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Genetics of Thyroid Dyshormonogenesis: From Molecular Mechanisms to Precision Management

Rosie Lee

Department of Pediatrics, Keimyung University Dongsan Hospital, Daegu, Korea

Congenital hypothyroidism (CH) is one of the most common endocrine disorders in newborns and an important preventable cause of intellectual disability. Thyroid dyshormonogenesis accounts for approximately 15%–20% of CH cases and results from defects in thyroid hormone synthesis. Recent advances in molecular genetics have identified several key genes involved in this process, including *SLC5A5, TPO, DUOX2, DUOXA2, TG, SLC26A4*, and *IYD*. These genes affect different steps of hormone production, such as iodide transport, organification, thyroglobulin synthesis, and iodide recycling. Clinical presentations vary widely, ranging from transient to permanent hypothyroidism, depending on the type and severity of genetic defects. A precise genetic diagnosis has important clinical implications. It can guide individualized treatment strategies and help predict disease courses, including the likelihood of transient versus permanent hypothyroidism. In addition, early identification of affected family members enables timely intervention and prevention of developmental complications. In conclusion, thyroid dyshormonogenesis represents a genetically heterogeneous group of disorders. Integrating genetic, biochemical, and clinical data is essential for precision management and may improve long-term outcomes in patients with congenital hypothyroidism.

Key words: Congenital hypothyroidism, Thyroid hormone synthesis disorders, Thyroid dyshormonogenesis

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Correspondence to: Rosie Lee, MD
Department of Pediatrics, Keimyung University Dongsan Hospital, 1035 Dalgubeol-daero, Dalseo-gu, Daegu 42601, Korea
Tel: +82-53-258-4852
Fax: +82-53-258-4875
E-mail: llrs0325@gmail.com

ORCID
https://orcid.org/0000-0003-3285-3916

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INTRODUCTION

Congenital hypothyroidism (CH) is the most common congenital endocrine disorder and an important preventable cause of intellectual disability [1]. CH is classified into two main categories: thyroid dysgenesis and thyroid dyshormonogenesis. Thyroid dyshormonogenesis causes 15%–20% of congenital hypothyroidism, while thyroid dysgenesis accounts for the majority [2]. Thyroid dyshormonogenesis has been associated with mutations in seven genes: *SLC5A5 (NIS)*, *SLC26A4 (PDS)*, *TG*, *TPO*, *DUOX2*, *DUOXA2*, and *IYD (DEHAL1)*. Defects can occur at any step of thyroid hormone synthesis, including iodine uptake *(SLC5A5)*, iodine organification (*TPO, DUOX2, DUOXA2, SLC26A4*), thyroglobulin synthesis (*TG*), and iodine recycling by iodotyrosine deiodinase (*IYD/DEHAL1*) [3]. A definite genetic diagnosis in CH offers several clinical benefits. It can guide treatment decisions, as some hormonogenesis defects may respond effectively to iodide supplementation rather than levothyroxine (L-T4). In addition, genetic testing can help identify patients with transient CH caused by partial defects in hormonogenesis and may also predict those who will require lifelong thyroid hormone replacement therapy [1].

THYROID HORMONE BIOSYNTHESIS

Thyroid hormone synthesis starts with the uptake of iodine (I) from the diet, which is absorbed in the form of iodide (I^-) and transported into thyroid cells by

Table 1. Clinical characteristics of thyroid dyshormonogenesis according to genetic defects

Gene	Biosynthesis Step	Goiter	Serum TG level	Radioiodine Uptake in Thyroid scintigraphy	Perchlorate discharge test	Treatment
SLC5A5	Iodide uptake	Present	Elevated	Decreased or absent	Negative	Iodide ± LT4
TPO	Iodine organification	Present (often large)	Elevated	Increased	Positive	Lifelong LT4
DUOX2	H_2O_2 generation (for organification)	Present	Elevated	Normal or increased	Positive	Iodide or LT4
DUOXA2	DUOX2 maturation	Present	Elevated	Normal or increased	Positive	LT4
SLC26A4	Iodide efflux (apical transport)	Present	Elevated	Normal or increased	Positive	LT4 if needed
TG	Thyroglobulin synthesis	Present (often large)	Low	Increased (high uptake)	Negative	Lifelong LT4
IYD	Iodide recycling	Present	Elevated	Initially increased, then declines	Negative	Iodide or LT4

