

GENETIC ANALYSIS OF THE *TPO* GENE ASSOCIATED WITH HYPOTHYROIDISM IN PAKISTANI FAMILIES

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DOI: <https://doi.org/10.5281/zenodo.18347276>

Keywords

TPO gene, hypothyroidism, Pakistani families, *TPO* protein, *TPO* mutations, congenital hypothyroidism.

Article History

Received: 18 November 2025

Accepted: 07 January 2026

Published: 23 January 2026

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Abstract

Congenital hypothyroidism is a severe metabolic disorder that is present at birth due to insufficient production of thyroid hormones. If not addressed early, it can lead to permanent growth delays and intellectual disabilities. One of the major genetic causes of congenital hypothyroidism is dysmorphogenesis, which disrupts the hormone synthesis pathway. The thyroid peroxidase (*TPO*) gene is crucial as it provides the enzyme needed for thyroid hormone synthesis within the thyroid gland. *TPO* catalyzes important steps in the iodination and coupling reactions in the thyroid. When this gene is mutated, enzyme activity is compromised, resulting in varying degrees of hypothyroidism. This article compiles information on *TPO* gene mutations associated with congenital hypothyroidism in Pakistani families. In Pakistan, consanguineous marriages are common, leading to a higher prevalence of inherited disorders, including congenital hypothyroidism. The mutations in the *TPO* gene identified to date range from missense mutations, which are single amino acid substitutions, to larger deletions of exons and issues at splice sites. This diversity reflects the variety of mutations present within local populations. In families affected by congenital hypothyroidism, the mutational load primarily stems from changes occurring in exons 8, 9, 10, 11, and 14. Molecular diagnostic tools, including next-generation sequencing and Sanger sequencing, are used to detect these mutations. Early genetic diagnosis followed by hormone replacement therapy, typically with levothyroxine, is effective in preventing developmental delays when administered promptly. Genetic testing and counselling can be instrumental in prevention efforts.

INTRODUCTION

Congenital hypothyroidism is one of the most common causes of intellectual disability, and it requires treatment (1). It happens when the thyroid gland does not produce enough thyroid hormones. These hormones, mainly thyroxine (T₄) and triiodothyronine (T₃), are crucial for proper growth and brain development, and their adequate levels regulate how our body works (2,3). These hormones keep our body temperature in check and are key players in energy metabolism (2). They are essential

for brain development in infants (1,4). If the diagnosis of this condition is not performed in early stage and start treatment, individuals with CH could end up facing severe, long-term delays in both physical and cognitive development (1,5). Congenital hypothyroidism (CH) usually falls into two main categories: thyroid dysgenesis and dysmorphogenesis. Thyroid dysgenesis, which makes up about 80% of cases, refers to situations where the thyroid gland is either missing, not fully

developed, or just in the wrong spot (6). The other 10 to 20%, dyshormonogenesis comes in, often due to Inherited issues (7,8) .

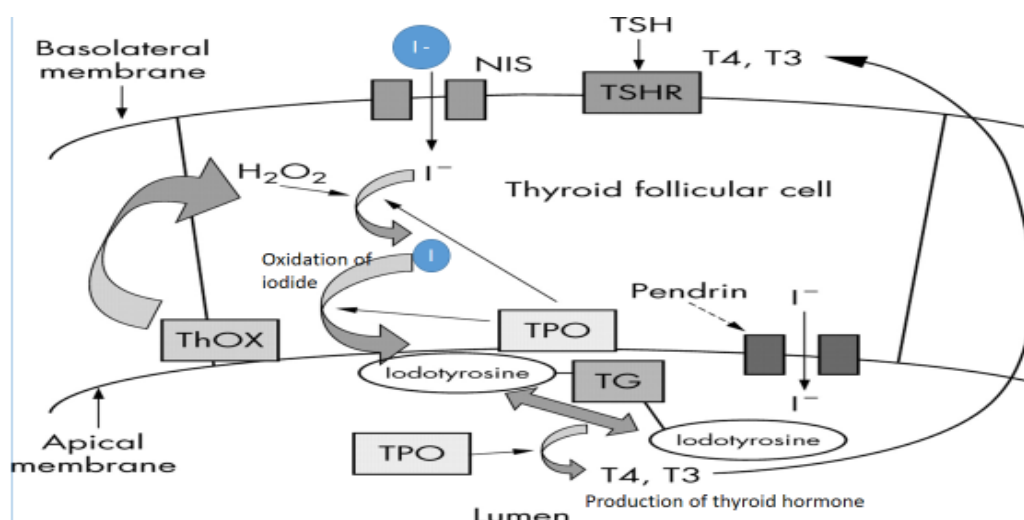


Figure 1: Schematic diagram showing thyroid hormone production. (Ref)

