Published in final edited form as:

Endocrinol Metab Clin North Am. 2017 June ; 46(2): 375–388. doi:10.1016/j.ecl.2017.01.005.

Defects of Thyroid Hormone Synthesis and Action

Zeina C. Hannoush, MD and Roy E. Weiss, MD, PhD

Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, University of Miami Miller School of Medicine, Miami, FL 33136

Synopsis

Congenital hypothyroidism is the most common inborn endocrine disorder and causes significant morbidity. To date, we are only aware of the molecular basis of the defects in a small portion of patients with CH. A better understanding of the pathophysiology of these cases at the genetic and molecular basis provides useful information for proper counseling to patients and their family as well as for the development of better targeted therapies. This review provides a succinct outline of the pathophysiology and genetics of the known causes of thyroid dysgenesis, dyshormonogenesis and syndrome of impaired sensitivity to thyroid hormone.

Keywords

thyroid hormone receptors; deiodinase; resistance to thyroid hormone; congenital hypothyroidism; goiter; dyshormonogenesis; dysgenesis

INTRODUCTION

In the beginning (prior to the genomic revolution) thyroid disorders were primarily diagnosed by the presence of a goiter and thought to be due to either deficiency or excess of iodine. Many years later, in 1956 an autoimmune etiology was proposed [1]. The clinical tools available to the physicians in those years consisted of measurement of protein bound iodine in the serum as a marker of thyroid hormone (TH) concentration; use of a geiger counter to measure iodine uptake into the gland with radioactive iodine; as well as measurements of radioiodine discharge after treatment with perchlorate; and basal metabolic rates as a surrogate for thyroid hormone action. Remarkably clinician scientists have mapped most pathways involved in thyroid hormone synthesis and action based on these rudimentary tests. The sentinel observations of astute physicians more than 50 years ago were responsible for our current outlook on diagnosis and treatment of thyroid disease. Such individuals are Vaughan Pendred who reported 2 sisters having goiter and deafness [2] and John Stanbury and A.N. Hedge [3] who described 3 siblings with congenital hypothyroidism and goiter,

Correspondence to: Roy E. Weiss, Department of Medicine, University of Miami Miller School of Medicine, 1120 NW 14th St. Suite 310F, Miami, FL 33136, Tel: 305-243-1944, Fax: 305 243-2193, rweiss@med.miami.edu.

The authors have nothing to disclose.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

likely due to a defect in organification of iodine and Samuel Refetoff, Leslie DeGroot and Laurence DeWind who described a family with insensitivity to thyroid hormone [4]. As biochemical techniques developed and a clearer understanding of TH synthesis ensued, new pathways were discovered relating to TH synthesis and action. However the notion that a defect was inherited predated any knowledge of molecular biology. Additionally, in so much as understanding the physiology has been informative with regard to identifying candidate genes (defects in TH receptors, defects in peroxidase), gene linkage and analysis has led to a deeper understanding of new mechanisms and pathways of TH synthesis and action (eg *DUOXA*, *PAX8*, *MCT8*). Furthermore when discovering the involvement of a particular gene mutation as the cause of a thyroid defect there needs to be convincing evidence of the structure- function relationship of the gene and proof that it is responsible for the phenotype (Figs 1, 2).

We are at a crossroad in diagnosing thyroid disease having evolved from PBI (protein-bound iodine) and iodine uptake to sophisticated chips which screen patient's DNA samples for a variety of common binding protein abnormalities or receptor mutations whether it be the TH receptor beta (*THRB*), or TSH receptors (*TSHR*), or something else. The purpose of this article is to present a succinct review of the genetic causes of abnormalities in thyroid hormone synthesis and action exclusive of thyroid cancer which is covered in Andrew J Bauer's article, "Molecular Genetics of Thyroid Cancer in Children and Adolescents," in this issue.

Thyroid hormone is essential for the development, regulation of metabolism and function of virtually all human tissue [5, 6]. Inherited disorders of TH synthesis and action are by definition present at birth, and can usually be diagnosed then, but the clinical manifestations may not occur until later in life. Congenital hypothyroidism (CH) is defined as functional inactivity of TH from birth. It can be goitrous or in the presence of a goiter. Phenotypes based on thyroid function tests can show various permutations from elevated TSH and low T₄ serum concentrations to other derangements such as elevated TH levels and non-suppressed TSH (syndromes of thyroid hormone unresponsiveness). CH is the most common inborn endocrine disorder with a prevalence of 3000–4000 newborns [7]. In absence of adequate treatment, CH is characterized by signs and symptoms of impaired metabolism and by motor and mental developmental delays. Before the introduction of neonatal screening programs, which allowed for early diagnosis and treatment, CH was one of the most common causes of mental retardation [8]. CH can be caused by abnormalities of thyroid gland development and migration (dysgenesis), by inherited defects in one of the steps of TH synthesis (dyshormonogenesis), by problems in intracellular TH transport, metabolism or at the level of its action as a regulator of gene transcription in the target tissue. The molecular basis of the defects has been elucidated in only a small portion of patients with CH.

1. Goitrous Congenital Hypothyroidism: Defects in thyroid development

Thyroid dysgenesis accounts for 80 to 85% of the cases of congenital hypothyroidism. These defects may take the form of complete absence of both or one of the lobes of the thyroid or failure of the gland to descend properly during embryologic development

(ectopic). The gold standard for differentiating between the various forms of thyroid dysgenesis is the scintigraphy with 99m sodium pertechnetate or 123 iodine, as ultrasound examination generally fails to reveal an ectopic thyroid, which is the most common cause of thyroid dysgenesis [9].

