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Review Article

Diagnostic options, physiopathology, risk factors and genetic causes of permanent congenital hypothyroidism: A narrative review

Zahra Rasoulizadeh (MD) [1]
Mahtab Ordooei (MD) [1*]
Elahe Akbarian (Msc) [1]

1. Children Growth Disorder Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

*** Correspondence:**
Mahtab Ordooei, Children Growth Disorder Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

E-mail: dr.ordooei@yahoo.com
Tel: +98 3531833502

Abstract

Background: In Permanent congenital hypothyroidism (PCH) is a lifelong condition characterized by a deficiency in thyroid hormone, leading to various neurodevelopmental complications. Early clinical signs are often nonspecific and easily overlooked, but newborn screening programs have improved early detection.

Methods: This narrative review aims to provide insights comparatively transient and permanent PCH and also the diagnosis, risk factors, underlying pathophysiology, and genetic causes associated with PCH. Relevant studies were identified through a comprehensive search using the term 'Permanent congenital hypothyroidism' (Mesh) across scientific databases of electronic databases such as PubMed, Scopus, and Web of Science.

Results: Prompt initiation of thyroid hormone replacement therapy, particularly within the initial two weeks postpartum, crucially enhances neurocognitive development outcomes. Multiple predictive approaches, encompassing screening TSH levels, maternal thyroid history, and levothyroxine dosage per kilogram assessment, aid in identifying PCH. Recent studies have demonstrated a mounting prevalence of PCH, contributing significantly to the overall rise in CH incidence. Genetic factors, primarily DUOX2 and DUOXA2 mutations, alongside environmental influences such as post-term birth, low birth weight, and macrosomia, may induce PCH. Nonetheless, reliable markers for early PCH prediction upon diagnosis remain elusive, leading to delayed recognition post-ceasing levothyroxine treatment around age 3.

Conclusions: Recent studies have observed an increased incidence of PCH, contributing substantially to the overall rise in cases of congenital hypothyroidism. Understanding the diagnostic options and genetic etiologies associated with PCH is crucial for the early identification and appropriate management.

Keywords: Permanent congenital hypothyroidism, Thyroid hormone deficiency, Newborn screening, Levothyroxine therapy, Genetic etiologies.

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1. Congenital hypothyroidism: Congenital hypothyroidism (CH) is a prevalent endocrine disorder that manifests as a deficiency in thyroid hormone present at birth. It encompasses various causes, including thyroid dysgenesis (TD) and dyshormonogenesis, which can result in permanent or transient thyroid hormone deficits (1, 2). This review aims to provide a comprehensive understanding of permanent CH, focusing on its definition, diagnostic methods, key epidemiological data and explaining the differentiation between transient and permanent CH. Additionally, we will explore the mechanism of thyroid hormone synthesis, highlighting the impact of genetic and environmental factors on the pathogenesis of permanent CH.

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1.1 Definition and diagnosis of permanent congenital hypothyroidism: CH is classified into two categories: permanent CH and transient CH. Permanent CH refers to a sustained deficiency of thyroid hormone that necessitates lifelong medication. On the other hand, transient CH is characterized by a temporary insufficiency of hormones that resolves spontaneously. Diagnostic criteria and screening methods for identifying permanent CH will be discussed, emphasizing the importance of early detection through newborn screening programs. We will also explore the timeline for levothyroxine therapy cessation in individuals with transient CH, as their thyroid hormone production typically normalizes by the end of the third year of life (1).

1.2 Pathogenesis of permanent congenital hypothyroidism:

1.2.1 Thyroid dysgenesis (TD): TD encompasses various structural abnormalities in the thyroid gland, including agenesis, ectopic location, orthotopic placement, hypoplasia, and thyroid ectopy. We will examine the underlying causes of TD, such as genetic mutations, and their impact on thyroid gland development. Additionally, the association between TD and maternal TSH receptor-blocking antibodies will be explored.

1.2.2 Dyshormonogenesis:

Dyshormonogenesis involves impairments in the production of thyroid hormone due to genetic defects throughout the thyroid hormone synthesis pathway. We will discuss the different stages of hormone production affected by genetic mutations and their contribution to permanent CH. Furthermore, the clinical manifestations associated with dyshormonogenesis, including goiter formation, will be addressed.

