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REVIEW

Genetics of Thyroid Disorders

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Background: Thyroid diseases are the most common endocrine pathologies second to diabetes. They have been shown to have high genetic impact, and variants in any of the genes involved in the metabolism of thyroid hormones have marked influence on the development of these diseases.

Aim: To identify the genes that have been most involved in the development of thyroid pathologies by reviewing the literature with recent relevant articles.

Materials and methods: We performed a literature search on the NCBI (National Center for Biotechnology Information) databases, and that of the European Bioinformatics Institute (EMBL-EBI) using keywords related to the topic of interest).

Results: Activation of oncogenes such as RAS, BRAF, RET/PTC and the overstimulation of the PI3K/AKT pathway plays an important role in thyroid tumorigenesis. SLC5A5, SLC26A4, TG, TPO, DUOX2, DUOXA2 are related to hypothyroidism. Risk factors for Graves' disease are associated with the presence of HLA-DR3, CTLA4, PTPN22, CD40, IL2RA (CD25), FCRL3, and IL23R. FOXE1 can be associated to hypothyroidism and papillary thyroid cancer.

Conclusions: Thyroid diseases are polygenetic, and while there are sufficient pathways affected by genetic changes, and there is, to our knowledge, no gene that has been found to be specifically causal, and the pathology has been the result of the interaction of many genetic variables such as polymorphisms or mutations.

BACKGROUND

Thyroid hormones (THs) are essential for the development of mammals playing an important role in the immune, cardiovascular, nervous, and reproductive systems. In fact, it has been shown that thyroid dysfunction exerts effects on the female reproductive capacity causing menstrual disorders, including amenorrhea, oligomenorrhea and polymenorrhea.[1] In addition, it has been known that THs also increase the basal metabolic rate and regulate energy homeostasis, which is evident in patients with thyroid dysfunction. THs have also been linked to obesity and it has been observed that individuals with hyperthyroidism eat more, but lose weight, while the individuals with hypothyroidism eat less, but gain weight. Previous hypotheses have directly connected THs with adipose tissue, skeletal muscle, and the heart.[2] In muscles, THs increase ATP consumption by acting on the Ca^{+} gradient between the sarcoplasmic reticulum and the cytoplasm, among other mechanisms.[3]

In bone development, THs also play an important role. In hypothyroid children, linear growth ceases and there is epiphyseal dysgenesis, whereas in children with thyrotoxicosis, linear growth increases and bone maturation accelerates, causing premature fusion of growth plaques, which causes children to have short stature.[4]

Finally, in the cardiovascular system, which has been the most studied in relation to the metabolism of THs, it has been documented that patients with primary thyroid dysfunction have adverse cardiovascular manifestations.[5] For example, hyperthyroidism is characterized by an increase in cardiac output and a reduction in peripheral vascular resistance, and it also increases cardiac preload as a result of increased blood volume, which increases the risk of heart damage.[6]

The previous physiological implications are only some of the many in which the THs intervene; therefore, their mechanism of action has been widely studied over the years keeping the enthusiasm to know the molecular and genetic

bases of the damage in thyroid metabolism that contribute to the development of a pathology and consequently to a failure in the human organism. These explanations are not easy as the T4 and T3 synthesis involves a complex of molecules whose alterations give rise to the diseases related to the gland.[7] This review describes the most representative genes that have been involved in the development of thyroid pathologies.

MATERIALS AND METHODS

We did a literature search on the National Center for Biotechnology Information (NCBI) and on the European Bioinformatics Institute (EBI) databases, using keywords related to the topic of interest.

RESULTS

Thyroid cancer

Homeostasis of the thyroid gland is maintained by the regulation of thyroid growth and differentiation, which occurs through a complex interaction between the thyroid stimulating hormone (TSH) and other growth factors and cytokines. There is evidence to support even the role of transforming growth factor beta 1 (TGF-β1) and epidermal growth factor (EGF) as a link in the regulation of thyroid differentiation and proliferation.[8]

It should be noted that the thyroid gland is the most common site for epithelial hyperplasia which affects 15% of the adult population. In fact, it sporadically presents a condition called nontoxic Goiter's multinodular disease, in which the gland usually contains well-defined nodules of variable size surrounded by abnormal epithelium. In relation to this issue, many studies have revealed evidence of autocrine stimulators involved in the growth and progression of Goiter disease, including TGF-β1.[8]