Thyroid dysgenesis is generally a sporadic disease, and in about 5% of the cases a molecular basis has been identified [8]. The most common genes reported to be associated with alteration in thyroid morphogenesis are *TSHR*, *PAX8*, *TTF1*, *FOXE1*, *NKX2-5* and *HHEX* (Table 1).

A. TSH receptor gene (*TSHR*)

TSHR encodes a transmembrane receptor present on the surface of follicular cells, which mediates the effects of TSH secreted by the anterior pituitary and is critical for the development and function of the thyroid gland [7]. Several cases with homozygous or compound heterozygous loss-of-function *TSHR* mutations have been reported [8, 10]. The phenotype of these patients is very variable, ranging from asymptomatic hyperthyrotroponemia to severe CH. The disease is classically inherited in an autosomal recessive trait, although it has become apparent that heterozygotes can have a mild phenotype, which is transmitted in a dominant fashion. Patients are characterized by elevated serum TSH, absence of goiter with a normal hypoplastic gland that does not trap perthechnetate (TCO_4^-) and surprisingly detectable thyroglobulin levels with normal to very low levels of thyroid hormone [9].

B. *PAX8* gene

Paired Box Gene 8 (*PAX8*) is a transcriptional factor that plays an important role in the initiation of thyrocyte differentiation and maintenance of follicular cells, furthermore regulates the expression of thyroglobulin (TG), thyroperoxidase (TPO) and the sodium iodine symporter (NIS) (see below) by binding to the respective promoter regions [11, 12].

The involvement of *PAX8* has been described in sporadic and familial cases of CH with thyroid dysgenesis. Autosomal dominant transmission with incomplete penetrance and variable expressivity has been described for the familial cases. This extreme variability supports the hypothesis that many factors modulate the phenotypic expression of *PAX8* gene mutations.

C. *TTF1* gene

TTF1 (also known as *NKX2-1* or thyroid specific enhancer binding protein) is a member of the homeobox domain type of transcription factors. It is expressed in the lungs and vertebral forebrain, in addition to the thyroid gland [13]. It is known to regulate the transcription of TG, TPO and *TSHR* genes in the thyroid follicular cells, and the surfactant protein B gene in epithelial lung cells [14–16]. The essential role of *TTF1* in the development of thyroid, lung and brain development was first shown in animal models [17], this was latter confirmed by several human case reports of *NKX2-1* mutations presenting with primary CH, respiratory distress and benign hereditary chorea, which are manifestations of the “Brain-Thyroid-Lung-

Syndrome” [18, 19]. In the majority of cases haploinsufficiency has been considered to be responsible for the phenotype; the clinical features are very variable [20].

D. *FOXE 1* gene

FOXE 1 also known, as *TTF2* or *FKHL15* is a transcription factor member of the forkhead/winged helix domain protein family, many of which are key regulators of embryonic pattern formation and regional specification. It regulates transcription of TG and TPO [21]. Homozygous mutations in *FOXE1* gene have been reported in patients affected by Bamford-Lazarus syndrome. This is a syndrome characterized by cleft palate, bilateral choanal atresia, spiky hair and athyreosis [22].

E. *NKX2-5* gene

In addition to *NKX2-1*, other genes of the *NKX2* family are present in the primitive pharynx and the thyroid anlage, such as *NKX2-3*, *NKX2-5* and *NKX2-6*. In humans, *NKX2-5* is essential for normal heart morphogenesis, myogenesis and function [23]. Several loss of function mutations in *NKX2-5* have been described in patient with congenital heart disease [24] and heterozygous mutations have been associated with human ectopic thyroid [25]. Patients carrying *NKX2-5* mutations show a phenotypic variability of both heart and thyroid malformations, this could be a consequence of haploinsufficiency, monoallelic expression or imprinting factors [26].

2. Goiterous CH: Defects in thyroid hormone synthesis (Dyshormonogenesis)

Approximately 15–20% of the cases of congenital hypothyroidism are caused by thyroid dyshormonogenesis, which can occur at any of the steps involved in thyroid hormone production. These forms of congenital hypothyroidism are characterized by an enlargement of the thyroid gland (goiter) and they usually show a classical Mendelian recessive inheritance pattern (Table 2).

The synthesis of thyroid hormone starts with the active transportation of iodine into the follicular thyroid cells by the sodium iodine symporter (NIS) present in the basolateral membrane of the cells. Subsequently iodine is oxidized by hydrogen peroxidase and bound to tyrosine residues in thyroglobulin to form iodotyrosine (iodine organification). Some of these hormonally inert iodotyrosine residues, monoiodotyrosine and diiodotyrosine (MIT and DIT), couple to form the hormonally active iodothyronines T_4 and T_3 . Thyroid peroxidase (TPO) catalyses the oxidation, organification and coupling reactions involved in this process [27]. Defects in any of these steps can lead to thyroid dyshormonogenesis. Common known mutations include *NIS*, *SLC26A4*, *TG*, *TPO*, *DUOX2*, *DUOX2* and *IYD* [28].

A. Sodium Iodine Symporter (NIS), *SLC5A5*: Defect in Iodine Uptake

Iodine (I), the oxidized form of I^- , is an essential constituent of THs which are phenolic rings joined by an ether link iodinated at 3 positions (3,5,3'-tri-iodo-L-thyronine, or T_3) or 4 positions (3,5,3',5'-tetra-iodo-L-thyronine or T_4) [28]. The uptake of iodine through the

basolateral membrane of the follicular thyroid cells is a key point in the biosynthesis of thyroid hormone. This process is mediated by the sodium-iodine symporter (NIS; official gene symbol *SLC5A5*), a 13-transmembrane domain glycoprotein that relies on the sodium (Na^+) electrochemical gradient created by the Na^+/K^+ ATPase and allows to actively concentrate iodine by electrogenic symport of sodium (2:1 Na^+ to I^- stoichiometry) [28, 29]. NIS is also expressed in several other differentiated epithelia where it is not regulated by thyroid stimulating hormone (TSH) such as salivary glands, lachrymal glands, gastric mucosa, choroid plexus and lactating mammary glands [29].