1.3 Epidemiological data and risk factors: A comprehensive overview of the epidemiological data surrounding permanent CH will be provided. This includes the incidence rates, geographic variations, and trends observed in different populations. We will also examine the role of both genetic and environmental risk factors in the development of permanent CH, shedding light on their contributions to the pathogenesis of the condition.

1.3.1 Evidence acquisition: To gather relevant information on the pathogenesis, etiology, and diagnosis of CH, a search was conducted using the term 'Permanent congenital hypothyroidism' (Mesh) across scientific databases, including PubMed, Scopus, and Web of Science. The search encompassed studies published up until January 2023, with inclusion criteria limited to studies published in English. The search term 'Permanent congenital hypothyroidism' (Mesh) was employed to retrieve pertinent studies from the databases.

The summarized findings presented in table 1 provide valuable insights into the prevalence, demographics, and clinical characteristics of permanent CH, thereby contributing to a better understanding of its pathogenesis, etiology, and diagnosis. This study has received full ethical approval from the Ethics Committee of Shahid Sadoughi University of Medical Sciences (Ethics Certificate Number: IR.SSU.REC.1402.012).

Table 1. Summary of prevalence, demographics and clinical characterization of patients with permanent CH

Author	Year	N (F,M)	Country	PCH incidence	Prevalence of PCH	FT4 levels	TSH levels	Ref
Evin F et al.	2022	105 (47,58)	Turkey	58.2%		0.90±0.35 (ng/dL)	97.11±76.40 (mIU/mL)	(3)
Beheshti Z et al.	2018	389 (172,217)	Iran (Northern)	43.4%	1;1043	7.5±15.6 (ug/dL)	55±15.6 (mIU/L)	(4)
Aminzadeh M et al.	2018	194 (94,100)	Iran (Southwest)	46%	1;970			(5)
Khazaei Z et al.	2017	855 (336,516)	Iran (Western)	22.6%		8.8±10.8 (mIU/L)	14.1±17.6 (mIU/L)	(6)
Marr A et al.	2022	469 (286,180)	Canada	78.6%		118.9 (mIU/L)	11.2 (mIU/L)	(7)
Bekhit Oem et al	2013	248 (107,141)	Egypt	82.3%	1;36			(8)
Tuli G et al.	2021	55 (21,34)	Italy	52.7%		197.3±44.5 (Pg/mL)	6.92±0.72 (Pg/mL)	(9)

Author	Year	N (F,M)	Country	PCH incidence	Prevalence of PCH	FT4 levels	TSH levels	Ref
Ordooei M et al.	2013	22 (9,13)	Iran (center)	45.5%				(10)
Nagasaki K et al.	2021	116 (62,54)	Japan		1;3000			(11)
Mehran L et al.	2021	1047 (491,556)	Iran	57.1%		11.85 (mU/l)		(12)
Höpfner S et al.	2005	129 (73,56)	Germany	53.4%	1;3313			(13)
Hemati Z et al.	2019	918 (461,457)	Iran (Central)	52.5%		42.26 (mIU/L)		(14)
Habib A et al.	2021	938 (304,634)	Iran (Southwest)	66.04%		28.33±47.62(mIU/L)		(15)

Abbreviations: PCH, permanent congenital hypothyroidism; TSH, thyroid stimulating hormone.

1.1 Physiological needs for the synthesis of thyroid hormone and the implications for CH: In individuals with normal thyroid function, the levels of circulating thyroid hormones are high during the newborn period but gradually decrease over the first year of life (16). This indicates a significant reduction in the physiological need for thyroid hormone during early development. However, temporary elevations in the requirements of thyroid hormone biosynthetic are observed during adolescence and pregnancy, particularly in females (17). For individuals with CH, maintaining adequate levels of thyroid hormone is crucial for optimal health (18).

Exogenous levothyroxine, a synthetic form of thyroid hormone, is used to supplement the deficient hormone production in CH patients. The dosage requirements of levothyroxine need to be adjusted regularly to ensure the maintenance of appropriate hormone levels. To achieve this, the goal is to maintain free thyroxine (FT_4) concentrations in the upper half of the normal age-specific reference range while bringing thyroid-stimulating hormone (TSH) levels within the normal range. In some cases, FT_4 levels slightly exceeding the upper limit of the reference range may be allowed if TSH levels are within the age-specific reference range (19, 20). Initiating levothyroxine treatment as early as possible after the diagnosis of CH is crucial because the initial dosage requirements typically range from 8 to 15 µg/kg. In newborns with reduced thyroid activity, such as those with ectopic or absent thyroid gland (ectopy or athyreosis), the required levothyroxine dosage changes predictably with age in a comparable manner (21). Therefore, closely monitoring thyroid hormone levels, particularly FT_4 and TSH, is essential to ensure adequate hormone replacement therapy in individuals with CH. Regular adjustments in levothyroxine dosage based on age and individual requirements help maintain optimal thyroid hormone levels, supporting normal growth and development in CH patients.