The thyroid peroxidase (*TPO*) gene is a key player. The enzyme produced by the *TPO* gene is involved in two vital steps in making thyroid hormones—first, it helps iodinate thyroglobulin (3). Then it's responsible for coupling iodotyrosine residues together (23). If there are mutations in this gene, thyroid hormone is not produced correctly. It can dysregulate or completely stop those processes, which means the body struggles to produce enough thyroid hormones (6). Moreover, that, in turn, can lead to varying degrees of CH (7). The *TPO* gene is located on chromosome 2p25 and is responsible for making a protein composed of 933 amino acids, mainly found in thyroid follicular cells (24). This enzyme, along with hydrogen peroxide and heme groups, ensures the proper function of thyroid hormone production (21). However, mutations in this gene can affect thyroid hormone production (9). It can affect everything from small changes in a single amino acid (those are called missense mutations) to more serious issues like nonsense mutations, splice site errors, frameshifts, or even big deletions (9). All these genetic changes can result in either a partial or complete loss of enzyme activity, which is why it shows varying degrees of how congenital hypothyroidism

(CH) shows up in different people and different populations, countries, etc (15).

Globally, hypothyroidism affects 5% of the general population, with a further estimation that 5% are underdiagnosed (5). The worldwide epidemiology patterns of hypothyroidism show that the women are more vulnerable to hypothyroidism as compared to men because they are 8 to 9 times more likely to get hypothyroidism as compared to men (16). The global genetic cause of hypothyroidism depends on any malfunctioning of the following twelve candidate genes, which are (*SLC5A5*, *TPO*, *TG*, *IYD*, *DUOXA2*, *DUOX2*, *TSHR*, *SLC26A7*, *GLIS3*, *FOXE1*, *TSHB*, *TRHR*) (18). In Pakistan, two significant factors add to the challenges of CH. The standard practices of consanguineous marriages in Pakistani families result in inheriting autosomal recessive conditions like CH due to *TPO* mutations (14), and Pakistan, being a developing country, lacks a nationwide newborn screening program in place. So, in many areas, children often don't get diagnosed until after they start showing symptoms and, in that case, significant damage has been happened (1). Recently, there has been an increasing focus on genetic studies involving Pakistani families affected

by congenital hypothyroidism (CH). These studies have revealed quite a few unique and population-specific mutations in the *TPO* gene, which helps us grasp this condition's local genetic landscape(13). These discoveries are of great importance. They can lead to better early detection, quicker treatments, and more effective family-centered management plans (7).

This review focuses on the common *TPO* gene mutations found in the Pakistani population that lead to hypothyroidism. In Pakistan, it is essential to improve access to genetic screening, establish robust newborn testing programs, and provide genetic counselling in order to manage this condition effectively. The review also presents practical suggestions to enhance national efforts to prevent and manage this significant but treatable health issue.

Methodology:

Search strategy inclusion and exclusion criteria:

The terms "Pakistani families + *TPO* gene OR hypothyroidism + hypothyroidism OR congenital hypothyroidism + mutations in *TPO* gene" were searched in Google Scholar. A total of 525 results were found. The review of the literature included full-text articles that were published in English between

2019 and 2026. Some of the related articles were also taken from PubMed, NCBI etc. Additionally, sources cited within the identified literature reviews were also sourced. All the articles which are not related to hypothyroidism, congenital hypothyroidism or are even related to thyroid disorders such as hyperthyroidism, are excluded.

Role and structure of the *TPO* gene:

Understanding the role of *TPO* Gene in Congenital Hypothyroidism:

The thyroid peroxidase (*TPO*) gene plays an important role in synthesizing thyroid hormone (23). It's a key element in figuring out some inherited cases of congenital hypothyroidism (CH) (7). The *TPO* enzyme is like this little anchor, stuck to the membrane of thyroid follicular cells, especially at the top part, where all the hormone-making magic happens (3). It's directly involved in properly producing the thyroid hormones triiodothyronine (T3) and thyroxine (T4). These hormones are crucial for healthy growth, brain development, and metabolism (2). This is especially vital during the early years of life—infancy and childhood are crucial times for it (1).