Perchlorate discharge test positive: indicating a defect in converting accumulated iodide to organically bound iodine.

the sodium/iodide symporter (NIS) [4]. Inside the cells, thyroglobulin (Tg), a large glycoprotein, is secreted into the follicle lumen [5], while thyroid peroxidase (TPO) at the apical membrane uses H_2O_2, generated by Duox, to oxidize iodide and attach it to Tg tyrosyl residues [6,7]. This iodination produces monoiodotyrosine (MIT) and diiodotyrosine (DIT), and the coupling of two DIT residues forms T4 [8]. When needed, Tg is endocytosed and degraded in endosomes and lysosomes, releasing T4 and T3 into the circulation. Non-hormonal iodide, about 70% of Tg iodine, is recovered by iodotyrosine deiodinase (IYD) or reuse within the gland [9]. Thyroid-stimulating hormone (TSH) regulates nearly every step, controlling both enzyme activity in the short term and gene expression in the long term. Imbalances in iodine or genetic defects in key proteins such as NIS, TPO, Duox, or Tg can lead to goiter or hypothyroidism. Clinical characteristics of thyroid dyshormonogenesis according to genetic defects are described in Table 1.

IODIDE TRANSPORT DEFECT: *SLC5A5(NIS)* MUTATIONS (OMIM #274400, THYROID DYSHORMONOGENESIS-1)

Thyroid dyshormonogenesis-1 (TDH1) results from homozygous or compound heterozygous mutations in the *SLC5A5* gene, which is located on chromosome 19p13. The NIS, encoded by the *SLC5A5* gene, is a 13-transmembrane protein that enables iodide to enter thyroid follicular cells via the basolateral membrane [1]. TDH1 is characterized by a failure of the thyroid gland to establish and maintain an iodide concentration gradient between the plasma and thyroid tissue. Therefore, patients usually present with goiter and show reduced or absent radioactive iodine uptake (RAIU) on thyroid scintigraphy. RAIU directly reflects residual NIS activity [10]. Patients can be treated with iodide supplementation alone or combined with L-T4 replacement therapy. Hypothyroidism may develop from the neonatal period through childhood and is influenced by the remaining functional activity of the mutant transporter. Identification of an index case enables early detection in other family members, preventing delayed diagnosis and potential developmental delay [11].

Stanbury and Chapman first reported iodide transport defect in 1960 [12]. Fujiwara [13] subsequently clarified the molecular mechanism underlying this defect, identifying a mutation in the *SLC5A5* gene in 1997. To date, 66 mutations in *SLC5A5* have been documented in the Human Gene Mutation Database (HGMD) [14].

IODIDE ORGANIFICATION DEFECT: *TPO* MUTATIONS (OMIM #274500, THD2A)

TDH2A results from homozygous or compound heterozygous mutation in the *TPO* gene located on chromosome 2p25. TPO catalyzes the iodination of tyrosine residues in thyroglobulin using H_2O_2 and mediates their coupling to generate thyroid hormones. *TPO* defects cause severe congenital hypothyroidism with goiter and a total or partial iodine organification defect. After sodium perchlorate administration, accumulated radioiodide is rapidly released from the thyroid, reflecting failure of iodide oxidation and binding to tyrosine residues in thyroglobulin [15]. *TPO* deficiency is the most common cause of thyroid dyshormonogenesis with permanent

CH [16]. If a newborn with congenital hypothyroidism has biallelic *TPO* mutations, lifelong thyroid hormone treatment is needed, and careful monitoring for fetal goiter is recommended in future pregnancies [17]. Although the condition follows a recessive inheritance pattern, about 20% of cases show only monoallelic *TPO* mutations are identified, likely due to undetected variants in intronic or regulatory regions [18]. Niu et al. [19] reported that even monoallelic *TPO* mutations may be associated with transient neonatal hypothyroidism.

