Genetics of Thyroid Disorders

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Received: 06 May 2018
Accepted: 12 Dec 2018
Published Online: 07 Jan 2019
Published: 30 June 2019

Key words: thyroid gland, thyroid digenesis, mutation, polymorphism, thyroid hormones

Citation: Cortés JMR, Zerón HM. Genetics of thyroid disorders. Folia Med (Plovdiv) 2019;61(2):172-9. doi: 10.2478/folmed-2018-0078

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 Ca²⁺ 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. 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 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

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 \( \textit{BRAF} (\textit{BRAF V600E}) \), which leads to the only molecular and pathological process that causes failures in radioactive treatment. Mutations in \( \textit{RAS}, \textit{PIK3CA}, \textit{PTEN}, \textit{TP53}, \beta\)-catenin (\( \textit{CTNNB1} \)), anaplastic lymphoma kinase (\( \textit{ALK} \)), and dehydrogenase is citrate 1 (\( \textit{IDH1} \)) have also been identified and, in addition to the latter, translocations have been associated in \( \textit{RET-PTC} \) genes and the \( \textit{PAX8} \) gene. Also, for the development of pathogenesis, modifications have been found in several cell signaling pathways, including the following: MAPK; P13K-AKT; NFK\( \beta \) 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 \( \textit{RET} \) 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 \( \textit{RET} \) and \( \textit{RET-PTC} \) are characteristic of the well-differentiated non-aggressive PTC, in addition to the \( \textit{BRAF V600E} \) mutation, which have been shown to be markers of PTC in refractory thyroid cancer. It should be noted that \( \textit{RET/PTC} \) significantly suppresses \( \textit{PAX8} \) expression.\(^{16} \)

In fact, another arrangement of the \( \textit{PAX8/PPAR\gamma} \) 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 predictable value of 100% for differentiating thyroid cancer. It should be noted that the \( \textit{PAX8/PPAR\gamma} \) array is formed through the translocation (t2; 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, \( \textit{PAX8} \), 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 \( \textit{PAX8} \) are manifested with hypothyroidism, accompanied by thyroid dysgenesis. The results obtained in 2016 by Rosignolo et al. show that the expression of \( \textit{PAX8} \) is diminished in tumors compared to healthy tissue.\(^{18} \)

Regarding \( \textit{PAX8} \) expression studies, in 2015 Lucci et al. studied the relationship between \( \textit{PAX8} \) 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 \( \textit{PAX8} \) expression decreased in tissues with thyroid carcinoma, that of NRP2 increased, directly influencing the pathogenesis of the disease.\(^{19} \)

\( \textit{PAX8} \) has been one of the most studied molecules in thyroid malignancies. In 2014, Filippone et al. studied the relationship of this transcription factor with \( \textit{WNT4} \), considering that \( \textit{WNTS} \) genes are powerful regulators of cell proliferation and differentiation. The association between these two molecules comprises an interesting research point. The authors found that \( \textit{PAX8} \) can modulate the expression of \( \textit{WNT4} \) 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, \( \textit{WNT4} \) 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 \( \textit{FOXM1} \), 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.

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.

**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 H₂O₂, which is a substrate of the TPO enzyme.
6. **DUOX1** (15q15.3): Encodes for DUOX maturation factor 2 and affects the generation of H₂O₂ which is a substrate of the TPO enzyme.
7. **IYD** (6q25): Encodes for deiodinase iodotyrosine (DEHAL1) 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.

**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. It is a member of solute transport family SLC26A4 that includes transporters with various anion exchange functions.

Mutations in SLC26A4 are responsible for the Pendred syndrome, an autosomal recessive disease characterized by sensorineural 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. 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.

**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 and c1978C> G of exon 11 were associated with toxic and non-toxic multinodular goiter and c1708 T at position 1708 of exon 10 of the TPO gene and c1978G> 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 genes 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.

REFERENCES
1. Kong L, Wei Q, Fedail JS, et al. Effects of thyroid hormones on the antioxidative status in the uterus of young adult rats. J Reprod Dev 2015; 61(3): 219-27.

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.

association between IL-23R and Graves’ ophthalmopathy.38-40 Table 1 illustrates some genes associated with Graves’ disease.

CONCLUSIONS
Thyroid diseases have complex inheritance pattern and they also need environmental factors and triggerers 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.

2. Martinez-Sánchez N, Alvarez CV, Fernø J, et al. Hypothalamic effects of thyroid hormones on metabolism. Best Pract Res Clin Endocrinol Metab 2014; 28(5): 703-12.

3. López M, Alvarez CV, Nogueiras R, et al. Energy balance regulation by thyroid hormones at central level. Trends Mol Med 2013; 19(7): 418-27.