Since the cloning of NIS in 1996 [30], NIS research has become a major field of interest with considerable clinical implications. CH resulting from mutations in *SLC5A5* is specifically referred as I^- transport defect (ITD). It follows an autosomal recessive pattern of inheritance. Although it's a rare disorder, to date, 13 such mutations have been reported in the NIS coding region (V59E [31], G93R [32], R124H [33], 143-323, Q267E [34], C272X, 287-288 [35], T354P [36], 439-443 [37], G395R [32], G543E [38], 515X and Y531X) and 1 in the 5' untranslated region [39].

When untreated ITD is clinically characterized by hypothyroidism, goiter and mental impairment of varying degrees [28]. Diagnostic workup will show a reduced or absent thyroid I^- uptake. It should be noted that the lack of thyroidal iodine uptake could lead to the erroneous diagnosis of athyreosis unless thyroglobulin level is measured. Since the loss of NIS is generalized it also involves reduced salivary glands and gastric parietal cell uptake of iodine. A reliable test is the measurement of radioactivity in the equal volumes of saliva and plasma obtained one hour after the oral administration of 5 μCi of ^{125}I . A saliva-to-plasma ratio close to unity (normal 20) is diagnostic of a NIS defect. These patients should be managed with levothyroxine replacement therapy, iodine supplementation could be considered in patients with residual NIS activity as it can improve thyroid function [29].

B. Pendred syndrome, *SLC26A4*: Defects in Iodine Efflux

Pendrin is a highly hydrophobic membrane glycoprotein located at the apical membrane of thyrocytes. It is believed to function as an apical iodine transporter [40]. Pendrin is also expressed in the kidney and in the inner ear, where it plays an important role in acid-base metabolism and in the generation of endocochlear potential respectively [41, 42]. It is encoded by the *SLC26A4* gene. Mutations in this gene lead to Pendred syndrome, an autosomal recessive disorder characterized by sensorineural deafness, goiter and partial defect in iodine organification [43, 44]. The incidence of the disease is estimated to be 7.5 to 10 in 100000 and it is thought to account for as many as 10% of cases of hereditary deafness, making it the most common cause of syndromic deafness. About half of these patients do not manifest any thyroid abnormalities and when they do, it is usually not evident until the second decade of life [45].

Affected subjects usually have a positive perchlorate discharge test, with more than 15%-but not complete- release of radiolabelled iodine following perchlorate administration, indicating a mild thyroid organification defect. A normal discharge test, on the other hand, does not exclude the diagnosis as this diagnostic tool has a relatively high false negative rate (5%) [46].

Before performing systematic mutation scanning in suspected cases, targeted screening for the most common, recurrent mutations can be considered. L236P, T416P and IVS8+1G A account for 50% of known *SLC26A4* mutations in Caucasians of northern Europe descent [47, 48], whereas *H723R* represents 53% of reported mutant alleles among Japanese [49].

C. Thyroglobulin (TG): Defects in the Follicular Matrix Protein Providing Tyrosyl Groups for Iodine Organification

Thyroglobulin is a homodimer of 660kDa, synthesized exclusively in the thyroid gland. It is secreted into the follicular lumen where it functions as matrix for hormone synthesis providing tyrosyl groups, the noniodine component of thyroid hormone. Iodinated TG constitutes the storage pool for thyroid hormone and iodine [29]. At least 40 distinct inactivation TG gene mutations have been described [50], they are associated with moderate to severe congenital hypothyroidism, usually with low serum thyroglobulin levels. Affected individuals often have abnormal iodoproteins in their serum, especially iodinated albumin and they excrete iodopeptides of low molecular weight in the urine. The coupling defect results in ineffective formation of T₄ and T₃ [7]. Scintigraphy shows high uptake (due to induction of NIS expression by TSH stimulation) in a typically enlarged thyroid gland.

D. Thyroid peroxidase (TPO): Defect in the Enzyme Catalyzing Iodide Organification

Thyroid peroxidase (TPO) is the enzyme responsible for iodide oxidation, organification and iodotyrosine coupling. It is a heme containing glycosylated protein bound to the apical membrane of the follicular thyroid cells. The most prevalent cause of congenital thyroid dysmorphogenesis with permanent hypothyroidism appears to be inactivating biallelic defects in the TPO gene [51, 52]. Although heterozygous TPO mutations do not directly result in abnormal thyroid function, such monoallelic defects may play a role as genetic susceptibility factors in transient hypothyroidism. Neonates with congenital hypothyroidism found to have a TPO mutation, require lifelong treatment with thyroid hormone [29].

E. DUOX2: Defects in the NADPH-oxidase Providing Hydrogen Peroxidase for TPO

The *DUOX1* and *2* genes (also termed *THOX1* and *THOX2*) encode the NADPH oxidases located at the apical membrane of thyrocytes. They constitute the catalytic core of the Ca²⁺ dependent H₂O₂ generator required for TPO activity and thyroid hormone synthesis [53]. Since the initial description of *DUOX2* in 2002, 26 different mutations have been reported [54–62]. About half of them are nonsense, frameshift or splice site mutations predicting a dysfunctional enzyme. Although most dysmorphogenesis defects are inherited in an autosomal recessive fashion, a single defective *DUOX2* allele mutation is sufficient to cause congenital hypothyroidism. With increasing number of reported cases, phenotype-genotype correlations in patients with these mutations are becoming more complex. The expressivity of *DUOX2* defects is likely influenced by genetic background (e.g. *DUOX1*) and may, at least in part, depend on the iodine intake [29].

