄ ratio [17]. Serum thyroglobulin concentration tends also to be high as the result of TSH induced thyroid gland over activity. The response of TSH to TSH-releasing hormone is normal or exaggerated, in proportion to the baseline TSH level. The relatively high TSH bioactivity explains why goiters develop despite normal levels of immunoreactive TSH [46]. Thyroidal radioiodide uptake is high and not dischargeable by perchlorate. The presence of thyroperoxidase and thyroglobulin antibodies does not exclude the diagnosis of RTH. As a matter of fact, their cooccurrence is slightly more frequent [47].

Tests assessing TH action on peripheral tissue are usually normal at baseline, but are not sensitive to small hormonal deficiencies or excess. A standardized protocol, using short-term administration of L-T₃ to determine the sensitivity of central and peripheral tissues to TH is available [17]. Three incremental doses given to adults, each for three consecutive days, are a replacement dose of 50 μ g/day and two supraphysiologic doses of 100 and 200 μ g/day, administered in split daily doses. Attenuated stimulation of sex hormone binding globulin and ferritin and reduced suppression of TSH, cholesterol and creatine kinase are compatible with RTH (Fig. 4).

Evaluation for other endocrine abnormalities has yielded negative results. Earlier, in-vivo tests, measuring hormonal turnover, and in-vitro tests, using the patients skin fibroblasts in culture, have provided valuable diagnostic information which, with the advent of genetic diagnosis, have lost their utility [17].

These laboratory results were not found in a subject with a *TR α* gene mutation (see Variants, above)

Mechanisms of the Disorder—The more common forms of TH hypersecretion are TSH independent and thus, as in primary hypothyroidism, there is a reciprocal relation between the serum TH and TSH concentrations. The absence of such correlation in RTH, has introduced the term "inappropriate secretion of TSH". This is unfortunate, as the increased secretion of TH as consequence of the reduced feedback action of TH, is compensatory and fully appropriate for the defect.

Individuals with one WT *TR β* allele due to deletion of the other allele are normal, while those expressing a mut *TR β* and a WT allele, have RTH. The former is not due to a compensatory over expression of the WT allele [48], and the reduced amount of TR β does not produce haploinsufficiency. In the latter situation, the presence of a defective mut TR β interferes with the function of the WT TR β , a phenomenon known as dominant negative effect (DNE). This explains the dominant form of RTH inheritance when caused by mut TR β s and recessive in subjects with *TR β* gene deletion [33, 49].

Expression of a DNE requires that the mut TRs with defective T₃-binding preserve a DNA-binding domain and the ability to dimerize with a homologous or heterologous partner (Fig. 2). Mut TRs interfere with WT TR function by occupying TREs on target genes and by engaging WT TR β in homodimerization. This explains why no mutations have been identified in CpGs located in regions of the TR β molecule involved in homodimerization [50]. Dominant negative effect can also manifest through altered association of a mut TR β with a cofactor, including increased affinity to or decreased release of a corepressor [42, 51], or reduced association with a coactivator [40]. In contrast, mut TR β s with complete inability to bind T₃ can paradoxically produce minimal dysfunction if association to corepressor is also reduced [41]. Less obvious was the reason for the reverse situation in which mut TR β s manifesting strong DNE have minimal impairment or even, intact T₃-binding. The two mutations R243Q and R243W, located in the hinge domain and with normal T₃-binding in solution, become resistant to T₃ when bound to TRE, thus maintaining repressive dimers [52, 53]. On some occasions, mut TR β s may show greater impairment of transactivation on genes negatively rather than positively regulated by T₃ [41, 54]. Recent work suggests that the mut TR β R429Q affects predominantly the TR β 2 mediated action [55] while mut TR β R338W, through its association with a single nucleotide polymorphism in the enhancer region, produces over expression of the mut TR β allele [56]. These two mechanisms give credence to the existence of predominantly pituitary RTH.

Different mechanisms are responsible for the variable phenotype of RTH. Homozygotes devoid of WT TR β are deaf and color blind even though the magnitude of thyroid function tests abnormalities are comparable to heterozygotes with mut TR β s. This is due to the total absence of TR β mediated action required for cochlear and photoreceptor development (see Mouse Models below). Conversely, the severe signs of hypothyroidism in bone and brain of homozygotes with mut TR β s can be explained by the DNE of the double dose of the mut TR β s that interfere with TR α function as well [26].

Differences in the magnitude of hormonal resistance in different tissue are due to the absolute and relative levels of TR β and TR α expression. For example, the hypothalamus and pituitary which are dependent on TR β , manifest relative hormone deprivation, while the heart which depends on TR α , exhibits signs of hormone excess in the form of tachycardia [17]. Thus, it is not surprising that the phenotype of the patient with *TR α* gene mutation was completely distinct [10].

Although differences in functional impairment and, rarely, level of expression of the mut TR β s can explain some of the clinical differences, the molecular basis for the heterogeneity of the RTH phenotype in individuals with the same mutation remains unknown. This phenotypic variation can occur across families [38] and within the same family [57]. Finding differences in the relative expression level of the mutant relative to the normal TR β allele has not been consistent [48, 58]. Genetic variability of factors other than TR β may modulate the phenotype of RTH.

Mouse Models

Gene targeting has allowed the generation of mice with *TR β* deletion (knockout, KO) and with various mutations (knockin, KI), which replicate defects observed in man. These animals have been invaluable in understanding the physiology of TR and the pathophysiology of RTH [59].

TR β gene manipulations

TR β KO mice exhibit all the features of humans with *TR β* gene deletion. Heterozygotes are normal and homozygotes have, in addition to the characteristic thyroid test abnormalities,

sensorineural deafness and monochromatic vision, indicating that the deaf-mutism and color blindness in humans can be fully explained by the complete absence of TR β . These mice allowed in-depth investigations establishing that TR β 2 deficiency was responsible for the color blindness [60] but not for the hearing loss [61]. TR β KO mice have increased heart rate that normalizes with reduction on the TH level [62, 63]. These findings, together with the lower heart rate in TR α 1KO mice [59], indicates that TH affects heart rate through TR α 1, and explains the tachycardia observed in some patients with RTH.

TR β KI mice, targeted to replicate known human TR β gene mutations (frame-shift PV and T337D) [64, 65], are true models of the dominantly inherited form of RTH. Heterozygous KI mice manifest many of the abnormalities observed in man. In addition, homozygotes develop metastatic thyroid cancer [64].

TR α gene manipulation

TR α gene deletions, total or only α 1, do not produce important alterations in TH or TSH concentrations [35]. Several mutations naturally occurring in the human TR β gene (PV, R438C and P453H) were targeted in homologous regions of the TR α 1 gene of the mouse [66–68]. The resulting phenotypes were variable but did not exhibit RTH as that found in TR β gene mutations. In the heterozygous state, the first two KIs mentioned show severe postnatal development and growth retardation, while the latter has increased body fat and insulin resistance. Decreased heart rate and cold-induced thermogenesis, as well as reduced fertility, were also observed. Serum thyroid tests were variable with the type of mutations and with age, but T₄ had the tendency to be low and T₃ high. Some of the abnormalities are reminiscent to those observed in the heterozygous human with TR α 1 gene mutation. All three types of TR α 1KIs did not survive in the homozygous state, recapitulating the noxious effect of unliganded TR α 1.

Combined TR and related gene deletions

Deletion of both α and β TRs is compatible with life [36, 37]. This contrasts with the complete TH deficiency in the athyreotic Pax8KO mouse that dies prior to weaning, unless rescued by TH. The survival in the absence of TR is not due to the presence of an unidentified TR but to the absence of the noxious effect of unliganded TRs. Indeed, removal of all TR α isoforms rescues the Pax8KO mice from death [69, 70]. Deletion of the TR α 1 gene also prevents the development of cerebellar abnormalities during TH deprivation [71]. The aporeceptor does not seem to be required for the upregulation of TSH.

NCoA-1 (SRC1) KO mice have resistance to TH in addition to sex-hormones [72]. Mice deficient in retinoid-X receptor γ , the dimerization partner of TR, are also mildly resistant to TH [73].

Thyroid hormone cell membrane transporter defect (THCMTD)

Cell membrane TH transporters

The previously accepted paradigm of passive TH diffusion into cells [74] has been abandoned with the identification of several classes of molecules that transport TH across cell membranes [75]. These proteins belong to different families of solute carriers. Among them, the X-linked monocarboxylate transporter 8 (MCT8) has been shown to be a potent and specific TH transporter [76]. The important role of MCT8 was convincingly demonstrated by the identification in two different laboratories of the first inherited THCMTD caused by mutations in the MCT8 (SLC16A2) gene [6, 7]. All affected subjects tested to date have 1) a complex and severe neurodevelopmental defect and 2) a

combination of pathognomonic test abnormalities of high serum T_3 , low rT_3 , low normal to reduced T_4 with TSH levels normal or slightly elevated.

Clinical features and course of the disorder

Male subjects later found to have *MCT8* gene mutations, are referred for medical investigation during infancy or early childhood because of neurodevelopmental abnormalities. Newborns have normal Apgar scores and in most cases there is history of normal gestation, though polyhydramnios and reduced fetal movements have been reported [77, 78] [Dumitrescu, A.M. and Refetoff, S, unpublished data].

sarcina normală sau cu polihidramnios și miscarile fetale reduse
dificultăți de alimentație și hipotonie centrală de la 6 luni
în timp -> hipertonie musculară și spasticitate
câteva familii în care au prezentat mers atactic și vorbere disbalică

-activitate reziduală

MCT8

Dystonia

purposeless movements

characteristic paroxysms of kinesigenic dyskinesias

true seizures occur 25%

Difficulty falling asleep and frequent awakenings Reflexes are usually brisk and clonus is often present.

cu timpul, creșterea liniară este pastrată dar creșterea în greutate stagnăza și apărea microcefaliei masa musculară redusă

facies: gura deschisă, buza sus ridicată(tented), urechi lungi, în forma de cupă

Genetics

Truncal hypotonia and feeding problems are the most common early signs of the defect, appearing in the first 6 months of life. Characteristically, the neurological manifestations progress from flaccidity to limb rigidity, which, with advancing age, leads to spastic quadriplegia. Most subjects are unable to walk, stand or sit independently and do not develop speech. Only members of three families [78, 79] were able to walk with ataxic gait or with support and had a limited, dysarthric speech. A possible explanation for milder neurological phenotype in these patients is a residual 15–37% TH-transport activity of their mutant *MCT8* molecules [80].

Dystonia and purposeless movements are common and characteristic paroxysms of kinesigenic dyskinesias have been reported in several patients [81, 82]. In addition, true seizures occur in one quarter of the patients. Difficulty falling asleep and frequent awakenings, can represent an important clinical issue for caregivers [82]. Reflexes are usually brisk and clonus is often present.

With advancing age, weight gain lags and microcephaly becomes apparent, while linear growth proceeds normally [83]. Muscle mass is diminished and there is generalized muscle weakness with typical poor head control, originally described as “limber neck” [84]. A prominent and common feature in *MCT8* deficient patients is the failure to thrive, which may require in some cases a gastric feeding tube. Possible reasons for low weight and muscle wasting are difficulty swallowing on neurological basis, and increased metabolism due to the thyrotoxic state of peripheral tissues caused by the high serum T_3 levels [82, 85–87].

