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Genetic and epigenetic markers in Hashimoto's thyroiditis (Review)

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Abstract. Hashimoto's thyroiditis is clinically characterized as a commonly occurring, painless, diffuse enlargement of the thyroid gland, which predominantly affects middle-aged females. The affected patients are often euthyroid, although hypothyroidism may develop. In the beginning of 20th century, Hashimoto first described the most notable signs of autoimmune thyroiditis, describing patients exhibiting atrophy of follicular cells, lymphocytic infiltration, goiter and fibrosis. Previous research has indicated the potential involvement of specific genetic variations, both inside and outside the human leukocyte antigen system, where immune control and thyroid function are focused, in the development of hypothyroidism. It has been discovered that both DNA methylation and histone modifications are involved in the development of hypothyroidism, and that these processes can affect immunological responses or gene expression in the thyroid gland. Knowledge of the interactions between the genetic and the epigenetic components which protect hypothyroidism uncovers a complex mechanism of causes and refinements. A combination of genetic and epigenetic data can be instrumental in tailoring meshes for hypothyroidism into diagnosis, prognosis and therapy. This particular line of investigation should be further pursued to determine the applicability of markers, investigate their functions and develop treatments based on these for hypothyroidism. The present review highlights the mechanisms through which genetic and epigenetic markers provide clues that could enhance the current understanding of hypothyroidism and provide disease management strategies. This may lead to the improved care of patients with this chronic autoimmune disease.

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1. Introduction

Hashimoto's thyroiditis (HT) is considered to be the reason for autoimmune Graves' disease that may eventually progress to hypothyroidism; HT causes inflammation that affects the thyroid gland and can lead to hypothyroidism. The condition is known as an autoimmune disease, which describes the complex interplay between predisposition from genetics/genes, and environmental factors and immune disorders which may also be the cause. In this case, the immune system of the body fails to differentiate the actual tissue of the thyroid, which it is supposed to be protective, but perceivably considers it as a type of foreign object and thus relentlessly keeps attacking its tissue (1). This results in the activation of an immune response, eventually leading to abnormal thyroid tissue, which causes inflammation of the thyroid cells, resulting in the very slow secretion of thyroid hormones. Clinically, the symptoms of HT appear to be the same as those of hypothyroidism, including but not confined, to a constant feeling of tiredness, an inability to tolerate cold and weight gain. The diagnosis will be based on the outcomes of thyroid function tests and serological markers detecting the association between thyroid gland carriers and antithyroid antibodies (2). Additionally, during the gestation period in females affected by HT, hormone replacement therapy is administered, which relieves symptoms and prevents possible related complications. However, HT indeed has profound implications on the quality of life of patients; patients are destined to outlive their pathology with appropriate and effective management for the malignancy. On the one hand, the intricate pathomechanism, which is the core of Chinese medicine, provides ample investigative aspects for

the researchers. On the other hand, possible research outcomes stimulate the development of the unique, European-based pharmacopeia that will help people cure their autoimmune disorders (3).

The mechanisms through which these genetic and epigenetic factors contribute to the development of HT have been identified as key factors in these complex phenomena. In addition, research that establishes the association between genetic predisposition and HT may be of value for determining which individuals are genetically susceptible, and may also determine the process of the disease pathogenesis. Clinicians are searching for the specific gene variant which triggers this genetic condition and for the genes which may function as risk factors for the condition (4). Consequently, HT may experience epigenetic regulation which differs from the normal DNA sequence, although the DNA does not change. Therefore, knowledge of the effects and countermeasures of these factors is a key prerequisite in building a solid genome-environment connection. The factor that modifies gene expression in heritable thyroid disorders is rich in epigenetic mechanisms, and it operates through a variety of mechanisms, which may be significant in the modification of immune responses and thyroid function. Furthermore, the scientific understanding of the mechanisms functioning at the level of the gene and at the epigenetic level may help identify other novel therapeutic targets that can be used for more successful personalized approaches. The latter specific genetic and epigenetic pathways, may be critical for the pathogenesis (complication processes) of HT and may guide the development of new intervention strategies which can be used to better manage autoimmune pathologies than what has previously been possible. Consequently, as a result, it can be comprehended that education at this level is necessary, not only for mankind, but also for influencing the development of treatment strategies (5).

