

## Review

# Recent advances in research on isolated congenital central hypothyroidism

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**Abstract.** Congenital central hypothyroidism (C-CH) is caused by defects in the secretion of thyrotropin-releasing hormone (TRH) and/or TSH, leading to an impairment in the release of hormones from the thyroid. The causes of C-CH include congenital anomalies of the hypothalamic-pituitary regions and several genetic defects. In terms of endocrinology, C-CH is divided into two categories: (1) accompanied by another pituitary hormone deficiency and called combined pituitary hormone deficiency, and (2) isolated C-CH, showing mainly TSH deficiency. For isolated C-CH, a mutation in the TSH gene (*TSHB*) encoding the  $\beta$ -subunit of the protein was first found in 1990 by Japanese researchers, and thereafter several mutations in *TSHB* have been reported. Mutations in the thyrotropin-releasing hormone receptor gene (*TRHR*), as well as genetic defects in immunoglobulin superfamily 1 (*IGSF1*), have also been identified. It was recently found that isolated C-CH is caused by mutations in transducin  $\beta$ -like 1 X-linked and insulin receptor substrate 4. It is noted that all patients with *TSHB* deficiency and some with *IGSF1* deficiency show severe hypothyroidism soon after birth. Among the causes of C-CH, high frequency of mutations in *IGSF1* is the most prevalent. This review focuses on recent findings on isolated C-CH.

**Key words:** congenital central hypothyroidism (C-CH), immunoglobulin superfamily 1 (*IGSF1*), *TRHR*, *TBL1X*

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## Introduction

Congenital central hypothyroidism (C-CH) is defined as hypothyroidism due to a lack of stimulation of the normal thyroid gland (1, 2). C-CH is caused by anatomical or

functional impairments in neurons that secrete hypothalamic-thyrotropin releasing hormone (TRH) and/or pituitary thyrotropes that secrete TSH. C-CH is more frequently recognized as a part of a combined pituitary hormone deficiency (CPHD), but a small proportion of C-CH cases demonstrate isolated C-CH where mainly TSH secretion is impaired.

The frequency of C-CH among the general population has been reported as 1/16,000 to 1/30,000 (2–4). In Japan, newborn screening for congenital hypothyroidism has been performed since 1979. While the main purpose of such screening is to detect primary hypothyroidism (thyroid origin), some regions in the country

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**Table 1.** Genetic causes, severity of hypothyroidism, and endocrine findings of isolated-Cent-H

Gene	Chromosome	Inheritance	Degree of hypothyroidism	Endocrinological findings
<i>TSHB</i>	1p13.1	Autosomal Recessive	Severe	Low TSH, normal ~ elevated PRL, blunted response of TSH after TRH stimulation
<i>TRHR</i>	8q23.1	Autosomal Recessive	Mild	Normal TSH, low ~ normal PRL, blunted responses of TSH and PRL after TRH stimulation
<i>IGSF1</i>	Xq26.1	X-linked	Severe ~ mild	Low ~ normal TSH Some patients shows PRL and GH deficiency together with TSH
<i>TBL1X</i>	Xp22.2	X-linked	Mild	Normal TSH, normal response of TSH after TRH stimulation
<i>IRS4</i>	Xq22.3	X-linked	Mild	Normal TSH, blunted response of TSH after TRH stimulation

employ simultaneous determination of blood TSH and free T4 (FT4) levels to diagnose C-CH in addition to primary hypothyroidism (2–4). Nagasaki et al. reported that C-CH occurs in about 10% of patients with congenital hypothyroidism in Japan (5).

In 1971, Miyai *et al.* (6) first reported a family with isolated TSH deficiency, and in 1989, a mutation in the TSH gene (*TSHB*) encoding the  $\beta$ -subunit of the protein was eventually discovered (7). Thereafter, over the following three decades, several genetic defects associated with isolated C-CH have been identified (Table 1) (1, 2, 8, 9). This review summarizes the current knowledge regarding the genetic causes and clinical features of isolated C-CH.