2. Diagnosis of permanent CH

2.1 Newborn screening: The majority of infants with CH are identified through newborn screening programs since they may not exhibit obvious symptoms at birth. This screening for CH is a major achievement in public health as it enables early detection and initiation of levothyroxine treatment, reducing the associated morbidity. Confirmation of the CH diagnosis is typically based on venous thyroid function tests, which reveal elevated TSH or subnormal thyroxine (T4) levels, depending on the regional newborn screening protocol (19).

2.2 Thyroid imaging: Thyroid imaging, such as thyroid scintigraphy, may be used to differentiate between thyroid dysgenesis and dyshormonogenesis, although it is not always necessary (20). Imaging can provide limited prognostic information but is not essential for diagnosis.

2.3 Distinguishing between permanent and transient CH: Differentiating between permanent CH and transient CH at the time of diagnosis can be challenging. However, several factors can help in this determination:

2.3.1 FT4 levels and levothyroxine dosage: FT4 levels at diagnosis and the dosage of levothyroxine at specific time points, such as the sixth month, first year, and second year, can be indicative of the type of CH. Additionally, the levothyroxine dose during therapy and TSH levels at

diagnosis may also aid in distinguishing between permanent and transient CH (22).

2.3.2 Thyroid Scintigraphy: In cases where an ectopic or agenesis gland is found, thyroid scintigraphy can help determine the presence of permanent hypothyroidism. However, in situations where an ectopic or agenesis gland is not detected, other factors need to be considered for differentiation (22).

2.3.3 Predictive tools: Various predictive tools have been developed to differentiate between transient and permanent CH. Factors such as screening TSH levels, maternal thyroid illness history, and levothyroxine dosage per kilogram can help identify transient CH. For example, a levothyroxine dose of less than 3 µg/kg at ages 1 and 2 years and less than 2.5 µg/kg at age 3 years may be indicative of transient CH (7).

2.3.4 Long-term monitoring: Long-term monitoring of levothyroxine needs and dosage can provide valuable information. For instance, a levothyroxine dose >3.2 µg/kg/day at 24 months is predictive of permanent CH, while a dose of 0.94 µg/kg/day is highly predictive of transient CH in children (23). Monitoring levothyroxine needs during the first years of therapy can also aid in the early differentiation between transient and permanent CH (24).

2.3.5 Increase in levothyroxine dosage: An increase in levothyroxine dosage beyond the age of 3 years is a significant indicator for distinguishing between persistent CH and transient CH, particularly in younger children prior to re-evaluation (25). By considering these factors, healthcare professionals can make more informed assessments to distinguish between permanent and transient CH, allowing for tailored management and treatment approaches.

Mehran et al. identified several factors that can be used as screening methods to predict the likelihood of developing permanent CH. These factors include higher confirmatory venous TSH, lower serum total thyroxine (TT_4), increased levothyroxine dose requirements, venous TSH 10 mU/l at 6 months of age, parental consanguinity, and family history of thyroid disorders (12). Ünüvar et al. found that symptoms present at the time of diagnosis can provide insight into the timing of the event, suggesting whether it occurred during the intrauterine period or early after birth. Lower levothyroxine dose requirements and shorter time for normalization of TSH levels may indicate transient CH (26). Srinivasan et al. determined that the incidence of permanent CH is similar in preterm and term babies. Transient CH can cause severe thyroid dysfunction in preterm infants. Screening techniques using a "once-only" TSH screening with a relatively low cut-off can diagnose both types of hypothyroidism (27). McGrath et al. discovered that delayed TSH rise is common in preterm newborns with CH. Therefore, repeated screening for CH is necessary in preterm infants to avoid missing cases of delayed TSH rise. Screening at different time points, such as 2 weeks and 4 weeks, is recommended to ensure the early detection of hypothyroidism (28).