Facial features, attributed to the prenatal and infantile hypotonia, include ptosis, open mouth, and a tented upper lip. Ears are long, thick and cup-shaped while there is a decrease in facial creases. Pectus excavatum and scoliosis are common.

Cognitive impairment is severe but *MCT8* deficient patients tend to be non-aggressive. Death during childhood or teens is common, usually caused by recurrent infections and/or aspiration pneumonia. However, survival beyond age 70 years has been observed in a few instances of more mild neurologic involvement [78].

Female carriers have none of the psychomotor abnormalities described above. Nevertheless, intellectual delay and frank mental retardation was reported in six carrier females [6, 78, 86, 88]. Although an unfavorable nonrandom X-inactivation could alter the phenotype in these females [78], cognitive impairment can be due to a variety of unrelated causes [89].

Inheritance and incidence—*MCT8* deficiency is a X-linked defect. Mutations have 100% penetrance in males who manifest both neuropsychomotor and characteristic thyroid tests abnormalities. Carrier females may show only mild thyroid test abnormalities [6, 89, 90]. A single female manifesting the typical features of *MCT8*-specific THCMTD had a *de*

de novo translocation disrupting the *MCT8* gene and unfavorable nonrandom X-inactivation [88]. The defect has been reported in individuals of all races and diverse ethnic origins. In a study of 448 subjects with X-linked mental retardation, *MCT8* gene mutations responsible for the phenotype were found in three [88]. Although no affected male has reproduced, *MCT8* gene mutations are maintained in the population due to the fact that carrier females are asymptomatic and fertile.

MCT8 gene and mutations—The *MCT8* gene was cloned in the process of characterizing the Xq13.2 region containing the X-inactivation center [91]. The deduced products are proteins of 613 and 539 amino acids (translated from two in-frame start sites) containing 12 transmembrane domains (TMD) with intracellular amino- and carboxyl- ends [92]. The upstream translation start site is absent in most species. Thus, the additional N-terminal sequence present in humans has unknown functional importance.

Mutations are distributed throughout the coding region of the gene with apparent increased distribution in the TMDs (Fig. 5). As mutations are relatively underrepresented in the extracellular and intracellular loops, it is likely that missense mutations in these domains result in a milder phenotype, escaping detection. In fact, sequences in these regions are less conserved across species compared to the TMD regions [93].

MCT8 gene mutations range from single nucleotide substitutions to large deletions involving one or more exons. Twelve different mutations occurred each in at least two or more unrelated families. The majority of single nucleotide substitutions are located in mutational hotspots such as CpG dinucleotides, or C and A repeats. Of cases who's mothers were genotyped, *de novo* mutations were identified in 25%.

Laboratory findings

Biochemical—Pathognomonic are the high serum total and free T₃ and low rT₃ concentrations. T₄ is reduced in most cases and TSH levels can be slightly elevated but rarely above 6 mU/L (Fig. 6A).

TSH is usually normal at neonatal screening. Neonatal T₄ levels available in 8 cases revealed low values in six and normal in two [78, 82] [Dumitrescu, A.M. and Refetoff, S, unpublished data], but information on T₃ and rT₃ concentration in the first days of life is not available. The typical thyroid tests abnormalities of MCT8 deficiency become apparent within one month.

Heterozygous female carriers have all three serum iodothyronine concentrations intermediate between affected males and unaffected family members [6, 78, 86]. Serum TSH concentrations are, however, normal (Fig. 6A).

la unii pacienti:
SHBG, transaminaze,
amoniac, lactat si
piruvat crescute
acid hidroxibutiric urinar
crescut
rezistenta hipofizara la
hh ty--> scadere
insuficienta a TSH la
administrarea de T3

Urinary organic acids, serum amino acids and fatty acids, CSF neurotransmitters, and glucose are usually normal. Other test results were abnormal only in some patients, such as, elevated serum SHBG, transaminases, ammonia, lactate and pyruvate; mildly elevated medium chain products in plasma acylcarnitine profile, elevated hydroxybutyric acid in urine [77, 86] [Dumitrescu, A.M. and Refetoff, S, unpublished data] and reduced serum cholesterol. While the relation of some test abnormalities with MCT8 deficiency is unclear, others, such as reduced cholesterol, and increased SHBG and lactate, can be ascribed to the effect of the high serum T₃ levels on peripheral tissues.

Other endocrine tests, including pituitary function were normal when tested in a several individuals. However, administration of incremental doses of L-T₃, using the protocol described for the study of patients with RTH, showed reduced pituitary sensitivity to the

hormone [Dumitrescu, A.M. and Refetoff, S, unpublished data]. This is probably caused by the reduced suppressive effect of T₃ on the hypothalamic-pituitary axis, as well as the diminished incremental effect of the hormone on peripheral tissues already exposed to high levels of T₃.

Altered activity of muscle mitochondrial complexes II and IV was identified in two cases [94] [Dumitrescu, A.M. and Refetoff, S, unpublished data]. Whether this is due to the abnormal TH status of the muscle or to a yet unidentified effect of MCT8 on the mitochondria, it remains unknown.

VO scazuta (4 cazuri) sau crescuta (1 caz)

demielinizare sau dismyelinizare usoara/severa, care nu poate fi adularata dupa varsta de 4 ani

alte modificari - atrofie corticala, subcorticala

sau cerebeloasa, **corpus callosum deosebit de scăzut** sau cerebeloasa, **corpus callosum deosebit de scăzut** ocazional

Mild to severe delayed myelination or dysmyelination [97, 98] [Dumitrescu, A.M. and Refetoff, S, unpublished data] is a common finding when brain magnetic resonance imaging (MRI) is performed in early life. Decreased myelination is less apparent by 4 years of age. This distinguishes MCT8 deficiency from other leukodystrophies with persistent myelination defect, one such example being the Pelizaeus-Merzbacher syndrome [97]. Other MRI abnormalities reported in single cases might be non-specific. They include subtle cortical and subcortical atrophy [85], mild cerebellar atrophy [86], putaminal lesions [99] and a small corpus callosum [Dumitrescu, A.M. and Refetoff, S, unpublished data]. Increased choline and myoinositol levels and decreased N-acetyl aspartate detected by MR-spectroscopy were associated with the degree of dysmyelination found on MRI [100].

Mechanisms of the disorder—Mct8-deficient (*Mct8KO*) mice [18, 101] replicate the characteristic thyroid tests abnormalities found in humans and, in this respect, have been invaluable in understanding the mechanisms responsible for the thyroid phenotype [102]. The variable availability of the circulating hormone to tissues, depending on the redundant presence of TH cell membrane transporters was demonstrated by measurement of tissue T₃. Tissues such as the liver, that express other transporters [12], have high T₃ concentrations reflecting the high levels in serum, despite the absence of Mct8. The effect of TH excess was demonstrated by an increase in the D1 enzymatic activity (Fig. 7A), decrease in serum cholesterol and increase in serum alkaline phosphatase concentrations. In contrast, tissues with limited redundancy in cell membrane TH transporters, such as the brain [12], have decreased T₃ content in *Mct8KO* mice, which together with the increase in D2, indicate local TH deprivation (Fig. 7B). The high D2 in the context of TH deficiency [13] has only partial compensatory effect. The coexistent tissue specific T₃ abundance and deficiency in the *Mct8KO* mouse explain, in part, the mechanisms underlying the manifestation of TH excess and deficiency in humans with MCT8 defects.

Mct8 also has a role in TH efflux and excretion in kidney and secretion from the thyroid gland, respectively [103, 104]. The content of T₄ and T₃ in kidney is increased, producing an increase in D1 activity. In the thyroid, Mct8 is localized at the basolateral membrane of thyrocytes. Thyroidal T₄ and T₃ content is increased in *Mct8KO* mice, while the rate of their secretion and appearance in serum is reduced [104].

The increased D1 and D2 activities, stimulated by opposite states of intracellular TH availability, have an additive consumptive effect on T₄ levels and together increase T₃ generation. The important role of D1 in maintaining a high serum T₃ level has become evident by the normalization of serum T₃ and rT₃ in *Mct8KO* mice also made deficient in D1 [105]. The low serum T₄ in Mct8 deficiency is not only the result of attrition through

soareci:

t nondep de MCT8 --> Nivele crescute de T3 si deiodinaza D1, compensator. ex: ficat t dep de MCT8 --> nivele scăzute de T3 si crescute de deiodinaza D2, compensator

in trichi, MCT8 are rol in excretia hh ty --> concentratii crescute de T3 si T4 si D1, cu o pierdere crescuta prin urina

in tiroida este situata in mb bazolateralala, determina o concentratie crescuta intratiroidiana cu eliminare diminuata de hh ty.

per total --> T4 scazut prin conversie ic crescuta, excretie renala crescuta, eliberare ty scazuta

deiodination but also caused by the reduced secretion from the thyroid gland and possibly increased renal loss.

Serum TSH is usually modestly increased in MCT8 deficient subjects, a finding compatible with the decrease in serum T₄ concentration but not with the elevated serum T₃ level. However, as MCT8 is expressed in the hypothalamus and pituitary, its inactivation likely interferes with the negative feedback of TH at both sites [106]. Hypothalamic TRH expression is markedly increased in *Mct8KO* mice, and high T₃ doses are needed to suppress it, indicating T₃ resistance at the hypothalamic level.

Mct8KO mice are useful for testing thyromimetic compounds with the potential of bypassing the Mct8 defect in tissues. The same dose of the TH analogue, diiodothyropropionic acid (DITPA), was found to be equally effective in the *Mct8KO* and WT animal to replace the TH requirements in animals rendered hypothyroid [107]. In contrast, 2.5 and 8-fold higher doses of L-T₄ and L-T₃, respectively, were necessary to produce a central effect in the *Mct8KO* compared to that in WT animal. These high doses of TH produced “hyperthyroidism” in peripheral tissues of the *Mct8KO* mice.

The absence of a clear neurological phenotype in *Mct8KO* mice limits their use in the understanding the mechanisms of the neurological manifestations in patients with MCT8 deficiency. If combined with deficiencies of other TH transporters in brain, Mct8 has the potential of producing an obvious neurological phenotype. This is being currently explored in several laboratories.

Mutant MCT8 molecules identified in humans and tested by transfection in heterologous systems, or in fibroblasts derived from affected individuals, show absent or greatly reduced ability to transport iodothyronines, primarily T₃ [80]. However, the magnitude of serum T₃ elevation does not correlate with the degree of T₃ transport defect probably due to the important contribution of the concomitant perturbation in iodothyronine metabolism on the production of T₃, as demonstrated in the *Mct8KO* mice. Similarly, there is no correlation between the magnitude of serum T₃ elevation or rT₃ reduction in affected males compared to corresponding values in their carrier mothers [Dumitrescu, A.M. and Refetoff, S, unpublished data]. Nevertheless, an imperfect correlation does exist between the degree of the MCT8 defect and clinical consequences. Less severely affected individuals, capable of some locomotion, have mutations with partial preservation of T₃ transport function. In contrast, early death is more common in patients with mutations that completely disrupt the MCT8 molecule. However, it should be kept in mind that genetic factors, variability in tissue expression of MCT8, and other iodothyronine cell membrane transporters could be responsible for the lack of a stronger phenotype/genotype correlation. The possibility that MCT8 is involved in the transport of other ligands, or has functions other than TH transport, cannot be excluded.