Haddad and Sidbury reported the first *in vitro* demonstration of impaired thyroid peroxidase activity in a patient with a thyroid hormone organification defect in 1959 [20]. Abramowicz et al. [21] identified a *TPO* gene mutation in 1992 in a patient presenting with partial iodide organification defect. To date, the HGMD has documented 287 mutations in the *TPO* gene [14].

IODIDE ORGANIFICATION DEFECT, H_2O_2 GENERATION DEFECT: *DUOX2* MUTATIONS (OMIM #607200, TDH6)

TDH6 is caused by homozygous or compound heterozygous mutations in the *DUOX2* gene located on chromosome 15q21. Duox plays a key role by producing H_2O_2 required for TPO-driven iodination and coupling reactions [22]. CH due to *DUOX2* mutations typically presents with goiter and elevated Tg, and most patients demonstrates a partial iodide organification defect (PIOD) on the perchlorate discharge test. Several studies have reported that biallelic *DUOX2* mutations are associated with permanent CH accompanied by PIOD. Iodide supplementation may be considered as an alternative to lifelong thyroid hormone replacement therapy [1]. Although most dyshormonogenesis defects follow an autosomal recessive inheritance pattern, a single defective *DUOX2* allele can cause transient CH due to haploinsufficiency, particularly during the neonatal period or pregnancy when thyroid hormone synthesis demand is highest [23].

Moreno et al. [23] first described patients with CH with total/partial iodide organification defect caused by *DUOX2* mutations in 2002. In the Korean populations, *DUOX2* variants represent a relatively common cause of CH, often accompanied by normal-sized or enlarged eutopic thyroid glands [24]. The HGMD currently lists 527 different *DUOX2* mutations [14].

IODIDE ORGANIFICATION DEFECT, H_2O_2 GENERATION DEFECT: *DUOXA2* MUTATIONS (OMIM #274900, TDH5)

TDH5 is caused by homozygous or compound heterozygous mutation in the *DUOXA2* gene on chromosome 15q21. DUOXA2 functions as a maturation factor for DUOX2 [22]. Zamproni et al. [7] identified homozygous *DUOXA2* mutation in a patient with permanent CH and dyshormonogenic goiter in 2008. The mutant protein failed to reconstitute DUOX2 activity *in vitro*. A perchlorate discharge test revealed partial iodide discharge [7]. However, a monoallelic *DUOXA2* mutation linked to transient CH was reported in 2015, highlighting the need for additional investigation. To date, 89 different mutations in *DUOXA2* have been reported in the HGMD [14].

IODIDE EFFLUX DEFECT: PENDRED SYNDROME, *SLC26A4* MUTATIONS (OMIM #274600, TDH2B)

Pendred syndrome (PDS) is caused by homozygous or compound heterozygous mutation in the *SLC26A4* gene on chromosome 7q22.3. Pendrin is expressed in the thyroid, inner ear, and kidney. In the thyroid, pendrin is in the apical membrane of follicular cells, where it is thought to play a role in transporting iodide across the apical surface [25]. PDS is the most common syndromic cause of deafness. It is characterized by sensorineural hearing loss, developmental abnormalities of the cochlea and diffuse thyroid goiter [26]. In perchlorate discharge test, patients exhibit partial discharge of iodide [27], and they typically develop enlarged thyroid glands beginning in childhood. Although most patients are euthyroid, an exaggerated response to thyrotropin-releasing hormone indicate compensated for hypothyroidism [28], and approximately 10% of patients have elevated TSH levels [29]. With sufficient dietary iodide, most patients are euthyroid.

Pendred syndrome was first described by Vaughan Pendred in 1896 [30]. Everett et al. [26] identified the gene mutated in Pendred syndrome, *SLC26A4*, using a positional cloning strategy in 1997. Currently, the HGMD lists 763 different mutations in *SLC26A4* [14].