Ford et al. investigated the incidence of permanent CH and transient CH in infants detected through the first and the second Newborn Screening (NBS) tests. Infants identified on the second NBS had a higher frequency of transient CH, while most newborns identified on the first NBS had permanent CH. The severity of hypothyroidism at the time of diagnosis was similar between the two groups, but those identified on the second NBS were kept on lower levothyroxine doses at the age of 3 years (29). The reasons for the difference in the frequencies of persistent and transient CH between the first and the second NBS screens are not clear.

Krishna Prasad et al. observed a high prevalence of CH in preterm babies, highlighting the need for follow-up venous testing regardless of the results of the first screening. They also found a high prevalence of persistent CH in preterm infants (30). These studies provide valuable insights into factors that can aid in the diagnosis and prediction of permanent CH, particularly in relation to screening methods, symptomatology, and the incidence of CH in different populations.

3. Physiopathology of permanent PCH: The physiopathology of permanent CH is characterized by thyroid dysgenesis as the major cause in iodine-rich countries, accounting for 85% of cases. Thyroid dysgenesis refers to the abnormalities in the embryological development of the thyroid gland. It can manifest as the absence of thyroid tissue (agenesis or athyreosis) in 35-40% of cases or partial absence of thyroid tissue (hypoplasia) in 40-45% of cases. Hypoplasia is often accompanied by the failure of the thyroid to descend into the neck (ectopy). Both boys and girls have similar rates of thyroid dysgenesis (2, 31).

Thyroid dysgenesis, the main cause of permanent CH, has been associated with both genetic and environmental factors. While most cases are sporadic, genetic factors play a role in thyroid dysgenesis. It has been observed that thyroid dysgenesis occurs more frequently in specific ethnic groups, in the children of parents with CH, and in female infants compared to male infants. It is also more common in infants with birth defects and chromosomal abnormalities (2). However, Deladoéy et al. found that the incidence of

thyroid dysgenesis remained constant over a 16-year period, and its monthly variations were random. They also suggested that environmental factors do not significantly impact the development of thyroid dysgenesis (32).

Advanced maternal age is a prevalent epidemiological feature in patients with thyroid dysgenesis, which may increase the likelihood of new mutations in genes involved in thyroid gland development (33). Approximately 2-5% of cases of thyroid dysgenesis have been attributed to loss-of-function mutations in genes involved in the development of thyroid follicular cells, such as *PAX8*, *NKX2.1 (TTF1)*, *FOXE1 (TTF2)*, *and NKX2.5* (34-36). Thyroid ultrasonography is often used as the initial diagnostic step in children suspected of having thyroid dysgenesis. If hypoplasia or aplasia is suggested on ultrasonography, a thyroid scan is needed to further evaluate the possibility of ectopia. The diagnosis of aplasia or ectopia should involve either a thyroid scan or ultrasonography (37).

Dyshormonogenesis, another cause of permanent CH, is typically associated with genetic causes. It is often inherited in an autosomal recessive manner, with mutations in a single gene. Mutations in genes such as *SLC5A5*, *SLC26A4* (*PDS* or *Pendred* gene), *TPO*, *DUOX2*, *DUOXA2*, *TG*, and *DEHAL1* are responsible for dyshormonogenesis (34). Depending on the type of *DUOX2* mutation, CH can manifest as both transient and permanent forms. Dyshormonogenesis caused by these genetic abnormalities is associated with a normally positioned thyroid gland that may be larger at birth. In contrast, most infants with TSH resistance have normal or hypoplastic glands (38, 39). Molecular diagnosis in suspected cases of dyshormonogenesis allows for genetic counseling, identification of asymptomatic mutation carriers at risk of recurrent hypothyroidism, and consideration of adjunct iodide supplementation (40).

3.1 Thyroid hormone biosynthesis: The biosynthesis of thyroid hormone involves several transporter molecules and enzymes synthesized in thyroid follicular cells. The process requires sufficient circulating iodide substrate and thyroglobulin (TG) for iodination. Iodide is taken up from the circulation by the sodium-iodide symporter (NIS, SLC5A5) on the basolateral membrane of thyrocytes. Pendrin (SLC26A4) and anoctamin-1 facilitate the efflux of iodide into the follicular lumen. In the lumen, iodide is oxidized in the presence of hydrogen peroxide (H_2O_2) and integrated into tyrosyl residues on the surface of thyroglobulin, forming monoiodotyrosine (MIT) and diiodotyrosine (DIT). MIT and DIT then join together to produce thyroid hormones T_4 and T_3. After endocytosis is back into the thyroid follicular cells, T_4 and T_3 are cleaved and released into the bloodstream. Thyroid peroxidase (TPO) catalyzes the oxidation of iodide to iodine (I^+) in a H_2O_2-dependent manner. H_2O_2 production is primarily mediated by DUOX2 and DUOXA2 proteins (41). Mutations in any of these essential molecules involved in thyroid hormone production can cause CH (figure.1).