Thyroid hormone metabolism defect (THMD)

Intracellular metabolism of TH

The proper intracellular hormone supply, dependent on cell types and the timing in development, is fine-tuned by intracellular TH metabolism, regulated by three selenoprotein iodothyronine deiodinases (Ds). The rare amino acid, selenocysteine (Sec), located in the center of these molecules, is required for their enzymatic activity. Their expression varies according to cell type and in response to alterations in the intracellular environment, regulated at the level of transcription, translation and metabolism [13]. D2 activity can change very rapidly being inactivated by T₄ through ubiquitination, a reversible process that can regenerate active D2 enzyme through de-ubiquitination.

mutatii recursive in SBP2 implicata in sinteza deiodinazelor, care sunt selenoenzime ce contin selenocisteina) T4+, T3-, rT3 +, TSH + seleniu seric scazut, activitatea enzimelor cu Se scazuta

Clinical features and course of the disorder

8 familii descrise cateva cazuri descrise - majoritatea semnelor sunt apar la unii copii, nu la toti retard de crestere din mica copilarie, retard neurologic si motor vertigo rotator hipacusie fotosensibilitate (la singurul adult cunoscut) infertilitate (idem) FARA GUSA

unii au modificarile hh descrise dar fara semne clinice

◊ VO scazuta

As other selenoproteins, deiodinases are synthesized through a unique mode of translation. Sec is encoded by UGA, a codon that in most circumstances serves as a signal to stop synthesis. The recoding of a specific UGA is determined by the presence of a selenocysteine insertion sequence (SECIS) in the 3'-untranslated region of the selenoprotein messenger RNA. A SECIS-binding protein 2 (in short SBP2) recognizes the SECIS and recruits multiple factors and the specific transfer RNA for the addition of Sec to the nascent protein chain (Fig. 8) [108].

Alterations of TH metabolism in man are typically acquired. The most frequent produces the "low T₃ syndrome" of non-thyroidal illness [109]. The first inherited thyroid hormone metabolism defect was identified in 2005 [8]. It was caused by recessive mutations in *SBP2* gene affecting selenoprotein synthesis, among which are the selenoenzymes deiodinases. Since this report a total of eight families were found to have mutations in the *SBP2* gene. Affected individuals have delayed growth and characteristic thyroid tests abnormalities: high serum T₄, low T₃, high rT₃ and normal or slightly elevated serum TSH. In addition they also have decreased serum selenium (Se) and selenoprotein levels or activities. The overall clinical phenotype is complex. The prominent findings in the 10 individuals so far identified are described in the following section.

The probands of the first three families were brought to clinical attention because of growth delay [8, 110]. All were boys ranging in age from 6 to 14.5 years. Two young siblings, one male and one female, had the biochemical but not clinical abnormalities. The proband of a fourth family was a 12 years old girl with delayed bone maturation, congenital myopathy, impaired mental and motor coordination development, and bilateral sensorineural hearing loss [111]. In a fifth family, a male child, presented at age 2 years with failure to thrive as infant, followed by global developmental delay and short stature. Other features were eosinophilic colitis, fasting nonketotic hypoglycemia with low insulin levels, muscle weakness and mild bilateral high-frequency hearing loss [112]. A more recent report is that of 10 years old Japanese boy who at 3 months had short stature and failure to thrive. Through childhood he had delayed motor and intellectual development carrying the diagnosis of mild mental retardation and pervasive development disorder. The patient had rotary vertigo, recurrent exudative otitis media and bilateral mild conductive hearing loss [113]. We identified another patient (unpublished), an 11 years old Turkish girl born to non-consanguineous parents with mental and motor retardation, poor growth and abnormal thyroid function tests, typical of SBP2 deficiency.

Only one adult with SBP2 deficiency has been identified. He presented at age 35 years with primary infertility, skin photosensitivity, fatigue, muscle weakness, severe digital vasospasm, impaired hearing, and rotatory vertigo [112]. He had a history of delayed motor and speech development. Hearing problems persisted despite myringotomies for secretory otitis media at 6 years of age. He had difficulty walking and running in adolescence, with genu valgus and external rotation of the hip. At 13 years of age, marked sun photosensitivity was noted. Pubertal development was normal but, at the age of 15 years, he developed unilateral testicular torsion requiring orchietomy and fixation of the remaining testis.

All affected subjects were found to have the characteristic serum thyroid test abnormalities but none had enlarged thyroid glands confirmed by ultrasound examinations. As most of the patients are young, the long-term evolution of this defect is unknown. While growth retardation is a common feature it is unknown whether adult stature would be impaired. Some of the patients have a complex phenotype involving multiple tissues and organs. It is conceivable that oxidative damage causing neoplasia, neurodegeneration, premature ageing may manifest with time.

Genetics

Incidence and inheritance—The incidence of THMD caused by *SBP2* deficiency is unknown. Although a total of 8 families have been identified over the period of 6 years [8, 110–113] [Dumitrescu, A.M. and Refetoff, S, unpublished data], failure of detection is likely due to the relatively mild clinical symptoms in some subjects. The inheritance is autosomal recessive and males and females are equally affected. The ethnic origins of the reported patients are Bedouin from Saudi Arabia, African, Irish, Brazilian, English, Turkish and Japanese.

SBP2 gene and mutations—The human *SBP2* gene, located on chromosome 9, encodes a protein of 854 amino acids widely expressed in tissues [114]. The C-terminal domain of the molecule is required for SECIS binding, ribosome binding and Sec incorporation [115]. Recent *in vitro* studies have shown a nuclear localization signal in the N-terminal part and a nuclear export signal in the C-terminal part, allowing SBP2 to shuttle between the nucleus and the cytoplasm [116]. The fourteen different mutations so far identified are shown in Table 1.

It is likely that defects in thyroid hormone metabolism caused by mutations in other genes will have different phenotypes. So far mutations in the deiodinase genes or in other proteins involved in selenoprotein synthesis have not been reported in humans.

Laboratory findings

Biochemical—The characteristic thyroid tests abnormalities in subjects with *SBP2* gene mutations are high total and free T₄, low T₃, high rT₃ and slightly elevated serum TSH [117] (Fig. 6B). *In vivo* studies showed that affected children required higher amounts of T₄, but not T₃, to reduce their serum TSH levels (Fig. 9A).

Cultured skin fibroblasts from affected individuals had reduced basal and cAMP-stimulated D2 enzymatic activity. However, basal and cAMP-stimulated D2 mRNA levels were not different than those in fibroblasts from normal individuals (See Fig. 9B).

Being epistatic to selenoprotein synthesis, SBP2 deficiency is expected to affect multiple selenoproteins. In fact, the concentrations of serum selenium, selenoprotein P are reduced, and skin fibroblasts have decreased D2 and glutathione peroxidase (Gpx) activities [117].

Detailed studies of three recent cases with severe SBP2 deficiency demonstrated multiple selenoproteins deficiencies [111, 112]: lack of testis-enriched selenoproteins producing a failure of the latter stages of spermatogenesis resulting in azoospermia; selenoprotein N (SEPN) like myopathy resulting in axial muscular dystrophy; cutaneous deficiencies of antioxidant selenoenzymes causing increased cellular reactive oxygen species (ROS); and reduced selenoproteins in peripheral blood cells resulting in immune deficits [112]. Deficiencies of other selenoproteins of unknown function, such as SELH, SELT, SELW, SELI, were found and their consequences are as yet unknown [112].

Imaging—T1-weighted MRI in three patients revealed connective tissue and fatty infiltration in the adductor muscle at the mid-thigh level [111–113]. Delayed bone age seems to be characteristic in this defect.

Mechanisms of the disorder—Investigations have established that the *SBP2* gene mutations fully explain the observed abnormalities, as SBP2 is crucial for the synthesis of selenoproteins. Complete lack of SBP2 function is predicted to be lethal, as its immunodepletion eliminates Sec incorporation. The survival of reported patients with SBP2

tabloul clinic este dat de
asocierea dintre diferitele
deficite enzimatice:

- ☆ selenoproteinele testiculare sunt scazute --> azoospermie
- ☆ selenoproteina N --> distrofie musculara proximală
- ☆ deficit de selenoproteinele antioxidente cutanate
- ☆ deficit de selenoproteine in limfocite -->deficite imune.

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deficiency is attributed to the preservation of partial SBP2 activity and to the hierarchy in selenoproteins synthesis.

The thyroid tests abnormalities found in all subjects with SBP2 deficiency are consistent with a defect in TH metabolism caused by deficiency in deiodinases. The mutant R540Q SBP2 behaves as a hypomorphic allele as shown in studies using the corresponding R531Q mutation of the rat Sbp2 [118]. The mutant molecule showed no binding to some but not all SECIS elements, resulting in selective loss in the expression of a subset of selenoproteins. In another family the compound heterozygous child expressed ~24% of a normal SBP2 transcripts. In the case of the homozygous R128X mutation, smaller SBP2 isoforms translated from downstream ATGs provided functional molecules containing the C-terminus domains.

Because the human selenoproteome comprises at least 25 selenoproteins [119, 120] it is not surprising that the phenotype of SBP2 deficiency is complex and has additional manifestations than the thyroid tests abnormalities. The more severe phenotype, recently reported in three families, is due to a more extensive impairment in SBP2 function [117]. In the patient with two nonsense mutations the R770X mutation truncates the C-terminal functional domain and likely abolishes SBP2 function, while the R120X allele likely generates smaller functionally active SBP2 isoforms [111]. However, the overall amount would be lesser than that of the homozygous R128X patient [110], thus explaining the more severe phenotype. Low expression of functional SBP2 is also at the basis of the phenotype of the two patients from the UK. Increased proteasomal degradation was demonstrated for the C691R mutation and Western blotting of skin fibroblasts from both probands showed lack of full length SBP2 protein expression [112]

There is no mouse model of a SBP2 defect or other components of the Sec incorporation machinery except for tRNA^{Sec} [121]. A partial synthesis defect results in uneven deficiency in the different types of selenoproteins, reflecting the hierarchy in selenoprotein expression known to occur under conditions of selenium deprivation.

Homologous recombination has created mice deficient in each of the three deiodinases [122–124]. *Dio1*KO mice have elevated levels of T₄ and rT₃ while the concentrations of T₃ and TSH are unimpaired. *Dio2*KO mice have significantly elevated serum T₄ and normal T₃ levels but, contrary to *Dio1*KO mice, TSH concentration is elevated. *Dio3*KO mice show also some growth retardation and defective auditory function [125]. Total deficiency in D3 is associated with partial embryonic and neonatal lethality. Surviving mice show severe growth retardation, impaired reproduction and central hypothyroidism [124]. Mice with combined D1 and D2 deficiency have high serum T₄, and rT₃, reminiscent of the phenotype in SBP2 deficient patients. However, different from the patients, their T₃ is normal while TSH is markedly elevated. The putative, partial and uneven involvement of all three deiodinases in the thyroid phenotype of SBP2 defect, might explain the noted difference in the thyroid tests abnormalities.

