Genetic Landscape of Congenital Hypothyroidism in Bangladesh: Implications for Personalized Therapeutics

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ABSTRACT

Congenital hypothyroidism (CH) is the most common neonatal endocrine disorder and a leading preventable cause of intellectual disability if not diagnosed and treated early. In Bangladesh, neonatal screening for CH was initiated in 1999 with support from the International Atomic Energy Agency using radioimmunoassay-based thyroid-stimulating hormone (TSH) measurement. Recent national data indicate an increasing incidence, highlighting the growing public health importance of CH in the country.

This review explores the genetic landscape of CH in Bangladesh and its implications for diagnosis and personalized therapeutics. CH is genetically heterogeneous, broadly classified into thyroid dysgenesis and dyshormonogenesis. Mutations in genes such as TSHR, PAX8, NKX2-1, and FOXE1 are associated with thyroid dysgenesis, while defects in TPO, TG, DUOX2, and SLC5A5 underlie dyshormonogenesis. Available studies from Bangladesh, though limited, reveal a predominance of TPO gene mutations, indicating dyshormonogenesis as a significant contributor. Additional mutations in TSHR and NKX2.5 genes further highlight genetic diversity and complexity.

Integrating genetic screening into neonatal CH programs in Bangladesh is essential for improving etiological diagnosis, enabling personalized treatment, and reducing healthcare burden. Strengthening national genomic research and screening strategies will be critical to advancing precision medicine in CH management.

Keywords: Congenital hypothyroidism, genetics, Bangladesh, personalized therapeutics, dyshormonogenesis, thyroid dysgenesis, neonatal screening

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INTRODUCTION

Thyroid hormones are crucial for standard growth and neurological progress during early life. Congenital hypothyroidism (CH) is the most common neonatal endocrine disease that can lead to severe neurodevelopmental impairment if not detected through newborn screening and ensure early treatment to prevent intellectual disability.

Neonatal screening for CH in Bangladesh began in 1999 through a regional project supported by the International Atomic Energy Agency (IAEA), using a cost-effective radioimmunoassay (RIA) method to measure thyroid-stimulating hormone (TSH). The initial estimated prevalence was approximately 1 in 2,000 newborns (1). Subsequently, a government-approved national screening program reported a higher incidence of 1 in 1,825 births between July 2018 and June 2022, based on screening around 500,000 newborns, suggesting an increasing trend (2).

CH has been broadly classified into two forms: 1) dysfunction of the hypothalamic–pituitary–thyroid (HPT) axis present at birth, resulting in insufficient thyroid hormone production or reduced function (dyshormonogenesis); and 2) thyroid dysgenesis (TD), characterized by a defect in thyroid gland development, which accounts for approximately 85% of cases (3, 4).

However, recent advances in molecular techniques have greatly enhanced our understanding of the effect of single-gene mutations and multiple-gene polymorphisms in CH pathogenesis. Global ongoing research into the genetic origin of CH is continually revealing new regulatory pathways, suggesting that a substantial proportion of primary congenital hypothyroidism may result from the combined effect of rare variants across multiple genes involved in thyroid development and function (5, 6). The ENDO-European Reference Network (ERN) initiative 2020-2021 consensus guidelines on CH recommend genetic testing to improve diagnosis, treatment, or prognosis of the patients (3).

Bangladesh lacks a comprehensive genetic characterization of CH and screening status. It is inevitable to investigate the genetic etiology of CH and thereby evaluate the impact of genetic testing on the management and prognosis of patients with CH. Few studies have been conducted to find

the genetic mutation in diagnosed CH patients attending tertiary hospitals. This systematic review summarizes published evidence on genetic causes of CH in Bangladesh and explores the priorities for genetic screening as diagnostic practices and clinical application to improve management of CH.

GENETIC MECHANISMS UNDERLYING CONGENITAL HYPOTHYROIDISM

CH is a genetically heterogeneous disorder. Numerous genetic mutations have been identified that disrupts cell signaling pathways affecting thyroid gland development, hormone synthesis, or regulation of the hypothalamic–pituitary–thyroid (HPT) axis (Figure 1). Key genes associated with thyroid dysgenesis include the thyroid-stimulating hormone receptor (TSHR) and thyroid-specific transcription factors expressed during early thyroid development, such as PAX8, NKX2–1, FOXE1, and others (7). Whereas several genes are implicated in the dyshormonogenesis, including thyroglobulin (TG), TSH receptor (TSHR), thyroperoxidase (TPO), sodium/chloride symporter (SLC5A5), dual oxidase 2 (DUOX2), membrane transporters pendrin (SLC26A4), monocarboxylate transporter 8 (SLC16A2), and dehalogenase (DEHAL1/IYD) (8). This group includes inherited defects in the biochemical steps required for thyroid hormone production. Mutations impair iodine uptake, organification, coupling, or hormone release, resulting in reduced thyroid hormone synthesis despite a structurally normal gland (9).