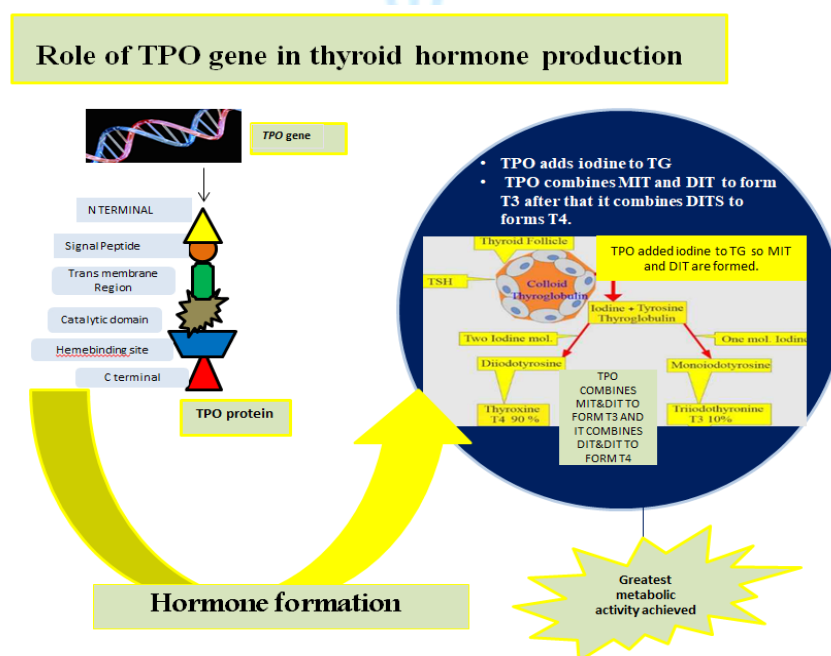


Figure 2: The production of TPO protein from its gene leads to the formation of thyroid hormones (REF)

Structure of the *TPO* Gene:

TPO gene spans about 150 kilobases of DNA. It's made up of 17 exons and 16 introns, with the coding region stretching over roughly 4.4 kb. In the end, this region encodes a protein that's made up of 933 amino acids (24).

Key structural components of the *TPO* protein include:

The key structural components of *TPO* protein include signal peptide, Trans membrane region, Catalytic Domain, heme-binding site, C-terminal and N-terminal. Signal Peptide is found at the N-terminal end; this short sequence helps direct the protein to the endoplasmic reticulum (ER) during formation. It's removed once the protein reaches its destination, allowing *TPO* to be transported to the thyroid cell surface. The transmembrane Region is the portion of the protein which anchors it firmly in the cell membrane, ensuring that the enzyme remains in place where it's needed for hormone production (23). The Catalytic Domain is that active part of the enzyme that faces the inside of the thyroid follicle and is responsible for its peroxidase activity—this is where iodine gets added to the hormone precursor (3). The heme-binding site holds a heme molecule essential for the enzyme's activity. It allows the oxidation of iodide, a key step in attaching iodine to amino acids in thyroglobulin (22). The C-terminal End region helps keep the enzyme stable and ensures it folds correctly and functions properly in hormone production (21). *TPO* is central to the chemical reactions that create T3 and T4. How T3 and T4 are made from *TPO* protein are mentioned as follows: *TPO* adds iodine to specific tyrosine molecules in a large protein called thyroglobulin, using hydrogen peroxide (H_2O_2) to help in this reaction. This forms two intermediate compounds—monoiodotyrosine (MIT) and diiodotyrosine (DIT). This step is known as iodination (3). Next, *TPO* links these iodinated tyrosines together. One MIT + one DIT gives T3, while two DITs form T4(13). This step is called a coupling reaction because it couples MIT and DITs to form T3 and T4. These hormones remain stored in the thyroid gland until needed. Then they are cleaved from thyroglobulin and released into the bloodstream, supporting critical body functions like energy balance, brain development, and growth (2).

TPO's activity is controlled by thyroid-stimulating hormone (TSH). When thyroid hormone levels in the blood drop, TSH increases, stimulating the thyroid to produce more *TPO* and other hormone-related proteins (25).

