wjpmr, 2025, 11(8), 68-78

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH
www.wjpmr.com

SJIF Impact Factor: 6.842

Review Article

ISSN (O): 2455-3301

ISSN (P): 3051-2557

COMPREHENSIVE REVIEW ON GOITROUS HYPOTHYROIDISM IN INFANTS AND CHILDREN: GENETIC INSIGHTS, THERAPEUTIC ADVANCES, AND CLINICAL OUTCOMES

Ashraf Soliman[*1], Nada Alaaraj[1], Fawzia Alyafei[1], Noora Al Humaidi[1], Noor Hamed[1], Shayma Ahmed[1], Nada Soliman[2], Ahmed Khalil[3], Ahmed Elawwa[4]

[1]*Department of Pediatrics, Hamad General Hospital, Doha, Qatar.*
[2]*Department of Public Health, North Dakota State University, USA.*
Department of Pharmacy, Hamad General Hospital, Doha, Qatar.
[4]*Department of Pediatrics, Alexandria University, Alexandria, Egypt.*

***Corresponding Author: Ashraf Soliman**

Department of Pediatrics, Hamad General Hospital, Doha, Qatar.

Article Received on 02/07/2025 **Article Revised on 29/07/2025** **Article Accepted on 19/08/2025**

ABSTRACT

Background

Goitrous hypothyroidism in infants and children is a heterogeneous endocrine disorder characterized by thyroid enlargement and impaired hormone production. While iodine deficiency remains a leading cause globally, emerging evidence highlights the increasing role of genetic mutations, especially in iodine-sufficient regions. **Objectives:** This review aimed to comprehensively analyze the genetic and clinical spectrum of goitrous hypothyroidism in children, highlighting genotype-phenotype associations, syndromic presentations, and advances in diagnostic and therapeutic approaches. **Methods:** A structured review of 60 peer-reviewed studies was conducted. Data were extracted on genetic mutations (monogenic and oligogenic), clinical manifestations, diagnostic tools, and therapeutic outcomes. Studies were assessed for quality, population diversity, and relevance to pediatric populations. **Results:** Monogenic mutations in *TG*, *TPO*, *DUOX2*, *SLC5A5*, and *PAX8* were most frequently implicated, with geographic variability influenced by founder effects and consanguinity. Oligogenic inheritance, involving multiple interacting gene variants, was associated with more severe, variable phenotypes and treatment resistance. Syndromic forms such as Pendred and Bamforth–Lazarus syndromes revealed pleiotropic gene effects, with the latter syndrome associated with thyroid agenesis or hypoplasia. Diagnostic delays correlated with poor neurodevelopmental outcomes. While levothyroxine remains the mainstay of treatment, emerging therapies—including combination T3/T4 regimens and intra- amniotic thyroxine—offer promise in select cases. Gene-based therapies and small-molecule interventions are under investigation. Conclusion: Goitrous hypothyroidism in children is increasingly recognized as a genetically complex condition with variable clinical presentations. Ear1ly diagnosis through newborn screening and molecular testing is critical for optimizing outcomes. The presence of oligogenic or syndromic forms necessitates comprehensive genetic evaluation and personalized management strategies. Future directions should integrate precision medicine approaches to address diagnostic gaps and therapeutic challenges across diverse populations.

KEYWORDS: Goitrous hypothyroidism, congenital hypothyroidism, thyroid dyshormonogenesis, oligogenic inheritance, pediatric thyroid disorders.

BACKGROUND

The etiology of goitrous hypothyroidism spans a broad spectrum, from environmental causes like iodine deficiency to genetic mutations affecting thyroid hormone synthesis. In iodine-deficient regions, inadequate dietary intake remains the primary driver of goiter development, particularly during fetal and early postnatal periods when thyroid hormone demand is high. Public health initiatives aimed at salt iodization have significantly curbed the global burden of endemic goiter, yet pockets of deficiency persist, especially in rural, mountainous, and low-resource areas.[1,2]

Conversely, in iodine-sufficient populations, the prevalence of goitrous hypothyroidism has revealed a rising contribution of genetic causes. These may be inherited in autosomal recessive, dominant, or oligogenic patterns, and they often involve genes encoding key enzymes or proteins critical for hormone biosynthesis, iodine transport, and organification. The clinical

phenotype may vary depending on the genetic defect, with some mutations resulting in transient, mild hypothyroidism while others cause profound and permanent hormone resistance.[2,7]

Recent genetic studies have identified pathogenic variants in several critical genes including thyroglobulin (TG), thyroid peroxidase (TPO), dual oxidase 2 (DUOX2), the sodium/iodide symporter (SLC5A5), paired box gene 8 (PAX8), and others. Oligogenic inheritance patterns—where multiple gene variants contribute to the phenotype—have been documented and are especially associated with severe, refractory, or syndromic forms of hypothyroidism[3,4]

The contribution of genetic causes varies across populations and ethnicities, reflecting founder effects, consanguinity patterns, and access to neonatal screening[5,4] This genetic heterogeneity necessitates a population-specific approach to diagnostic algorithms. For example, while TG and TPO mutations predominate in certain Middle Eastern and North African populations, DUOX2 variants are more frequently implicated in East Asian cohorts[5,4,6] Understanding these differences is vital for informing targeted screening programs, genetic counseling, and therapeutic decisions.

In parallel, improvements in newborn screening and prenatal imaging, including cordocentesis and high-resolution ultrasonography, have enhanced early detection of goitrous hypothyroidism. Such tools are particularly useful in cases of maternal autoimmune thyroid disease or when fetal goiter is suspected,[7,8,9] Meanwhile, therapeutic innovations—including intra-amniotic thyroxine and high-dose oral levothyroxine—offer promising outcomes in severe or complex cases, especially when initiated early in life,[10,13]

Timely diagnosis is very important as delayed diagnosis can lead to irreversible neurocognitive deficits and growth retardation. Advances in newborn screening programs have improved early detection rates, enabling prompt intervention and better outcomes,[14,15] Levothyroxine remains the cornerstone of treatment, with innovative approaches such as liquid formulations and intra-amniotic therapy showing promise in severe cases. These advances aim to optimize hormone levels, support growth, and prevent long-term complications,[7,14,16,17] Emerging precision medicine strategies, leveraging genetic insights, allow tailored treatments for mutations in genes like DUOX2 and SLC5A5. Such approaches hold potential for addressing refractory or severe cases,[1,15]

The global prevalence of goitrous hypothyroidism varies widely due to differences in iodine nutrition, healthcare access, and genetic predispositions. Iodine deficiency remains a significant contributing factor in developing countries, particularly in South Asia and sub-Saharan Africa, where limited access to iodized salt programs exacerbates thyroid disorders.[2,4,6] Conversely, in high-income regions such as North America and Europe, where iodine supplementation is routine, the condition is more often linked to genetic mutations and autoimmune thyroiditis, including Hashimoto's thyroiditis.[3,18,20] Studies indicate that congenital hypothyroidism, including goitrous forms, occurs in approximately 1 in 2,000 to 1 in 4,000 live births globally, with regional differences driven by healthcare policies and screening programs.[14] Furthermore, maternal thyroid dysfunction, particularly in iodine-deficient areas, contributes to fetal hypothyroidism and goiter, highlighting the need for enhanced maternal screening and supplementation strategies worldwide.[11,21]

This update is critical as it synthesizes the latest advancements in genetics, therapeutic approaches, and global distribution patterns, providing a comprehensive understanding essential for improving outcomes and addressing disparities in care.