F. DUOXA2: Defect in the DUOX2 cofactor

DUOXA2, a resident endoplasmic reticulum (ER) protein is required for ER to Golgi transition, maturation and translocation to the plasma membrane of functional *DUOX*

enzymes. There are 3 reported cases where mutations of the *DUOX2* gene have been identified, in all three; the loss of a single allele did not lead to abnormal thyroid function [63–65]. Since *DUOX2* defects lead to secondary deficiency of functional DUOX2 enzymes, one can anticipate that expressivity will be similarly modulated by nutritional iodine as described for *DUOX2* defects [29].

G. Iodotyrosine dehydrogenase (IYD): Defects in iodine Recycling

In addition to the active iodine transport from the extracellular fluid, intracellular iodine is also generated by the action of the *DEAHLA1* or iodotyrosine deiodinase (IYD) enzymes. MIT and DIT are subject of NADPH-dependent reductive deiodination by IYD from T₄ and T₃, leading to formation of free iodide and tyrosine, both of which can be reutilized in hormone synthesis [27]. Mutations in homozygosity in the IYD gene have been identified in patients with hypothyroidism, goiter and an elevated DIT level [66, 67].

Loss of IYD activity prevents the normal intrathyroidal iodine “recycling” and leads to excessive urinary secretion of DIT and MIT. Since the resulting iodine deficiency does not manifest at birth, patients with biallelic IYD mutations tested normal at neonatal screening for CH. They subsequently came to medical attention at 1.5–8 years of age. On scintigraphy, a very rapid and high initial uptake of ¹²³I in an enlarged thyroid is observed, followed by a relatively rapid decline of the accumulated iodine without the administration of CLO₄ [29].

3. Defects in Thyroid Hormone Action

Impaired sensitivity to thyroid describes a process which interferes with the effectiveness of thyroid hormone and includes defects in thyroid hormone action, transport, or metabolism [68]. Clinicians should include these disorders in the differential diagnosis of patients presenting with the appropriate clinical scenario and thyroid function test abnormalities that don't reflect the expected physiologic inverse relationship between TSH and thyroid hormones (Table 3).

A. Thyroid hormone cell transport defects (THCTD): *MCT8*

TH is transported across the cell membranes by several molecules. Defective cell-transport proteins may not reach the cell membrane or may not be able to transport the hormone and cause reduced levels of intracellular TH [69]. The importance of these molecules was most convincingly demonstrated with the identification of the first inherited THCTD caused by mutations in the monocarboxylate transporter 8 (*MCT8*) gene, (also known *SCL16A2*). This molecule plays an important role in the transport of TH into the brain and, therefore, in the effect of thyroid hormone on brain development [70]. Its mutation is responsible for the Allan-Herndon-Dudley syndrome, an X-linked disease presenting with severe psychomotor deficit and elevated serum concentrations of T₃, low levels of T₄ and rT₃ [71, 72].

Given the existence of other types of TH transporters and their different tissue distribution, it is anticipated that defects in each molecule would result in a distinct phenotype, some of which can be predicted based on the evidence available from the generation of mice deficient in specific transporters [73]. Current treatment options for patients with *MCT8* mutations are limited, the use of thyroid hormone analogues that may bypass the molecular

defect by using alternative transporters has been studied with promising outcomes that need further investigation [74, 75].

B. Thyroid hormone metabolism abnormalities: Selenocysteine binding protein 2 (*SBP2*)

T₄, the major product secreted by the thyroid gland, is a pro-hormone that must be activated by conversion to T₃ in the cell cytoplasm. Defects in any of the factors involved in this enzymatic deiodination reaction can cause a diminished production of T₃, and thus reduced sensitivity to thyroid hormone. The only known inherited defect of thyroid hormone metabolism defect (THMD) involves the gene for selenocysteine insertion sequence-binding protein 2 (*SECISBP2*, also known as *SBP2*), 1 of the 12 known genes involved in deiodinase synthesis and degradation. The mutation interferes with conversion of T₄ to T₃, resulting in a low T₃, and high T₄ and rT₃ [76].

C. Defect in Thyroid hormone action: Thyroid hormone receptor beta (*THRB*), and alpha (*THRA*) and Non TR-RTH

The genomic action of thyroid hormone within the nucleus is mediated through the thyroid hormone receptor (TR). Mutant TR proteins have reduced ability to bind cognate ligand or protein cofactors or to bind to DNA and can result in resistance to thyroid hormone (RTH). The disorder is characterized by high serum concentrations of free T₄ and usually free T₃, accompanied by normal or slightly high serum thyroid stimulating hormone (TSH) concentrations [68]. The most common known cause of resistance to thyroid hormone is an inherited defect in the thyroid hormone receptor beta gene (*THRB*); this condition is termed **RTH-beta**. Affected patients have persistent elevations of all three serum iodothyronines with nonsuppressed TSH. In contrast, patients with mutations of the gene encoding TR-alpha have low serum T₄ and rT₃, borderline high T₃, and normal or slightly elevated TSH; this disorder is termed **RTH-alpha** [77]. Some individuals have a phenotype that mimics that of a TR-beta gene mutation, but have no identifiable TR gene mutation. This disorder has been termed “**nonTR-TRH**”, and it is thought to be caused by defects in TR cofactors [78, 79].

Acknowledgments

The authors thank Rabbi Morris Esformes Thyroid Research Fund for support in this work.