### TSHB Deficiency

As mentioned, a family in Japan showing TSH deficiency was first reported by Miyai *et al.* (6), and eventually a mutation in *TSHB* was discovered in 1989 (7). In the first report, patients showed symptoms of severe congenital hypothyroidism, such as failure to thrive, prolonged jaundice, and developmental delay. Despite very low levels of serum T4 and T3, TSH was not measurable, indicating C-CH. A TRH stimulation test did not increase TSH level at

all, but showed a normal PRL response. Finally, their group identified a homozygous mutation p.Gly29Arg in *TSHB*. Miyai *et al.* (1) further found several Japanese patients with *TSHB* deficiency. Genetic analysis showed that all patients had p.Gly29Arg, suggesting a founder effect (1).

Since the first report, several patients with *TSHB* mutations have been reported worldwide (10–20). In all cases, the inheritance of *TSHB* defects is autosomal recessive. Almost all patients with a *TSHB* defect develop severe symptoms of congenital hypothyroidism after birth. A delay in diagnosis and thyroid hormone replacement therapy results in poorer psychomotor development.

Regarding mutations, nonsense mutations (p.Glu32Ter and p.Gln69Ter), frameshift mutations (p.Cys125ValfsTer10), missense mutations (p.Met1?, p.Glu32Lys, p.Gly49Arg, p.Cys108Tyr, and p.Cys105Arg), and a splice site mutation (c.1625+5G>A) have been identified. One mutation (c.162G>A) did not cause an amino acid change, but it was located at the 5' donor splice site of exon/intron2, leading to the skipping of exon 2. In addition, a homozygous deletion of *TSHB* was also reported (16). Among these mutations and deletions, p.Cys125ValfsTer10 has been most frequently reported in Europe,

Argentina, and the USA (10, 12, 18–20). This mutation has been found in various unrelated families, but several studies using haplotype analysis in Germany, the UK, and Ireland showed that this mutation was derived from common ancestors (18–20).

### TRHR Deficiency

To date, three homozygous mutations in the thyrotropin-releasing hormone receptor (*TRHR*) gene of five individuals from three unrelated families and a compound heterozygous mutation in a case from another family have been reported (21–24). In contrast to cases with TSHB deficiency, cases with TRHR deficiency do not show severe symptoms of congenital hypothyroidism or developmental delay despite a delay in the start of thyroxine replacement.

The first case with a *TRHR* mutation was identified through clinical evaluation because of the observation of a short stature at 8.9 yr of age (21). The patient showed low serum T4 and normal TSH levels. Neither TSH nor PRL responded upon TRH stimulation. Genetic analysis revealed that the patient was a compound heterozygote for p.Arg17Ter and p.Ser115-Tyr117del;Ala118Thr. Furthermore, two missense mutations in two unrelated families were reported. One patient who was homozygous for p.Pro81Arg, a recently identified TRHR missense mutation, showed prolonged jaundice; a subsequent endocrine examination was performed and low free T4 and normal TSH levels at 18 d of age were found (23). Thyroid hormone replacement therapy was initiated at 2 mo of age. The patient showed normal growth and development at 4 yr of age. A functional study of p.Pro81Arg revealed that mutant TRHR was normally expressed in the cell membrane, but showed reduced capacities for binding TRH and signal transduction through G $\alpha_q$ , a member of the G alpha q family of GTP-binding proteins.