Mutations in the *TPO* Gene and Their Consequences:

Any alterations in the *TPO* gene can alter *TPO* enzyme activity, leading to insufficient thyroid hormone production(6). This is one of the known causes of congenital hypothyroidism, especially in cases related to dysmorphogenesis (a defect in hormone synthesis)(7). Various types of mutations can affect the *TPO* gene.

Missense Mutations change one amino acid in the protein. For example, a mutation like p.Arg396His affects the catalytic region and can significantly reduce the enzyme's activity and render it a nonfunctional protein (9). Such mutations usually cause severe hypothyroidism (26). Splice Site Mutations affect how the gene's instructions are assembled, potentially leading to an unstable or malformed protein (9). In the case of Large Deletions, entire exons or parts of the gene are sometimes deleted. This typically causes a complete loss of enzyme function and leads to more severe forms of the disease (11). Complex Rearrangements are rare but can cause big changes in the chromosome's structure, disrupting the gene and leading to *TPO* deficiency (12).

Clinical Importance of Mutations in *TPO* Gene:

The type of mutation in the *TPO* gene often affects how severe the hypothyroidism is (6). Some children may have mild hormone deficiencies, while others may be born with a complete lack of hormone production, which—if untreated—can result in developmental delays and intellectual disabilities (1). This is why early detection through genetic screening and timely treatment with hormone replacement (like levothyroxine) is crucial (26). Especially in countries with high rates of consanguinity, such as Pakistan, knowing the specific genetic mutations can help with family counselling, early diagnosis, and preventive care in future pregnancies (14).

Global prevalence and mutation spectrum of genes causing hypothyroidism:

Hypothyroidism is the most common disease in both developing and developed countries (5). According to an epidemiological study in the USA, UK and Denmark, the prevalence of subclinical hypothyroidism is between 3% to 10% (16). On the other hand, the study conducted in eight cities of India concluded that the prevalence of hypothyroidism was 10.95% (17). So the occurrence of hypothyroidism in both developing and developed countries is common. The 29 genes were known to have some link with hypothyroidism. A study took place in China which identified the most common causative genes out of these 29 genes and those common genes were *DUOX2*, *TG*, *TPO*, and *TSHR*. The study showed that some of the patients also had more than one gene mutation leading to hypothyroidism (18). The following genes *TSHR*, *FOXE1*, *NKX2-1*, *PAX8* and *NKX2-5* are the primary cause of CH in 85% of cases, and mutations in seven genes in thyroid dysmorphogenesis *SLC5A5*, *TPO*, *DUOX2*, *DUOXA2*, *SLC6A4*, *Tg*, and *DEHAL1* are also common (6).

Genotype Phenotype Correlations:

Hypothyroidism exhibits a strong genotype-phenotype correlation, as confirmed by various studies (6). One study involving 30 Japanese patients with hypothyroidism found mutations in the *TG* gene (27). Biallelic truncating mutations in these patients resulted in severe hypothyroidism without the presence of a goitre, while missense variants were associated with mild hypothyroidism and the presence of a goitre (27). Additionally, a study on newborns with hypothyroidism in China screened the *DUOX2* gene to examine the relationship between *DUOX2* variants and thyroid size (18). The observed phenotypic differences can be attributed to the types of mutations and different gene combinations (27).

Case study of Somali siblings:

A case series of three Somali siblings who were given levothyroxine at ages 0.5, 7.7, and 14.8 years. The newborn had the best outcome because he was treated at the best time, when mental and physical development is at its peak during the first 2 years of life; the oldest suffered with severely short height and

had static encephalopathy, which means that delayed diagnosis and treatment of congenital hypothyroidism led to irreversible neurocognitive and physical damage (1).

Genetic Landscape of *TPO* Mutations in Pakistani Families:

In Pakistan, there is a high rate of consanguineous marriages, which sets the stage for investigating inherited disorders such as congenital hypothyroidism (CH) (14). When examining the genetics involved, mutations in the thyroid peroxidase (*TPO*) gene have been identified as a major cause of hypothyroidism in the Asian population (7). The *TPO* enzyme plays a vital role in producing thyroid hormones, so any alterations in this gene can significantly impact hormone production (3). The consequences of these mutations can vary widely, ranging from mild thyroid issues to more severe problems such as developmental delays and cognitive challenges (26). Recent research conducted between 2018 and 2026 has greatly enhanced our understanding of the range of *TPO* gene mutations among Pakistani families, uncovering both known and previously undocumented variants (13).