Thyroid cancer is one of the most common diseases of this gland, and is classified as papillary, medullary, follicular, or anaplastic, being the papillary thyroid cancer (PTC) one of the malignant tumors with highest incidence, whose molecular mechanism of development is not at all clear due to their complexity, but what is certain is the role of some genetic factors that may increase the risk of suffering from PTC.[9] In fact, it has been shown that activation of oncogenes such as *RAS, BRAF, RET/PTC* and the overstimulation of the PI3K/AKT pathway plays an important role in thyroid tumorigenesis.[8]

On the other hand, simple nucleotide polymorphisms (SNP) have also been found in *FOXE1* and *NKX2* transcription factors: in fact, *FOXE1* rs965513 and *NKX2-1* rs94428 have been associated with differentiated thyroid cancers in Caucasian population.[10] In relation to *FOXE1* it is a thyroid-specific transcription factor with an essential role in thyroid development; even more, this gene aids in maintaining cellular differentiation in the adult thyroid and recognizes sites in thyroglobulin (Tg) and thyroperoxidase (TPO), among others. There is evidence that *Adamts9*, *Cdh1*, *Duox2*, and *S100a4* genes increase their expression in the absence of *FOXE1*, whereas *Casp4*, *Creld2*, *Dusp5*, *Etv5*, *Hsp5a*, *Nr4a2*, and *Tm4sf1* decrease.[11] Interestingly, *FOXE1* is involved in cleft lip and cleft palate, hypothyroidism and PTC, probably causing a new syndrome that integrates these three diseases.[12]

The genes coding for thyroid transcription factors 1 and 2 (*TTF1* and *TTF2*) have been extensively studied in thyroid carcinomas because they regulate other genes essential to thyroid function. *TTF1* and *TTF2* are expressed in different tissues, and their anomalies are involved in several types of cancer; *TTF1* plays an important role in thyroid differentiation and is expressed in numerous tissues and cell types, including the posterior pituitary tract and hypothalamus. On the other hand, *TTF2* has also been found involved in embryonic development and thyroid formation. In fact, SNP rs944289 in the *TTF1* gene was associated with increased risk of PTC, as was SNP rs96513 in the *TTF2* gene, and were considered as susceptible genetic factors in Asians and Caucasians.[9]

Two new variants of *TTF-2* (C, 200C> G) and (c510C> A) have also been identified in thyroid carcinoma. C, 200C> G was associated with lower expression of TPO in tumors, suggesting that this variant may alter the transcription of TPO, normally regulated by *TTF-2*, in addition to that, the *RET* mutation in PTC is considered the most common genetic alteration in this tumor.[13]

RET/PTC reactivity is very frequent in the PTC, through the activation of tyrosine kinase domain in the follicular cell, which in turn starts a signaling pathway through MAPK, leading to uncontrolled cell proliferation. The most commonly known rearrangements are *RET/PTC-1* and *RET/PTC-3*, both attributed to an environmental risk factor, such as exposure to ionizing radiation, which has been previously mentioned.[14] In addition, among the well-known environmental risks for PTC, there is an additive risk in case of deficiency in iodine intake.[13]

It is noteworthy that the genetic and epigenetic alterations that lead to thyroid cancer are many, not solely those named earlier. Examples of other alterations leading to thyroid cancer include mutation in *BRAF (BRAF V600E)*, which leads to the only molecular and pathological process that causes failures in radioactive treatment. Mutations in *RAS*, *PIK3CA*, *PTEN*, *TP53*, β-catenin (*CTNNB1*), anaplastic lymphoma kinase (*ALK*), and dehydrogenase is citrate 1 (*IDH1*) have also been identified and, in addition to the latter, translocations have been associated in RET-PTC genes and the PAX8 gene. Also, for the development of pathogenesis, modifications have been found in several cell signaling pathways, including the following: MAPK; P13K-AKT; NFKβ and RASSF1, concluding that the progression of thyroid cancer is a result of a process of the accumulation of alterations that lead to secondary molecular damage involving the tumor cells and the microenvironment, acting in cooperation by amplifying and acting synergistically on the impact of thyroid tumorigenesis.[15]