The present review on HT and its genetic and epigenetic markers aimed to contribute to the scientific understanding of this disease and to further improve clinical management. The present review provides an overview of currently existing evidence on the genetic and epigenetic mechanisms of HT (6). The present review aimed to not only provide explanations of the possible disease-causal pathways of the disease, but also to enhance the understanding of the pre-existing and causative factors of the disease. Similarly, the present review provides an assessment of the strength and weakness of research on HT, in an aim to enhance the quality of evidence. The present review also identifies inconsistencies and discontinuities that can be sought in the field of research based on the review of the existing secondary sources, thereby presenting an opportunity for further analysis and conclusions. It is also important to highlight the fact that utilizing these genetic and epigenetic markers of HT opens a line of clinical relevance that can be used for more decisive risk assessments and for the better prediction of disease outcomes, as adequate therapeutic interventions can be developed. It is hoped that he information presented herein may expand the available knowledge of the disease, which in turn may help to improve clinical expertise. This may also help to encourage further practice and may improve quality of treatment of the patients with this complex autoimmune disease (7).

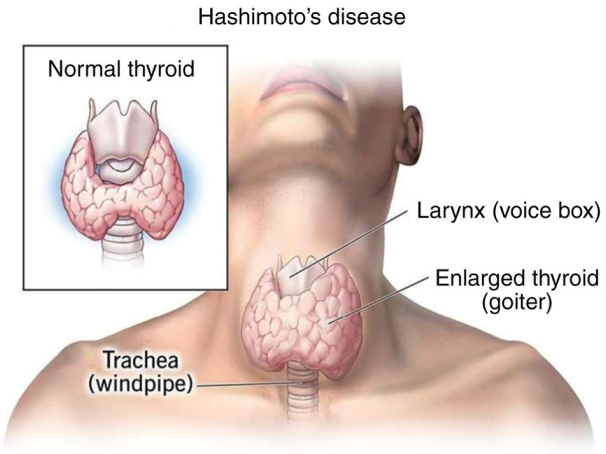

Figure 1. Image of thyroid gland in both conditions (normal and affected by Hashimoto's thyroiditis).

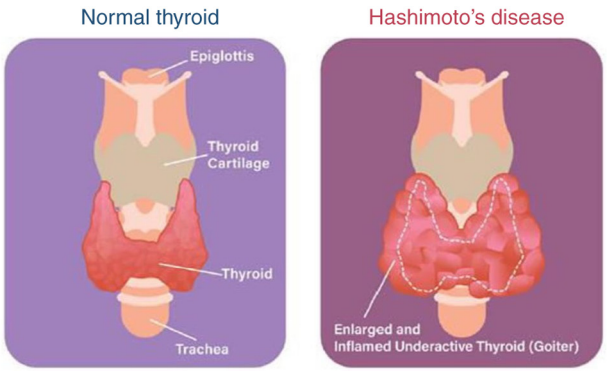

Figure 2. Illustration of the differences between a normal and affected thyroid gland.

2. Definition of Hashimoto's thyroiditis

HT is the most frequent autoimmune disorder of the thyroid gland and is the leading cause of hypothyroidism in iodine-sufficient areas worldwide. Approximately 20-30% of patients suffers from HT, the cause of which is considered to be a combination of genetic susceptibility and environmental factors that causes the loss of immunological tolerance. This leads to an autoimmune attack of the thyroid tissue and the development of the disease. The thyroid gland becomes inflamed in this type of autoimmune disease. An image of the thyroid gland in both normal conditions and in HT conditions is presented in Fig. 1 (8).

