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Unraveling Hypothyroidism: The Genetic Predisposition And Molecular Basics

Rana Rahimova, Sabina Gulieva, Fakhranda Rzaeva, Ellada Huseynova, Firangiz Gulieva
Biochemistry Department, Azerbaijan Medical University, Baku, Azerbaijan

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Hypothyroidism, a prevalent endocrine disorder affecting millions globally, manifests due to insufficient thyroid hormone production. While environmental factors undoubtedly contribute, recent advancements in genetic and molecular research have illuminated the complex interplay between genetic predisposition and molecular mechanisms. Among the key players, pendrin, an iodide transporter in thyroid follicular cells, and iodothyronine deiodinases (DIOs) stand out, shedding light on the intricate pathophysiology of hypothyroidism. In this article, we delve into the genetic underpinnings of hypothyroidism, explore the multifaceted role of pendrin, and unravel the significance of iodothyronine deiodinases, supported by contemporary research evidence.

I. Genetic Predisposition: Unraveling The Genetic Tapestry

Growth, brain development, reproduction, and the control of energy metabolism all depend on thyroid hormones. Worldwide, all populations are impacted by the prevalent illnesses hypothyroidism and hyperthyroidism, which can have disastrous health effects. The epidemiology of thyroid disease is influenced by a number of factors, including age, smoking status, genetic susceptibility, ethnicity, endocrine disruptors, and the development of innovative therapies such immune checkpoint inhibitors. One important driver of thyroid disease risk is iodine diet. The prevalence of undetected thyroid disease is probably declining in the developed world as a result of common thyroid function testing and comparatively low treatment initiation thresholds [14]. It has long been acknowledged that there is a substantial hereditary component to hypothyroidism, with twin studies and familial clustering offering strong evidence of heredity. The genetic landscape of hypothyroidism has been further clarified by recent genome-wide association studies (GWAS), which have identified a large number of susceptibility loci and genetic variants linked to the condition.

For example, familial types of hypothyroidism have been associated with polymorphisms in genes encoding important thyroid-related proteins, such as thyroglobulin (TG), thyroid peroxidase (TPO), and the thyroid-stimulating hormone receptor (TSHR). Iodine deficiency-induced hypothyroidism has also been linked to changes in genes involved in iodine metabolism, such as the sodium-iodide symporter (NIS) gene and the pendrin-encoding SLC26A4 gene [1].

Moreover, studies on congenital hypothyroidism have identified mutations in genes critical for thyroid development and function, providing insights into the genetic basis of early-onset hypothyroidism. Despite these advancements, further research is needed to unravel the complex genetic interactions underlying hypothyroidism and its diverse clinical manifestations [2].

A normally developing thyroid gland, a healthy hypothalamic-pituitary-thyroid axis, and an adequate iodine intake are necessary for the manufacture of thyroid hormones. Goiter development is typically linked to deficiencies in hormone synthesis, assuming that thyrotropin (TSH) bioactivity and function are unaffected. On the other hand, developmental abnormalities, bioinactive TSH, or resistance to TSH at the receptor or signaling pathway level could result in gland hypoplasia. On the other hand, gain of function mutations in genes controlling growth and function may cause hyperthyroidism [10].

II. Pendrin: Navigating Iodide Transport In Thyroid Follicular Cells

Thyroid follicular cells produce pendrin, a versatile anion transporter that is encoded by the SLC26A4 gene. It is crucial for thyroid hormone synthesis and secretion because of its critical function in iodide transport inside the thyroid gland. A crucial stage in the production of thyroid hormone is the efflux of iodide from thyroid follicular cells into the follicular lumen, which is facilitated by pendrin [3].

One of the causes of congenital hypothyroidism resulting from thyroid dyshormonogenesis is Pendred syndrome (OMIM274600). The hallmark symptoms of this autosomal recessive illness include sensorineural deafness and dyshormonogenetic goiter. It is brought on by mutations in the PDS/SLC26A4 gene, which codes for the anion transporter pendrin, which is mostly expressed in the inner ear and thyroid. Only 80% of those with Pendred syndrome experience thyroid dysfunction, which manifests as a euthyroid or hypothyroid goitre. This condition is rarely evident at birth and can be identified by neonatal screening for congenital hypothyroidism [4]. There are researches to identify infants with congenital or postnatal non-autoimmune hypothyroidism who were patients of Pendred syndrome, and then to confirm the diagnosis by identifying mutations in the PDS/SLC26A4 gene [11].

Regulation of pendrin expression is tightly controlled by various factors, including thyroid-stimulating hormone (TSH), iodine availability, and inflammatory cytokines. Dysregulation of pendrin function can disrupt iodide transport, impairing thyroid hormone synthesis, and contributing to the pathogenesis of hypothyroidism [5].

Recent research utilizing advanced molecular techniques such as CRISPR/Cas9 genome editing has provided further insights into pendrin's role in thyroid function and its potential as a therapeutic target for hypothyroidism. Moreover, studies investigating the molecular mechanisms underlying pendrin dysfunction in hypothyroidism offer promising avenues for targeted therapeutic interventions [6].

III. Iodothyronine Deiodinases: Orchestrating Thyroid Hormone Metabolism

Selenium-dependent enzymes called iodothyronine deiodinases (DIOs) are essential for the metabolism of thyroid hormones. The processes of deiodinating T4 and T3 to inactive metabolites and converting thyroxine (T4) to triiodothyronine (T3) are catalyzed by DIO1, DIO2, and DIO3. These enzymes are essential for controlling tissue-specific thyroid hormone signaling as well as general thyroid hormone levels [7].

The pathophysiology of hypothyroidism is influenced by dysregulation of DIO expression or activity. Despite normal or high serum T4 levels, decreased DIO1 expression in peripheral tissues in primary hypothyroidism reduces T3 synthesis, aggravating symptoms of systemic hypothyroidism. On the other hand, elevated DIO3 expression exacerbates thyroid hormone insufficiency in hypothyroidism by limiting the conversion of T4 to T3 [8].

Since deiodinase-deficient animals are readily available, the significance of the deiodinases in thyroid hormone homeostasis has become more evident. The deiodinases either activate or inactivate thyroid hormone. Simultaneously, increased curiosity has been created in the area as a result of the finding that type 2 deiodinase can play a significant role in the G protein-coupled bile acid receptor 1-mediated (GPBAR1-mediated) signaling cascade and the Hedgehog signaling pathway. The identification of these novel functions for the deiodinases suggests that tissue-specific deiodination has far wider implications than previously believed, encompassing the fields of metabolism and developmental biology [12].

Clinically, the importance of the deiodinases in the regulation of thyroid hormone bioactivity is apparent when their activity is affected by patho-physiological conditions. Examples of such conditions are iodine insufficiency, thyroidal and non-thyroidal illness and malnutrition.

Genetic variations in DIO genes have been associated with autoimmune thyroid diseases, congenital hypothyroidism, and resistance to thyroid hormone. Understanding the role of DIOs in thyroid hormone metabolism provides insights into the molecular mechanisms underlying hypothyroidism and offers potential therapeutic targets for intervention [9].

IV. Conclusion

Hypothyroidism represents a multifaceted disorder influenced by genetic predisposition and intricate molecular mechanisms. The roles of pendrin as an iodide transporter in thyroid follicular cells and iodothyronine deiodinases in thyroid hormone metabolism underscore the complexity of hypothyroidism pathophysiology. Continued research efforts leveraging modern genomic and molecular techniques offer promise for elucidating the genetic underpinnings and molecular pathways of hypothyroidism, paving the way for targeted therapeutic interventions and improved patient outcomes.

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