Differential diagnosis

Common to the syndromes of reduced sensitivity to thyroid hormone is the non-suppressed TSH despite an increase in TH levels. Indeed, the combination of non-suppressed (normal or slightly elevated) serum TSH with increased concentrations of T₄, T₃ or both, is characteristic of the three syndromes of reduced sensitivity to TH (Table 2). This applies to a lesser degree to the single patient with TRα gene mutation. The ratio of T₃ to rT₃ is characteristically high in MCT8 deficiency while it is normal or low in RTH and low in other causes of abnormal T₃ and rT₃ levels, such as binding defects, iodine deficiency and non-thyroidal illness.

Exclusion of serum TH transport protein abnormalities by direct assessment or measurement of the free TH levels (preferably by equilibrium dialysis) is recommended before proceeding with further testing. The laboratory test abnormalities must be confirmed by repeated testing. Laboratory errors, transient changes in thyroid function tests and the consequence of a variety of non-thyroidal illnesses and drugs should be excluded. Other rare causes of increased TH concentration, such as the presence of iodothyronine antibodies should be considered when thyroglobulin and/or thyroperoxidase antibodies are positive. It should be noted that in *MCT8* and *TRα* gene mutations serum T₄ concentration is usually low, rather than high.

Although the clinical presentation of THCMD involving other cell-membrane transporters than MCT8 is unknown, the latter always presents in males and is accompanied by psychomotor abnormalities, including truncal hypotonia, limb spasticity, poor head control, dyskinetic movements and absent or garbled speech. However, presence of the characteristic thyroid function test abnormalities is mandatory. Sequencing of the *MCT8* gene in subjects with similar psychomotor manifestations but no characteristic thyroid tests abnormalities have yielded negative results.

Because the clinical presentations of RTH and defects of SBP2, are variable and non-specific, the differential diagnosis includes all possible causes of hyperthyroxinemia accompanied by non-suppressed TSH (Table 3). A typical feature of RTH and SBP2-linked THMD is high free T₄ concentration. It should be noted that in mutant albumins with high affinity for T₄, free T₄ can be falsely elevated when measured by a direct method. A distinguishing feature of SBP2 defects is the low serum T₃ and the absence of goiter. In RTH the possibility of a TSH producing pituitary adenoma should be considered, particularly when first presenting in an adult and when the parents have normal thyroid function tests or are not available for testing. Measurement of the α-subunit of pituitary glycoproteins should precede imaging studies.

Most rewarding and cost effective is to obtain thyroid function tests in first-degree relatives. In RTH, which usually is dominantly inherited, testing both parents may suffice. Identification of affected siblings and children can help in sorting out symptoms and signs that are unrelated to the condition under investigation. Mothers of males suspected of having *MCT8* gene defect, should be also tested as they could present a mild thyroid phenotype.

Genetic testing can be sufficient to provide the diagnosis under the following circumstances: identification of a mutation in the candidate gene is pathognomonic if it results in a functionally defective protein or failure to synthesize the protein. Linkage analysis, if informative, can exclude the involvement of a specific gene. However, absence of a mutation does not rule out the suspected defect, particularly when dealing with mosaicism, nonTR-RTH or TH metabolism defect caused by a mutation in a gene other than *SBP2*. In such instances a biochemical diagnosis should be secured by measuring the responses to incremental doses of L-T₄ and/or L-T₃, as described in the respective section of Laboratory Tests.

Routine neonatal testing for hypothyroidism by measurement of blood TSH is inadequate of identifying affected subjects. However, measurement of blood T₄ will detect RTH [31, 32], especially the more severe cases. Low T₄ concentrations are commonly found at birth in MCT8 defects. Unfortunately low T₄ values are not uncommon, and are more often associated with low levels of T₄-binding protein and prematurity.

Treatment

Because the syndromes of reduced sensitivity to TH manifest in the same individual, at the same time, either cell dependent TH deficiency, sufficiency or excess, manipulation of the TH level cannot fully and specifically correct the defects. Furthermore, treatment depends on the timing of the diagnosis, age of the subject and the effect of prior treatment. It should be kept in mind that routine neonatal screening based on the measurement of TSH will rarely lead to the identification of the defects, though measurement of blood T₄ would identify neonates with TR β or non-TR RTH. On the other hand, in all syndromes of reduced sensitivity to TH, a prenatal diagnosis can be made in mothers known to carry a specific mutation by genotyping DNA obtained by chorionic villus sampling or amniocentesis. When contemplating treatment, most important is not to intervene with the sole purpose of normalizing the TH levels.

RTH

tachicardia - beta blocante, uneori ajuta si la sindrom hiperkinetic, daca nu sunt suficiente -> trt specific.

In pacientii la care s-a facut ablatie ty - trb de obicei doze suprafiziologice de hh ty pt substitutie, pe baza TSH.

la unii paciencti cu mutatii de la functie mult scazuts, ty nu compenseaza suficient si trb administrati hh ty, uneori in doze mari. urmaresc profilul metabolic si SHBG pt a nu avea exces, cresc progresiv dozele. pe termen lung monitorizez VO.

la copii cu hipermetabolism si tachicardie - blochez sinteza de TSH cu somatostatina si eventual ATS. pot administra TRIAC, care are o afinitate mai mare centrala decat periferica si scade TSH-ul, determinand si scaderea hipermetabolismului.

The common occurrence of sinus tachycardia can be controlled with the β -adrenergic blocking agent, atenolol. In many cases, this treatment also improves the hyperactivity. However, more severe attention deficit disorder may require treatment aimed at this condition. Fortunately, in most subjects with RTH, the partial tissue resistance to TH is reasonably well compensated by an increase in the endogenous supply of TH. This is not the case in patients with limited thyroidal reserve due to prior ablative therapy. In these patients, the serum TSH level can be used as a guideline for hormone dosage. Sometimes the compensation is incomplete and requires the judicious administration of supraphysiological doses of the hormone. This is particularly common in homozygotes for TR β gene mutations. In such cases, attention must be paid to growth, bone maturation and mental development in children. It is suggested that TH be given in incremental doses and that the basal metabolic rate, nitrogen balance and serum SHBG be monitored at each dose, and bone age and growth on a longer term. Development of a catabolic state is an indication of overtreatment.

Even more rarely, infants may present with failure to thrive accompanied by hypermetabolism and severe tachycardia not controlled by beta-blockers. This has been observed with frameshift mutations producing a TR β with an extended nonsense carboxyl-terminal sequence [126]. In such instances, temporary reduction of the TH level with somatostatin, and if ineffective, the judicious administration of antithyroid drugs could be tried. Among the TH analogues used to alleviate symptoms of apparent TH excess [127], triiodothyroacetic acid (TRIAC) has had the widest use [128, 129]. The combination of greater affinity for TRIAC than T₃ of some mutant TR β s [130] and its short half-life, produce greater effect centrally than on peripheral tissues. This reduces TSH and TH secretion with apparent amelioration of hypermetabolism. The value of treatment with D-T₄ is questionable.

Prenatal diagnosis and counseling is particularly important in families whose affected members show evidence of growth or mental retardation. In addition, women with RTH, that carry unaffected fetuses, have increased risk of abortion and to give birth to infants with low weight for gestational age [131]. This effect, caused by the excess of maternal TH reaching the normal fetus, may be averted by not allowing the maternal free T₄ to rise more than 20% above the upper limit of normal [Dumitrescu, A.M. and Refetoff, S, unpublished data]. The wisdom of in-utero treatment is questionable.

The indications for treatment of RTH in infancy have not been established. This is often an issue when the diagnosis is known or made at birth or in early infancy. Any signs of hypothyroidism, other than serum TSH elevation, such as retarded bone development and failure to thrive deserve consideration for treatment with TH. Though experience is lacking,

treatment with high doses of TH may be indicated in homozygotes for TR β gene mutations that often manifest stigmata indicative of hormone deficiency. The outcome of affected older members of the family who did not receive treatment may serve as a guideline. Longer follow-up and psychological testing of infants who have been given treatment will determine the efficacy of early intervention.

Reducing goiter size, without causing side effects, can be achieved with supraphysiological doses of L-T₃, given as a single dose every other day [132]. Such treatment is preferable as postoperative recurrence of goiter is the rule. The L-T₃ dose must be adjusted until TSH and thyroglobulin are suppressed.

MCT8 defects

Treatment options for patients with *MCT8* gene mutations are currently limited. Supportive measures include the use of braces to prevent mal-position contractures that could lead to orthopedic surgery. Aspiration should be prevented by diet adjustment. Dystonia might be improved with medications such as anticholinergics, L-DOPA, carbamazepine and lioresol. Drooling might be reduced with glycopyrrolate or scopolamine. Seizures should be treated with standard anticonvulsants. When refractory, ketogenic diet has been successful as well as administration of supraphysiologic doses of L-T₄. Experience with such treatments is, however, limited to only a few cases.

Early treatment with L-T₄ doses used for generalized hypothyroidism was not beneficial, presumably because of the impaired uptake of the hormone in MCT8-dependent tissues. Treatment with supraphysiological doses of L-T₄ to increase the availability of TH to the brain will aggravate the hypermetabolism caused by an excess of D1 generated T₃ on peripheral tissues. Therefore, high L-T₄ dose treatment has been used in combination with propylthiouracil (PTU), which is a specific inhibitor of D1. Benefit was limited to reduction of the hypermetabolism and weight loss, without improvement of the neuropsychomotor deficit [87] [Dumitrescu, A.M. and Refetoff, S, unpublished data]. It is unknown what effect such treatment will have if initiated at birth.

The use of thyromimetic drugs that do not require MCT8 to enter tissues are currently under investigation. One such TH analogue, DITPA, is effectively transported into mouse brain in the absence of Mct8 [107]. Preliminary results show normalization of the thyroid tests and possible improvement in the nutritional status but no objective change in the neuropsychiatric deficit [Dumitrescu, A.M. and Refetoff, S, unpublished data]. TH metabolites, such as TRIAC and its precursor TETRAC (tetraiodothyroacetic acid) are being tested. It is possible that for any TH mediated treatment to be effective on brain development, that it will have to be initiated at, or before birth.

SBP2

Although all subjects with *SBP2* gene defects have deficiency in selenoprotein synthesis, in some cases the phenotype is mild, owing to the fact that the deficiency is not complete. The common clinical abnormality of growth retardation, due to reduced generation of T₃, can be corrected by the administration of L-T₃ [110]. Although administration of selenium, in the form of selenomethionine normalized the serum selenium concentration it did not increase the selenoprotein P levels nor restored the TH metabolism dysfunction [133].

More severe consequences caused by the defect require supportive treatment. The benefit of treatment with anti-oxidants has not been established.

Conclusions

Syndromes of reduced sensitivity to thyroid hormone are more common than formerly suspected. The coexistence of cell-specific TH deprivation and excess is characteristic of these syndromes.

