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Genetic causes of congenital hypothyroidism due to dyshormonogenesis

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Abstract

Purpose of Review—Overview of congenital hypothyroidism (CH) caused by thyroid hormone synthesis defects, the current understanding of their pathophysiology, and clinical implications of molecular diagnoses.

Recent Findings—Genetic defects in all known thyroid-specific factors required for thyroid hormone synthesis have been described. These include defects in iodide trapping (NIS), in the facilitated iodide efflux across the apical membrane (PDS), the organification of iodide within the follicular lumen (TPO, DUOX2, DUOX2A2), the substrate for thyroid hormone synthesis (TG) and the ability to recover and retain intrathyroidal iodine (IYD). Clinical and biochemical evaluation aids in selecting the most appropriate candidate gene(s).

A definite molecular diagnosis of thyroid dyshormonogenesis allows genetic counselling, and has prognostic value in differentiating transient from permanent CH and predicting the response of patients to iodine supplementation as adjunct or alternative treatment to L-T₄ replacement.

Summary—CH due to thyroid dyshormonogenesis is a heterogenic disorder that may be caused by mutations in any of the known steps in the thyroid hormone biosynthesis pathway. An exact molecular diagnosis allows genetic counselling, the identification of asymptomatic mutation carriers at risk of recurrent hypothyroidism, and provides a rationale for adjunct iodide supplementation.

Keywords

congenital hypothyroidism; genetics; thyroglobulin; thyroid peroxidase; dual oxidase

Introduction

With a prevalence of 1 in 3,000–4,000 newborns, congenital hypothyroidism (CH) is the most common inborn endocrine disorder and a common cause of preventable mental retardation. While most cases are sporadic and associated with abnormalities of thyroid gland development and migration (thyroid dysgenesis), 15–20% are caused by inherited defects in one of the steps of thyroid hormone synthesis (thyroid dyshormonogenesis) (Fig. 1). When the synthesis defect results in reduced hormone secretion, the ensuing diminished negative feedback on the anterior pituitary thyrotrophs leads to an increase in thyrotropin (TSH) secretion stimulating the thyroid gland. Consequently, patients are either born with an enlarged thyroid gland (goiter) or develop goiter postnatally, especially when diagnosis and

levothyroxine (L-T₄) supplementation are delayed. With the exceptions indicated below, these defects are inherited in an autosomal recessive fashion and are amenable to detection by the newborn screening for CH.

The etiological classification of CH is based on clinical and biochemical evaluation. Useful tests are measurement of serum TSH, thyroxine (T₄), triiodothyronine (T₃), and thyroglobulin (TG); thyroid ultrasound and scintigraphy, using ^{99m}Tc pertechnetate or, preferably, ¹²³I [1] and when indicated, the perchlorate (ClO₄⁻) discharge test. Often infants with CH, confirmed by the TSH and T₄ values, are started on thyroid hormone replacement without etiologic diagnosis. The latter is usually postponed until 2 or 3 years of age, following a one-month withdrawal of L-T₄ replacement.

With the identification of the key steps involved in thyroid hormone synthesis, a molecular genetic diagnosis should be feasible for the vast majority of patients with dysmorphogenesis. A complete diagnostic work up facilitates the selection of the likely candidate gene(s) for genetic confirmation (Table 1). While the distinguishing features of each particular hormone synthesis defect are outlined in the following sections, it should be noted that early genetic screening might be justified even without complete clinical workup. Other than providing useful information for genetic counselling, there are additional benefits to a definite genetic diagnosis. One is the potential impact on treatment as some defects may be efficiently treated with iodide supplementation rather than with L-T₄. Another benefit is in the identification of a subset of patients with transient CH due to partial morphogenesis defects. Even if euthyroid at a particular point in time, increased demand for thyroid hormone synthesis may precipitate hypothyroidism. An early molecular diagnosis predicts the necessity for life-long hormone replacement therapy. Finally, some genetic defects may not manifest at birth but produce hypothyroidism later in life. The definitive diagnosis of an index case will enable early identification of subsequent cases in the same family and help to avoid the negative consequences on mental development associated with delayed diagnosis and treatment of hypothyroidism.