Also, the *RET* protooncogene encodes a receptor tyrosine kinase (RTK) that mediates extracellular neurotropic signaling to intracellular transduction pathways including the MAPK/ERK pathway, which is crucial for the initiation of PTC. In fact, mutations in *RET* and RET/PTC are characteristic of the well-differentiated non-aggressive PTC, in addition to the *BRAF* V600E mutation, which have been shown to be markers of PTC in refractory thyroid cancer. It should be noted that *RET/PTC* significantly suppresses *PAX8* expression.[16] In fact, another arrangement of the *PAX8/PPARγ* array is found in follicular thyroid cancers (FTC) and eventually, in PTC. Armstrong et al. reported in 2014 that this arrangement was found in thyroid nodules and that it had a predictive value of 100% for differentiating thyroid cancer. It should be noted that the *PAX8/PPARγ* array is formed through the translocation t(2; 3)(q13;25) and has been found in approximately 30-35% of FTC, and that, despite that PTC is low in frequency, it has been documented in follicular variants of this type of malignancy.[17]

The importance of studying transcription factors in the development of thyroid cancer is that these factors are critical for the development and function of the gland; for example, *PAX8*, which belongs to the PAX family of proteins, plays a critical role in the development of the thyroid to the point that there is evidence that mutations with loss-of-function in *PAX8* are manifested with hypothyroidism, accompanied by thyroid dysgenesis. The results obtained in 2016 by Rosignolo et al. show that the expression of *PAX8* is diminished in tumors compared to healthy tissue.[18]

Regarding *PAX8* expression studies, in 2015 Lucci et al. studied the relationship between *PAX8* and neuropilin 2. In this regard, neuropilins (NRP1 and NRP2) are transmembrane glycoproteins that play a central role in neuronal and blood vessel development, are expressed in various tissues including endothelial cells, neurons, pancreatic islet cells, hepatocytes, melanocytes, osteoblasts, and frequently in malignant tumor cells. The authors found that the relationship between the two molecules was inversely proportional and that, while PAX8 expression decreased in tissues with thyroid carcinoma, that of *NRP2* increased, directly influencing the pathogenesis of the disease.[19]

PAX8 has been one of the most studied molecules in thyroid malignancies. In 2014, Filippone et al. studied the relationship of this transcription factor with *WNT4,* considering that *WNTS* genes are powerful regulators of cell proliferation and differentiation. The association between these two molecules comprises an interesting research point. The authors found that *PAX8* can modulate the expression of *WNT4* in thyroid cells and correlate the expression of this substance with the epithelial integrity of the thyroid because it is reduced in carcinomas. In fact, *WNT4* regulation is required for the progression of thyroid epithelial tumors to a complete malignant phenotype.[20]

Deiodinases have also been studied in relation to cancer, since their expression is altered in some malignancies. For example, it is thought that they contribute to the loss-of-control in cell division followed by tumor development. First, it should be remembered that deiodinase 1 (D1) and deiodinase 2 (D2) transform T4 into T3, while deiodinase 3 (D3) inactivates the thyroid hormone and ends the action of T3. It has been observed that the expression of D1 varies depending on the pathology; for example, in PTC, D1 decreases or increases, whereas in FTC and anaplastic thyroid carcinoma increases. On the other hand, D2 is increased in FTC, in anaplastic thyroid cancer (ATC), and in medullary thyroid cancer (MTC), whereas in PTC, glioblastomas and astrocytomas is diminished.[21]

Meanwhile, in ATC, which is quite aggressive, alterations have been identified in *FOXM1*, which codes for the protein Forkhead Box M1, that be-

longs to a family of transcription factors involved in the control of cell proliferation, chromosomal stability, and angiogenesis and is highly increased in non-differentiated thyroid cancer. Moreover, high levels of *FOXM1* have been linked to a loss of p53 function and uncontrolled activation of the phosphatidylinositol-3 kinase/AKT/FOXO3a pathway. In fact, it has been probed how the inhibition of *FOXM1* can reduce the aggressiveness of this cancer type and can reduce the risk of metastasis. The latter has been corroborated to reveal results, whereas inhibiting *FOXM1* not only reduces cell invasion, but also decreases the expression of *FOXM1* target genes, such as cyclin B1 (*CCNB1*), polo-like kinase 1 (*PLK1*), and Aurora kinase B (*AURKB*), among others.[22]