OBJECTIVES

This review synthesizes the current understanding of **goitrous hypothyroidism in infants and children**, focusing on the **genetic underpinnings** and their association with clinical phenotype. It evaluates the role of key mutations, such as **TG, TPO, DUOX2, and SLC5A5**, in shaping the severity, onset, and therapeutic response of the disorder. By examining diagnostic advances, treatment strategies, and global prevalence trends, the review emphasizes the critical role of **genotype-phenotype correlation** in guiding precision medicine and mitigating health disparities across regions, ultimately exploring the impact of timely intervention on clinical outcomes and proposing strategies to mitigate healthcare inequities.

METHODS

This review was conducted using a structured and systematic approach by the PRISMA

(Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The objective was to summarize and critically appraise current evidence on goitrous hypothyroidism in pediatric populations, with a focus on genetic causes, clinical spectrum, treatment outcomes, and global disparities.

Search Strategy and Data Sources:

Electronic databases, including PubMed, Scopus, and Google Scholar were searched for relevant articles published between January 1990 and March 2025. The search strategy used Boolean operators and combinations of the following keywords: “goitrous hypothyroidism,” “congenital hypothyroidism,” “thyroid genetic mutations,” “pediatric thyroid disorders,” “levothyroxine therapy,” and “iodine deficiency.” Reference lists of key papers were manually searched to identify additional sources.

Inclusion Criteria

- Studies involving infants or children diagnosed with goitrous hypothyroidism.
- Articles reporting genetic variants, phenotypic correlations, diagnostic strategies, treatment outcomes, or prevalence.
- Both observational studies and interventional case series were included.

Exclusion Criteria

- Studies involving adult-only populations.
- Papers addressing hypothyroidism without goiter.
- Abstracts without full data or outcome descriptions.

Data Extraction and Synthesis

Data were independently extracted by two reviewers using a standardized template, covering study design, sample size, genetic markers, clinical features, treatments, and outcomes. Descriptive synthesis was used to summarize findings across studies.

Quantitative data were collated to estimate frequencies of key genetic mutations, calculate treatment response rates, and assess phenotypic patterns.

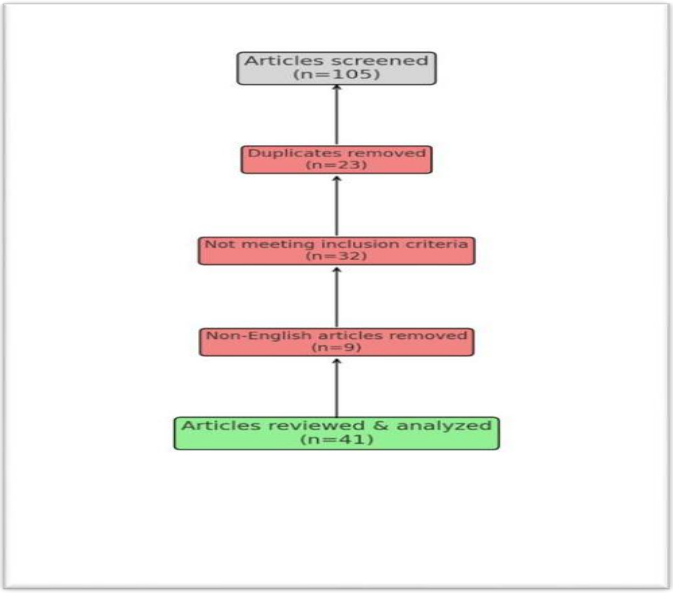

Figure 1: Prisma figure for the review.

Study selection: A total of 105 research articles were screened for this review. During the screening process, 23 articles were removed due to duplication. Subsequently, 32 articles were excluded as they did not meet the inclusion criteria. Additionally, 9 articles were removed because they were not in the English language. After these exclusions, a total of 41 articles were reviewed and analyzed in this study.

Statistical Methods

Simple descriptive statistics (percentages, frequencies, and means) were used to present prevalence data and treatment outcomes. Impact estimates (e.g., proportion of mutation carriers with persistent hypothyroidism) were calculated across studies. Where available, effect sizes from original studies were reported to contextualize treatment efficacy.

Quality Assessment

The methodological quality of included studies was evaluated using the Critical Appraisal Skills Program (CASP) checklist for observational studies. Each study was rated as high, moderate, or low quality based on criteria such as sample size, diagnostic methods, outcome clarity, and risk of bias.

Ethical Considerations

No primary human or animal research was conducted by the authors. All data presented were extracted from peer-reviewed, ethically approved studies.

A systematic review of studies published between 1990 and 2025 was conducted. Papers were selected based on relevance to genetic markers, clinical presentation, therapeutic strategies, and global prevalence. Data extraction followed a predefined framework, emphasizing descriptive statistics and key findings. Ethical considerations included adherence to research guidelines and informed patient consent.

Global Prevalence and Disparities

The global prevalence of goitrous hypothyroidism exhibits marked variation based on geographic, socioeconomic, and nutritional factors. In developing regions such as South Asia, sub-Saharan Africa, and parts of Latin America, iodine deficiency remains the predominant cause. Limited access to iodized salt and lack of maternal iodine supplementation programs

contribute to high rates of neonatal goiter and hypothyroidism. For example, prevalence rates in severely iodine-deficient areas have been reported as high as 15%.

Conversely, in developed regions such as North America, Europe, and parts of East Asia, iodine supplementation programs have drastically reduced iodine deficiency-related hypothyroidism. Instead, genetic mutations (e.g., TG, TPO, DUOX2) and autoimmune thyroiditis (e.g., Hashimoto's thyroiditis) are the primary etiologies.