TPO Gene Mutations in Pakistan

The Research Team: Khan *et al.*, (2020) identified a Homozygous missense mutation in p.Tyr772Cys (c.2315A>G). The clinical features of this mutation are Congenital hypothyroidism (CH) with mild intellectual disability (two siblings). The mutation is located in the *TPO*'s complement control protein (CCP)-like domain. *TPO* spans 17 exons, and this mutation occurs in exon 12. The WES technique predicted variation, which was validated by Sanger sequencing, in 200 healthy controls and 145 exomes (13). The Research Team: Naqvi *et al.*, (2023) identified mutations in two families through Molecular genetic analyses which showed homozygous variants in *TPO*: novel missense variant c.719A>G (p.Asp240Gly) in family 1 and rare c.2315A>G (p.Tyr772Cys) in family 2. The Clinical Features of these mutations are CH with intellectual disability, goitre, developmental delay, short stature, and sensory impairments. (14). The Research Team: Iqbal *et al.*, identified a Homozygous Deletion of Exons 11–15. This mutation is a Homozygous

intragenic deletion. The Clinical Features are CH with intellectual disability (11). The Research Team: Mittal *et al.*, 2016 identified p.Arg412His (c.1235G>A). This is a Homozygous missense mutation (7). The Clinical Features of the mutation are CH with intellectual disability and facial dysmorphism. Targeted sequencing confirmed the mutation in exon 8. The Research Team: Mittal *et al.*, 2016 identified mutation p.Glu596* and Arg412His. This is a Homozygous nonsense mutation. The

Clinical Features of the mutation is CH, goiter, mild ID. The mutation is located in exon 8 and 11 leading to an early stop codon and truncation of the protein (7). In these cases, Exons 7, 8, 11, 12, 13, 14, 15 are hotspots for TPO mutations. The deletion spanning exons 11-15 represents a major gene-disrupting alteration (11). These mutations reflect a diverse pathogenic spectrum: missense changes, nonsense truncations, and multi-exon deletions (7).

Table 1: Highlights mutations of *TPO* gene, their types, zygosity, clinical features and exons.

Mutation	Types	Zygosity	Clinical Features	Exons
p.Tyr772Cys	missense	homozygous	CH+ID	12
p.Asp240Gly	missense	homozygous	CH+ID+Goiter and sensational issues	7
Deletion exons 11-15	deletion	homozygous	CH+ID	11-15
p.Arg412His	missense	homozygous	CH+ mild ID+ goiter	8
p.Glu596*	nonsense	homozygous	CH+ mild ID+ goiter	11

Relationship Between Genetic Changes and Clinical Symptoms:

The impact of *TPO* mutations on health outcomes in Pakistani families is influenced by both the **type and location** of the mutation. For instance, mutations in highly conserved enzyme regions typically lead to more severe disease (9). However, even relatively mild mutations can result in significant cognitive issues if not diagnosed and managed early (1). This variability makes it challenging to predict clinical outcomes based solely on genetic data, emphasizing the need for **early genetic testing** and **newborn screening** programs (6).

Implications for Clinical Practice:

The growing body of evidence on *TPO* mutations in Pakistan underscores the urgent need for **widespread genetic screening**, particularly among consanguineous families at elevated risk (14). Diagnosing congenital hypothyroidism early is essential. When we identify those at risk right

away, it opens the door for timely treatment with thyroid hormone replacement. It can boost health and cognitive development in the long run (1).

Some unique mutations in certain areas, like p.Tyr772Cys and those large deletions that affect Exons 11 to 15. This highlights a real need for diagnostic tools tailored specifically for people in Pakistan (13). We can get more accurate diagnoses by customizing how we screen for these issues (11). Furthermore, that is crucial for families, particularly in communities with common consanguineous marriages. It gives them better insight into reproductive planning and helps with genetic counselling (14). It's all about ensuring families have the information they need for a healthier Future. The diagnostic tools that were used for detecting hypothyroidism in different studies are mainly Next generation sequencing (18), whole exome sequencing (13), Sanger sequencing (13) insilico pathogenicity prediction tools (30).