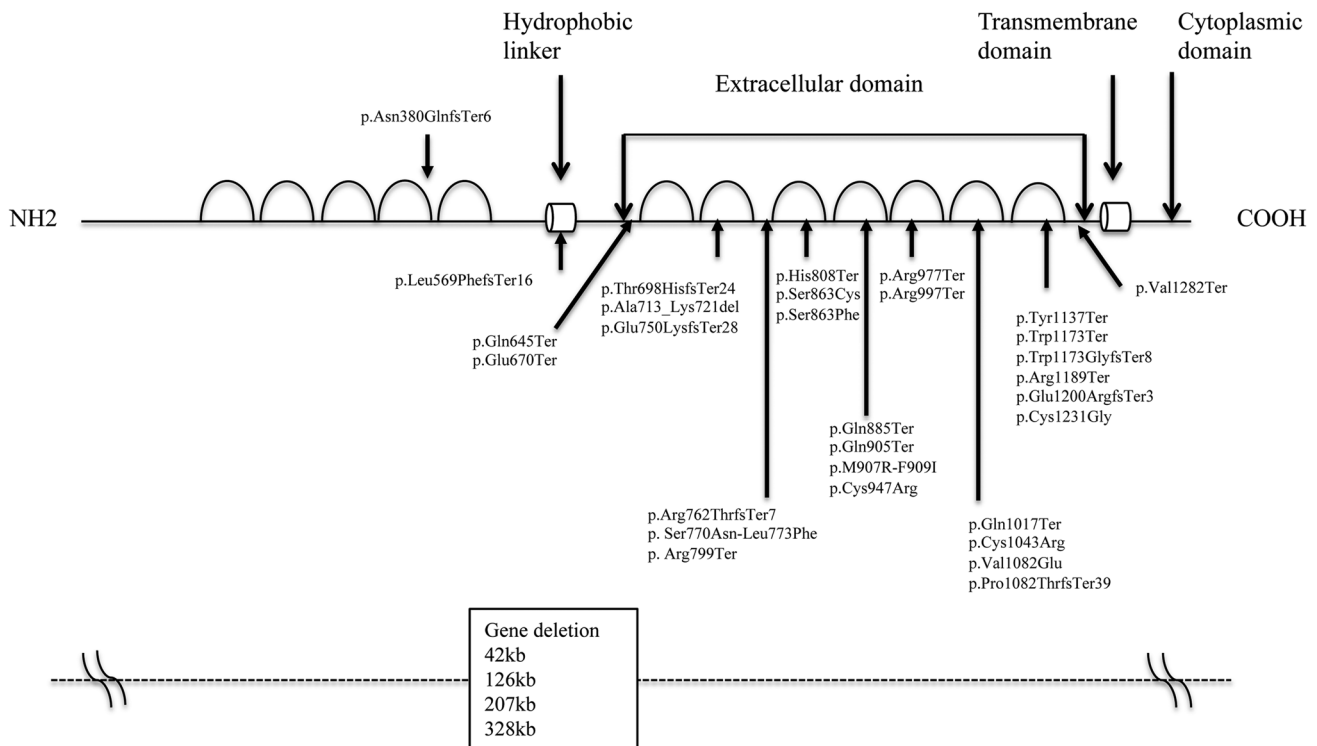
The other homozygous TRHR missense mutation, p.Ile131Thr, was reported in an 8-yr-

old boy (24). He showed mildly low free T4 and normal TSH levels and was overweight (body mass index (BMI): 20.4 kg/m<sup>2</sup>). This mutation was also associated with decreased TRH binding affinity. In addition, two cases with a homozygous nonsense mutation (p.Arg17Ter) have been reported (22). A boy was medically evaluated because of short stature and easy fatigue at 11 yr of age. His neurological development was normal. Endocrinological evaluation showed low free T4 and normal TSH levels, but TRH stimulation did not increase either serum TSH or PRL level. Thyroxine replacement improved the boy's symptoms. Interestingly, his 33-yr-old sister was also found to be homozygous for p.Arg17Ter in a family screen. She showed normal growth and neurological development. She had two deliveries and subsequent lactation was normal. This finding indicates that, while TRHR is expressed in lactotropes as well as thyrotropes, TRH-stimulated PRL is not necessary for human pregnancy and lactation. In this case, thyroid hormone replacement therapy was reported to improve the sister's quality of life (8).

As mentioned previously, in contrast to cases with TSHB deficiency, cases with TRHR deficiency did not show severe symptoms of congenital hypothyroidism and had normal neurological development. The T4 levels in cases with TRHR deficiency were reduced by approximately 50–80% for the lower limit range, but were at higher levels than those in cases with TSHB deficiency. These findings indicate that, without TRHR-mediated TRH stimulation, thyrotropes can secrete bioactive TSH, leading to the secretion of thyroid hormone to achieve normal neurological development.