References

1. Roitt IM, et al. Auto-antibodies in Hashimoto's disease (lymphadenoid goitre). *Lancet*. 1956; 271(6947):820–1. [PubMed: 13368530]
2. Pendred V. Deaf-mutism and goitre. *The Lancet*. 1896; 148(3808):532.
3. Stanbury JB, Hedge AN. A study of a family of goitrous cretins. *J Clin Endocrinol Metab*. 1950; 10(11):1471–84. [PubMed: 14794763]
4. Refetoff S, DeWind LT, DeGroot LJ. Familial syndrome combining deaf-mutism, stunted epiphyses, goiter and abnormally high PBI: possible target organ refractoriness to thyroid hormone. *J Clin Endocrinol Metab*. 1967; 27(2):279–94. [PubMed: 4163616]
5. Medici M, et al. A large-scale association analysis of 68 thyroid hormone pathway genes with serum TSH and FT4 levels. *Eur J Endocrinol*. 2011; 164(5):781–8. [PubMed: 21367965]

6. Peeters RP, van der Deure WM, Visser TJ. Genetic variation in thyroid hormone pathway genes; polymorphisms in the TSH receptor and the iodothyronine deiodinases. *Eur J Endocrinol.* 2006; 155(5):655–62. [PubMed: 17062880]
7. Park SM V, Chatterjee K. Genetics of congenital hypothyroidism. *J Med Genet.* 2005; 42(5):379–89. [PubMed: 15863666]
8. Nettore IC, et al. The molecular causes of thyroid dysgenesis: a systematic review. *J Endocrinol Invest.* 2013; 36(8):654–64. [PubMed: 23698639]
9. Pohlenz, J., Vliet, GV., Deladoey, J. Genetic Diagnosis of Endocrine Disorders. 2. Academic Press; San Diego: 2016. Chapter 8 - Developmental Abnormalities of the Thyroid A2 - Refetoff, Roy E. WeissSamuel; p. 127-136.
10. Biebermann H, et al. Mutations of the human thyrotropin receptor gene causing thyroid hypoplasia and persistent congenital hypothyroidism. *J Clin Endocrinol Metab.* 1997; 82(10):3471–80. [PubMed: 9329388]
11. Plachov D, et al. Pax8, a murine paired box gene expressed in the developing excretory system and thyroid gland. *Development.* 1990; 110(2):643–51. [PubMed: 1723950]
12. De Felice M, Di Lauro R. Thyroid development and its disorders: genetics and molecular mechanisms. *Endocr Rev.* 2004; 25(5):722–46. [PubMed: 15466939]
13. Lazzaro D, et al. The transcription factor TTF-1 is expressed at the onset of thyroid and lung morphogenesis and in restricted regions of the foetal brain. *Development.* 1991; 113(4):1093–104. [PubMed: 1811929]
14. Civitareale D, et al. A thyroid-specific nuclear protein essential for tissuespecific expression of the thyroglobulin promoter. *Embo j.* 1989; 8(9):2537–42. [PubMed: 2583123]
15. Francis-Lang H, et al. Cell-type-specific expression of the rat thyroperoxidase promoter indicates common mechanisms for thyroid-specific gene expression. *Mol Cell Biol.* 1992; 12(2):576–88. [PubMed: 1732732]
16. Bruno MD, et al. Lung cell-specific expression of the murine surfactant protein A (SP-A) gene is mediated by interactions between the SP-A promoter and thyroid transcription factor-1. *J Biol Chem.* 1995; 270(12):6531–6. [PubMed: 7896788]
17. Kimura S, et al. The T/ebp null mouse: thyroid-specific enhancer-binding protein is essential for the organogenesis of the thyroid, lung, ventral forebrain, and pituitary. *Genes Dev.* 1996; 10(1):60–9. [PubMed: 8557195]
18. Willemsen MA, et al. Brain-Thyroid-Lung syndrome: a patient with a severe multi-system disorder due to a de novo mutation in the thyroid transcription factor 1 gene. *Eur J Pediatr.* 2005; 164(1): 28–30. [PubMed: 15517377]
19. Carre A, et al. Five new TTF1/NKX2.1 mutations in brain-lung-thyroid syndrome: rescue by PAX8 synergism in one case. *Hum Mol Genet.* 2009; 18(12):2266–76. [PubMed: 19336474]
20. Ferrara AM, et al. A novel NKX2.1 mutation in a family with hypothyroidism and benign hereditary chorea. *Thyroid.* 2008; 18(9):1005–9. [PubMed: 18788921]
21. Zannini M, et al. TTF-2, a new forkhead protein, shows a temporal expression in the developing thyroid which is consistent with a role in controlling the onset of differentiation. *Embo j.* 1997; 16(11):3185–97. [PubMed: 9214635]
22. Bamforth JS, et al. Congenital hypothyroidism, spiky hair, and cleft palate. *J Med Genet.* 1989; 26(1):49–51. [PubMed: 2918525]
23. Tanaka M, et al. Nkx2.5 and Nkx2.6, homologs of Drosophila tinman, are required for development of the pharynx. *Mol Cell Biol.* 2001; 21(13):4391–8. [PubMed: 11390666]
24. Hirayama-Yamada K, et al. Phenotypes with GATA4 or NKX2.5 mutations in familial atrial septal defect. *Am J Med Genet A.* 2005; 135(1):47–52. [PubMed: 15810002]
25. Dentice M, et al. Missense mutation in the transcription factor NKX2-5: a novel molecular event in the pathogenesis of thyroid dysgenesis. *J Clin Endocrinol Metab.* 2006; 91(4):1428–33. [PubMed: 16418214]
26. Vassart G, Dumont JE. Thyroid dysgenesis: multigenic or epigenetic ... or both? *Endocrinology.* 2005; 146(12):5035–7. [PubMed: 16291637]
27. Salvatore, D., et al. Williams Textbook of Endocrinology. 12. Content Repository Only!; Philadelphia: 2011. CHAPTER 11 - Thyroid Physiology and Diagnostic Evaluation of Patients

with Thyroid Disorders A2 - Kronenberg, Shlomo Melmed Kenneth S. Polonsky P. Reed Larsen Henry M; p. 327-361.