The whole exome sequencing technique detects mutations in coding regions of all genes. The purpose of this technique is that the *TPO* gene mutations are mostly novel and allow for the examination of all exomes (13). The Sanger sequencing technique involves gene sequencing via the chain termination method. This is mainly done to confirm the tests done through WES and NGS (11). Next-generation sequencing involves the sequencing of exact thyroid-related genes. This is an effective screening of genes (18). The in silico pathogenicity prediction tools involve using all computational tools to predict whether the mutations will likely cause protein defects (30). There are many research gaps in the studies related to hypothyroidism because no specific study can tell about the occurrence of any specific gene in causing hypothyroidism, and from a lot of identified genes, none of the genes is taken explicitly into account to see their effects and occurrence in any specific area. This review targets this gap by considering one specific gene *TPO* gene, to see its occurrence in a specific area of the world. This study will help researchers and scientists in their studies so that, by just getting a glimpse of this review, which involves all scattered data related to this specific gene in a specific area, they can deduce their opinion about its occurrence, etc. It can open the doors of future research of this potential culprit gene in causing hypothyroidism by helping scientists to predict its treatment plans or other options to mask its effects.

Recent expert commentary emphasizes that hypothyroidism is a lifelong condition requiring individualized management, with careful consideration of age, comorbidities, and symptom burden rather than reliance on biochemical thresholds alone. Moreover, delayed diagnosis and suboptimal treatment remain major contributors to preventable morbidity, highlighting the need for improved awareness and early detection strategies (31).

Conclusion:

Identifying individuals at risk for congenital hypothyroidism early is crucial. Starting thyroid hormone replacement therapy promptly can lead to effective outcomes. When we detect specific mutations common in Pakistan, such as

p.Tyr772Cys or large deletions affecting Exons 11 to 15, it highlights the importance of having diagnostic tools specifically designed to address this condition. It's vital to ensure we have the proper methods in place. By customizing our screening techniques, we can achieve more accurate diagnoses. This is particularly beneficial for families, especially in regions with prevalent consanguineous marriages. Families will have a clearer path for reproductive planning and improved access to genetic counselling. In conclusion, while significant progress has been made in identifying the genetic causes of congenital hypothyroidism in Pakistan, continued efforts are needed to enhance diagnostics, strengthen healthcare systems, and raise awareness. Through collaboration, research, and investment in public health infrastructure, Pakistan can work toward early detection, better treatment outcomes, and a brighter, healthier future for children affected by this preventable condition.

Acknowledgments:

I would like to thank Dr. Komal Aslam, Dr. Roeha Akhtar, Dr. Samina Hassan, and Kinnaird College for Women University in Lahore for their guidance and support during the preparation of this article.

Declarations:

- Funding: The authors received no external funding for this work.
- Conflict of Interest: The authors declare that there is no conflict of interest.
- Ethical Approval: Ethical approval was not required for the present study.
- Authors' Contributions: Mahnoor Abdullah conducted the literature search and wrote every intricate detail related to the subject. Dr. Komal Aslam, Ms. Roeha Akhtar, Dr. Saba Riaz and Dr. Samreen Riaz supervised the project.

REFERENCES:

- Hamdoun E, Karachunski P, Nathan B, et al. Case report: The specter of untreated congenital hypothyroidism in immigrant families. *Pediatrics*. 2016;137(5):e20153418.