With this illness, it is not the gland that produces the thyroid hormone whose production is damaged; the immune system of the body targets the gland, attacking it gradually until it reaches the stage of complete destruction over a course of time. An image of the differences between the normal and affected thyroid gland is presented in Fig. 2.

The inhibition of iodine influx deadlocks the capability of the immune system and the consequence is a hypofunction of the gland, directly related to the decrease of the amount of produced hormones, the equilibrium of which is followed by hypothyroidism, which is, in turn, leads to a deterioration of health (9). HY may predispose to goitrous hypothyroidism,

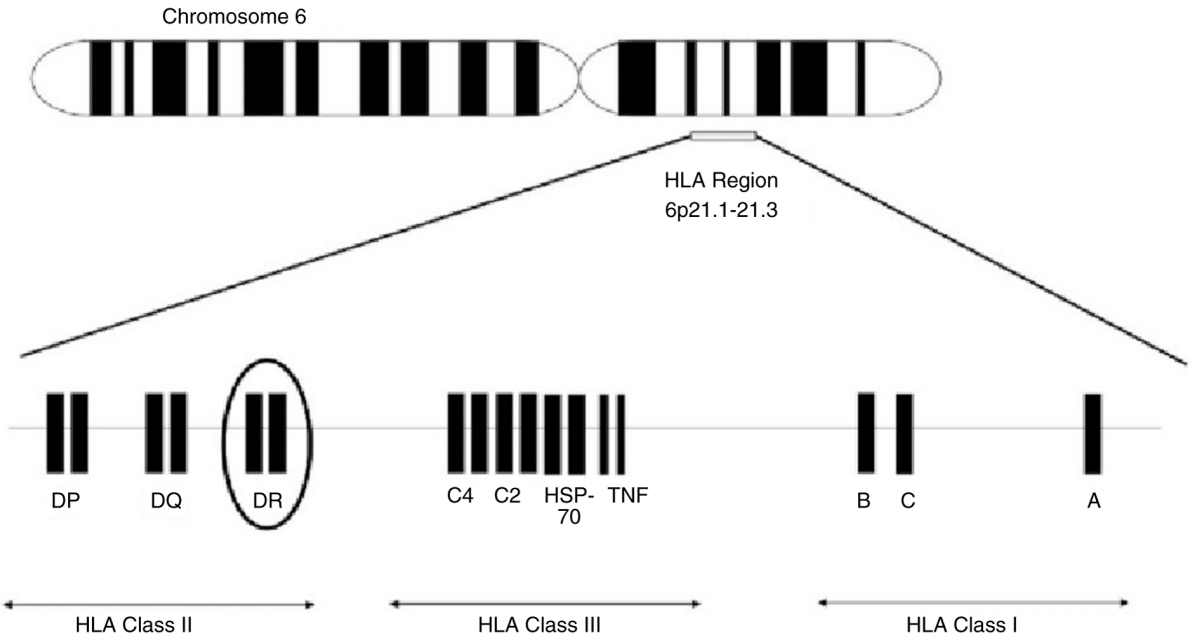

Figure 3. Illustration depicting chromosome 6 within the HLA region (10). HLA, human leukocyte antigen.

which involves an adequate of iodine; this condition mainly affects middle-aged females. However, it can also occur in males and among the elderly of both sexes. The symptoms mentioned above are instrumental in diagnosis of the disease via clinical evaluation, testing for thyroid function, and the search for autoimmune markers, such as anti-thyroid markers. Treatment approaches involve strategies which lead to the secretion of normal hormone levels and maintain the same clinical state via ongoing substitute therapy throughout life (9). Despite the fact that the disease is chronic and it requires proper medical attention for a life-long period, it is possible to maintain a normal lifestyle, and numerous patients with the disease live healthy lives (1).

3. Genetic and epigenetic markers in autoimmune diseases

HT is a complex disease combining genetic and epigenetic factors affecting autoimmunity development; it is well known as a susceptibility factor for the development of other autoimmune diseases (4).