Additionally, in PATZ1 protein, a ring of zinc has been recently investigated as a regulator in the development of cancer, the molecule is postulated as a tumor suppressor in thyroid carcinoma; thyroid malignant tissue compared to normal has reduced expression and is has been found that PATZ1 activates *P53*-dependent protective pathways, preventing cell proliferation, migration, and invasion.[23]

Hypothyroidism

Congenital hypothyroidism (CH) is the most common endocrine disorder, with an incidence of 1 per 3000-4000 newborns, and it can be caused by thyroid dysgenesis (80%) or thyroid dyshormogenesis (15%). The importance of this endocrine disease lies in the mental retardation and cognitive difficulties that can present in children with the disorder. Therefore, over the years, several studies have been designed to get more evidence of the molecular mechanism involved in the development of CH by dyshormogenesis, finding the following genes:

1. *SLC5A5* (19p13): Encodes the sodium iodide (NaI) transporter and, on being altered, reduces entrapment of I.
2. *SLC26A4* (7q31): Encodes for pendrin and affects the flow of I into the follicular lumen.
3. *TG* (8q 24): Encodes for thyroglobulin (TG) and affects the hormonal synthesis of thyroid hormones.
4. *TPO* (2q25): Encodes for thyroperoxidase (TPO) and affects the organization and attachment of iodine (I).
5. *DUOX2* (5q15.3): Encodes the dual oxidase 2 and affects the generation of H_2O_2, which is a substrate of the TPO enzyme.
6. *DUOXA2* (15q15.3): Encodes for DUOX maturation factor 2 and affects the generation of H_2O_2 which is a substrate of the TPO enzyme.
7. *IYD* (6q25): Encodes for deiodinase iodotyrosine (DEHALI) and affects the intrathyroid process of recycling I.

A 2010 study by Di Cosmo et al. showed that reduced expression of monocarboxylate transporter 8 (MCT8) occurs with low serum concentrations of T4, which gives an idea of how mutations in the MCT8-producing gene can alter the levels of THs, leading to surge of some diseases.[7,24]

Pendred Syndrome

Pendrin is a protein transporter that exchanges chlorine for anions such as iodine (I) in the thyroid and is located on the apical membrane of the thyrocytes.[25] It is a member of solute transport family *SLC26A4* that includes transporters with various anion exchange functions.[26]

Mutations in *SLC26A4* are responsible for the Pendred syndrome, an autosomal recessive disease characterized by sensoneural association, including hearing loss and a partial defect in I organification; 80% of patients present with goiter, but only a minority have hypothyroidism. In 2011, Dosena et al. found that mutations in *V239D*, *G334V X335*, and *I487Y FSX39* reduce pendrin activity in Israeli and Palestinian populations.[25] In the same year, this same group identified other changes in Spanish population that gave rise to loss of function of pendrin, and these were *P70L*, *P301L*, and *F667C*, while *V609G* and *D687* that caused reduction of significant function, different from those found in Middle Eastern population.[27]

Goiter

Goiter, defined as an increase in the size of the thyroid tissue, is a continuous and important global health problem. It can be present in a diffuse or nodular manner, whereas its prevalence can range from 5% to 50%, although this may vary according to the detection method used as well as the study population. In nodular goiter, prevalence is higher in women living in areas of iodine deficiency and it increases with advanced age.[28]

In 2014, Faisal and colleagues analyzed 63 Iraqi patients and found that mutations c1078C> T at position 1708 of exon 10 of the TPO gene and c1978C> G of exon 11 were associated with both toxic and non-toxic multinodular goiter and considering that goiter in general occurs in more than 10% of the population, these findings have an important epidemiological impact. It should

be recalled that in non-toxic multinodular goiter, an enlargement of the gland is observed without an increase in T4 and T3, but with an increase in TSH, while the toxic multinodular goiter can occur as Graves' disease, toxic adenoma, and toxic nodular goiter, resulting in hypersensitivity to Immunoglobulin G (IgG) directed against TSH receptors. In these pathologies, T3 and T4 levels are high with low TSH levels. In addition to this, it must be taken into account that more than 50 mutations in *TPO* have been identified, including deletions and insertions that generate an abnormal TPO, which triggers a production of null or reduced thyroid hormones and which in turn leads to congenital hypothyroidism, goiter, and other thyroid disorders.[29]