THYROGLOBULIN SYNTHESIS: *TG* MUTATIONS (OMIM #274700, TDH3)

TDH3 is caused by homozygous or compound heterozy-

gous mutation in the *TG* gene on chromosome 8q24. Thyroglobulin (Tg), a glycoprotein generated within the endoplasmic reticulum of thyroid follicular cells, is delivered to the colloid by exocytotic vesicles through the apical membrane [5]. It functions as a structural platform for hormone production by offering tyrosyl residues, which form the non-iodide portion of thyroid hormones. The severity of thyroid dysfunction differs among individuals with impaired Tg production. The condition is characterized by undetectable or very low serum Tg levels despite elevated TSH, often accompanied by markedly enlarged goiter [5]. Thyroid scintigraphy typically shows high uptake in an enlarged gland, and no perchlorate discharge is observed because iodide organification remains intact [1]. CH caused by *TG* mutations is usually permanent, requiring lifelong L-T4 medication [31]. Sugisawa et al. reported that monoallelic variants in *DUOX2*, *TSHR*, *TG*, and *TPO* are more frequent in hypothyroidism patients (16.8%) than in the general population (3.3%) and act as risk factors rather than direct causes of disease [32].

Riddick et al. reported hypothyroidism patients with absence of Tg in 1969 [33], and the first *TG* gene mutation was reported by Ieiri et al. in 1991 [34]. The HGMD currently lists 480 different mutations in *TG* [14].

IODIDE RECYCLING DEFECT: *IYD* MUTATIONS (OMIM #274800, TDH4)

TDH4 is caused by homozygous mutation in the iodotyrosine deiodinase gene (*IYD*) on chromosome 6q25. Deiodinases are membrane-bound isoenzymes that require NADPH and FAD for activity and are expressed in multiple tissues, including the thyroid, kidney, and liver. In affected patients, the inability to deiodinate radiolabeled MIT and DIT leads to ongoing urinary loss of iodine and tyrosine. On scintigraphy, an enlarged thyroid usually demonstrates a rapid and high initial uptake of ^{123}I, followed by a spontaneous decline without perchlorate administration. Elevated urinary MIT and DIT detected by tandem mass spectrometry may aid in diagnosis [1]. Iodine supplementation, such as Lugol's solution, has been reported as a potential alternative to L-T4 treatment in patients with *IYD* deficiency [35]. Iodide deficiency due to biallelic *IYD* mutations may not manifest at birth. Affected patients can have normal neonatal CH screening results but later present between 1.5 and 8 years of age with complications of untreated hypothyroidism. Therefore, even if initial thyroid function is normal, careful follow-up is clinically important [36]. A heterozygous carrier of an inactivating mutation was recently reported to develop overt hypothyroidism, suggesting a possible dominant pattern of inheritance [37].

Moreno et al. identified *IYD* mutations in patients with hypothyroidism in 2008 [36]. A total of 32 mutations in *IYD* have been reported in the HGMD [14].

CONCLUSIONS

CH due to thyroid dyshormonogenesis represents a genetically heterogeneous group of disorders affecting multiple steps of thyroid hormone synthesis. Mutations in genes such as *SLC5A5*, *TPO*, *DUOX2*, *DUOXA2*, *TG*, *SLC26A4*, and *IYD* lead to variable clinical phenotypes, ranging from transient to permanent hypothyroidism. Recent advances in molecular genetics have improved understanding of genotype–phenotype correlations and revealed that some defects may show atypical inheritance patterns or partial functional impairment. A precise genetic diagnosis can guide individualized treatment strategies, predict disease course, and allow early identification of affected family members. In addition, distinguishing transient from permanent hypothyroidism can help avoid unnecessary lifelong treatment. Future studies integrating genetic, biochemical, and clinical data will further improve risk stratification and support the development of precision medicine approaches in congenital hypothyroidism.

CONFLICTS OF INTEREST

There are no conflicts of interest.

REFERENCES

1. Grasberger H, Refetoff S. Genetic causes of congenital hypothyroidism due to dyshormonogenesis. Curr Opin Pediatr 2011;23(4):421-8. doi:10.1097/MOP.0b013e32834726a4.
2. Kwak MJ. Clinical genetics of defects in thyroid hormone synthesis. Ann Pediatr Endocrinol Metab 2018;23(4):169-75. doi:10.6065/apem.2018.23.4.169.
3. Szinnai G. Clinical genetics of congenital hypothyroidism. Endocr Dev 2014;26:60-78. doi:10.1159/000363156.
4. Spitzweg C, Heufelder AE, Morris JC. Thyroid iodine transport. Thyroid 2000;10(4):321-30. doi:10.1089/thy.2000.10.321.
5. Targovnik HM, Esperante SA, Rivolta CM. Genetics and phenomics of hypothyroidism and goiter due to thyroglobulin mutations. Mol Cell Endocrinol 2010;322(1-2):44-55. doi:10.1016/j.mce.2010.01.009.
6. Muzza M, Fugazzola L. Disorders of H_2O_2 generation. Best Pract