Basolateral iodide transport defect (ITD) due to mutations in the *SLC5A5* (NIS) gene

The sodium-iodide symporter (NIS; official gene symbol: *SLC5A5*) is a 13-transmembrane domain glycoprotein that mediates the uptake of iodide through the basolateral membrane of thyroid follicular cells (Fig. 1). Iodide is actively concentrated into these cells by the electrogenic symport of Na⁺ (2 Na⁺ for 1 I⁻) down the electrochemical gradient maintained by the activity of Na⁺/K⁺-ATPase.

Shortly after cloning of the gene [2], mutations in the *SLC5A5* gene were described as cause of congenital ITD [3]. The incidence is unknown as the characteristic clinical findings of absent thyroidal iodide has led to the erroneous diagnosis of athyreosis especially when goiter was absent or missed and when serum TG was not measured. Individuals with ITD were found to be homo- or compound heterozygous for 13 different *SLC5A5* inactivating mutations (V59E, G93R, R124H, Q267E, C272X, G395R, T354P, fs515X, Y531X, DelM143-Q323, DelV287-G288, DelA439-P443, and G543E) [4]. The onset of hypothyroidism has varied from birth to childhood and seems to correlate with the residual *in vitro* activity of the mutant transporter [5].

Scintigraphy reveals blunted or absent radioactive iodide uptake (RAIU) in a normally located thyroid gland. RAIU in ITD is 0–5% (normal 10–40%) and imaging may suggest athyreosis especially when the presence of a thyroid gland is missed [6]. Since the loss of *SLC5A5* function is generalized, it also involves reduced iodide uptake in salivary glands

and gastric parietal cells, hence, failure to visualise these organs during ^{123}I scintiscanning. Ultrasound examination further helps to distinguish defects in *SLC5A5* from other conditions with reduced iodide uptake as it shows, characteristically, a normally located enlarged thyroid gland, excluding thyroid gland hypoplasia due to TSH receptor defects.

Genetic screening should be considered in all patients with permanent goitrous hypothyroidism in conjunction with low or absent RAIU. Without RAIU results, patients with goitrous hypothyroidism associated with high serum TG are better first evaluated for defects in TPO and DUOX2. Apart from establishing a definite diagnosis, finding *SLC5A5* gene mutations has further implications. Identification of an index case will allow subsequent preclinical diagnoses of other cases in the same family as patients with delayed onset of CH in ITD had already signs of developmental delay at time of diagnosis [5]. Concerning treatment options, iodide supplementation can improve thyroid function in patients with residual NIS activity and should be considered, either alone or together with L-T₄ replacement.

Defect in apical iodide efflux due to mutations in the *SLC26A4* (PDS) gene

SLC26A4 is a member of the multifunctional SLC26 transporter family facilitating the passive efflux of iodide across the apical thyrocyte membrane into the follicular lumen (Fig. 1). In the inner ear, chloride/bicarbonate exchange by *SLC26A4* is crucial for acid-base homeostasis of the endolymphatic fluid.

Biallelic inactivating mutations of the *SLC26A4* gene are a cause of Pendred syndrome (PDS) [7]. It is clinically defined by congenital bilateral sensorineural hearing loss (associated with vestibular dysfunction) combined with diffuse or multinodular goiter. The latter usually develops in late childhood or early adolescence, and is the consequence of a partial iodide organification defect consistent with the function of *SLC26A4* as an apical iodide efflux channel in thyrocytes. However, about half of patients with *SLC26A4* defects do not manifest thyroid abnormalities (designated non-syndromic hearing loss with familial enlarged vestibular aqueduct or DFNB4). Nutritional iodide intake is an important modifier of the thyroid phenotype in PDS. With sufficient dietary iodide, about 90% of patients are clinically and biochemically euthyroid. In the remaining 10% with elevated TSH level, goiter is always present [8].

PDS is rarely detected by neonatal screening for congenital hypothyroidism [9]. Rather, patients present because of severe congenital deafness. In patients with CH, screening for mutations in the *SLC26A4* gene is only justified when hearing impairment is present without the additional need to perform a (ClO_4^-) discharge test. Before systematic mutation scanning, targeted screening for the most common, recurrent mutations can be considered: L236P, T416P, and IVS8+1G>A in Caucasians of northern European descent [10, 11], and H723R in Japanese patients [12].

Mutations in the thyroglobulin (TG) gene

TG, a glycoprotein homodimer of 660 kDa, is the most abundantly expressed protein in the thyroid gland. It is secreted into the follicular lumen where it functions as matrix for hormone synthesis providing tyrosyl groups, the non-iodide component of thyroid hormone (Fig. 1). Iodinated TG constitutes the storage pool for thyroid hormone and iodide.