### IGSF1 Deficiency

The immunoglobulin superfamily 1 (*IGSF1*) gene was cloned from the X chromosome in 1998 and found to encode a transmembrane glycoprotein containing 12 extracellular immune loops, a single transmembrane domain, and



**Fig. 1.** Schema of IGSF1 and mutations/deletions. Immunoglobulin superfamily 1 (IGSF1) has 12 immune loops. The protein is cleaved at N- and C-terminal domains between immunoglobulin loops 5 and 7. Whereas the C-terminal domain moves to the cell membrane, the N-terminal domain remains in the endoplasmic reticulum. Deletions, nonsense, frameshift, missense, and splicing mutations reported are summarized.

a short cytoplasmic domain (25) (Fig. 1). The protein is cleaved by peptidase between immune loops 5 and 6, and only the C-terminal region moves to and is expressed in the cell membrane (25). It was suggested that IGSF1 has a role as a coreceptor of inhibin; however, *Igsf1* knockout mice showed normal fertility and FSH levels, indicating that IGSF1 does not function as a coreceptor of inhibin (26). In 2012, Sun *et al.* (27) reported that mutations and deletions of *IGSF1* were causal to C-CH. In Japan in 2013, our group reported four mutations in *IGSF1* in patients with C-CH (28, 29). Thereafter, to date, several reports of IGSF1 deficiency have been made (30–38).

Regarding genetic defects of *IGSF1*, deletion, nonsense, missense, and splicing mutations have been identified, and all mutations except

**Table 2.** Clinical features of male patients with IGSF1 deficiency

Features	Prevalence
Hypothyroidism	100%
Macroorchidism	80%
Low testosterone levels in adult	70%
Attention deficit disorder	65%
Increased BMI in children	30%
Increased BMI in adult	75%
PRL deficiency	60%
GH deficiency in childhood	10%

These data is collected from published literatures (27–41).

one (p.Asn380GlnfsTer6) (30) were found to be located in the C-terminal region of IGSF1 (Fig. 1). Regarding missense mutations, since an *in vitro* study demonstrated that mutant proteins

could not traffic to the cell membrane, these were thought to be loss-of-function mutations (27, 29, 34, 37).

Clinical features of IGSF1 deficiency and the frequency of these features are summarized in Table 2 (27–40). Almost all male individuals with IGSF1 deficiency had C-CH, but the severity of C-CH varied widely. Whereas some individuals showed symptoms of hypothyroidism such as failure to thrive, constipation, icterus, and growth failure from early childhood, family screening of thyroid function accidentally detected several asymptomatic individuals when affected family members were first diagnosed.

It is notable that one of the characteristic features of IGSF1 deficiency is macroorchidism. In the study by Joustra *et al.*, approximately 80% of adult cases showed macroorchidism (40). Some patients also showed a delayed rise in LH and FSH levels during puberty. In addition, serum testosterone levels were low in adult male patients, but male fertility was likely to be normal. Furthermore, about 50% of adult patients developed obesity despite appropriate thyroxine replacement. It was also reported that 65% of patients showed attention deficit disorder. Attention deficit disorder has been found in patients despite early initiation of thyroxine treatment (41). Since IGSF1 is expressed in the brain, any neurological deficits may be due to a direct effect of IGSF1 deficiency.

To date, in Japan, 10 patients described in six publications within the medical literature have been identified (28–30, 32, 38, 39). Clinical features and endocrine findings are summarized in Table 3. Patients 1 and 2 were siblings and their detailed clinical courses have been reported (38). In brief, patient 1 developed a failure to thrive, marked abdominal distention, and icterus at 5 d of age; a subsequent examination of thyroid function showed marked low FT4 and free T3 levels (Table 3). To our knowledge, this patient presented the most severe case to have been reported so far in the literature. However, patient 2, who was an older brother of patient 1, did not

develop severe symptoms of hypothyroidism, but showed a mild psychomotor developmental delay at 1 yr of age and was followed regularly. After his younger brother was diagnosed with C-CH, he was evaluated for thyroid function and diagnosed with C-CH. Thyroid hormone replacement was started at 3 yr of age, but his psychomotor development was mildly delayed.