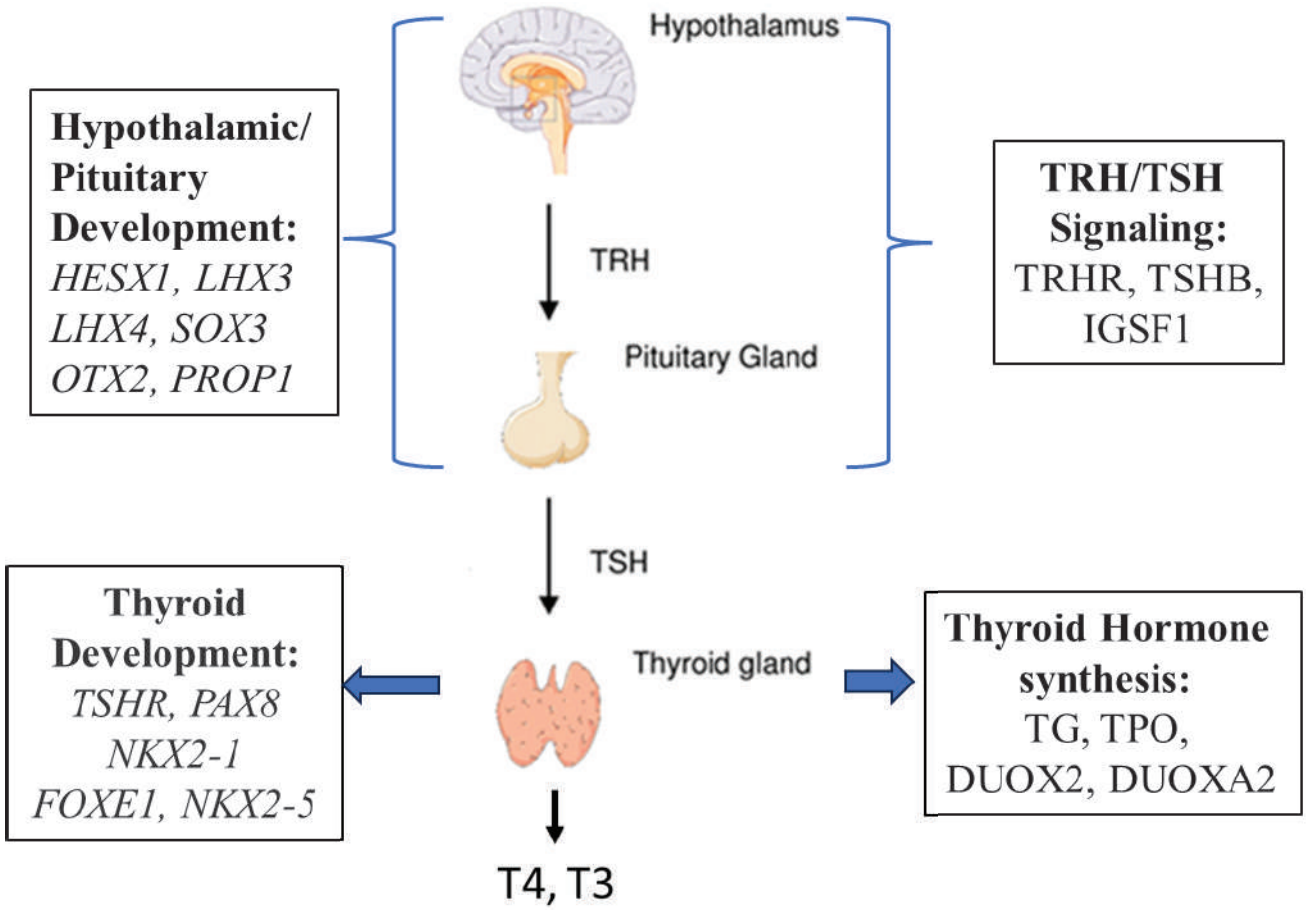

Figure 1: Genetic involvement with congenital hypothyroidism. TRH- Thyrotropin releasing hormone; TSH-Thyroid stimulating hormone; T4- Thyroxine; T3-Triiodothyronine

GENETIC STUDIES FOR CONGENITAL HYPO-THYROIDISM IN BANGLADESH

The present systematic review has summarized available genetic investigations for CH in Bangladesh to show the frequencies of the common mutagenic trend in CH (Table 1). Although there is limited data, the studies include both thyroid dysgenesis (TD) and dyshormonogenesis (TDH).