Following the first description of an inactivating mutation in the *TG* gene by Ieiri et al. [13], at least 40 others have been reported [14]. Defects in TG as cause of CH have been most extensively studied in Japanese for whom the estimated incidence is 1:67,000 [15], equivalent to ~1/4 to ~1/3 of all cases with thyroid dysmorphogenesis.

Patients with biallelic *TG* gene defects typically manifest elevated serum TSH levels on neonatal screening. Serum T₃ levels are usually disproportionately higher than T₄ concentrations, apparently because of increased intrathyroidal type 2 iodothyronine deiodinase activity [16]. Most typical is undetectable or very low serum TG level despite the elevated serum TSH. Goiters are often remarkably large, although early treatment should prevent goitrogenesis. Scintigraphy shows high uptake in a typically enlarged thyroid gland. Since the iodide organification process is not affected, there is no discharge after administration of ClO₄⁻. In the absence of TG iodide is covalently bound to other proteins, such as albumin. Mild TG secretion defects can manifest as compensated hypothyroidism (isolated hyperthyrotropinemia). Screening for *TG* gene mutations may be justified when absent or an unexpectedly low serum TG level is found in a patient with CH having an enlarged thyroid gland.

Defects in iodination and coupling of tyrosyl moieties due to mutations in the thyroid peroxidase (*TPO*) gene

TPO is a thyroid-specific heme peroxidase anchored via a C-terminal transmembrane domain at the apical membrane surface of thyroid follicular cells (Fig. 1). Using hydrogen peroxide as oxidative equivalents, TPO catalyzes the iodination of tyrosyl residues in TG and the subsequent phenoxo ether bond formation between pairs of iodotyrosines to generate iodothyronines (T₄ and, to lesser degree, T₃ and reverse T₃).

Abramowicz et al. [17], demonstrated the first inactivating, biallelic mutation in the *TPO* gene. Defects in this gene appear to be the most frequent cause of inherited dyshormonogenesis with permanent CH [18–20] and are present in virtually all patients with permanent total iodide organification defects (TIOD; >90% ClO₄⁻ discharge) [21]. The incidence of TIOD owing to biallelic TPO defects has been estimated at 1:66,000 for a Dutch population [21].

In about 20% of cases with TIOD only monoallelic defects of *TPO* are found, presumably due to unidentified cryptic mutations in unexamined intronic or regulatory regions of the gene. Indeed, in a patient with TIOD and single allele mutation, *TPO* mRNA analysis of thyroid tissue obtained at surgery revealed monoallelic expression of only the mutant allele indicating an unidentified defect on the other allele [22]. Although heterozygous *TPO* mutations do not directly result in abnormal thyroid function, such monoallelic defects may play a role as genetic susceptibility factor in transient hypothyroidism. In a Chinese population, heterozygosity for a common *TPO* gene founder mutation (2268insT) is 16 times more common in infants with transient neonatal hypothyroidism [23].

TPO is the indisputable candidate gene in patients with permanent TIOD. In contrast, non-syndromic PIOD is heterogeneous including defects in the hydrogen peroxide generator driving TPO activity (see below). When ClO₄⁻ discharge test is not available, screening for *TPO* mutations is still reasonable. For instance, 10 of 53 unrelated Portuguese with permanent CH, orthotopic thyroid glands and elevated serum TG levels harboured TPO defects [18]. In an Eastern European population with unusually high frequency of dyshormonogenesis (34% of CH), 18 of 39 apparently unrelated patients with permanent CH, normal or enlarged gland *in situ*, and normal or high serum TG were found to have *TPO* gene mutations. In 12 only a single heterozygous mutation (1273_1276dupGGCC) was detected [19]. The high prevalence of *TPO* gene mutations can also lead to pseudodominant inheritance of goitrous CH as described for a family segregating three different TPO mutations [24].

Finding *TPO* gene mutations in a neonate with CH indicates that the subject will require life-long treatment with thyroid hormone and that future pregnancies should be carefully monitored for the presence of prenatal goiter. The latter can be detected by ultrasonography and treated by a single intra-amniotic injection of L-T₄ to prevent goiter-related dystocia and improve neurological development [25].