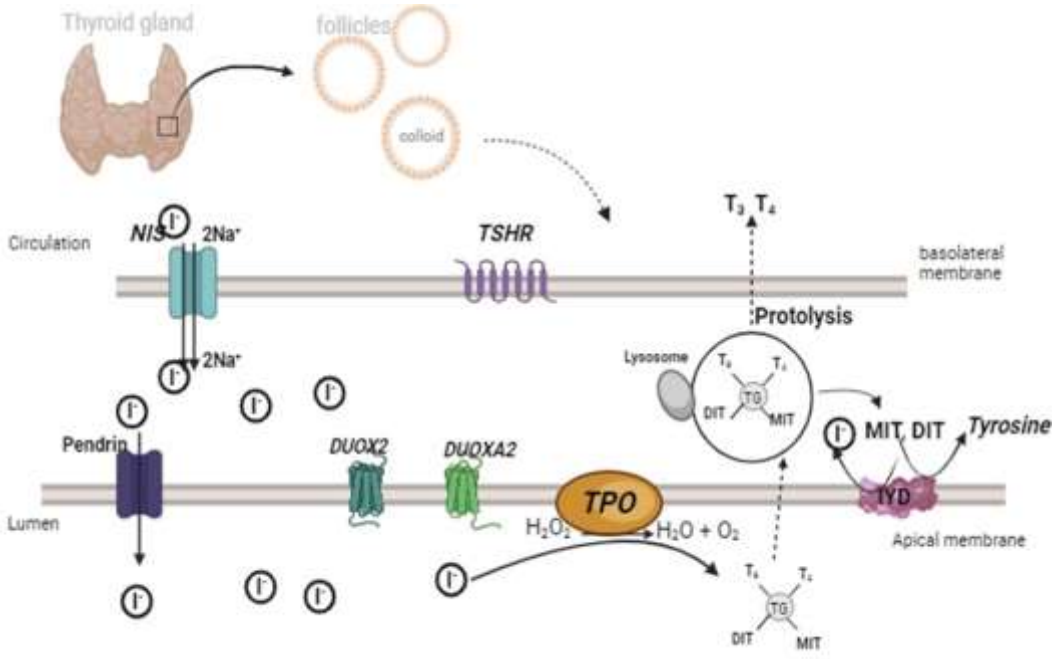

Figure 1. This schematic illustrates the key stages involved in thyroid hormone production. Mutations in components such as TSHR, NIS, Pendrin, TG, TPO, DUOX2, DUOXA2, and IYD can lead to congenital hypothyroidism (CH). Adapted from BioRender.com

2. Risk factors of permanent CH

2.1 Environmental risk factors: Recent studies suggest that there are environmental risk factors that may contribute to the onset and progression of permanent CH, and modifying these factors could potentially help prevent the disease (42, 43). Recent studies have suggested that there are environmental risk factors that may contribute to the onset and progression of permanent CH, and modifying these factors could potentially help prevent the disease (43). Additionally, post-term infants, low birth weight infants, and macrosomic newborns had a significantly higher incidence of permanent CH compared to normal birth weight infants (42). On the other hand, Khazaei et al. did not observe any statistically significant differences in the types of permanent CH and transient CH based on gender, place of birth, delivery method, or time of year of birth (6).

2.2 Genetic cause of permanent CH: The genetic causes of permanent CH are significant, particularly considering the high rate of consanguinity between parents of affected infants (44).