Res Clin Endocrinol Metab 2017;31(2):225-40. doi:10.1016/j.beem.2017.04.006.
7. Zamproni I, Grasberger H, Cortinovis F, Vigone MC, Chiumello G, Mora S, 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. doi:10.1210/jc.2007-2020.
8. Knobel M, Medeiros-Neto G. An outline of inherited disorders of the thyroid hormone generating system. Thyroid 2003;13(8):771-801. doi:10.1089/105072503768499671.
9. Moreno JC. Identification of novel genes involved in congenital hypothyroidism using serial analysis of gene expression. Horm Res 2003;60 Suppl 3:96-102. doi:10.1159/000074509.
10. Lakshmanan A, Scarberry D, Green JA, Zhang X, Selmi-Ruby S, Jhiang SM. Modulation of thyroidal radioiodide uptake by oncological pipeline inhibitors and Apigenin. Oncotarget 2015;6(31):31792-804. doi:10.18632/oncotarget.5172.
11. Szinnai G, Kosugi S, Derrien Cl, Lucidarme N, David Vr, Czernichow P, et al. Extending the clinical heterogeneity of Iodide Transport Defect (ITD): a novel mutation R124H of the Sodium/Iodide Symporter Gene and Review of Genotype-Phenotype Correlations in ITD. J Clin Endocrinol Metab 2006;91(4):1199-204. doi: 10.1210/jc.2005-1832.
12. Stanbury JB, Chapman EM. Congenital hypothyroidism with goitre. Absence of an iodide-concentrating mechanism. Lancet 1960;1(7135):1162-5. doi:10.1016/s0140-6736(60)91042-4.
13. Fujiwara H. Congenital hypothyroidism caused by a mutation in the Na+/l-symporter. Nat Genet 1997;17(1):122. doi:10.1038/ng0997-122a.
14. The Human Gene Mutation Database Cardiff (UK); [Available from: http://www.hgmd.cf.ac.uk.
15. Bakker B, Bikker H, Vulsma T, de Randamie JS, Wiedijk BM, De Vijlder JJ. Two decades of screening for congenital hypothyroidism in The Netherlands: TPO gene mutations in total iodide organification defects (an update). J Clin Endocrinol Metab 2000;85(10):3708-12. doi:10.1210/jcem.85.10.6878.
16. Park SM, Chatterjee VK. Genetics of congenital hypothyroidism. J Med Genet 2005;42(5):379-89. doi:10.1007/s42000-020-00267-x.
17. Agrawal P, Ogilvy-Stuart A, Lees C. Intrauterine diagnosis and management of congenital goitrous hypothyroidism. Ultrasound Obstet Gynecol 2002;19(5):501-5. doi:10.1089/thy.2005.15.1341.
18. Fugazzola L, Cerutti N, Mannavola D, Vannucchi G, Fallini C, Persani L, et al. Monoallelic expression of mutant thyroid peroxidase allele causing total iodide organification defect. J Clin Endocrinol Metab 2003;88(7):3264-71. doi:10.1210/jc.2002-021377.
19. Niu DM, Lin CY, Hwang B, Jap TS, Liao CJ, Wu JY. Contribution of genetic factors to neonatal transient hypothyroidism. Arch Dis Child Fetal Neonatal Ed 2005;90(1):F69-72. doi:10.1136/adc.2003.039065.
20. Haddad HM, Sidbury JB, Jr. Defect of the iodinating system in congenital goitrous cretinism: report of a case with biochemical studies. J Clin Endocrinol Metab 1959;19:1446-57. doi:10.1210/jcem-19-11-1446.
21. Abramowicz MJ, Targovnik HM, Varela V, Cochaux P, Krawiec L, Pisarev MA, et al. Identification of a mutation in the coding sequence of the human thyroid peroxidase gene causing congenital goiter. J Clin Invest 1992;90(4):1200-4. doi:10.1172/JCI115981.