Asakura *et al.* (30) pointed out that patients with IGSF1 deficiency are born larger than the mean for a specific gestational age. Furthermore, Japanese cases reported after the publication of the study by Asakura *et al.* (30) also described a heavy birth weight (Table 3). The BMI data of 10 reported Japanese patients are summarized in Table 3. Most patients showed an increased BMI, concordant with a study from Europe (40). Interestingly, the patient described by Asakura *et al.* (30) showed hypoplastic anterior and ectopic posterior lobes in the pituitary by magnetic resonance imaging (MRI), accompanying a growth hormone deficiency. So far, hypoplasia of the corpus callosum in one patient and in the small stalk region in another as shown by MRI have been identified (27). Whether these anatomical findings observed through MRI occurred by accident or were a direct effect of IGSF1 deficiency is still unknown.

While it is now clear that IGSF1 deficiency causes C-CH, the physiological role of IGSF1 in humans has not yet been determined. The expression of *IGSF1* and murine *Igsf1* mRNAs were observed in Rathke's pouch and the adult pituitary gland (27), suggesting that IGSF1 is probably involved in the regulation of TRH and/or the secretion of TSH. In this regard, a study using *Igsf1* knockout mice may be useful. Turgeon *et al.* (42) recently reported about *Igsf1* knockout mice that showed a loss-of-function mutation in the C-terminal domain of *Igsf1*. In this study, the TSH content of the pituitary was reduced compared with that of wild-type mice. In addition, mRNA levels of *Tshb* and *Trhr* in thyrotropes were decreased. A low iodine diet together with propylthiouracil-induced hypothyroidism in

**Table 3.** Biochemical, clinical features and mutations of Japanese patients with IGSF1 deficiency

Pt	Age at DG <sup>a)</sup>	Symptoms at DG	Free T4 at DG (ng/dl)	Free T3 at DG (pg/ml)	TSH at DG (mU/l)	PRL	Birth weight (SD)	Birth length (SD)	BMI (kg/m <sup>2</sup> )	Macroorchidism	Mutation	Ref
1 <sup>b)</sup>	5 d	Icterus, failure to thrive, abdominal distension	0.38	1.04	1.10	Low	+ 2.2	+ 1.4	22.6 (5 yr)	ND <sup>c)</sup>	W1173GfsX8	39
2 <sup>b)</sup>	3 yr	Developmental delay	0.57	2.38	0.67	Low	+ 2.9	+ 2.0	23.5 (7 yr)	ND	W1173GfsX8	39
3	14 yr	Short stature, constipation	0.73	NA <sup>d)</sup>	1.11	Normal	+ 2.0	+ 1.5	22.0 (16 yr)	+	c.2065+1G>A	38
4	1 mo	Icterus	0.56	2.47	1.84	Normal	+ 1.4	+ 1.0	19.7 (3 mo)	ND	Q905X	28
5	16 d	NBS <sup>e)</sup>	0.51	NA	0.6	Low	+ 1.2	+ 0.7	22.1 (17 yr)	-	P1082TfsX39	29
6	22 d	NBS	0.57	3.60	2.70	Low	+ 1.1	+ 1.1	18.9 (12 yr)	+	R1189X	29
7	4 yr	Short stature	0.76	2.35	2.35	Low	+ 1.9	+ 1.7	26.7 (12 yr)	ND	R1189X	29
8	24 d	NBS	0.52	1.96	3.5	Normal	+ 1.6	- 0.2	18.2 (5 yr)	ND	V1082E	29
9	21 d	Failure to thrive, constipation	0.78	3.82	<0.01	Normal	+ 3.2	+ 2.2	22.3 (5 yr)	ND	Q645X	32
10	4 yr	Short stature	0.85	NA	1.94	Normal	+ 3.0	+ 2.6	19.7 (16 yr)	-	N380QfsX6	30

<sup>a)</sup> DG, diagnosis. <sup>b)</sup> The patients 1 and 2 are siblings. <sup>c)</sup> ND, not determined. These patients were before puberty. <sup>d)</sup> NA, not available. <sup>e)</sup> NBS, newborn screening.