Defects in hydrogen peroxide generation due to mutations in the *DUOX2* or *DUOX2* genes

Hydrogen peroxide is the essential electron acceptor for the TPO-catalyzed iodination and coupling reactions. It is produced at the apical membrane of follicular thyroid cells by dual oxidase (DUOX)/dual oxidase maturation factor (DUOXA) NADPH oxidase complexes [26, 27]. The DUOX2-based enzyme appears to be most critical for maintaining normal thyroid function, since only mutations in *DUOX2* and *DUOX2*, but not *DUOX1* or *DUOX1* genes, have been identified as cause of CH.

Since the first description of *DUOX2* gene mutations in patients with CH [28], 28 different mutations have been reported [29]. About half of these are nonsense, frameshift or splice site mutations predicting a dysfunctional enzyme lacking the C-terminal NADPH oxidase domain (G201fs, W414X, Y425X, R434X, L479fs, K530X, K628fs, Q686X, R701X, R842X, S965fs, Q1023X, Q1026X, g.IVS19-2A>C). Of the missense mutations (Q36H, R110Q, R376W, Y475C, D506N, A649E, H678R, E879K, R885Q, S911L, C1052Y, G1518S), six have been studied *in vitro* and shown to cause either complete trafficking defects or partial defects in cell surface expression of an oxidase complex with normal or absent intrinsic activity [30–32]. Based on a finding of loss-of-heterozygosity for common polymorphisms, two groups recently identified larger deletions affecting the *DUOX2* locus in CH patients [32, 33].

Although most dysmorphogenesis defects are inherited in an autosomal recessive fashion, a single defective *DUOX2* allele suffices to cause CH. When patients with mono-allelic defects were re-evaluated at three years of age after withdrawal of L-T₄, they often showed normal thyroid function tests indicating that the CH was transient [28]. In addition, adult heterozygotes in these and other families with *DUOX2* gene defects had normal serum TSH concentrations. In the absence of dominant negative effects of the mutant DUOX2 proteins [30], these patients appear to have *DUOX2* haploinsufficiency with manifestation limited to the neonatal period when thyroid hormone synthesis requirements are highest.

Several studies have linked biallelic *DUOX2* gene defects to permanent CH with PIOD. Based on the type of mutations (nonsense, frameshift) or the *in vitro* study of missense mutations found in homozygous or compound heterozygous state in these patients, most are predicted to express no residual DUOX2 activity. In contrast to the complete inactivation of TPO, which consistently leads to TIOD, a complete loss of DUOX2 activity does not completely abrogate the ability to synthesize thyroid hormone [34]. Limited iodide organification is likely maintained by the activity of DUOX1, which is also expressed in thyrocytes, albeit at lower level.

The expressivity of *DUOX2* gene defects is likely influenced by genetic background and may, at least in part, depend on the iodide intake. Since iodination by TPO requires both iodide and hydrogen peroxide, a diet containing excessive amounts of iodide would lead to better utilization of hydrogen peroxide provided by DUOX1. Credence to an important role of iodide intake in expressivity of DUOX2 defects is provided by a report of two siblings compound heterozygous for the same *DUOX2* gene mutations. In one sibling, perinatal

iodine overload produced completely normal TSH levels in the early postnatal period [35] indicating compensation of the defect.

While the incidence of *DUOX2* gene mutations in CH has not been determined, they appear to be frequent in patients with PIOD. For instance, 7 of 20 such unrelated patients from Italy were found to have pathogenetic *DUOX2* gene mutations [36]. Sequencing of the *DUOX2* gene is therefore recommended in patients with non-syndromic PIOD. In those with suspected non-syndromic organification defect (normal sized to enlarged thyroid gland with high serum TG concentration) without confirmation by ClO_4^- discharge test, the *TPO* gene should be screened first especially in cases where CH is profound. Concerning follow-up, patients with transient CH due to *DUOX2* haploinsufficiency are at risk for recurrent hypothyroidism at times of increased hormonogenesis requirements, such as pregnancy. With regard to treatment after the neonatal period, we would advocate to assess iodide supplementation as an alternative to potentially life-long L-T₄ replacement therapy.