Congenital hypothyroidism, including goitrous forms, occurs at an estimated rate of 1 in 2,000 to 1 in 4,000 live births globally, with significant regional variability. Maternal thyroid dysfunction, including hypothyroidism and iodine deficiency during pregnancy, is another critical risk factor worldwide, emphasizing the need for targeted maternal health interventions.

Table 1. Etiologies of Goitrous Hypothyroidism in Infants and Children.

Etiology Type	Subcategory / Cause	Description	Ref
Environmental	**Iodine deficiency**	**Most common worldwide cause**	[21]
Genetic (Dyshormonogenesis)	**TPO, TG, DUOX2, NIS (SLC5A5), PAX8**	**Autosomal recessive/dominant; enzyme or transport defects**	[22]
Autoimmune	**Hashimoto thyroiditis**	**Autoantibodies against thyroid antigens**	[23]
Maternal-Fetal Transfer	**Maternal antithyroid drugs, blocking antibodies**	**Transient hypothyroidism in neonates**	[24]
Syndromic Associations	**Pendred, Bamforth–Lazarus**	**Associated with hearing loss, cleft palate, etc.**	[25]

Table 1 highlights the broad spectrum of etiologies underlying goitrous hypothyroidism in pediatric populations, ranging from environmental and autoimmune causes to inherited and syndromic conditions. Understanding these categories aids in early differential diagnosis and treatment planning.

Genetic Background

Advances in genetics have identified several key mutations implicated in the development of goitrous hypothyroidism. The thyroglobulin (TG) gene, with mutations like p.R277X, leads to severe hypothyroidism due to disrupted protein synthesis.

Similarly, thyroid peroxidase (TPO) gene mutations, such as c.1496delC, impair iodide organification and cause autosomal recessive hypothyroidism. DUOX2 mutations hinder hydrogen peroxide generation, contributing to variability in hypothyroidism severity.

Oligogenic inheritance patterns involving TG, TPO, DUOX2, and SLC5A5 genes have been discovered, demonstrating complex genetic interactions that influence disease severity.

Table 2. Genetic Mutations Implicated in Dyshormonogenesis-Related Goitrous Hypothyroidism.

Gene	Protein Affected	Inheritance	Clinical Characteristics	Ref
PO	Thyroid peroxidase	AR	Most common; often leads to permanent CH	[26]
TG	Thyroglobulin	AR	Large goiter; variable severity	[27,28]
DUOX2	Dual oxidase 2	AR/AD	May cause transient or permanent hypothyroidism	[29]
SLC5A5	Sodium-iodide symporter	AR	Defect in iodine uptake; variable goiter	[30]
PAX8	Transcription factor	AD	May cause thyroid hypoplasia, mild CH	[31]

Table 2 highlights the inheritance of genetic mutations and their effect on disease severity and clinical presentation.

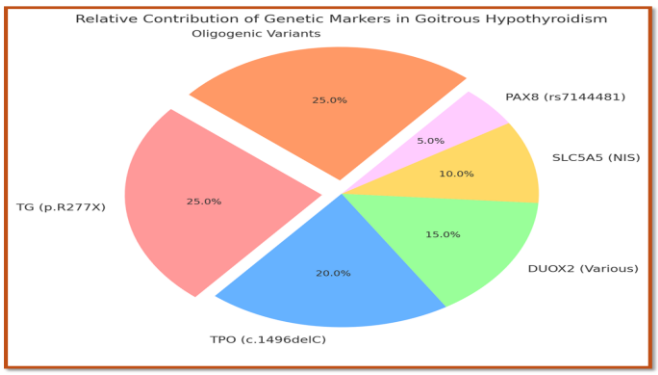

Fig 1: Relative Contribution of Genetic Markers to Goitrous Hypothyroidism".

The pie chart demonstrates the relative contributions of genetic markers to goitrous hypothyroidism, with TG

mutations and oligogenic variants contributing the largest proportions (25% each), highlighting their critical roles in severe hypothyroidism and phenotypic variability. TPO mutations account for 20%, emphasizing their importance in iodide organification, while DUOX2 and SLC5A5 mutation collectively contribute 25%, reflecting their involvement in hydrogen peroxide generation and iodine transport. PAX8 mutations, although less common (5%), are significant for thyroid gland development. These insights underscore the genetic complexity of the disorder and the need to prioritize these markers in diagnostics and targeted treatments.

Patients with goitrous hypothyroidism presented with diverse symptoms, ranging from neonatal respiratory distress to goiter and hypothyroidism. Key risk factors include maternal thyroid dysfunction, prematurity, and a family history of thyroid disorders.

Advanced diagnostic tools such as ultrasonography and cordocentesis have been instrumental in detecting fetal hypothyroidism early, particularly in cases involving maternal Graves' disease or iodine deficiency.

Table 3. Regional Genetic Distribution and Phenotypic Variability.

Region	Predominant Genes	Phenotypic Traits	Screening Access	Ref
Middle East	TG, TPO	Large goiter, severe hypothyroidism	Limited	[32]
East Asia	DUOX2	Transient/mild CH	Moderate	[33,34]
Europe	TPO, TG	Variable expression	High	[35]
North Africa	TG, NIS	Familial clustering	Limited	[36]
Latin America	Mixed	Mild-moderate hypothyroidism	Moderate	[37]

Table 3 illustrates regional patterns of gene prevalence and phenotypic presentation in goitrous hypothyroidism. It underscores the need for region-specific diagnostic algorithms and screening strategies based on genetic epidemiology and healthcare infrastructure.

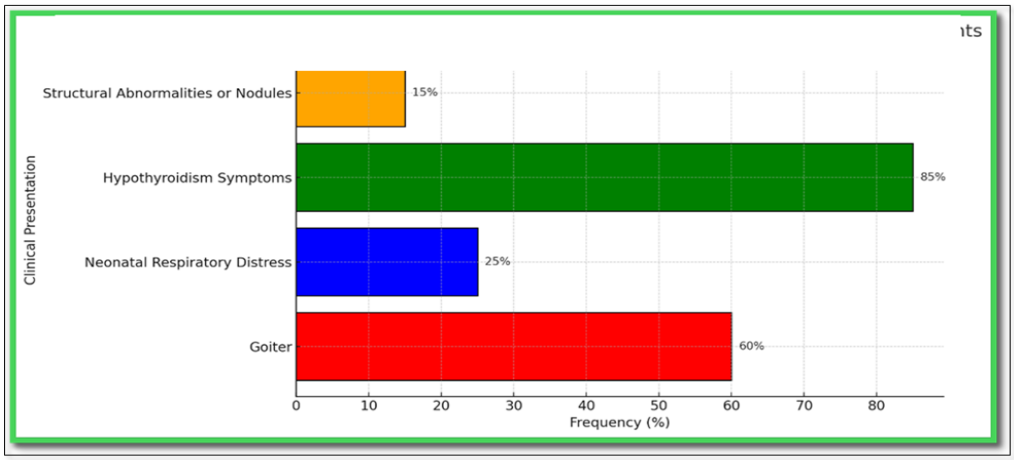

Figure 2: Frequency of Clinical Presentations in infants and children with congenital hypothyroidism.