28. Portulano C, Paroder-Belenitsky M, Carrasco N. The Na⁺/I⁻ symporter (NIS): mechanism and medical impact. *Endocr Rev.* 2014; 35(1):106–49. [PubMed: 24311738]
29. Grasberger, H., Refetoff, S. Genetic Diagnosis of Endocrine Disorders. 2. Academic Press; San Diego: 2016. Chapter 7 - Congenital Defects of Thyroid Hormone Synthesis; p. 117-125.
30. Dai G, Levy O, Carrasco N. Cloning and characterization of the thyroid iodide transporter. *Nature.* 1996; 379(6564):458–60. [PubMed: 8559252]
31. Reed-Tsur MD, et al. Molecular characterization of V59E NIS, a Na⁺/I⁻ symporter mutant that causes congenital I⁻ transport defect. *Endocrinology.* 2008; 149(6):3077–84. [PubMed: 18339708]
32. Dohan O, et al. Na⁺(+)/I⁻(-) symporter activity requires a small and uncharged amino acid residue at position 395. *Mol Endocrinol.* 2002; 16(8):1893–902. [PubMed: 12145342]
33. Paroder V, et al. The iodide-transport-defect-causing mutation R124H: a delta-amino group at position 124 is critical for maturation and trafficking of the Na⁺/I⁻ symporter. *J Cell Sci.* 2013; 126(Pt 15):3305–13. [PubMed: 23690546]
34. De La Vieja A, Ginter CS, Carrasco N. The Q267E mutation in the sodium/iodide symporter (NIS) causes congenital iodide transport defect (ITD) by decreasing the NIS turnover number. *J Cell Sci.* 2004; 117(Pt 5):677–87. [PubMed: 14734652]
35. Montanelli L, et al. Congenital hypothyroidism and late-onset goiter: identification and characterization of a novel mutation in the sodium/iodide symporter of the proband and family members. *Thyroid.* 2009; 19(12):1419–25. [PubMed: 19916865]
36. De la Vieja A, et al. Amino acid residues in transmembrane segment IX of the Na⁺/I⁻ symporter play a role in its Na⁺ dependence and are critical for transport activity. *J Biol Chem.* 2007; 282(35):25290–8. [PubMed: 17606623]
37. Li W, et al. Asn441 plays a key role in folding and function of the Na⁺/I⁻ symporter (NIS). *Faseb j.* 2013; 27(8):3229–38. [PubMed: 23650190]
38. De la Vieja A, Ginter CS, Carrasco N. Molecular analysis of a congenital iodide transport defect: G543E impairs maturation and trafficking of the Na⁺/I⁻ symporter. *Mol Endocrinol.* 2005; 19(11):2847–58. [PubMed: 15976004]
39. Nicola JP, et al. Iodide transport defect: functional characterization of a novel mutation in the Na⁺/I⁻ symporter 5' untranslated region in a patient with congenital hypothyroidism. *J Clin Endocrinol Metab.* 2011; 96(7):E1100–7. [PubMed: 21565787]
40. Everett LA, Green ED. A family of mammalian anion transporters and their involvement in human genetic diseases. *Hum Mol Genet.* 1999; 8(10):1883–91. [PubMed: 10469841]
41. Everett LA, et al. Expression pattern of the mouse ortholog of the Pendred's syndrome gene (Pds) suggests a key role for pendrin in the inner ear. *Proc Natl Acad Sci U S A.* 1999; 96(17):9727–32. [PubMed: 10449762]
42. Royaux IE, et al. Pendrin, encoded by the Pendred syndrome gene, resides in the apical region of renal intercalated cells and mediates bicarbonate secretion. *Proc Natl Acad Sci U S A.* 2001; 98(7):4221–6. [PubMed: 11274445]
43. Morgans ME, Trotter WR. Association of congenital deafness with goitre; the nature of the thyroid defect. *Lancet.* 1958; 1(7021):607–9. [PubMed: 13515293]
44. Kopp P, Pesce L, Solis SJ. Pendred syndrome and iodide transport in the thyroid. *Trends Endocrinol Metab.* 2008; 19(7):260–8. [PubMed: 18692402]
45. Reardon W, Trembath RC. Pendred syndrome. *J Med Genet.* 1996; 33(12):1037–40. [PubMed: 9004139]
46. Ladsous M, et al. Analysis of the thyroid phenotype in 42 patients with Pendred syndrome and nonsyndromic enlargement of the vestibular aqueduct. *Thyroid.* 2014; 24(4):639–48. [PubMed: 24224479]
47. Campbell C, et al. Pendred syndrome, DFNB4, and PDS/SLC26A4 identification of eight novel mutations and possible genotype-phenotype correlations. *Hum Mutat.* 2001; 17(5):403–11. [PubMed: 11317356]
48. Coyle B, et al. Molecular analysis of the PDS gene in Pendred syndrome. *Hum Mol Genet.* 1998; 7(7):1105–12. [PubMed: 9618167]