RTH

Goiter, attention deficit hyperactivity disorder and tachycardia are the most common reasons that lead to the testing and ultimately, the diagnosis of RTH. Genetic analysis of subjects suspected of having RTH provides a short cut to diagnosis. Failure to identify a *TR β* gene mutation in genomic DNA from circulating mononuclear cells of subjects presenting the RTH phenotype could be due to mosaicism in a de-novo mutation or to a yet unidentified etiology of the syndrome (nonTR RTH). Ablative treatment in RTH complicates the follow up and outcome, as adjustment of TH replacement is not easy.

THCMTD

The neurological manifestations of MCT8 deficiency cannot be explained by the thyroid serum tests abnormalities observed in childhood and adult life. The phenotype is different than that of global TH deficiency or excess. Psychomotor abnormalities without characteristic serum thyroid tests abnormalities are unlikely to be caused by a MCT8 defect. As carrier females are asymptomatic, the presence of a MCT8 defect is not suspected until the birth of the first affected male. Aspiration pneumonia is the most common cause of death in affected males. Treatment with physiological doses of L-T₄ has not corrected the phenotype in several patients.

THMD

The phenotype of SBP2 deficiency is variable and depends on the severity of functional impairment of the mutant protein. Thyroid tests abnormalities are always present, and delayed growth and puberty are seen even in the more mild cases. Treatment with physiological doses of L-T₃ may accelerate growth and maturation but does not correct other manifestations of the defect.

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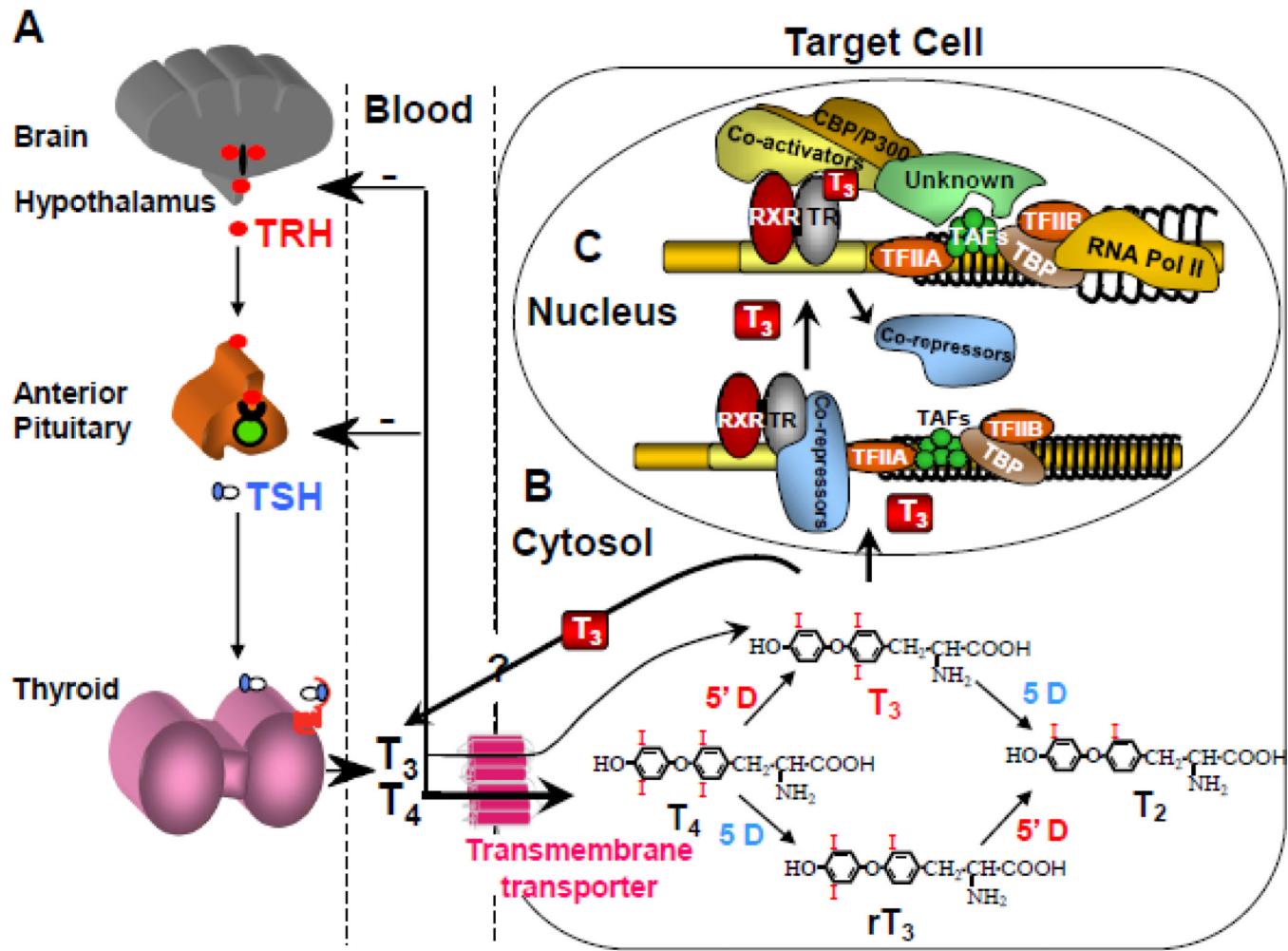
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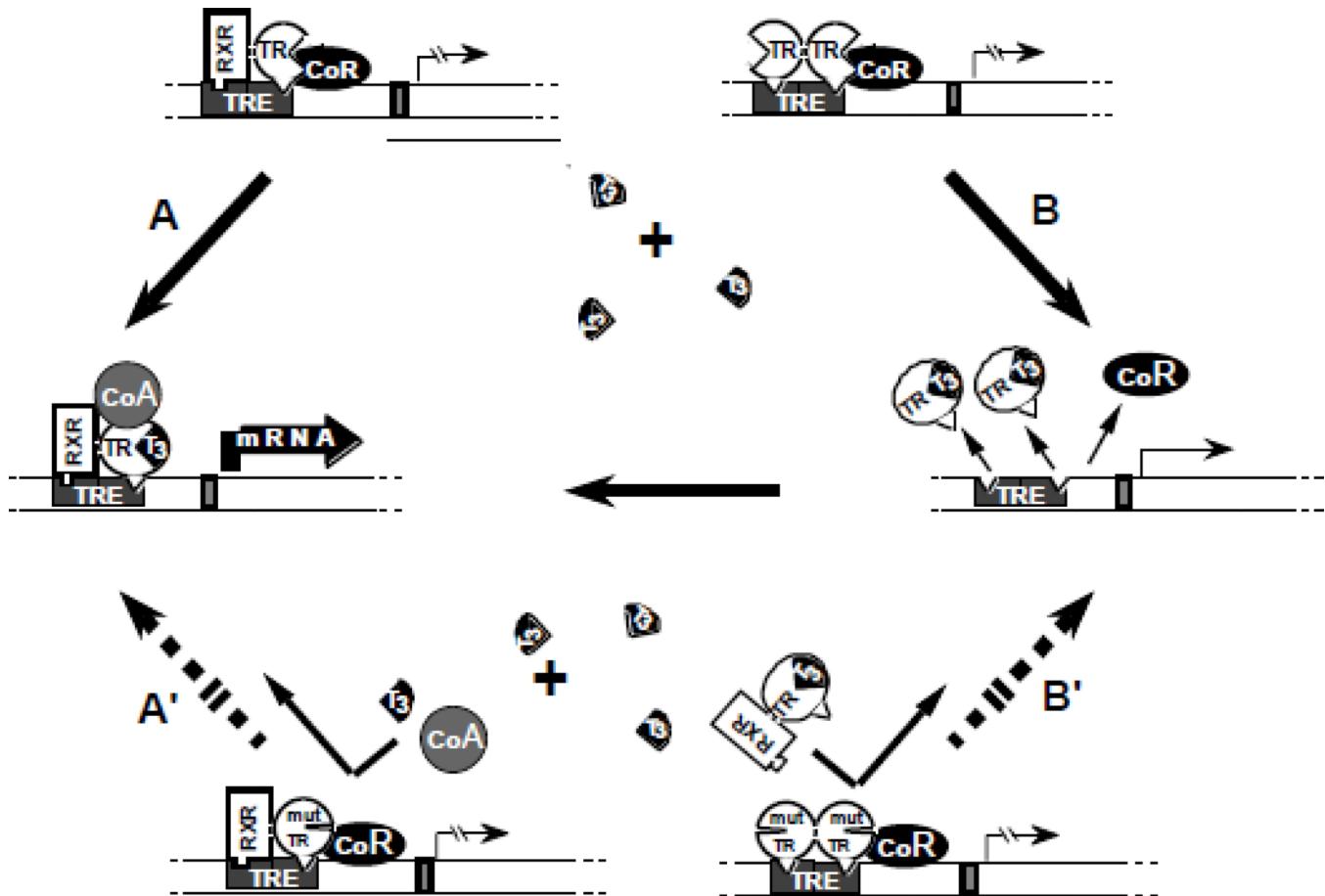
Highlights

- Defects of TH action manifest as tissue and cell specific TH deficiency and excess
- The syndrome of resistance to TH has helped elucidate the mechanism of TH action
- Neurological deficits of MCT8 defects are more severe than in congenital hypothyroidism
- SBP2 defects reduce selenoprotein synthesis and alter intracellular TH metabolism