knockout mice lead to a TSH elevation in response to hypothyroidism that was less than that of wild-type mice. Furthermore, TRH-stimulated TSH release was blunted compared with that of wild-type mice. These findings suggest that TRH stimulated signaling through TRHR in thyrotropes is impaired by IGSF1 deficiency. *In vitro*, Garcia *et al.* (35) analyzed the effect of IGSF1 on *TSHR* transcription. According to their study, transforming growth factor (TGF)  $\beta$  suppressed *Trhr* gene expression in rat pituitary GH4C1 cells and somato-lactrope cell lines, but transfection of *IGSF1* into GH4C1 cells cancelled the repression of transcription of *Trhr* induced by TGF $\beta$ . Therefore, it is speculated that, in IGSF1 deficiency, the transcription of *TRHR* is constantly suppressed by TGF $\beta$ , resulting in reduced TRHR numbers in the cell membrane and eventually leading to decreased TSH secretion from thyrotropes. Since it was just an *in vitro* study, further studies on IGSF1 function in the hypothalamic-pituitary thyroid axis are necessary. Furthermore, the mechanisms involved in macroorchidism, heavy birth weight, and increased BMI are still unknown. Elucidation of the physiological role of IGSF1 in the future will yield answers to these questions in addition to the development of C-CH.

### TBL1X Deficiency

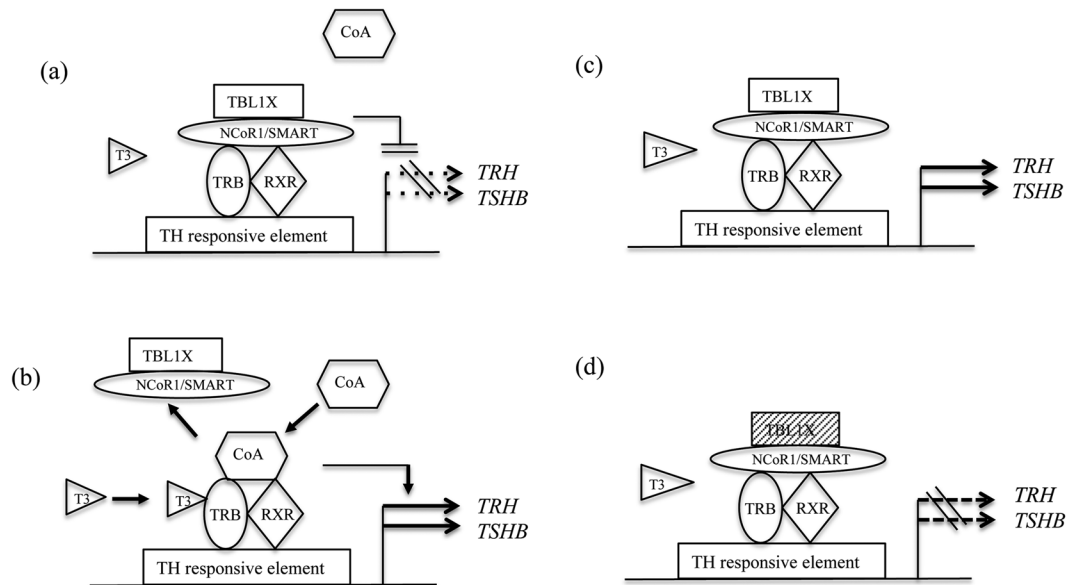
In 2016, Heinen *et al.* reported that mutations in the transducing  $\beta$ -like protein, X-linked gene (*TBL1X*) caused C-CH (43). *TBL1X* is one of components of the nuclear receptor repressor (NCoR) and is a silencing mediator of retinoid and thyroid receptors (SMRT). Its expression is observed in hypothalamic nuclei, including the paraventricular nucleus, and in the pituitary gland (44). In Heinen's study, five missense mutations (p.Asn365Tyr, p. His453Tyr, p.Ala366Thr, p.Tyr458Cys, and p.Trp369Arg) and one splice site mutation (c.1312-1G>A) were identified in eight patients from six families. Further analysis identified mutations in 11 other

asymptomatic individuals. Previously, partial deletion of *TBL1X* was identified in two unrelated patients with hearing loss (45). Indeed, 12 of 19 individuals harboring mutations in *TBL1X* had mild to moderate hearing loss. Garcia *et al.* (46) also reported a patient with p.Arg433Ter in *TBL1X*. In addition to low FT4, the patient had encopresis, constipation, and attention deficit/hyperactivity disorder. Patients thus far reported with mutations in *TBL1X* have shown lower limit of normal to normal concentrations of FT4, and thus whether these patients show true hypothyroidism at the organ level is not clear.