Genetic markers

Genetic predisposition. In the majority of autoimmune diseases, it is considered that inheritance plays a crucial, including the existence of genetic mutations. On the other hand, gene variation is highly implicated in autoimmune diseases; subjects vulnerable to such diseases carry increased levels of susceptibility genes (9).

Human leukocyte antigen (HLA) genes. One of the most powerful tools for fighting infectious diseases is, without a doubt, the HLA gene located on the chromosome 6 (Fig. 3) (10); the HLA genes constitute the strongest and the most common, if not the only common, susceptibility factor for numerous autoimmune diseases, such as type 1 diabetes, celiac disease and rheumatoid arthritis; they continue to be the most extensively studied genes with relation to immunity (10).

Non-HLA genes. In addition to the HLA genes, the non-HLA genes, can be as essential as the HLA genes for the analysis of the disease. Part of these analyses would be genetic and these genes would mainly promote immune functioning, as well as the regulation of inflammation involved in immunity. Some examples of such genes are protein tyrosine phosphatase, non-receptor type 22, insulin gene, cytotoxic T-lymphocyte-associated protein 4, nucleotide-binding oligomerization domain containing 2 and tumor necrosis factor) (10).

Gene-environment interactions. It was after the genealogy constituent was discovered that a new ecological base was added to the risk of being predisposed to autoimmune diseases. The environmental factors involved include diet and nutrition, toxins and pollutants, stress and mental health, sun exposure and physical activity. Gene-environment interactions produce elicitors, which increase the risk of developing autoinflammatory diseases (11).

Epigenetic markers

DNA methylation. DNA methylation, which adds a methyl group to the DNA on the cytosine base primarily at cytosine-guanine (CpG) dinucleotides (two nucleotides), is the fundamental building block of epigenetic modification. HT-associated abnormal DNA methylation was noted with the genes involved in the thyroid function and immunity regulation involves the target genes of these epigenetic changes (12). Hypermethylation of the thyroid specific gene, including thyroid-stimulating hormone (TSH) receptor and thyroid peroxidase may serve as a predisposing cause to thyroid deficiency in patients with HT (13). A schematic illustration of DNA methylation is presented in Fig. 4.

Histone modifications. An essential element of the epigenetic control of gene expression is histone modification. Histones are considered to be proteins that contribute to nucleosomes, which are structural units of DNA. The abnormal modifications of histone, for instance, the acetylation and the methylation