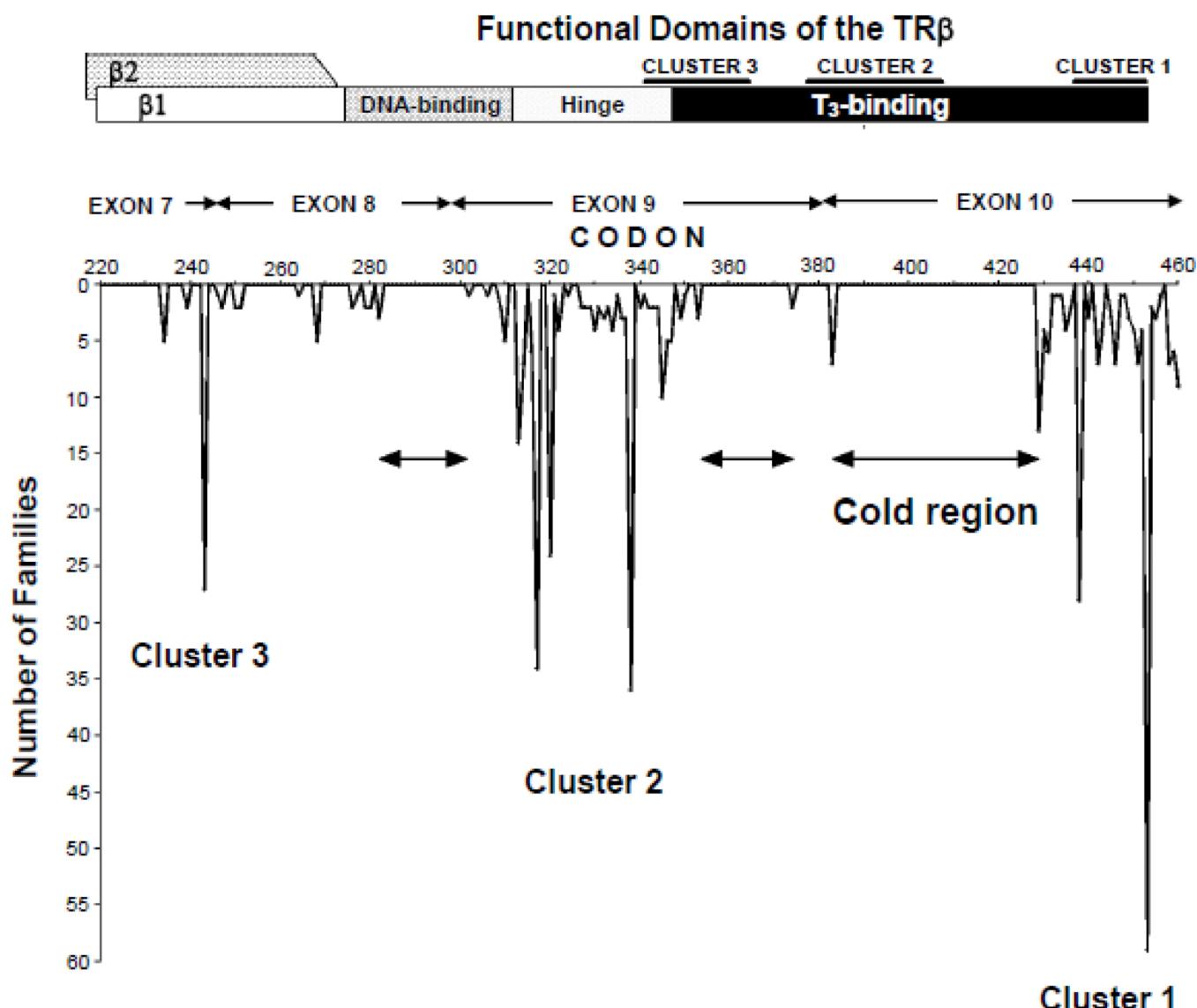
**Figure 1.**

Regulation of TH supply, metabolism and genomic action. (A) Central feedback control that regulates the amount of TH in blood. (B) Intracellular metabolism of TH, regulating TH bioactivity. (C) Genomic action of TH. For details see text.

CBP/P300, cAMP-binding protein/general transcription adaptor; TFIIA and TFIIB, transcription intermediary factor II, A and B; TBP, TATA-binding protein; TAF, TBP-associated factor. (Modified from Refetoff S, Dumitrescu AM. Syndromes of reduced sensitivity to thyroid hormone: genetic defects in hormone receptors, cell transporters and deiodination. Best Pract Res Clin Endocrinol Metab. 2007 Jun;21(2):277–305.)

**Figure 2.**

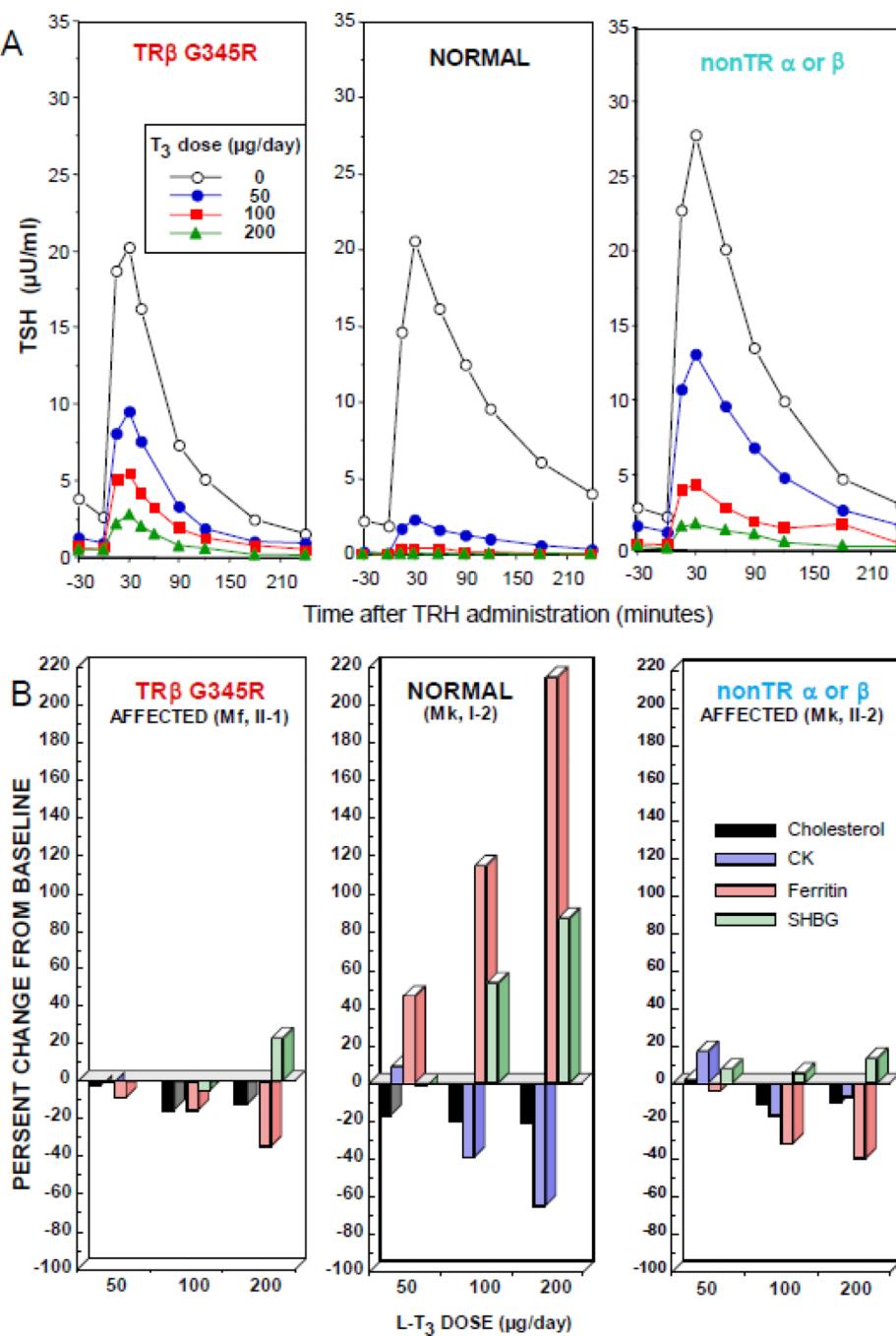
Schematic representation of the DNE mechanism: In the absence of T₃, occupancy of TRE by TR heterodimers (TR-RXR) or dimers (TR-TR) suppresses transactivation through association with a corepressor (CoR). (A) T₃-activated transcription mediated by TR-RXR heterodimers involves the release of the CoR and association with coactivators (CoA) as well as (B) the removal of TR dimers from TRE releases their silencing effect and liberates TREs for the binding of active TR-RXR heterodimers. The DNE of a mutant TR (mut TR), that does not bind T₃, can be explained by the inhibitory effect of mut TR-containing-dimers and heterodimers that occupy TRE. Thus, T₃ is unable to activate the mut TR-RXR heterodimer (A') or release TREs from the inactive mut TR homodimers (B'). (Modified from Refetoff S, Weiss RE, Usala SJ. The syndromes of resistance to thyroid hormone. *Endocr Rev* 1993;14:348–399.)

**Figure 3.**

Location of natural mutations in the TR β molecule associated with RTH.

TOP PORTION: Schematic representation of the TR β and its functional domains for interaction with TREs (DNA-binding) and with hormone (T₃-binding). Their relationship to the three clusters of natural mutations is also indicated. TR β 2 has 15 more residues than TR β 1 at the amino-terminus.

BOTTOM PORTION: The location of the 170 different mutations detected and their frequencies in the total of 459 unrelated families (published and our unpublished data). Amino acids are numbered consecutively starting at the amino terminus of the TR β 1 molecule according to the consensus statement of the First International Workshop on RTH [134]. "Cold regions" are areas devoid of mutations associated with RTH.

**Figure 4.**

Responses to the administration of L-T₃ in subjects with RTH, with and without mutations in the *TR β* gene and in a normal individual. The hormone was given in three incremental doses, each for 3 days. Results are shown at baseline and after each dose of L-T₃ in patients with RTH in the presence (left) or absence (right) of a *TR β* gene mutation, and the unaffected mother of the patient with nonTR-RTH (center). (A) TSH responses to TRH stimulation. (B) Responses of peripheral tissues. Note the stimulation of ferritin and sex hormone binding globulin (SHBG) and the suppression of cholesterol and creatine kinase (CK) in the normal subject. Responses in affected subjects, with or without a *TR β* gene mutation, were blunted or paradoxical. (Modified from Refetoff S, Dumitrescu AM.

Syndromes of reduced sensitivity to thyroid hormone: genetic defects in hormone receptors, cell transporters and deiodination. Best Pract Res Clin Endocrinol Metab. 2007 Jun;21(2): 277–305.)