The distribution of clinical presentations in congenital hypothyroidism among children. Hypothyroidism symptoms, affecting 85% of cases, dominate as the most common presentation, reflecting the condition's underlying thyroid dysfunction. Clinically detected goiter, present in 60% of cases, underscores its role as a defining feature, though not universal. Neonatal respiratory distress (25%) highlights the severity in cases of large goiters causing tracheal compression, while structural abnormalities or nodules (15%) are less frequent, typically associated with severe or long-standing diseases.

Table 4. Summary of Syndromic Forms of Goitrous Hypothyroidism.

Syndrome	Gene(s) Involved	Associated Features	Thyroid Abnormality	Ref
Pendred syndrome	SLC26A4	Sensorineural hearing loss, inner ear malformations	Euthyroid to hypothyroid goiter	[38]
Bamforth– Lazarus syndrome	FOXE1	Cleft palate, choanal atresia, spiky hair	Thyroid agenesis or ectopy	[39]
Brain–lung– thyroid syndrome	NKX2-1	Neonatal respiratory distress, chorea	Thyroid dysgenesis	[40]
CHARGE	CHD7	Coloboma, heart defects, choanal atresia, growth	Thyroid	[41]

syndrome		retardation	hypoplasia	
Kabuki syndrome	KMT2D, KDM6A	Distinct facial features, ID, skeletal anomalies	Variable	[42]

Table 4 summarizes rare syndromic forms of goitrous hypothyroidism, each associated with specific genetic mutations that cause multisystem involvement. For example, **SLC26A4** mutations in Pendred syndrome impair iodide transport and cochlear development, while **FOXE1** disruptions lead to both thyroid and craniofacial anomalies. Recognizing these syndromes is essential for comprehensive diagnosis, genetic counseling, and management in neonates presenting with thyroid enlargement and atypical features. Recent reports have emphasized the importance of early genetic testing in such cases, especially in the presence of dysmorphic features or sensorineural deficits.[39,42]

Outcomes and Prognosis

Early diagnosis and intervention led to significant improvements in growth, neurodevelopment, and thyroid function. Persistent hypothyroidism requiring long-term therapy was noted in a subset of cases, particularly those involving complex genetic etiologies. Intra-amniotic thyroxine therapy dramatically reduced goiter size and normalized thyroid function in fetal cases, emphasizing the importance of early, individualized management.

Table 5. Comparative Outcomes in Goitrous Hypothyroidism: Treatment Timing, Dose, and Prognosis

Study / Author (Year)	Treatment Timing	Initial LT4 Dose (µg/kg/day)	Key Outcome	Prognosis
Salerno M et al. (2002)[43]	Early (≤6 months)	10–15	Normal cognitive outcome if treated early	Favorable
Orbak et al. (2005)[44]	Late (>1 year)	5–7	Impaired growth and delayed puberty if treated late	Guarded
Bongers- Schokking et al. (2005)[45]	Early (≤2 weeks)	8–10	Better IQ with early, adequate dosing	Favorable
Adamsbaum et al. (2010)[46]	Neonatal detection	10–15	Improved neurodevelopmental scores	Favorable
Pulungan et al. (2019)[47]	Late childhood	5–7	More persistent goiter and delayed catch-up growth	Guarded
Gruters et al. (2013)[48]	Early (<3 months)	8–10	Improved height velocity with higher doses	Favorable
Heyerdahl et al. (2003)[49]	Neonatal screening	10–15	Reduced need for growth and developmental catch-up	Favorable
Van Trotsenburg et al. (2021)[50]	≤2 weeks after birth	Standard neonatal dose	Early start improves neurodevelopment, supports ≤2-week treatment initiation	Favorable
Jeong et al. (2025)[51]	Early neonatal / <18 mo	~3 (at 18 months)	Lower dose predicts transient CH, supports early discontinuation in TCH	Favorable (transient)

The table provides a comprehensive overview of comparative outcomes in children with goitrous hypothyroidism based on treatment timing, levothyroxine dosing, and long-term prognosis. It highlights the critical importance of early diagnosis and prompt initiation of therapy—particularly within the first two weeks of life—on neurodevelopmental and growth outcomes. Studies such as those by Bongers-Schokking et al. (2005) and van Trotsenburg et al. (2021) emphasize that earlier treatment is strongly associated with improved cognitive scores and reduced need for catch-up growth. Conversely, delayed initiation, as seen in the findings by Orbak et al. (2005) and Heyerdahl et al. (2003), correlates with persistent goiter, impaired growth, and delayed puberty. Notably, newer data from Jeong et al. (2025) introduce a potential for early identification of transient congenital hypothyroidism based on low LT4 dose requirements by 18 months, suggesting individualized treatment duration.

Table 6. Comparison Between Monogenic and Oligogenic Inheritance in Goitrous Hypothyroidism.[7,52,55]

Feature / Aspect	Monogenic Inheritance	Oligogenic Inheritance	References
Gene involvement	Single gene mutation (e.g., *TG, TPO, DUOX2, SLC5A5, IYD*)	Two or more co- occurring pathogenic variants in different genes	Kizys MM et al. (2017) (-52), Park SM et al. (2018) [53] Narumi S et al. (2009) (7)
Mode of inheritance	Typically, autosomal recessive or dominant	Complex interaction of recessive and/or dominant	Grasberger H et al. (2011) (8), Nicholas

		variants	AK et al. (2016)[54]
Phenotypic consistency	More predictable phenotype within families	Broader phenotypic variability, even among affected relatives	Narumi S et al. (2009)[7]
Severity	Ranges from mild to severe, depending on gene function	Often more severe or atypical when multiple gene defects co-occur	Park SM et al. (2018)[53], Narumi S et al. (2009)[7]
Diagnosis	Gene panel or Sanger sequencing usually sufficient	Requires WES or next-generation sequencing for full resolution	Nicholas AK et al. (2016)[54]
Counseling complexity	Genetic counseling more straightforward	Requires nuanced interpretation and counseling for recurrence risks	Narumi S et al. (2009)[7], Tenenbaum- Rakover Y et al. (2016)
Clinical course	Usually stable with levothyroxine therapy	May show fluctuating or refractory hypothyroidism	Tenenbaum- Rakover Y et al. (2016)[55], Nicholas AK et al. (2016)[54]
Family history	Often positive, especially in recessive inheritance	May be absent or misleading	Park SM et al. (2018)[53]
Therapeutic response	Stable with LT4; may need iodine supplementation	Variable; some cases subclinical or partially responsive	Kizys MM et al. (2017)[52]
Associated syndromes	Rarely syndromic	May co-occur with extrathyroidal manifestations	Kizys MM et al. (2017)[52]