In 2008, the first mutation in the *DUOX2* gene was reported in a nonconsanguineous Chinese patient with PIOD and mild, permanent CH [37]. The patient was homozygous for an Y246X nonsense mutation that resulted in a complete loss of *DUOX2* function *in vitro*. The frequency of Y246X homozygosity has been estimated at one out of 34,000 newborns in the Shanghai Chinese population. Heterozygous carriers of this mutation had normal thyroid function tests including negative neonatal screening for CH and ClO_4^- discharge tests. Accordingly, in contrast to monoallelic *DUOX2* gene mutations, the loss of a single *DUOX2* allele does not lead to haploinsufficiency. Apart from the intact *DUOX1*/*DUOX2* system, an additional mechanism for maintaining adequate hydrogen peroxide supply in patients with *DUOX2* deficiency is the partial activation of *DUOX1* by *DUOX2*, as demonstrated *in vitro* [37].

A more complex genetic alteration of the *DUOX/DUOX2* system was recently found in an infant with transient CH born to euthyroid non-consanguineous parents [33]. Genetic analysis revealed a C189R missense mutation on the maternal *DUOX2* allele causing complete loss of function *in vitro*. On the paternal allele, a large deletion comprising *DUOX2*, *DUOX1*, and *DUOX1* genes was identified. Thus, in this patient, near normal thyroid function is maintained after the neonatal period despite having only a single functional *DUOX2* allele (maternal *DUOX2*). The high degree of functional redundancy for defects in *DUOX2* is likely due to molar excess of *DUOX2* over *DUOX1* protein in the ER owing to reduced synthesis efficiency of the more complex *DUOX2* subunit.

Defects in recycling of intrathyroidal iodine due to mutations in the iodotyrosine deiodinase (*IYD*, also known as *DEHAL1*) gene

The lysosomal proteolysis of endocytosed iodinated TG liberates the iodothyronines (T₄ and T₃). However, most iodide contained in TG is released as uncoupled mono- and diiodotyrosines (MIT, DIT). The latter are subject to NADPH-dependent reductive deiodination by *IYD* leading to formation of free iodide and tyrosine, both of which can be reutilized in hormone synthesis (Fig. 1). In addition to the thyrocyte, the enzyme is expressed in liver and kidney. The expression in the latter tissue serves for the execution of a pathognomonic *in-vivo* test.

In 2008, mutations in *IYD* underlying impaired intrathyroidal dehalogenation were described in four unrelated consanguineous families [38, 39]. Six affected individuals were homozygous for either a missense mutation (R101W, I116T, or A220T) or a combined missense/deletion mutation c.315delCAT (resulting in replacement of both F105 and I106 by leucine at position 105). All mutations map to the flavin-binding domain and virtually

abolished the capacity of IYD to dehalogenate MIT and DIT *in vitro*. Notably, one heterozygous carrier of A220T developed non-autoimmune goitrous hypothyroidism at 15 years of age pointing to a possible dominant behaviour of the mutation in some individuals [39].

Loss of IYD activity prevents the normal intrathyroidal iodide 'recycling' and leads to excessive urinary secretion of MIT and DIT. Since the resulting iodide deficiency may not manifest at birth, the reported patients with biallelic *IYD* mutations tested normal at neonatal screening for CH [38]. They subsequently came to medical attention at 1.5 to 8 years of age because of sequelae of untreated hypothyroidism. On scintigraphy, a very rapid and high initial uptake of ^{123}I in the enlarged thyroid is observed, followed by a relatively rapid spontaneous decline of the accumulated iodine without the administration of ClO_4^- . The detection of high urinary MIT and DIT by tandem mass spectroscopy may become a useful diagnostic test.

The incidence of *IYD* mutations is unknown. Although not a viable candidate gene for CH, a potential role for *IYD* variants in susceptibility to endemic goiter remains to be investigated. We suggest that screening of *IYD* may be considered in patients developing 'idiopathic' diffuse or multinodular goiter between the neonatal period and adolescence, while early and late images during ^{123}I scintigraphy are compatible with *IYD* defects. However, deficient nutritional iodide intake, as in areas of endemic goiter, dietary goitrogens, and autoimmune thyroid disease have to be excluded. An autosomal recessive inheritance pattern of the disorder as well as consanguinity of the parents would likely increase the yield of mutation screening. Anecdotal evidence indicates that iodine supplementation (Lugol's solution) is an effective alternative to L-T₄ treatment in *IYD* deficiency [40].