- Shahid MA, Ashraf MA, Sharma S. Physiology, Thyroid Hormone. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Updated 2023 Jun 5.
- Rousset B, Dupuy C, Miot F, Dumont J. Thyroid hormone synthesis and secretion. In: Feingold KR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDTText.com, Inc.; 2000-. Updated 2015 Sep 2.
- Pang ALY, Chan WY. Molecular basis of diseases of the endocrine system. In: Zhang L, Orr BA, editors. Essential Concepts in Molecular Pathology. 1st ed. San Diego: Academic Press; 2010. p. 203-225.
- Chiovato L, Magri F, Carlé A. Hypothyroidism in context: where we've been and where we're going. *Autoimmun Rev*. 2019;18(10):102368. doi:10.1016/j.autrev.2019.102368.
- Kostopoulou E, Miliordos K, Spiliotis B. Genetics of primary congenital hypothyroidism—a review. *Rev Endocr Metab Disord*. 2021;22(2):287-297. doi:10.1007/s42000-020-00267-x.
- Mittal K, Rafiq MA, Rafiullah R, et al. Mutations in the genes for thyroglobulin and thyroid peroxidase cause thyroid dysmorphogenesis and autosomal-recessive intellectual disability. *J Hum Genet*. 2016;61:867-872. doi:10.1038/jhg.2016.62.
- Bakker B, Bikker H, Vulsma T, et al. Two decades of screening for congenital hypothyroidism: TPO gene mutations in total iodide organification defects. *J Clin Endocrinol Metab*. 2000;85(10):3708-3712.
- Ghosh A, Ghosh S, Das HK, et al. Functional analysis of thyroid peroxidase gene mutations detected in patients with thyroid dysmorphogenesis. *Int J Endocrinol*. 2014;2014:817135.
- 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.
- Iqbal Z, Neveling K, Razzaq A, et al. Targeted next-generation sequencing reveals a novel intragenic deletion of the TPO gene in a family with intellectual disability. *Arch Med Res*. 2012;43:312-316.
- Wang H, Wang W, Chen X, et al. Screening and functional analysis of TPO gene mutations in a cohort of Chinese patients with congenital hypothyroidism. *Front Endocrinol*. 2021;12:774941.
- Khan A, Umair M, et al. Novel homozygous variant in the TPO gene associated with congenital hypothyroidism and mild intellectual disability. *Hum Genome Var*. 2020;7:41.
- Naqvi SF, Mumtaz S, et al. Homozygous mutations in TPO associated with hypothyroidism, intellectual disability, developmental delay, and sensory anomalies in Pakistani families. *Yale J Biol Med*. 2023;96(3):347-365.
- Park KS. Analysis of worldwide carrier frequency and predicted genetic prevalence of autosomal recessive congenital hypothyroidism. *Genes*. 2021;12(6):863.
- Schübel J, Feldkamp J, Bergmann A, et al. Latent hypothyroidism in adults. *Dtsch Arztebl Int*. 2017;114(25):430-438.
- Unnikrishnan AG, Kalra S, Sahay RK, et al. Prevalence of hypothyroidism in adults: an epidemiological study in eight cities of India. *Indian J Endocrinol Metab*. 2013;17(4):647-652.
- Wang H, Kong X, Pei Y, et al. Mutation spectrum analysis of 29 causative genes in congenital hypothyroidism. *Mol Med Rep*. 2020;21(6):4987-5000.
- Arteaga-Jacobo MC, Roco-Videla Á, et al. Frequency of mutations in the TPO gene in congenital hypothyroidism due to dysmorphogenesis in Chile. *Medicina (Kaunas)*. 2024;60(7):1145.
- Mirzarahimi M, Panahi M, Rahimi B, et al. Genetic insights into congenital hypothyroidism in Iranian Azeri families. *Discov Appl Sci*. 2024;6:572.
- Baker S, Núñez Miguel R, Thomas D, et al. Cryo-electron microscopy structures of human thyroid peroxidase in complex with TPO antibodies. *J Mol Endocrinol*. 2023;70(3):e220149.
- Doerge DR, Chang HC. Inactivation of thyroid peroxidase by soy isoflavones. *J Chromatogr B*. 2002;777:269-279.

- Boi F, Mariotti S. Thyroid Peroxidase – an overview. In: Encyclopedia of Endocrine Diseases. Elsevier; 2004.
- NCBI. TPO thyroid peroxidase [Homo sapiens] – Gene. National Library of Medicine; 2025.
- Jang D, Eliseeva E, et al. TSH stimulation of thyroglobulin and thyroid peroxidase gene transcription. *Cell Signal*. 2022;90:110212.
- Tenenbaum-Rakover Y, Chertok-Shacham E, et al. Long-term outcome of patients with TPO mutations. *Thyroid*. 2021;31(6):867–875.
- Tanase-Nakao K, Iwahashi-Odano M, et al. Genotype–phenotype correlations in Japanese patients with congenital hypothyroidism due to TG defects. *J Clin Endocrinol Metab*. 2024;109(4):e198–e210.
- Ramesh BG, Bhargav PR, Rajesh BG, et al. Genotype–phenotype correlations of dyshormonogenetic goiter in South India. *Indian J Endocrinol Metab*. 2016;20(6):811–817.
- Creative Enzymes. Thyroid Peroxidase (TPO), recombinant human. Product information; 2025.
- Molina MF, Pio MG, Scheps KG, et al. Curating the gnomAD database: novel variants in the TPO gene. *Clin Chim Acta*. 2022;525:47–56.
- Chaker L, Papaleontiou M. A Review of Hypothyroidism—Reply. *JAMA*. Published online January 5, 2026. doi:10.1001/jama.2025.21662.