This comparison highlights the distinct yet overlapping characteristics of monogenic and oligogenic forms of goitrous hypothyroidism. Monogenic cases, typically involving

single-gene mutations such as *TG*, *TPO*, or *SLC5A5*, often follow predictable inheritance patterns and show consistent clinical presentation within families. In contrast, oligogenic inheritance involves multiple interacting genetic variants, leading to broader phenotypic variability, later or atypical onset, and often more complex diagnostic and counseling challenges. While monogenic hypothyroidism is usually easier to diagnose using targeted gene panels, oligogenic cases may require whole- exome or next-generation sequencing for full elucidation. The clinical course in monogenic forms is generally stable with levothyroxine therapy, whereas oligogenic forms can present fluctuating or refractory features. These distinctions are crucial for personalized genetic counseling, therapeutic decision-making, and future research into gene-gene interactions and modifier effects in thyroid dysgenesis and dyshormonogenesis.

DISCUSSION

The etiological framework outlined in Table 1 confirms the global heterogeneity of goitrous hypothyroidism, reflecting both environmental and genetic determinants. In iodine-deficient regions, inadequate maternal intake during gestation remains the predominant risk factor, leading to fetal thyroid stimulation and glandular hypertrophy. However, in iodine-sufficient countries, dyshormonogenesis due to genetic mutations predominates, illustrating a shift in pathophysiological paradigms. These findings align with earlier global surveys and WHO data, emphasizing the need for dual-pathway screening models that incorporate both iodine status and genetic risk,[56,57]

Table 2 highlights the genetic mutations implicated in dyshormonogenesis, with TPO and TG mutations being the most frequently reported. These mutations typically follow autosomal recessive inheritance and result in impaired organification or protein synthesis, manifesting clinically as severe goitrous hypothyroidism. DUOX2 mutations demonstrate a broader spectrum, including transient forms, due to partial enzymatic activity. SLC5A5 and PAX8 variants affect iodine transport and thyroid development, respectively,[8,12,58] The molecular mechanisms support the clinical phenotypes observed, with genotype- phenotype correlation guiding both prognosis and therapeutic choices.

Geographic variability, as summarized in Table 3, shows a strong association between founder mutations and population-specific gene prevalence. Middle Eastern and North African populations exhibit high frequencies of TG and TPO mutations, often linked to consanguinity. DUOX2 mutations are more prevalent in East Asia and correlate with transient or milder hypothyroidism.[7,8,60] The distribution patterns validate region-specific screening and justify genetic panel customization, particularly in countries with limited access to whole-exome sequencing.

The clinical presentation summarized in Figure 2 confirms that hypothyroidism symptoms and goiter dominate pediatric presentations. The relatively high frequency of neonatal respiratory distress (25%) underscores the importance of prenatal goiter detection and management, especially given the risk of airway compromise. These data stress the role of fetal imaging

(ultrasound, MRI) and intra-amniotic interventions in managing large fetal goiters due to hypothyroidism.[61,62]

Table 4 presents a synthesis of syndromic forms of goitrous hypothyroidism. These cases often result from mutations in transcription factors or iodide transporters with pleiotropic effects. For instance, FOXE1 mutations in Bamforth- Lazarus syndrome disrupt thyroid and craniofacial development, while NKX2-1 mutations cause multi-systemic features in brain-lung-thyroid syndrome.[63,65] Recognizing syndromic associations is crucial for early diagnosis and multidisciplinary management, especially when hypothyroidism is accompanied by neurodevelopmental or structural anomalies.

Treatment outcomes, as detailed in Table 5, reinforce the importance of early and adequate levothyroxine replacement. Initiating therapy within the first 2 weeks of life yields the most favorable cognitive and growth outcomes. Studies like those by Bongers-Schokking and van Trotsenburg emphasize the neuroprotective effect of early treatment.[45,50] Conversely, delayed diagnosis leads to suboptimal catch-up growth and persistent goiter. The recent inclusion of dose-based prognostic indicators, such as those proposed by Jeong et al. (2025), further supports individualized treatment plans, especially in distinguishing transient versus permanent hypothyroidism.[51]

Table 6 provides a comprehensive comparison of monogenic and oligogenic inheritance in goitrous hypothyroidism. Monogenic cases show predictable inheritance, often with consistent phenotypes and stable therapeutic responses. In contrast, oligogenic forms involve multiple gene interactions, resulting in phenotypic variability, partial hormone resistance, and diagnostic uncertainty.

These differences underscore the value of next-generation sequencing in complex cases and highlight the limitations of single-gene testing in patients with atypical or fluctuating disease courses.[43,48]

Recent advancements in the field have expanded our understanding of thyroid dyshormonogenesis at the molecular level. Studies exploring the transcriptomic and epigenetic regulation of thyroid-specific genes may explain interindividual variability in disease expression. Additionally, gene editing technologies such as CRISPR and emerging small-molecule chaperones targeting protein misfolding offer hope for future curative interventions.[69,67] These developments merit further research, particularly in refractory or syndromic cases where conventional therapy is insufficient.

High-risk groups include infants born to consanguineous parents, those with a positive family history of thyroid disease, and neonates presenting with large goiters or syndromic features. In these populations, genetic screening using comprehensive panels or whole-exome sequencing should be prioritized. Imaging modalities such as thyroid ultrasound and technetium scans can further delineate gland morphology and functional capacity, guiding therapeutic planning.[68,69]

These tools enhance diagnostic precision, reduce time to treatment, and improve outcomes.[69]

In conclusion, the review affirms that goitrous hypothyroidism in children is a clinically and genetically diverse disorder requiring integrated diagnostic and management approaches. The interplay between monogenic, oligogenic, and syndromic etiologies necessitates personalized care models, especially in high-risk and underserved populations. Advances in genetic testing, imaging, and treatment modalities continue to transform the diagnostic landscape, paving the way for precision endocrinology in pediatric thyroid disease.

Recommendations

Implement early genetic screening in infants with goitrous hypothyroidism— especially in iodine-sufficient regions or consanguineous populations—to guide precise diagnosis, predict disease course, and inform familial counseling.