4. Wojcicka A, Bassett JHD, Williams GR. Mechanisms of action of thyroid hormones in the skeleton. Bio-
5. Moureu la I, Forini F, Pantos C, et al. Thyroid hormone and cardiac disease: from basic concepts to clinical application. J Thyroid Res 2011; 2011: 958626.

6. Biondi B. Heart failure and thyroid dysfunction. Eur J Endocrinol 2012; 167(5): 609-18.

7. Grasberger H, Refetoff S. Genetic causes of congenital hypothyroidism due to dysshormonogenesis. Curr Opin Pediatr 2011; 23(4): 421-8.

8. Mincione G, Di Marcantonio MC, Tarantelli C, et al. EGF and TGF-β1 effects on thyroid function. J Thyroid Res 2011; 2011: 431718.

9. Gao Y, Chen F, Niu S, et al. Replication and meta-analysis of common gene mutations in TTF1 and TTF2 with papillary thyroid cancer. Medicine (Baltimore) 2015; 94(36): e1246.

10. Penna-Martinez M, Epp F, Kahles H, et al. FOXE1 association with differentiated thyroid cancer and its progression. Thyroid 2014; 24(5): 845-51.

11. Fernández LP, López Márquez A, Martínez AM, et al. New insights into FOXE1 functions: identification of direct FOXE1 targets in thyroid cells. PLoS One 2013; 8(5): e62849.

12. Fernández LP, López Márquez A, Martínez AM, et al. FOXE1 association with differentiated thyroid cancer and its progression. Thyroid 2014; 24(5): 845-51.

13. Espadinha C, Silva AL, Cabrera R, et al. Molecular analysis of TTF-1 and TTF-2 genes in patients with early onset papillary thyroid carcinoma. J Oncol 2012; 2012: 359246.

14. Romei C, Elisei R. RET/PTC translocations and thyroid cancer genome. Front Endocrinol (Lausanne) 2016; 7: 131.

15. Armstrong MJ, Yip L, et al. PAX8/PPARγ rearrangement in thyroid nodules predicts follicular-pattern carcinomas, in particular the encapsulated follicular variant of papillary carcinoma. Thyroid 2014; 24(9): 1369-74.

16. Rosignolo F, Sponziello M, Durante C, et al. Expression of PAX8 target genes in papillary thyroid carcinoma. PLoS One 2016; 11(6): e0156658.

17. Lucci V, Palma T Di, Zannini M. Neuropilin-2 is a newly identified target of PAX8 in thyroid cells. PLoS One 2015; 10(6): e0128315.
In this paper, we discuss the genetic contribution to Graves’ ophthalmopathy. The focus is on the genetic basis of Graves’ disease, clinical outcomes of radiotherapy, and the genetic contribution to the need for decompressive surgery. References include articles on genetic contributions, clinical outcomes, and genetic associations.

35. Ploski R, Szymanski K, Bednarczuk T. The genetic basis of Graves’ disease. Curr Genomics 2011; 12(8): 542-63.
36. Prabhu RS, Liebman L, Wojno T, et al. Clinical outcomes of radiotherapy as initial local therapy for Graves’ ophthalmopathy and predictors of the need for post-radiotherapy decompressive surgery. Radiat Oncol 2012; 7: 95.
37. Huber AK, Jacobson EM, Jazdzewski K, et al. Interleukin (IL)-23 receptor is a major susceptibility gene for Graves’ ophthalmopathy: The IL-23/T-helper 17 axis extends to thyroid autoimmunity. J Clin Endocrinol Metab 2008; 93(3): 1077-81.
38. Morshed SA, Latif R, Davies TF. Delineating the autoimmune mechanisms in Graves’ disease. Immunol Res 2012; 54(1-3): 191-203.
39. Planck T, Shahida B, Sjogren M, et al. Association of BTG2, CYR61, ZFP36, and SCD gene polymorphisms with Graves’ disease and ophthalmopathy. Thyroid 2014; 24(7): 730-6.
40. Xiong H, Wu M, Yi H, et al. Genetic associations of the thyroid stimulating hormone receptor gene with Graves diseases and Graves ophthalmopathy: A meta-analysis. Sci Rep 2016; 6: 30356.
41. Jurecka-Lubieniecka B, Ploski R, Kula D, et al. Association between age at diagnosis of Graves’ disease and variants in genes involved in immune response. PLoS One 2013; 8(3): e59349.
42. Jurecka-Lubieniecka B, Bednarczuk T, Ploski R, et al. Differences in gene-gene interactions in Graves’ disease patients stratified by age of onset. PLoS One 2016; 11(3): e0150307.
43. Jurecka-Lubieniecka B, Ploski R, Kula D, et al. Association between polymorphisms in the TSHR gene and Graves’ orbitopathy. PLoS One 2014; 9(7): e102653.