The development of multinodular goiter is associated with several factors, such as genetic abnormalities and iodine deficiency, among others. Genetic abnormalities have identified a germ mutation of the Kelch-like ECH-protein-1 gene (KEAP1), which was reported as a new molecular cause of familial multinodular goiter.[30] *KEAP1* was originally identified as a protein associated with nuclear factor (erythroid-derived 2) (NRF2); this factor is associated with increased cell replication. *KEAP1* also performs functions as a substrate binding protein for an ubiquitin E3-dependent complex ligase of Cul3, which generates the degradation of NRF2 by the proteasome.[31] Mutations in *KEAP1* are sufficient to lead to constitutive activation of NRF2 by disruption in *KEAP1-NRF2* interaction. This mutation is given by a mutant fragment in *KEAP1* (D294T, fs * 23), which is derived from a *KEAP1* mutant protein that is not synthesized by the modification. Since there is no control over NRF2, constitutive activation of *NRF2* leads to the production of a multinodular goiter of familial origin. Two mutations have been reported for this gene mutation: (D294T, fs * 23) and mutation (R483H).[29,32]

Graves' disease

Graves' disease (GD) is an autoimmune disorder in which the antibodies activate the TSH receptor, causing hyperfunction of the thyroid gland. This activation stimulates follicular hypertrophy and consequent hyperplasia, causing an enlargement of the thyroid and an increase in hormone production. GD affects approximately 0.5% to 2% of Caucasian population and is a major cause of hyperthyroidism.[33]

A variety of polymorphisms in genes have been established with a direct, or with a possible, association with the generation of GD. These genes have been classified into two groups. The first group are genes that are common to several autoimmune diseases, in which genes that stimulate or regulate the immune response can be found. These genes include *HLA-DR3*, *CTLA4*, *PTPN22*, *CD40, IL2RA (CD25)*, *FCRL3*, and *IL23R*. The second group includes genes that are specific to the thyroid gland: *TSHR* and the thyroglobulin gene.[34] Currently, it is clear that the genetic predisposition for GD is not only associated with a gene, but that it is presented by a set of genes with modest individual effects. Most of the previously identified loci confer a low risk for the disease (~1.2-1.5).[35]

One of the main complications of GD is ophthalmopathy or orbitopathy, which occurs in 25-50% of patients with GD Graves' ophthalmopathy is characterized by the enlargement and inflammation of the retrobulbar content, mainly the extraocular muscles of the eye, with the consequent increase in intraocular pressure. This sign is due to a cross-reaction of the antibodies present in GD. Anti-TSH receptor antibodies that although found mainly in the thyroid tissue, have also been found in connective tissue and adipose-tissue retrobulbar content. In addition, some patients may present with this disease with antibodies that interact with orbital fibroblasts, leading to the secretion and deposition of collagen and mucopolysaccharides behind the eyeball, resulting in an increase in intraocular pressure.[36]

Although the immunological mechanisms in Graves' ophthalmopathy have been clarified, it is necessary to know which genetic mechanisms are associated with this clinical feature of GD. Studies have found associations between different genes, but it has been possible to characterize a gene that has been specifically associated with Graves' ophthalmopathy: *I-23R*. This gene codes for a transmembrane 1 protein that binds to the *IL23* to activate the Janus kinases, leading to the transcription of proinflammatory genes, including IL-17 and Interferon-gamma. It is already known that polymorphisms in *IL-23R* confer susceptibility to various autoimmune diseases, including Crohn's disease, psoriasis, rheumatoid arthritis, etc.[34]

It has been possible to find a specific association of Graves' ophthalmopathy and SNP and different mechanisms have been postulated:

1. SNP on *IL-23R* (possibly rs10889677) may cause receptor overexpression, leading to a differ-

entiation of Th1 to TH17, resulting in an increase in the synthesis of IL-17 by these cells. This could subsequently lead to an increase in the release of TNF, causing chronic inflammation of the affected organ, in this case, the eyes.