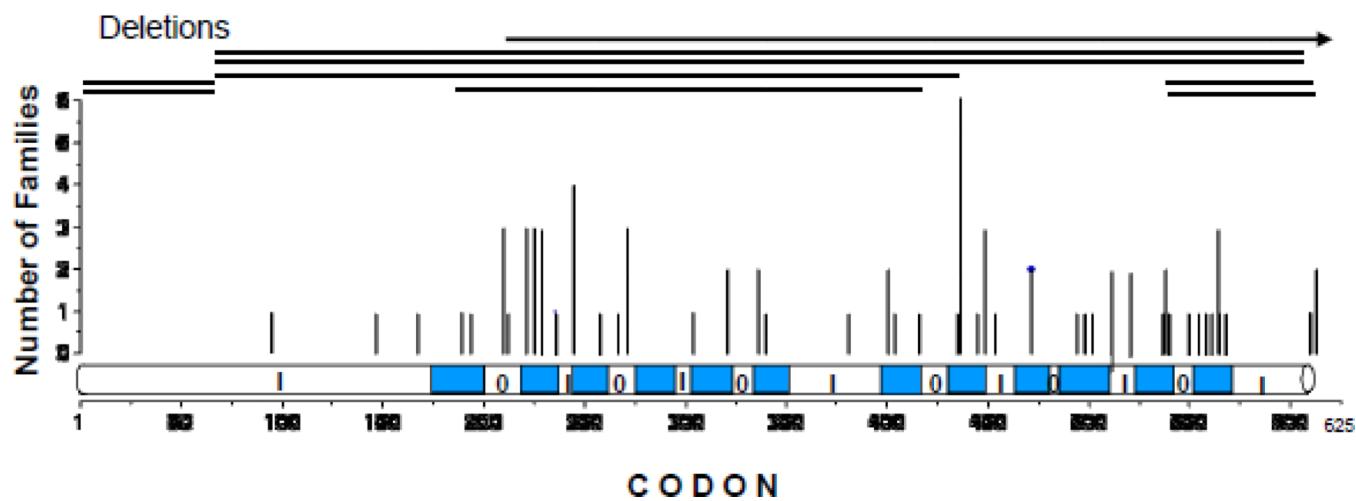
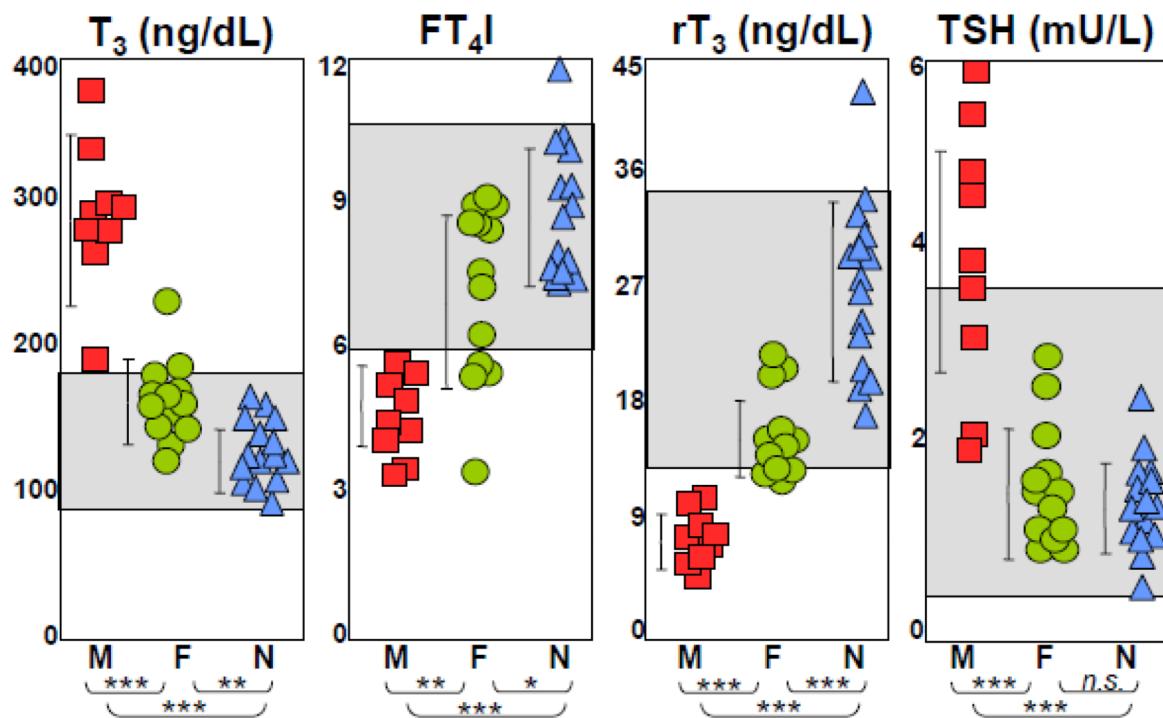
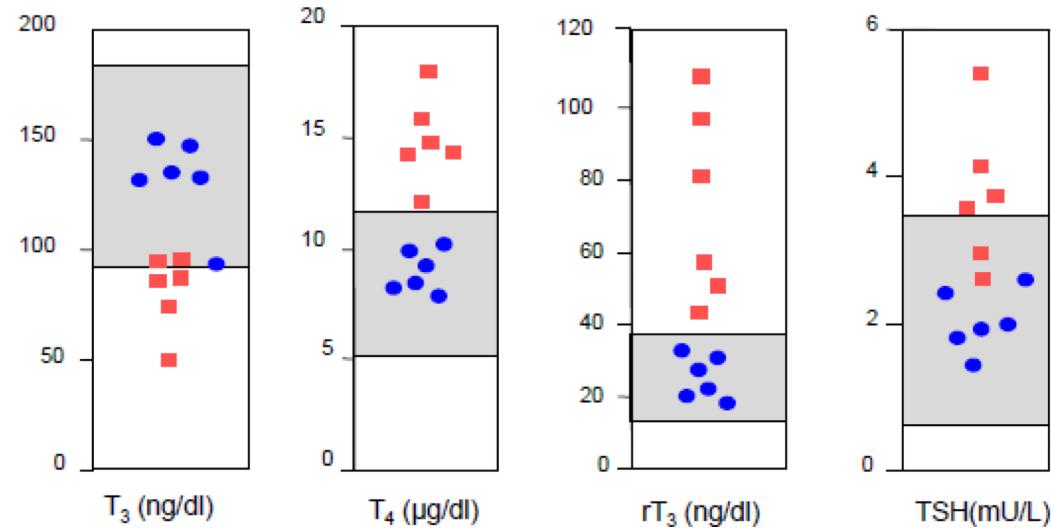


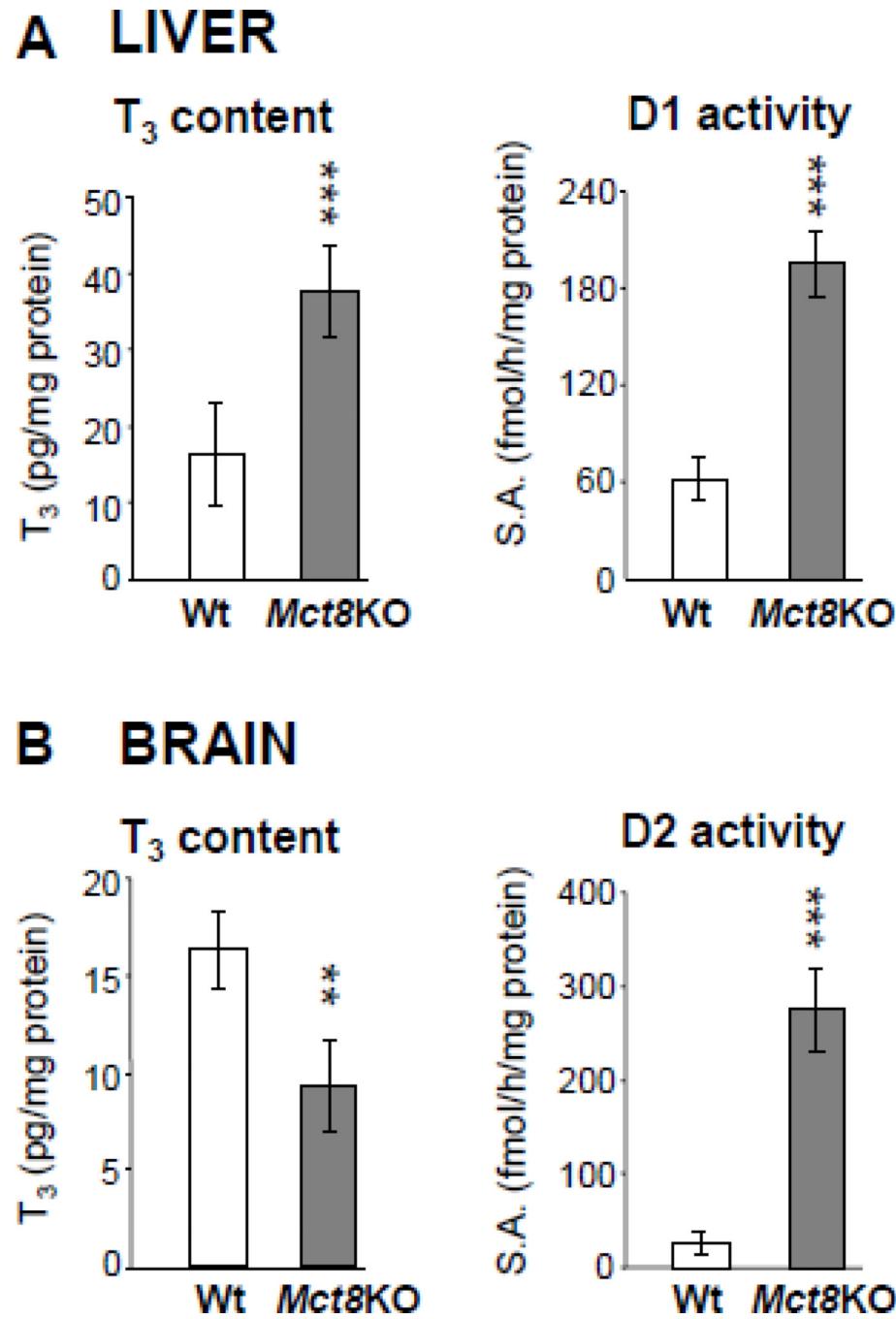
Figure 5.

Location of mutations in the MCT8 molecule associated with THCM TD Shown by vertical lines are 58 known mutant MCT8 proteins and their frequency in 80 families (published and our unpublished data). Horizontal lines indicate the mutations with deletions of large regions. Numbering is consecutive, starting at the amino terminus of the 613 amino acid human molecule. The 12 TMDs are indicated in blue. Loops predicted to be outside the cell are indicated by an O and those inside the cell, by an I.

A MCT8**B SBP2****Figure 6.**

(A) Thyroid function tests in several families with MCT8 deficiency studied in the authors' laboratory. Grey regions indicate the normal range for the respective test. Hemizygous males (M) are represented as red squares, heterozygous carrier females (F), as green circles and unaffected members of the families, as blue triangles (N). With the exception of TSH, mean values of iodothyronines in carrier females are significantly different than those in affected males and normal relatives. (B) Thyroid function tests in subjects from 4 families with SBP2 deficiency studied in the authors' laboratory. Grey regions indicate the normal range for the respective test. Affected individuals are represented as red squares and unaffected members of the families, as blue circles. (Modified from Refetoff S, Dumitrescu

AM. Syndromes of reduced sensitivity to thyroid hormone: genetic defects in hormone receptors, cell transporters and deiodination. Best Pract Res Clin Endocrinol Metab. 2007 Jun;21(2):277–305.)

**Figure 7.**

Tissue T_3 content *Mct8KO* and Wt mice and its corresponding effect. A. T_3 content and D1 enzymatic activity in liver. B. T_3 content and D2 enzymatic activity in brain. Data from *Mct8KO* mice are represented as grey bars and those from Wt littermates are in open bars. ** p-value <0.01, *** p-value <0.001. S.A., specific activity. (Modified from Refetoff S, Dumitrescu AM. Syndromes of reduced sensitivity to thyroid hormone: genetic defects in hormone receptors, cell transporters and deiodination. Best Pract Res Clin Endocrinol Metab. 2007 Jun;21(2):277–305.)