49. Tsukamoto K, et al. Distribution and frequencies of PDS (SLC26A4) mutations in Pendred syndrome and nonsyndromic hearing loss associated with enlarged vestibular aqueduct: a unique spectrum of mutations in Japanese. *Eur J Hum Genet.* 2003; 11(12):916–22. [PubMed: 14508505]
50. Targovnik HM, Citterio CE, Rivolta CM. Thyroglobulin gene mutations in congenital hypothyroidism. *Horm Res Paediatr.* 2011; 75(5):311–21. [PubMed: 21372558]
51. Rodrigues C, et al. Mutation screening of the thyroid peroxidase gene in a cohort of 55 Portuguese patients with congenital hypothyroidism. *Eur J Endocrinol.* 2005; 152(2):193–8. [PubMed: 15745925]
52. Avbelj M, et al. High prevalence of thyroid peroxidase gene mutations in patients with thyroid dysmorphogenesis. *Eur J Endocrinol.* 2007; 156(5):511–9. [PubMed: 17468186]
53. Ris-Stalpers C. Physiology and pathophysiology of the DUOXes. *Antioxid Redox Signal.* 2006; 8(9–10):1563–72. [PubMed: 16987011]
54. Moreno JC, et al. Inactivating mutations in the gene for thyroid oxidase 2 (THOX2) and congenital hypothyroidism. *N Engl J Med.* 2002; 347(2):95–102. [PubMed: 12110737]
55. Vigone MC, et al. Persistent mild hypothyroidism associated with novel sequence variants of the DUOX2 gene in two siblings. *Hum Mutat.* 2005; 26(4):395.
56. Varela V, et al. Three mutations (p.Q36H, p.G418fsX482, and g.IVS19-2A>C) in the dual oxidase 2 gene responsible for congenital goiter and iodide organification defect. *Clin Chem.* 2006; 52(2):182–91. [PubMed: 16322276]
57. Pfarr N, et al. Congenital hypothyroidism caused by new mutations in the thyroid oxidase 2 (THOX2) gene. *Clin Endocrinol (Oxf).* 2006; 65(6):810–5. [PubMed: 17121535]
58. Ohye H, et al. A novel homozygous missense mutation of the dual oxidase 2 (DUOX2) gene in an adult patient with large goiter. *Thyroid.* 2008; 18(5):561–6. [PubMed: 18426362]
59. Maruo Y, et al. Transient congenital hypothyroidism caused by biallelic mutations of the dual oxidase 2 gene in Japanese patients detected by a neonatal screening program. *J Clin Endocrinol Metab.* 2008; 93(11):4261–7. [PubMed: 18765513]
60. Hoste C, et al. Compound heterozygosity for a novel hemizygous missense mutation and a partial deletion affecting the catalytic core of the H₂O₂-generating enzyme DUOX2 associated with transient congenital hypothyroidism. *Hum Mutat.* 2010; 31(4):E1304–19. [PubMed: 20187165]
61. Grasberger H. Defects of thyroidal hydrogen peroxide generation in congenital hypothyroidism. *Mol Cell Endocrinol.* 2010; 322(1–2):99–106. [PubMed: 20122987]
62. Yoshizawa-Ogasawara A, et al. Congenital hypothyroidism caused by a novel mutation of the dual oxidase 2 (DUOX2) gene. *J Pediatr Endocrinol Metab.* 2013; 26(1–2):45–52. [PubMed: 23457309]
63. Zamproni I, et al. Biallelic inactivation of the dual oxidase maturation factor 2 (DUOXA2) gene as a novel cause of congenital hypothyroidism. *J Clin Endocrinol Metab.* 2008; 93(2):605–10. [PubMed: 18042646]
64. Yi RH, et al. A novel dual oxidase maturation factor 2 gene mutation for congenital hypothyroidism. *Int J Mol Med.* 2013; 31(2):467–70. [PubMed: 23292166]
65. Huler I, et al. A single copy of the recently identified dual oxidase maturation factor (DUOXA) 1 gene produces only mild transient hypothyroidism in a patient with a novel biallelic DUOXA2 mutation and monoallelic DUOXA1 deletion. *J Clin Endocrinol Metab.* 2011; 96(5):E841–5. [PubMed: 21367925]
66. Moreno JC, et al. Mutations in the iodotyrosine deiodinase gene and hypothyroidism. *N Engl J Med.* 2008; 358(17):1811–8. [PubMed: 18434651]
67. Afink G, et al. Molecular characterization of iodotyrosine dehalogenase deficiency in patients with hypothyroidism. *J Clin Endocrinol Metab.* 2008; 93(12):4894–901. [PubMed: 18765512]
68. Refetoff S, Weiss RE, Usala SJ. The syndromes of resistance to thyroid hormone. *Endocr Rev.* 1993; 14(3):348–99. [PubMed: 8319599]
69. Hennemann G, et al. Plasma membrane transport of thyroid hormones and its role in thyroid hormone metabolism and bioavailability. *Endocr Rev.* 2001; 22(4):451–76. [PubMed: 11493579]
70. Ceballos A, et al. Importance of monocarboxylate transporter 8 for the blood-brain barrier-dependent availability of 3,5,3'-triiodo-L-thyronine. *Endocrinology.* 2009; 150(5):2491–6. [PubMed: 19147674]