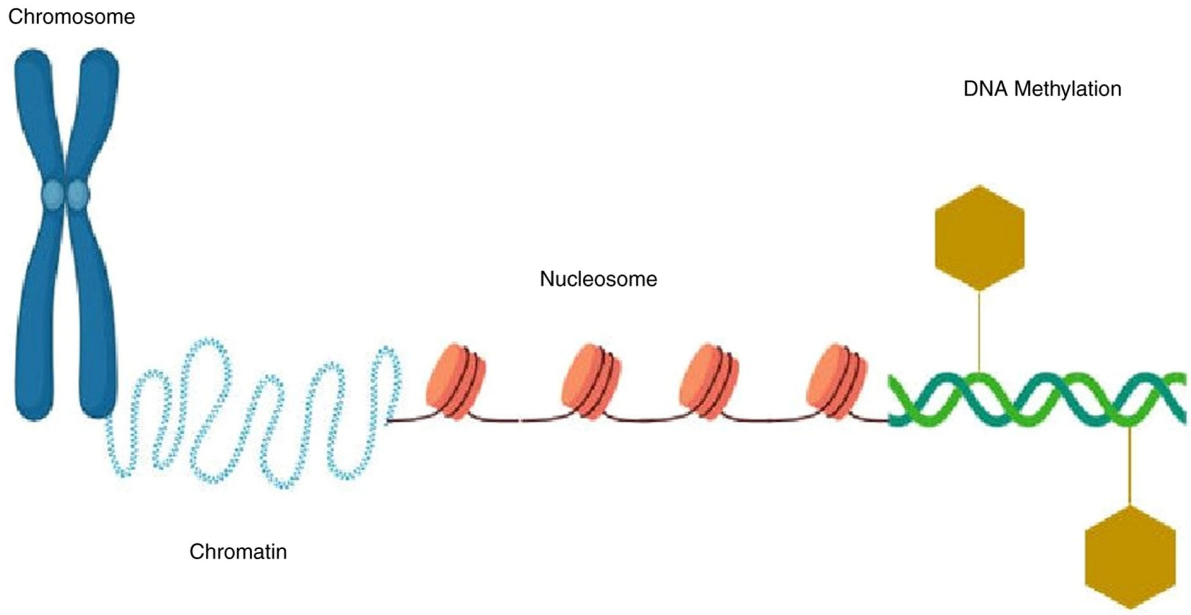

Figure 4. Illustration depicting DNA methylation (39).

which affect the chromatin's structure and the transcription of genes, may be associated with HT. The epigenetic mechanisms of histone modifications may exert effects on the expression of thyroid genes associated with auto-immunity and inflammatory responses (14,15). A schematic illustration of the modification of histones is presented in Fig. 5.

MicroRNAs (miRNAs/miRs). Various genes accelerate the development of HT. For example, altered levels of miRNAs can modulate the immune responses, as well as the proliferation and apoptosis of thyroid cells in HT. To identify miRNA expression levels in the thyroid gland in HT, the technique used is known as miRNA microarray analysis using RNA obtained from primary HT cases, three cases of HT and papillary thyroid cancer, and three normal thyroid cases, as previously described (16). A representative image of the role of miRNAs in thyroid regulation is presented in Fig. 6.

4. Significance and relevance of Hashimoto's thyroiditis in the context of autoimmune diseases

HT is one of the most common autoimmune diseases that affects thousands of individuals worldwide. Women are the most vulnerable to this disease. As it is indicated as a common autoimmune disease, this reduces the importance of convincing the public to improve awareness and proper diagnosis. Hashimoto's disease affects the normal function of the thyroid gland, which is manifested as an inflammation caused by an attack on the thyroid tissue by the immune system which leads to its destruction. In this condition, the body tends to produce autoantibodies that react to its own tissues. This is the main reason affected individuals are tested for anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies (17,18).

Association with other autoimmune diseases. There is frequently a situation in HT when the disease occurs simultaneously with other autoimmune disease, such as Graves' disease, rheumatoid arthritis, type 1 diabetes and celiac disease. This association thus uncovers common genetic predispositions and immunological components, which are disordered among the autoimmune diseases (19).

Clinical manifestations and impact on health. HT can eventually develop into hypothyroidism; the most common symptoms in adults are fatigue, lethargy, cold intolerance, weight gain, constipation, a change in voice and dry skin; however, the clinical presentation can differ with age and sex, among other factors, as well as cognitive impairments. HT can not only cause not only thyroid-related symptoms, but also some autoimmune-related complications, including the enlargement or presence of nodules in the thyroid gland, as well as a very low percentage of thyroid hormones. Furthermore, persistent or inappropriately managed hypothyroidism can have severe detrimental effects on human health and on the wellbeing of the affected individual (20).

Diagnostic and therapeutic implications. The diagnosis of HT is mostly based on an ultrasonography, which is a useful and essential tool for diagnosis based on the characteristics of the disease. In the differential diagnosis of thyroid nodules, ultrasound-guided fine-needle biopsy is an effective method used to distinguish HT from other thyroid disorders by the histological features of HT. A notable and recent advancement is that non-invasive ultrasound-based methods have supplemented fine-needle aspiration to diagnose HT under more complex conditions. The development of screening tests for thyroid function and antithyroid antibodies has enabled the rapid detection of the disease during the early stages. Primary treatment brings relief of the symptoms and prevents long-term complications is thyroid hormone replacement with levothyroxine (21).