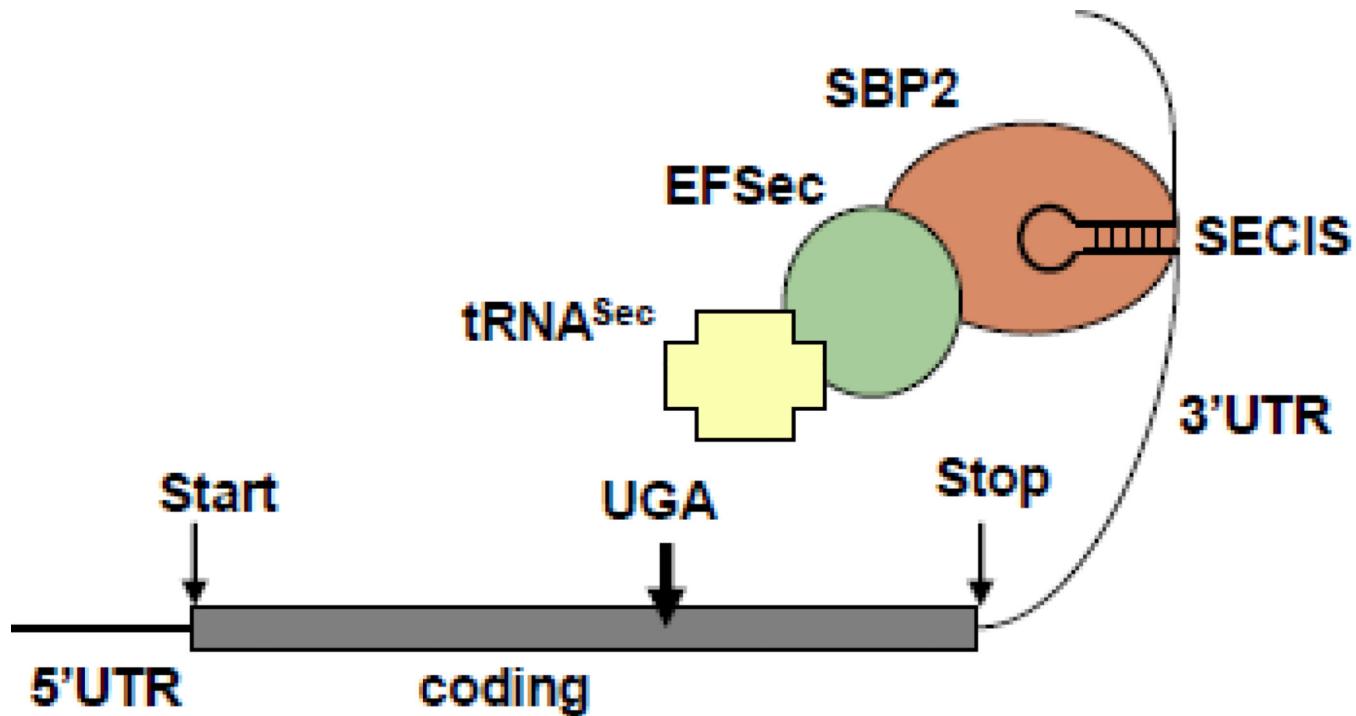
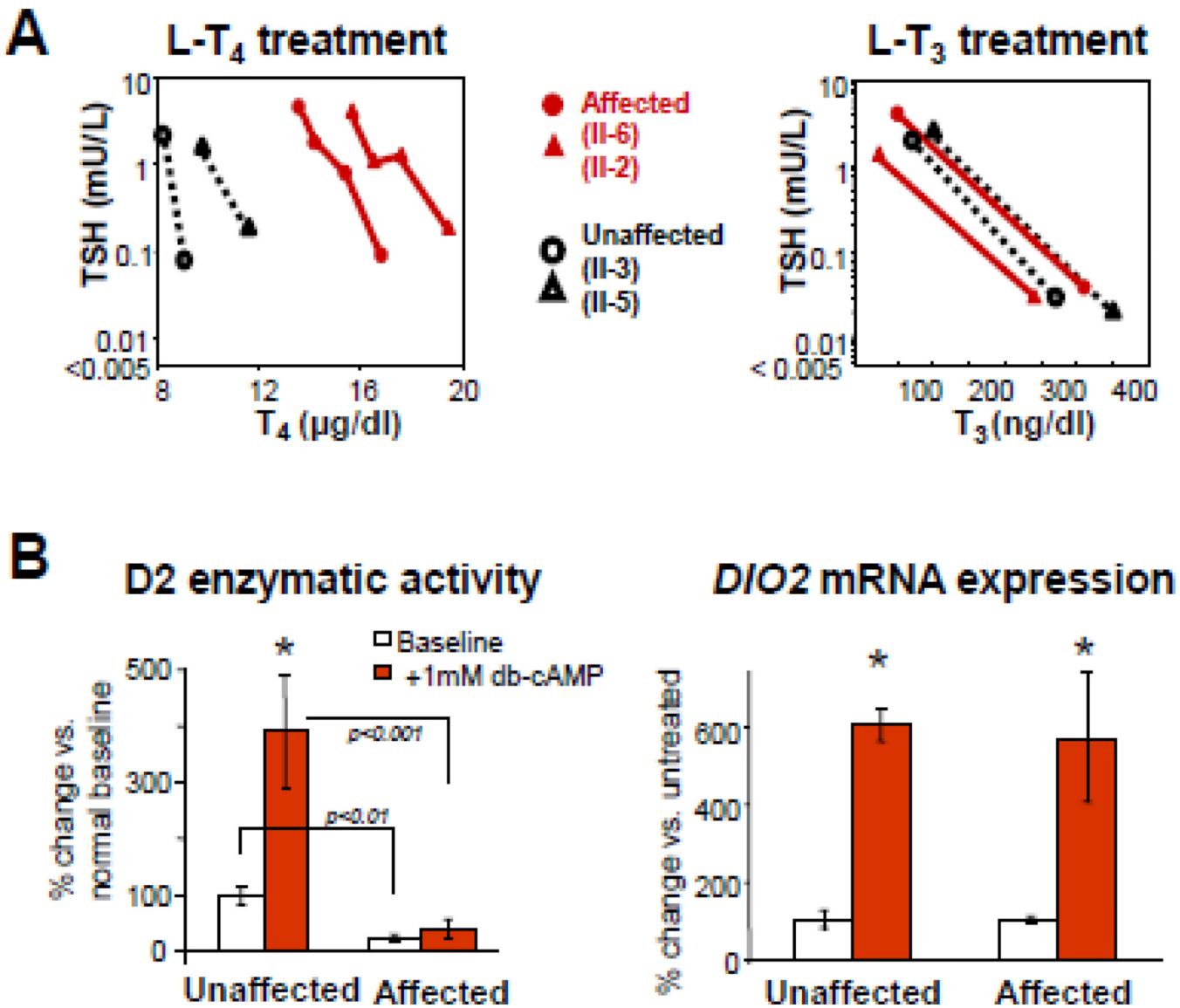


Figure 8.

Schematic representation of the components involved in Sec incorporation that are central to the synthesis of selenoproteins. Elements present in the mRNA of selenoproteins are an in frame UGA codon and Sec incorporation sequence (SECIS) element, a stem loop structure located in the 3'UTR (untranslated region). SBP2 binds SECIS and recruits the Sec-specific elongation factor (EFSec) and Sec-specific tRNA ($tRNA^{Sec}$) thus resulting in the recoding of the UGA codon and Sec incorporation.

**Figure 9.**

In-vivo and *in-vitro* studies in subjects with SBP2 deficiency. (A) *In-vivo* studies: Serum TSH and corresponding serum T₄ and T₃ levels, before and during the oral administration of incremental doses of L-T₄ and L-T₃. Note the higher concentrations of T₄ required to reduce serum TSH in the affected subjects; (B) *In-vitro* studies of deiodinase 2 in cultured skin fibroblasts: Baseline and stimulated D2 activity is significantly lower in affected individuals. There is significant increase of DIO2 mRNA with dibutyryl cyclic adenosine monophosphate [(db)-cAMP], in both unaffected and affected (*p < 0.001) while there are no significant differences in baseline (db)-cAMP stimulated DIO2 mRNA in affected versus the unaffected. (Modified from Refetoff S, Dumitrescu AM. Syndromes of reduced sensitivity to thyroid hormone: genetic defects in hormone receptors, cell transporters and deiodination. Best Pract Res Clin Endocrinol Metab. 2007 Jun;21(2):277–305.)

SBP2 gene mutations

Table 1

SBP2 gene	Protein	Comments on putative defect	No of affected	Defect	Ref
c.1619 G>A	R540Q	hypomorphic allele	3	homozygous	[8]
c.1312 A>T	K438X	missing C terminus	1	compound heterozygous	[8]
IVS8ds+29 G>A	fs	abnormal splicing			
c.382 C>T	R128X	smaller isoforms *	1	homozygous	[110]
c.358 C>T	R120X	smaller isoforms *	1	compound heterozygous	[111]
c.2308 C>T	R770X	disrupted C-terminus			
c.668delT	F223 fs 255X	truncation and smaller isoforms *	1	compound heterozygous	[112]
intron 6-155 delC	fs	abnormal splicing, missing C-terminus			
c.2071 T>C	C691R	increased proteasomal degradation	1	compound heterozygous	[112]
intronic SNP	fs	transcripts lacking exons 2–4, or 3–4	1	compound heterozygous	[112]
c.1529_1541dup CCAGGGCCCCACT	M515 fs 563X	missing C terminus	1	compound heterozygous	[113]
c.235 C>T	Q79X	smaller isoforms *			
c.2344 C>T	Q782X	missing C terminus	1	compound heterozygous	**
c.2045_2048 delAAACA	K682 fs 683X	missing C terminus			

* generated from downstream ATGs;

** Dumitrescu, A.M. and Refetoff, S, unpublished data

fs – frame shift

Table 2

Comparison of TFT Abnormalities in Syndromes of RSTH

Gene defect	Common clinical manifestations				
Syndrome	FT ₄	FT ₃	rT ₃	TSH	
RTH β *	↑↑	↑ N	↑↑	N, sl ↑	Attention deficit disorder, learning disability, tachycardia, goiter
RTH α #	↓	N, sl ↑	↓	N	Bradycardia, constipation, mental retardation, short lower limbs, delayed bone age
THCMTD **	↓	↑↑	↓	N, sl ↑	Severe psychomotor impairment (no talk, no walk, poor head control)
THMD	↑↑	↓	↑↑	N, sl ↑	Growth delay
					SBP2

* Includes non TR-RTH

** Males

based on three cases.

RSTH = reduced sensitivity to thyroid hormone

THCMTD = thyroid hormone cell membrane transport defect

THMD = thyroid hormone metabolism defect

sl, slight; ↑, increased; ↓, decreased; N, normal.

Table 3

Conditions Associated with Hyperthyroxinemia

Defect	Thyroid Function Tests				
	T ₄	T ₃	rT ₃	TSH	FT ₄ direct
↑TBG	↑	↑	↑	N	N
↑TTR *	↑	N	↑	N	N
FDH	↑	↑ or N	↑	N	↑
RTH β **	↑	↑ or N	↑	s↑ or N	↑
SBP2	↑	↓	↑	s↓ or N	↑
Acute NTL	↑	↓↓	↑	N	↑ or N
				N	N

* Refers to TTR with increased affinity for T₄ and rT₃

** Includes nonTTR-RTH

TBG, T₄ binding globulin; TTR, transthyretin;
FDH, familial dysalbuminemic hyperthyroxinemia;
SBP2, selenocysteine insertion binding sequence protein;
NTL, nonthyroidal illness;
s↓, slight; ↑, increased; ↓, decreased; N, normal.