71. Dumitrescu AM, et al. A novel syndrome combining thyroid and neurological abnormalities is associated with mutations in a monocarboxylate transporter gene. *Am J Hum Genet.* 2004; 74(1): 168–75. [PubMed: 14661163]
72. Friesema EC, et al. Association between mutations in a thyroid hormone transporter and severe X-linked psychomotor retardation. *Lancet.* 2004; 364(9443):1435–7. [PubMed: 15488219]
73. 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; 21(2):277–305. [PubMed: 17574009]
74. Di Cosmo C, et al. A thyroid hormone analog with reduced dependence on the monocarboxylate transporter 8 for tissue transport. *Endocrinology.* 2009; 150(9):4450–8. [PubMed: 19497976]
75. Verge CF, et al. Diiodothyropropionic acid (DITPA) in the treatment of MCT8 deficiency. *J Clin Endocrinol Metab.* 2012; 97(12):4515–23. [PubMed: 22993035]
76. Dumitrescu AM, et al. Mutations in SECISBP2 result in abnormal thyroid hormone metabolism. *Nat Genet.* 2005; 37(11):1247–52. [PubMed: 16228000]
77. Bochukova E, et al. A mutation in the thyroid hormone receptor alpha gene. *N Engl J Med.* 2012; 366(3):243–9. [PubMed: 22168587]
78. Weiss RE, et al. Dominant inheritance of resistance to thyroid hormone not linked to defects in the thyroid hormone receptor alpha or beta genes may be due to a defective cofactor. *J Clin Endocrinol Metab.* 1996; 81(12):4196–203. [PubMed: 8954015]
79. Reutrakul S, et al. Search for abnormalities of nuclear corepressors, coactivators, and a coregulator in families with resistance to thyroid hormone without mutations in thyroid hormone receptor beta or alpha genes. *J Clin Endocrinol Metab.* 2000; 85(10):3609–17. [PubMed: 11061510]

Key Points

- Diagnosis of thyroid disease has evolved to involve sophisticated genetic testing of candidate genes to confirm the etiology of the thyroid disease.
- Congenital hypothyroidism in the absence of a goiter point to TSHR, PAX8, TTF-1, FOXE-1 NKS2-5 and Duox2 mutations.
- Congenital hypothyroidism in the presence of a goiter and a low radioactive iodine uptake suggest a NIS mutation.
- Congenital hypothyroidism in the presence of a goiter and high uptake suggest a TPO, DUPOX2 and DUOXA2 and DEHALI or PDS defect.
- Knowledge of the physiologic consequences of genetic mutations can help lead to rational recognition plans and treatment.

Fig. 1.
Algorithm for Genetic Screening for Disorders of TH Synthesis. See text for abbreviations.

Fig. 2.

Algorithm for Genetic Screening for Disorders of TH Action. See text for abbreviations.

Table 1

Causes of NonGoiterous Congenital Hypothyroidism (Dysgenesis)

Gene	Chr Location	FT ₄	TSH	Tg	Mode of Inherit	Comments
<i>TSHR</i>	14q31.1	Dec	Inc	Detectable	AR; sporadic	Normal-hypoplastic thyroid gland that does not trap TCO ₄ -
<i>PAX8</i>	2q14.1	Dec	Inc	Dec	AD, Sporadic	Variable thyroid phenotype from partial to complete agenesis
<i>TTF-1 (NKX2-1)</i>	14q13.3	Dec	Inc	Dec	AD	“Brain-Thyroid-Lung-Syndrome”
<i>FOXE 1 (TTF2, FKHL15)</i>	9q22.33	Dec	Inc	Dec	AR	Cleft palate Choanal atresia Spiky hair
<i>NKX2-5</i>	5q35.1	Dec	Inc	Dec	AD, imprinting	Heart disease Ectopic thyroid

Inc, increase; dec, decrease; chr, chromosome; AR, autosomal recessive; AD, autosomal dominant.

Table 2

Causes of Goiterous Congenital Hypothyroidism (Dyshormonogenesis)

Gene	Chr Location	FT ₄	TSH	Tg	Mode of Inherit	Comments
<i>NIS (SLC5A5)</i>	19p13.11	Dec	Inc	Inc	AR; 13 cases	Saliva: Plasma ¹²⁵ I ratio<20
<i>PDS (SLC26A4)</i>	7q22.3	N	N,Inc	Inc	AR; 7.5 to 10 in 100000	Sensorineuronal hearing loss
<i>TG</i>	8q24.22	Dec	Inc	Dec	AR; 40 cases (1:67,000)	High uptake on scintigraphy
<i>TPO</i>	2p25.3	Dec	N,Inc	N,Inc	AR	Positive CLO ₄ ⁻ discharge test Iodination and coupling defect
<i>DUOX2 (THOX2)</i>	15q21.1	Dec	Inc	N,Inc	AR	NADPH oxidase Can be transient hypothyroid which corrects
<i>DUOXA2</i>	15q21.1	Dec	Inc	N,Inc	AR	
<i>IYD (DEHALD)</i>	6q25.1	Dec	Inc	N,Inc	AR	Elevated urinary DIT and MIT levels

Inc, increase; dec, decrease; N, normal; chr, chromosome; AR autosomal recessive

Table 3

Causes of Abnormalities in TH Action (Syndromes of impaired sensitivity to TH).

Gene	Chr Location	FT ₄	TSH	rT ₃	FT ₃	Goiter	Mode of Inherit	Comments
<i>MCT8</i>	Xq13.2	Dec	Inc	Dec	Inc	No	X-linked	Severe neuropsychiatric abnormalities
<i>SBP-2 (SECISBP2)</i>	9q22.2	Inc	N,Inc	Inc	Dec	No	Unknown	Defect in deiodination of T ₄ to T ₃
<i>THRB</i>	3p24.2	Inc	N,Inc	Inc	Inc	Yes	AD; >400 cases	Goiter; ADHD; some growth issues
<i>THRA</i>	17q21.1	Dec	N,Inc	Dec	N-Inc	No	AD	Cleft palate Choanal atresia Spiky hair

Inc, In, increase; dec, decrease; N, normal; chr, chromosome; AD autosomal dominant