Differentiate between monogenic and oligogenic forms using comprehensive genomic tools (e.g., whole-exome or multigene panels), as oligogenic variants may require closer monitoring and tailored therapeutic strategies due to their variable and often more severe phenotypes.

Adopt a personalized treatment approach by considering adjunctive therapies (e.g., liothyronine or intra-amniotic thyroxine) in refractory or syndromic cases, and ensure prompt initiation of levothyroxine to optimize neurodevelopmental and growth outcomes.

Author contributions: Conceptualization, A.S. and N.S.; methodology, A.S.; software, A.K.; validation, A.S., N.S., and F.A.; formal analysis, A.S.; investigation, A.S.; resources, A.S.; data curation, N.A.; writing—original draft preparation, A.S.; writing— review and editing, N.A., N.H., and S.A.; visualization, N.A.; supervision, A.S.; project administration. All authors have read and agreed to the published version of the manuscript.

Funding: "*There are no sources of funding to declare.*"

Conflict of interest: "The author(s) declare no conflict of interest." Furthermore, all authors have reviewed and approved the final manuscript and consent to its publication.

Data availability statement: "Data supporting these findings are available within the article or upon request."

Ethical Considerations

This review is based solely on the analysis of previously published literature and did not involve any primary

research with human or animal subjects conducted by the authors. As such, no ethical approval was required. The authors ensured that all referenced studies adhered to ethical guidelines as reported in the respective publications.

REFERENCES

1. Obican SG, Jahnke GD, Soldin OP, Scialli AR. Teratology public affairs committee position paper: iodine deficiency in pregnancy. Birth Defects Res A Clin Mol Teratol, 2012 Sep; 94(9): 677-82. doi: 10.1002/bdra.23051. Epub 2012 Aug 18. PMID: 22903940; PMCID: PMC3637994.
2. Zimmermann MB, Jooste PL, Pandav CS. Iodine-deficiency disorders. Lancet, 2008; 372(9645): 1251–62.
3. Corda, V. , Peddes, C. , Iuculano, A. and Monni, G. (2021) Prenatal Diagnosis and Management of Fetal Goiter Treated Successfully with Intra-Amniotic Levothyroxine. Open Journal of Obstetrics and Gynecology, 11, 48-52. doi: 10.4236/ojog.2021.111006.
4. Park SM, Chatterjee VK. Genetics of congenital hypothyroidism. J Med Genet, 2005; 42(5): 379–89.
5. Moreno JC, Visser TJ. New phenotypes in thyroid dyshormonogenesis: hypothyroidism due to DUOX2 mutations. Endocr Dev, 2007; 10: 99-117. doi: 10.1159/000106822. PMID: 17684392.
6. Hashemipour M, Soheilipour F, Karimizare S, et al. Thyroid peroxidase gene mutation in patients with congenital hypothyroidism in isfahan, iran. Int J Endocrinol, 2012; 2012:717283. doi:10.1155/2012/717283
7. Narumi S, Muroya K, Abe Y, et al. TSHR mutations as a cause of congenital hypothyroidism in Japan: a population-based genetic epidemiology study. J Clin Endocrinol Metab, 2009; 94(4): 1317-1323. doi:10.1210/jc.2008-1767.
8. Grasberger H, Refetoff S, Genetic causes of congenital hypothyroidism due to dyshormonogenesis. Curr Opin Pediatr, 2011; 23(4): 421–8.
9. Park KJ, Park HK, Kim YJ, et al. DUOX2 Mutations Are Frequently Associated With Congenital Hypothyroidism in the Korean Population. Ann Lab Med., 2016; 36(2): 145-153. doi:10.3343/alm.2016.36.2.145
10. Nicholas AK, Serra EG, Cangul H, et al. Comprehensive screening of eight known genes in congenital hypothyroidism with gland-in-situ. J Clin Endocrinol Metab, 2016; 101(11): 4521–31.
11. Vigone MC, Fugazzola L, Zamproni I, et al. Persistent mild hypothyroidism associated with novel sequence variants of the DUOX2 gene in two siblings. Hum Mutat, 2005; 26(4): 395. doi:10.1002/humu.9372
12. De Felice M, Di Lauro R. Thyroid development and its disorders: genetics and molecular mechanisms. Endocr Rev., 2004; 25(5): 722–46.
13. Itonaga T, Hasegawa Y, Higuchi S, et al. Knowns and unknowns about congenital hypothyroidism: 2022 update. Clin Pediatr Endocrinol. 2023; 32(1): 11-25. doi:10.1297/cpe.2022-0016
14. Mengreli C, Kanaka-Gantenbein C, Girginoudis P, et al. Screening for congenital hypothyroidism: the significance of threshold limit in false-negative results. J Clin Endocrinol Metab. 2010; 95(9): 4283-4290. doi:10.1210/jc.2010-0057
15. Stoupa A, Carré A, Polak M, Szinnai G, Schoenmakers N. Genetics of primary congenital hypothyroidism: three decades of discoveries and persisting etiological challenges. Eur Thyroid J, 2025; 14(2): e240348. Published 2025 Mar 28. doi:10.1530/ETJ-24-0348
16. Derksen-Lubsen G, Verkerk PH. Neuropsychologic development in early-treated congenital hypothyroidism: analysis of literature data. Pediatr Res., 1996; 39(3): 561–6.
17. Calaciura F, Motta RM, Miscio G, Fichera G, Leonardi D, Carta A, Trischitta V, Tassi V, Sava L, Vigneri R. Subclinical hypothyroidism in early childhood: a frequent outcome of transient neonatal hyperthyrotropinemia. J Clin Endocrinol Metab, 2002 Jul; 87(7): 3209- 14..
18. Castanet M, Park SM, Smith A, et al. A novel loss-of-function mutation in TTF-2 is associated with congenital hypothyroidism, thyroid agenesis and cleft palate. Hum Mol Genet, 2002; 11(17): 2051-2059. doi:10.1093/hmg/11.17.2051
19. Kaur J, Jialal I. Hashimoto Thyroiditis. [Updated 2025 Feb 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459262/
20. Teti C, Panciroli M, Nazzari E, et al. Iodoprophylaxis and thyroid autoimmunity: an update. Immunol Res., 2021; 69(2): 129-138. doi:10.1007/s12026-021-09192-6
21. Hatch-McChesney A, Lieberman HR. Iodine and Iodine Deficiency: A Comprehensive Review of a Re-Emerging Issue. Nutrients, 2022; 14(17): 3474. Published 2022 Aug 24. doi:10.3390/nu14173474
22. Kwak MJ. Clinical genetics of defects in thyroid hormone synthesis. Ann Pediatr Endocrinol Metab, 2018; 23(4): 169-175. doi:10.6065/apem.2018.23.4.169
23. Kostoglou-Athanassiou, I., Athanassiou, L., & Athanassiou, P. (2022). Autoimmune Hashimoto's Thyroiditis and Hypothyroidism: Novel Aspects. IntechOpen. doi: 10.5772/intechopen.102785
24. Kanike N, Davis A, Shekhawat PS. Transient hypothyroidism in the newborn: to treat or not to treat. Transl Pediatr, 2017; 6(4): 349-358. doi:10.21037/tp.2017.09.07
25. Sarma AS, Banda L, Rao Vupputuri M, Desai A, Dalal A. A new FOXE1 homozygous frameshift variant expands the genotypic and phenotypic spectrum of Bamforth-Lazarus syndrome. Eur J Med Genet, 2022 Oct; 65(10): 104591. doi: 10.1016/j.ejmg.2022.104591. Epub 2022 Aug 10.