22. Morand S, Ueyama T, Tsujibe S, Saito N, Korzeniowska A, Leto TL. Duox maturation factors form cell surface complexes with Duox affecting the specificity of reactive oxygen species generation. FASEB J 2009;23(4):1205-18. doi: 10.1096/fj.08-120006.
23. Moreno JC, Bikker H, Kempers MJ, van Trotsenburg AS, Baas F, de Vijlder JJ, et al. Inactivating mutations in the gene for thyroid oxidase 2 (THOX2) and congenital hypothyroidism. N Engl J Med 2002;347(2):95-102. doi:10.1056/NEJMoa012752.
24. Jin HY, Heo SH, Kim YM, Kim GH, Choi JH, Lee BH, et al. High frequency of DUOX2 mutations in transient or permanent congenital hypothyroidism with eutopic thyroid glands. Horm Res Paediatr 2014;82(4):252-60. doi:10.1159/000362235.
25. 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. doi:10.1093/hmg/8.10.1883.
26. Everett LA, Glaser B, Beck JC, Idol JR, Buchs A, Heyman M, et al. Pendred syndrome is caused by mutations in a putative sulphate transporter gene (PDS). Nat Genet 1997;17(4):411-22. doi:10.1038/ng1297-411.
27. Fraser GR, Morgans ME, Trotter WR. The syndrome of sporadic goitre and congenital deafness. Q J Med 1960;29:279-95.
28. Gomez-Pan A, Evered DC, Hall R. Pituitary-thyroid function in Pendred's syndrome. Br Med J 1974;2(5911):152-3. doi:10.1136/bmj.2.5911.152.
29. Reardon W, Coffey R, Phelps PD, Luxon LM, Stephens D, Kendall-Taylor P, et al. Pendred syndrome--100 years of underascertainment? Qjm 1997;90(7):443-7. doi:10.1093/qjmed/90.7.443.
30. Pendred V. Deaf mutism and goitre. The Lancet 1896;148(3808):532
31. Targovnik HM, Citterio CE, Rivolta CM. Thyroglobulin gene mutations in congenital hypothyroidism. Horm Res Paediatr 2011;75(5):311-21. doi:10.1159/000324882.
32. Sugisawa C, Uehara E, Tanase-Nakao K, Inoue K, Iida T, Otsuka F, et al. Clinical and genetic characteristics of adult nonautoimmune hypothyroidism: a single-institution study. J Clin Endocrinol Metab 2025;111(1):e32-e40. doi: 10.1210/clinem/dgaf352.
33. Riddick FA, Desai KB, Stanbury JB, Murison PJ. Familial goiter with diminished synthesis of thyroglobulin. Z Gesamte Exp Med Einschl Exp Chir 1969;150(3):203-12. doi: 10.1007/BF02044425.
34. Ieiri T, Cochaux P, Targovnik HM, Suzuki M, Shimoda S, Perret J, et al. A 3' splice site mutation in the thyroglobulin gene responsible for congenital goiter with hypothyroidism. J Clin Invest 1991;88(6):1901-5. doi:10.1172/JCI115513.
35. Hirsch HJ, Shilo S, Spitz IM. Evolution of hypothyroidism in familial goitre due to deiodinase deficiency: report of a family and review of the literature. Postgrad Med J 1986;62(728):477-80.

doi:10.1136/pgmj.62.728.477.
36. Moreno JC, Klootwijk W, van Toor H, Pinto G, D'Alessandro M, Lèger A, et al. Mutations in the iodotyrosine deiodinase gene and hypothyroidism. N Engl J Med 2008;358(17):1811-8. doi: 10.1056/NEJMoa0706819.
37. Afink G, Kulik W, Overmars H, de Randamie J, Veenboer T, van Cruchten A, et al. Molecular characterization of iodotyrosine dehalogenase deficiency in patients with hypothyroidism. J Clin Endocrinol Metab 2008;93(12):4894-901. doi:10.1210/jc.2008-0865.