Usually in the absence of T3, NCoR/SMRT complexes bind thyroid hormone receptor  $\beta$  (TRB) with retinoid X receptor (as a heterodimer; Fig. 2a). These complexes bind to a thyroid hormone (TH) response element in the promoter region of TH targeting genes to repress their transcription (Fig. 2a). When T3 binds TRBs, the dissociation of the repressor complex and the recruitment of a coactivator complex occur, thus activating the transcription of TH target genes (Fig. 2b). However, several *in vitro* studies showed that cotransfection of NCoR/SMRT with TRBs conversely stimulates the transcription of *TSHB* and *TRH* in the absence of T3 (47, 48). Recently, Takamizawa *et al.* (49) have demonstrated that the ligand-independent thyroid hormone receptor-mediated stimulation of *TSHB* and *TRH* promoters was enhanced by *TBL1X* alone or by cotransfection with *TBL1X* and NCoR (Fig. 2c); however, the stimulating effect was attenuated by cotransfection with *TBL1X* mutants (p.Asn365Tyr and p.Tyr458Cys) and NCoR (Fig. 2d). The authors speculated that, despite low thyroid hormone levels, *TSHB* and *TRH* transcription is not up-regulated by *TBL1X* mutations, resulting in C-CH.

### IRS4 Deficiency

Most recently, four different mutations (one nonsense and three frameshift) from five families of insulin receptor substrate 4 (*IRS4*)



**Fig. 2.** Mechanism of C-CH: Mutations in *TBL1X*. (a) In the absence of T3, NCoR/SMRT complexes bind thyroid hormone receptor  $\beta$  (TRB) with RXR (as a heterodimer). These complexes bind to the thyroid hormone response element in the promoter region of thyroid hormone (TH) targeting genes and repress the transcription of these genes. (b) When T3 binds TRBs, the dissociation of the repressor complex and the recruitment of coactivator (CoA) occur, thus activating the transcription of TH target genes. (c) Several *in vitro* studies showed that cotransfection of NCoR/SMRT with TRBs conversely stimulates the transcription of *TSHB* and *TRH* in the absence of T3. The ligand-independent thyroid hormone receptor-mediated stimulation of *TSHB* and *TRH* promoters was enhanced by TBL1X. (d) TBL1X (shaded box) mutants of N365Y and Y458C impaired the stimulating effect. TBL1X, transducin  $\beta$ -like 1 X-linked; NCoR, nuclear receptor repressor; SMRT silencing mediator of retinoid and thyroid receptors; TRB, thyroid hormone receptor  $\beta$ ; RXR, retinoid X receptor; CoA, coactivator; TH, thyroid hormone.

have been reported (9). These patients showed 72 to 92.5% of the lower limit of the normal range of FT4 concentrations, but normal T3 levels. The expression of *IRS4* mRNA was observed in the hypothalamus, pituitary gland, thyroid, and ovaries, but the mechanism for developing low FT4 is unknown.

## Conclusion

It is noteworthy that IGSF1 deficiency is the most prevalent cause of C-CH, with some patients developing severe hypothyroidism soon after birth, similar to that seen with TSHB deficiency. In Japan, although TSH-based newborn screening is usually performed for congenital hypothyroidism, except in some

regional areas, pediatricians must bear in mind that the screen may overlook C-CH. This highlights the importance of suspecting severe to moderate C-CH based on the clinical symptoms of hypothyroidism during infancy and childhood, with a prompt diagnosis and subsequent initiation of thyroid hormone replacement in severe cases.

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