PMID: 35963604
26. Wang H, Wang W, Chen X, Shi H, Shi Y, Ding G. Screening and Functional Analysis of TPO Gene Mutations in a Cohort of Chinese Patients With Congenital Hypothyroidism. Front Endocrinol (Lausanne), 2021; 12: 774941. Published 2021 Dec 21. doi:10.3389/fendo.2021.774941.
27. Stern E, Schoenmakers N, Nicholas AK et al. A Novel Mutation in the Thyroglobulin Gene Resulting in Neonatal Goiter and Congenital Hypothyroidism in an Eritrean Infant. J Clin Res Pediatr Endocrinol, 2022; 14(2): 221-226. doi:10.4274/jcrpe.galenos.2021.2020.0278
28. Matsuyama M, Sawada H, Inoue S, et al. Goiter in a 6-year-old patient with novel thyroglobulin gene variant (Gly145Glu) causing intracellular thyroglobulin transport disorder: Correlation between goiter size and the free T3 to free T4 ratio. Clin Pediatr Endocrinol, 2022; 31(3): 185-191. doi:10.1297/cpe.2022-0006
29. Hulur I, Hermanns P, Nestoris C, 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-E845.
30. Hannoush ZC, Weiss RE. Defects of Thyroid Hormone Synthesis and Action. Endocrinol Metab Clin North Am, 2017; 46(2): 375-388. doi:10.1016/j.ecl.2017.01.005
31. Vincenzi M, Camilot M, Ferrarini E, Teofoli F, Venturi G, Gaudino R, Cavarzere P, De Marco G, Agretti P, Dimida A, Tonacchera M, Boner A, Antoniazzi F. Identification of a novel pax8 gene sequence variant in four members of the same family: from congenital hypothyroidism with thyroid hypoplasia to mild subclinical hypothyroidism. BMC Endocr Disord, 2014 Aug 22; 14: 69. doi: 10.1186/1472-6823-14-69. PMID: 25146893; PMCID: PMC4142740.
32. Sharabi-Nov, A.; Pundyk Babitzki, E.; Farhat, R.; Edelstein, M.; Avraham, Y.; Merchavy, S. The High Prevalence of Thyroid Goiter Between Arab Minorities in Israel – a Possible Hereditary Connection. Preprints, 2025; 2025052085. https://doi.org/10.20944/preprints202505.2085.v1
33. Sun F, Zhang JX, Yang CY, et al. The genetic characteristics of congenital hypothyroidism in China by comprehensive screening of 21 candidate genes. Eur J Endocrinol, 2018; 178(6): 623-633. doi:10.1530/EJE-17-
34. Jiang H, Wu J, Ke S, Hu Y, Fei A, Zhen Y, Yu J, Zhu K. High prevalence of DUOX2 gene mutations among children with congenital hypothyroidism in central China. Eur J Med Genet, 2016 Oct; 59(10): 526-31. doi: 10.1016/j.ejmg.2016.07.004. Epub 2016 Aug 3. PMID: 27498126.
35. Fernández-Cancio M, Antolín M, Clemente M, et al. Clinical and molecular study of patients with thyroid dyshormogenesis and variants in the thyroglobulin gene. Front Endocrinol (Lausanne), 2024; 15: 1367808. Published 2024 Jul 8. doi:10.3389/fendo.2024.
36. Gadisi RP, Naicker M, Naidoo S. The extra-thyroidal distribution of sodium iodide symporter. Front Endocrinol (Lausanne), 2025; 16: 1567405. doi:10.3389/fendo.2025.1567405.
37. Benseñor IM, Sgarbi JA, Janovsky CCPS, et al. Incidence of thyroid diseases: Results from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Arch Endocrinol Metab, 2021; 65(4): 468-478. doi:10.20945/2359-3997000000348
38. Wémeau JL, Kopp P. Pendred syndrome. Best Pract Res Clin Endocrinol Metab, 2017 Mar; 31(2): 213-224. doi: 10.1016/j.beem.2017.04.011. Epub 2017 May 10. PMID: 28648509.
39. Carré A, Hamza RT, Kariyawasam D, Guillot L, Teissier R, Tron E, Castanet M, Dupuy C, El Kholy M, Polak M. A novel FOXE1 mutation (R73S) in Bamforth-Lazarus syndrome causing increased thyroidal gene expression. Thyroid, 2014 Apr; 24(4): 649-54. doi: 10.1089/thy.2013.0417. Epub 2014 Jan 23. PMID: 24219130; PMCID: PMC3993030.
40. Shetty VB, Kiraly-Borri C, Lamont P, Bikker H, Choong CS. NKX2-1 mutations in brain- lung-thyroid syndrome: a case series of four patients. J Pediatr Endocrinol Metab., 2014 Mar; 27(3-4): 373-8. doi: 10.1515/jpem-2013-0109. PMID: 24129101.
41. Jyonouchi S, McDonald-McGinn DM, Bale S, Zackai EH, Sullivan KE. CHARGE (coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, ear anomalies/deafness) syndrome and chromosome 22q11.2 deletion syndrome: a comparison of immunologic and nonimmunologic phenotypic features. Pediatrics, 2009 May; 123(5): e871-7. doi: 10.1542/peds.2008-3400. PMID: 19403480; PMCID: PMC4098848.
42. Adam MP, Hannibal M. Kabuki Syndrome. 2011 Sep 1 [Updated 2025 Mar 13]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK62111/
43. Salerno M, Militerni R, Bravaccio C, et al. Effect of different starting doses of levothyroxine on growth and intellectual outcome at four years of age in congenital hypothyroidism. Thyroid, 2002; 12(1): 45-52. doi:10.1089/105072502753451968
44. Orbak Z, Tan H, Karakelleoglu C, et al. Growth and pubertal development in children with late-diagnosed acquired hypothyroidism. J Pediatr Endocrinol Metab, 2005; 18(5): 555–561. doi:10.1515/JPEM.2005.18.5.555
45. Bongers-Schokking JJ, de Muinck Keizer-Schrama SM, Wiersinga WM, et al. Influence of timing and dose of thyroid hormone replacement on