Patient type	Patient no.	Gene studied	Mutation identified	Reference
Dyshormon ogenesis	36	TPO Gene	Four mutations: three nonsynonymous c.1117G>T (p.Ala373Ser), c.1193G>C (p.Ser398Thr), c.2173A>C (p.Thr725Pro), and one synonymous c.2145C>T (p.Pro715Pro).	Begum et al., 2019 (10)
Dysgenesis	40	NKX2.5	Nucleotide substitutions (c.1051G>T) in 9, deletions (c.1143 delT-) in 8, and both substitution and deletion in 4 patients	Khatun et al., 2020 (11)
Dysgenesis	01 (case study)	Thyroid transcription factor 2	Exon2; Nucleotide substitution (c.1051G>T)	Khatun et al., 2021 (12)
Dysgenesis	21	TSHR	Exon10: Two nonsynonymous mutations (p.Ser508Leu, p.Glu727Asp).	Begum et al., 2023 (13)
Dyshormon ogenesis (n=19); Dysgenesis (n=08)	27	TPO, TSHR, PAX8	TPO: four mutations- c.1117G>T, c.1193G>C, c.2145 C>T, and c.2173A>C TSHR: three mutations- c.2181G>C, c.2161G>C, and c.1523C>T. PAX8: no mutation in exon 3	Konika et al., 2024 (14)
Dyshormon ogenesis	36	TPO	Non-synonymous mutations c.1117G>T, c.1193G>C, and c.2173A>C	Begum et al., 2024 (15)

Table 1: Genetic analysis of congenital hypothyroidism in Bangladesh

The most prevalent gene mutation found is thyroperoxidase (TPO), which is frequently associated with TDH (10,14,15). TPO (a glycosylated hemoprotein) is the major enzyme in thyroid hormone biosynthesis, and it catalyzes both iodination and coupling of iodotyrosine residues in TG (thyroglobulin) (Figure 2).

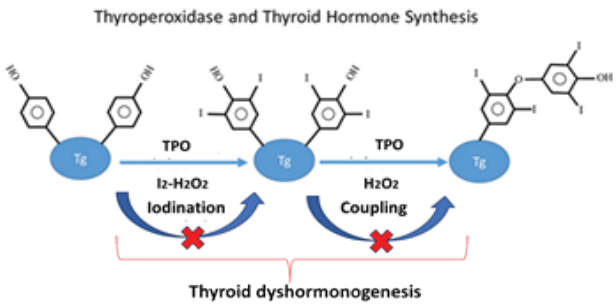

Figure 2: Enzymatic role of TPO in the synthesis of thyroxine (T4). Impairment of enzymatic function results reduced hormone production.

Begum et al. (10) analyzed how mutations affect the structural integrity, domain arrangement, and folding patterns of the TPO protein using molecular docking with heme, as heme is crucial for TPO's catalytic activity. Molecular simulation with heme showed that mutant TPO proteins have lower binding affinity than the wild type, indicating that mutations could reduce enzyme activity, thereby decreasing thyroid hormone synthesis. Researchers also found mutations in genes responsible for TD, including TSHR, Thyroid transcription factor NKX2.5, and PAX8 (Table 1) (11-14). A study investigated mutations in the *TSHR* gene in 21 patients with dysgenesis and found that mutant proteins exhibited reduced binding affinity for small-molecule thyrogenic drugs compared with the wild type, as determined by molecular docking and molecular dynamics simulations

(13). Thus, the findings demonstrated that TSHR mutations can impair drug binding, providing insights for targeted drug design and therapeutic strategies in congenital hypothyroidism with dysgenesis.

Another study used high-resolution melting (HRM) analysis, a rapid, high-throughput real-time PCR method that detects DNA variations based on melting behavior (15). This study evaluated HRM as an effective screening tool for congenital hypothyroidism (CH) in Bangladeshi patients with dyshormonogenesis and found it to be a reliable, cost-effective approach for identifying common TPO gene mutations (c.1117G>T, c.1193G>C, c.2173A>C).

IMPACT OF GENETIC TESTING ON DIAGNOSIS AND PERSONALIZED TREATMENT OF CH

Studying mutations in genetic disorders like congenital hypothyroidism is crucial for understanding disease development and severity. Congenital hypothyroidism can be categorized as permanent or transient, influencing treatment duration. Transient congenital hypothyroidism may resolve itself and can be linked to maternal factors such as iodine imbalance, anti-thyroid drugs, or thyroid antibodies during pregnancy. Genetic testing aids in differentiating between transient and permanent forms, potentially allowing for the cessation of thyroxine therapy in certain patients. Kara et al. (16) found that genetic analysis re-evaluated diagnoses in a study cohort and resulted in treatment discontinuation for five patients with specific gene mutations such as, monoallelic THSR (thyroid-stimulating hormone receptor) or DUOX2 (Dual oxidase 2). Timely identification of transient cases can significantly reduce unnecessary medical treatments and healthcare usage.

CONCLUSION

Several studies highlight the importance of genetic screening for congenital hypothyroidism. Identifying the specific genetic cause can determine if a patient requires lifelong hormone replacement therapy, as is the case for genetic causes, or if a temporary treatment plan is sufficient for acquired cases such as those related to iodine deficiency. Early diagnosis and treatment are crucial to prevent severe developmental delays and cognitive impairments. In Bangladesh, since there is increasing trend of CH incidence, it is urgent to develop and practice early newborn genetic screening that may outweigh the burden of lifelong follow-up and treatment.

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