2. SNP in *IL-23R* (possibly rs7530511) may cause a change in the affinity of IL-23 to its receptor, altering the activation of *IL-23R*.[37]

However, several studies have not found direct association between *IL-23R* and Graves' ophthalmopathy.[38-40] **Table 1** illustrates some genes associated with Graves' disease.

Table 1. Genes associated with Graves' disease

Population	Genes	Results
735 GD patients and 1216 healthy controls from Poland.[41]	*HLA-DRB1, TNF, CTLA4, CD40, NFKB, PTPN22, IL4* and *IL10.*	Polymorphism in the *HLA-DRB1*, *TNF* and *CTLA4* genes were associated with GD. The carriers of the HLA DRB1*03 allele were more frequent in patients with age at GD diagnosis ≤30 years than in patients with older age at GD diagnosis.
256 Caucasian patients with GO (n=199) and less severe GO (n=57), and 90 patients with GD but no clinically apparent GO.[35]	*HLA-DR3, TSHR* [rs2268458], *CTLA4* [A49G], *IL23R* [rs10889677], *IL23R [rs2201841].*	Patients with GO did not have a distinct genetic susceptibility to their eye disease confirming the interaction between environment and epigenetics.
709 patients with GD.[42]	*HLADRB1, PTPN22, CTLA4* and *TSHR.*	Interactions between the *HLADRB1/PTPN22* and *HLADRB1/CTLA4* genes more closely predicted the risk of GD onset in young patients.
768 GD patients were included in the study. 359 of them had clinically evident orbitopathy.[43]	*TSHR, HLA-DRB1, CTLA4* and *PTPN22.*	Allele A of the rs179247 polymorphism in the *TSHR* gene was associated with lower risk of GO in young GD patients.
594 patients (109 male and 485 female) with GD with (n=267) or without (n=327) ophthalmopathy and 1147 controls (204 male and 943 female), in southern Sweden.[39]	*BTG2, CYR61, ZFP36, EGR1, DUSP1, PTGS2, NR4A2, CXCL2, SOCS3, RGS2, SCD, CTLA4.*	SNPs in IEGs and SCD were associated with GD and/or GO.

GD: Graves' disease, GO: Graves' ophthalmopathy, IEGs: adipocyte-related immediate early genes, SCD: stearoyl-coenzyme A desaturase.

CONCLUSIONS

Thyroid diseases have complex inheritance pattern and they also need environmental factors and triggers for their development. They represent a broad field of study in clinical research and genes related to the development of pathologies are key in the smooth functioning of several metabolic pathways.

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Генетика заболеваний щитовидной железы

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Введение: Заболевания щитовидной железы являются наиболее распространённой эндокринной патологией после диабета. Доказано, что они оказывают большое генетическое воздействие, а вариации любого из генов, участвующих в метаболизме гормонов щитовидной железы, оказывают выраженное воздействие на развитие этих заболеваний.

Цель: Идентифицировать гены, которые в наибольшей степени участвуют в развитии патологий щитовидной железы, путём обзора литературы новых статей.

Материалы и методы: Мы провели литературный обзор базы данных NCBI (Национального центра биотехнологической информации) и Европейского института биоинформатики (EMBL-EBI), используя ключевые слова, относящиеся к разрабатываемой теме.

Результаты: Активация онкогенов, таких как RAS, BRAF, RET / PTC и избыточная стимуляция сигнального пути PI3K / AKT, играет важную роль в онкогенезе щитовидной железы. SLC5A5, SLC26A4, TG, TPO, DUOX2, DUOXA2 связаны с гипотиреозом. Факторами риска для развития Базедовой болезни (Graves' disease) являются наличие HLA-DR3, CTLA4, PTPN22, CD40, IL2RA (CD25), FCRL3 и IL23R. FOXE1 может быть связан с гипотиреозом и папиллярным раком щитовидной железы.

Выводы: Заболевания щитовидной железы являются полигенетическими, и, хотя генетические изменения затрагивают достаточно много путей, и, насколько нам известно, не существует гена, который являлся бы подтверждённой специфической причиной, а патология является результатом взаимодействия многих генетических переменных, таких как полиморфизмы или мутации.