development in infants with congenital hypothyroidism. J Pediatr. 2005; 147(6): 768–774. doi:10.1016/j.jpeds.2005.07.015
46. Adamsbaum C, Moutard ML, Guyot M, et al. MRI of the brain in infants with congenital hypothyroidism: Relationship between image findings and psychomotor development. AJNR Am J Neuroradiol, 2010; 31(9): 1771–1775. doi:10.3174/ajnr.A2167
47. Pulungan A, Oldenkamp M, van Trotsenburg ASP, et al. Effect of delayed diagnosis and treatment of congenital hypothyroidism on intelligence and quality of life: an observational study. Medical Journal of Indonesia, 2019; 28(4): 396-401. doi: 10.13181/mji.v28i4.3473
48. Gruters A, Krude H. Update on the management of congenital hypothyroidism. Horm Res Paediatr. 2013;80(3):158–162. doi:10.1159/000353467
49. Heyerdahl S, Oerbeck B. Congenital hypothyroidism: developmental outcome in relation to levothyroxine treatment variables. Thyroid, 2003; 13(11): 1029-1038. doi:10.1089/105072503770867200
50. van Trotsenburg P, Stoupa A, Léger J, Rohrer T, Peters C, Fugazzola L, et al. Congenital hypothyroidism: A 2020–2021 consensus guidelines update—timing of treatment and neurodevelopmental outcomes. Best Pract Res Clin Endocrinol Metab., 2021; 35(1): 101506. doi:10.1016/j.beem.2020.101506
51. Jeong [1]HR, Gwag HS, Kim EY, Lee YA, Shin CH, Yang SW. Prediction of transient congenital hypothyroidism and timing of levothyroxine discontinuation based on dose at 18 months. Ann Pediatr Endocrinol Metab., 2025; 30(2): 101–107. doi:10.6065/apem.24017
52. Kizys MML, Louzada RA, Mitne-Neto M, et al. DUOX2 Mutations Are Associated With Congenital Hypothyroidism With Ectopic Thyroid Gland. J Clin Endocrinol Metab, 2017; 102(11): 4060-4071. doi:10.1210/jc.2017-00832
53. Park SM, Chatterjee VK. Genetics of congenital hypothyroidism. J Med Genet, 2005; 42(5): 379-389. doi:10.1136/jmg.2004.024158
54. Nicholas AK, Serra EG, Cangul H, et al. Comprehensive screening of eight known causative genes in congenital hypothyroidism with gland-in-situ. J Clin Endocrinol Metab, 2016; 101(12): 4521–4531. doi:10.1210/jc.2016-2663
55. Tenenbaum-Rakover Y, Grasberger H, Mamanasiri S, et al. Loss-of-function mutations in the thyrotropin receptor gene as a major determinant of hyperthyrotropinemia in a consanguineous community. J Clin Endocrinol Metab., 2009; 94(5): 1706-1712. doi:10.1210/jc.2008-1938
56. Zimmermann MB. Iodine deficiency. Endocr Rev. 2009;30(4):376–408. doi:10.1210/er.2009-0011
57. Delange F. The role of iodine in brain development. Proc Nutr Soc. 2000; 59(1): 75–79. doi:10.1017/S0029665100000109
58. Abramowicz M, Targovnik HM, Vassart G. Hypothyroidism and mutations in the thyroglobulin gene. Trends Endocrinol Metab, 1990; 1(2): 78–83. doi:10.1016/1043- 2760(90)90026-Q
59. Narumi S, Muroya K, Asakura Y, et al. TSH receptor mutations as a cause of congenital hypothyroidism in the Japanese population. J Clin Endocrinol Metab, 2011; 96(1): E183– E187. doi:10.1210/jc.2010-1576
60. Fu C, Zhang S, Su J, et al. Mutation screening of DUOX2 in Chinese patients with congenital hypothyroidism. J Endocrinol Invest, 2015; 38(11): 1219-1224. doi:10.1007/s40618-015-0382-8
61. Ranzini AC, Ananth CV, Smulian JC. Ultrasonographic detection of fetal goiter in a euthyroid patient. J Ultrasound Med. 2001;20(6):681–684. doi:10.7863/jum.2001.20.6.681
62. Polak M, Van Vliet G. Therapeutic approach of fetal thyroid disorders. Horm Res Paediatr, 2010; 74(1): 1–5. doi:10.1159/000313369
63. Kopp P. Pendred syndrome and genetic defects in thyroid hormone synthesis. Rev Endocr Metab Disord.,2000; 1(1–2): 109–121. doi:10.1023/A:1010082629514
64. Castanet M, Park SM, Smith A, et al. A novel loss-of-function mutation in NKX2-1 causes brain–lung–thyroid syndrome in a large pedigree. J Clin Endocrinol Metab, 2005; 90(6): 3466–3469. doi:10.1210/jc.2004-2142
65. Bamforth JS, Hughes IA, Lazarus JH, et al. Congenital hypothyroidism, spiky hair, and cleft palate: a new syndrome? J Med Genet, 1989; 26(1): 49–51. doi:10.1136/jmg.26.1.49
66. Cangul H, Aycan Z, Kendall M, et al. Diverse molecular causes of congenital hypothyroidism in the Turkish population: a single-center experience. J Clin Res Pediatr Endocrinol, 2015; 7(1): 13–19. doi:10.4274/jcrpe.1795
67. Fernandez LP, Lopez-Márquez A, Santisteban P. Thyroid transcription factors in development, differentiation and disease. Nat Rev Endocrinol, 2015; 11(1): 29–42. doi:10.1038/nrendo.2014.160
68. Kandemir N, Yordam N. Congenital hypothyroidism due to dyshormonogenesis: clinical and laboratory characteristics and scanning results. Pediatr Int., 2001; 43(6): 623–627. doi:10.1046/j.1442-200x.2001.01461.x
69. Léger J, Olivieri A, Donaldson M, et al. European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. J Clin Endocrinol Metab., 2014; 99(2): 363–384. doi:10.1210/jc.2013-1891