Conclusion

The cloning of important genes involved in thyroid hormone synthesis provides the basis for a molecular diagnosis in patients with CH due to dysmorphogenesis. A genetic diagnosis is crucial to further explore the complete phenotype of these disorders. For instance, in analogy to studies on the DUOX homolog of invertebrates [41], the high expression of human DUOX enzymes in the barrier epithelia of human intestine and airways may indicate an yet unrecognized role in innate immunity. For the clinician treating patients with thyroid dysmorphogenesis, a precise molecular diagnosis allows genetic counselling, identification of asymptomatic mutation carriers at risk for developing hypothyroidism, and identification of the subset of patients likely to respond to iodide supplementation (all *SLC26A4*, *DUOX2*, *DUOX2* and *IYD* defects, and partial defects in *SLC5A5*).

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Key points

- CH due to hormone synthesis defects is heterogeneous, but amenable to precise molecular diagnosis.
- Clinical and biochemical evaluation aids in selecting the most appropriate candidate gene(s) among *SLC5A5*, *SLC26A4*, *TPO*, *TG*, *DUOX2*, *DUOX2A2*, and *IYD*.
- A molecular diagnosis allows genetic counselling, the identification of asymptomatic mutation carriers at risk of recurrent hypothyroidism, and provides a rationale for adjunct therapy with iodide supplementation.

Fig. 1. Schematic drawing of a follicular thyroid cell illustrating the key players involved in thyroid hormonogenesis

The distinct steps comprise 1) the active uptake of iodide from the blood circulation via the sodium-iodide symporter (SLC5A5); 2) the facilitated efflux of iodide into the colloid via an apical anion channel (SLC26A4); 3) iodination of tyrosine groups of thyroglobulin (TG) catalyzed by thyroid peroxidase (TPO); 4) subsequent coupling of iodinated tyrosines within TG via ether-bond formation to iodothyronines; steps 3 and 4 require hydrogen peroxide as co-substrate, which is provided by a hydrogen peroxide generating NADPH-oxidase constituted by dual oxidase 2 (DUOX2) and its maturation factor (DUOXA2); 5) following endocytosis, iodothyronines (T₄>T₃) are liberated by lysosomal degradation of the TG matrix protein; 6) concomitantly released iodothyrosines are dehalogenated by iodotyrosine deiodinase (IYD) allowing 'recycling' of iodide for further hormone synthesis.

Table 1

Known Gene Defects Causing Dyshormonogenesis

Affected Process	Substance/Gene	Gene Symbol	Chromo-somal Location	Characteristic Features	Diagnostic Test
iodide trapping	sodium iodide symporter	<i>SLC5A5</i> (NIS)	19p13	<ul style="list-style-type: none"> reduced thyroidal iodide or pertechnetate uptake 	<ul style="list-style-type: none"> saliva/plasma RAI ratio <10
iodide efflux into follicular lumen	pendrin	<i>SLC26A4</i> (PDS)	7q31	<ul style="list-style-type: none"> sensorineural deafness enlarged vestibular aqueduct PIOD and goiter 	<ul style="list-style-type: none"> MR1/CT of temporal bones
matrix protein for hormone synthesis	thyroglobulin	<i>TG</i>	8q24	<ul style="list-style-type: none"> hypothyroidism goiter absent or very low serum TG level 	<ul style="list-style-type: none"> serum TG level
iodide organification/coupling reaction	thyroid peroxidase	<i>TPO</i>	2p25	<ul style="list-style-type: none"> TIOD or PIOD 	<ul style="list-style-type: none"> CLO_4^- discharge test
H_2O_2 generation (co-substrate for TPO)	dual oxidase 2	<i>DUOX2</i> (THOX2)	15q15.3	<ul style="list-style-type: none"> permanent or transient CH PIOD 	<ul style="list-style-type: none"> CLO_4^- discharge test
H_2O_2 generation (co-substrate for TPO)	DUOX_2 maturation factor	<i>DUOXA2</i>	15q15.3	<ul style="list-style-type: none"> mild CH PIOD 	<ul style="list-style-type: none"> CLO_4^- discharge test
Intrathyroidal iodide recycling	iodotyrosine deiodinase	<i>IYD</i> (<i>DEHAL1</i>)		<ul style="list-style-type: none"> negative CH screen goiter, hypothyroidism (after neonatal period) 	<ul style="list-style-type: none"> iodotyrosines in urine rapid thyroidal loss of iodine

IOD, Iodide organification defect; **PIOD**, Partial IOD; **TIOD**, Total IOD.

RAI, radioactive iodide