2.2.1 DUOX*2* gene mutations and their association with PCH: *DUOX2* mutations are considered the most prevalent cause of persistent CH with normal-sized or enlarged ectopic thyroid glands (45, 46), and the manifestations caused by *DUOX2* mutations may be milder compared to other factors (47). Mutations in the *TSHR* gene have been identified as a cause of persistent CH due to thyroid gland hypoplasia (39). The functional type of altered genes, rather than the form of mutations, influences the transient or permanent outcome in patients with CH. Individuals with thyroid dysgenesis-related mutations are more likely to experience persistent CH. However, there is no association between mutations and transient or permanent results in individuals with mutant *DUOX2* (48). DUOX2 is an enzyme involved in hydrogen peroxide production, while DUOXA2 is essential for DUOX2 trafficking. Both proteins have functional interactions with TPO at the apical membrane. DUOX1, encoded by the *DUOX1* gene, is a thyroidal NADPH-oxidase that shares similarities with *DUOX2*. However, DUOX2 is considered the dominant isoenzyme in the thyroid. Mutations in *DUOX2* and *DUOXA2* have been implicated in CH, particularly in individuals of East Asian heritage. Furthermore, according to an examination of known CH-associated genes in the gnoMAD population database, *DUOX2* had the greatest prevalence of pathogenic variant carriers (49).

The frequency of pathogenic variants in these genes in apparently healthy populations exceeds the incidence of CH, which may be due to false-negative neonatal screening findings in mutation carriers. It is possible that *DUOX2* and *DUOXA2* mutations predispose individuals to CH in the presence of certain genetic or environmental factors, but they may not be causal in isolation (50). Loss of *DUOX2* activity is associated with severe, persistent CH in murine models and is believed to cause permanent hypothyroidism and slow metabolic rate in giant pandas (51, 52). In humans, the correlation between the number of *DUOX2* mutations and the persistence or transience of CH has yielded mixed findings. CH caused by one or two *DUOX2* mutations is more likely to be subclinical or transient, whereas CH caused by three or more *DUOX2* mutations is more likely to be persistent (53). It is worth noting that patients with thyroid dysgenesis (TD) require increasing doses of levothyroxine supplementation with age, while those with *DUOX2* variations require lower levels (46).

4.2.2 Other genetic factors contributing to PCH: Mutations in other genes involved in thyroid hormone production or thyroid development usually result in persistent CH, albeit in a milder form. This may be because, unlike *DUOX2*, there are no alternate compensatory pathways for specific deficiencies caused by mutations in genes such as *thyroglobulin (TG)* or *thyroid peroxidase (TPO)*. In these cases, transient CH would require an additional reversible factor, such as a temporary iodine deficiency, to unmask the phenotype. *TSH receptor (TSHR)* mutations may lead to compensated hypothyroidism, which is a persistent condition in which TSH production is upregulated and the hypothalamic-pituitary-thyroid axis is "reset" to maintain elevated TSH levels despite normal pituitary sensitivity to circulating thyroid hormones (38).

Conclusions

In conclusion, CH stands as a prevalent childhood endocrine disorder, raising significant health concerns due to its potential impact on neurocognitive development in affected individuals. Early identification through newborn screening remains pivotal for prompt intervention. Physicians must assess the likelihood of permanent or transient hypothyroidism in a child with CH by the age of three or earlier, and subsequently tailor levothyroxine treatment. Given that most CH cases are permanent, lifelong thyroid hormone supplementation becomes a necessity. Vigilant monitoring of the free T4 to total T4 ratio and serum TSH levels assumes importance in appropriately adjusting thyroid hormone replacement dosages. PCH can be detected by screening TSH levels, maternal thyroid disease history, and levothyroxine dosage per kilogram. Although certain genetic factors, such as alterations in the DUOX2 and DUOXA2 genes, and environmental variables

are well-established, predicting PCH based solely on early newborn screening biochemistry or thyroid scintigraphy remains elusive. It is crucial to note that the duration of CH cannot be definitively determined solely based on genetics. In cases where PCH has a genetic influence, ongoing monitoring is advisable to detect potential recurrence of thyroid malfunction, particularly in the context of pregnancy. Furthermore, while the correlation between PCH and mutations in DUOX2 and DUOXA2 is widely acknowledged, further research is imperative to delineate their relative contributions and decipher the underlying causes of the differing incidences of PCH across various geographical regions. As our understanding evolves, continued investigation promises to shed light on the intricate interplay of genetics and environmental factors in the landscape of PCH. This narrative review has synthesized a comprehensive overview of diagnostic options, physiopathology, risk factors, and genetic causes of PCH. The amalgamation of clinical insights and scientific findings underscores the multifaceted nature of this disorder and paves the way for informed clinical management and future research endeavors.

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Authors' contribution: M.O., designed the study; E.A. collected the data; Z.R. wrote the manuscript. All authors reviewed the manuscript and approved.

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