5. Pathophysiology of Hashimoto's thyroiditis

The clinical characteristics of Hashimoto's disease are a result of the interplay and interaction of the genetic and environmental

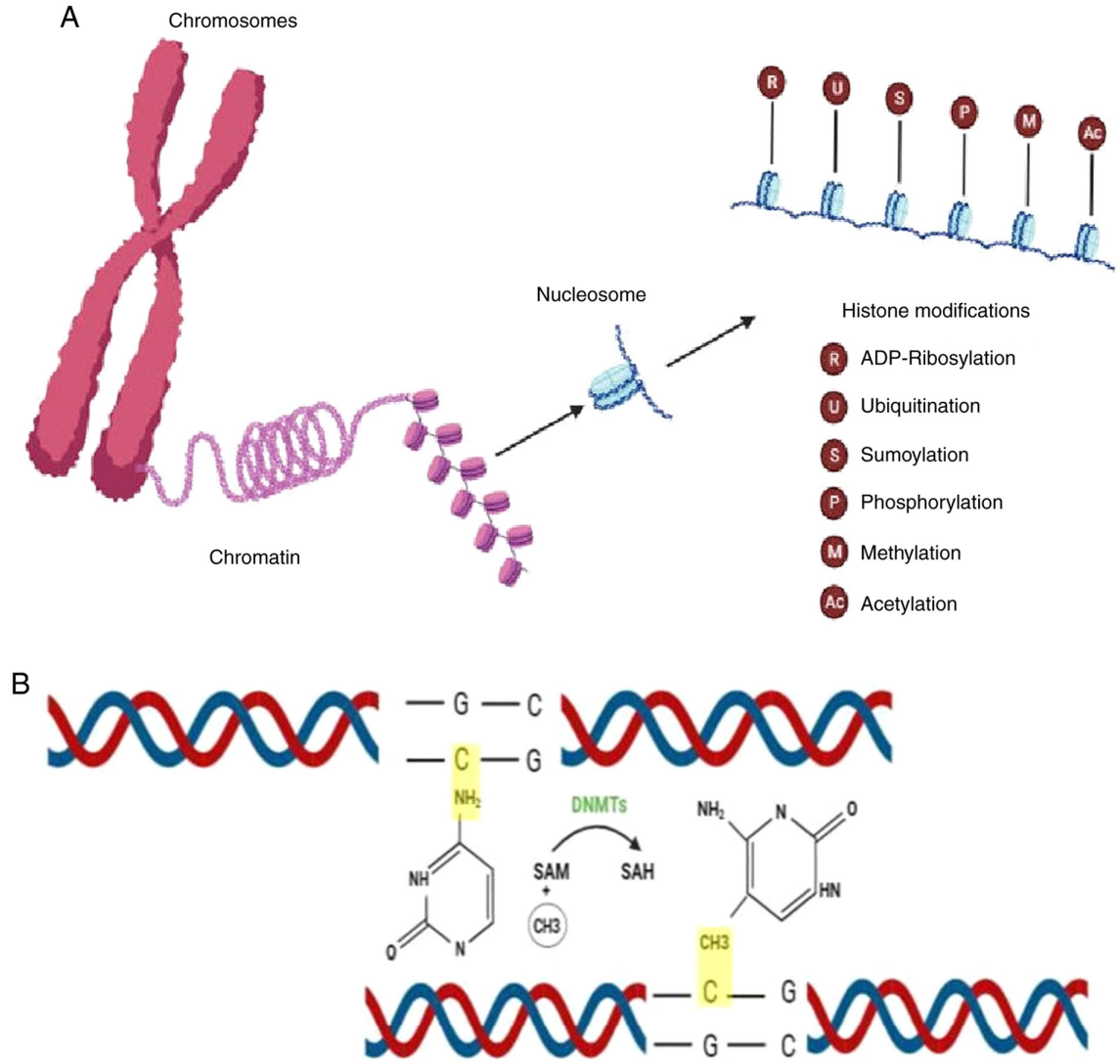

Figure 5. Histone modification process (40). (A) Modification of histones and (B) molecular level of the modification.

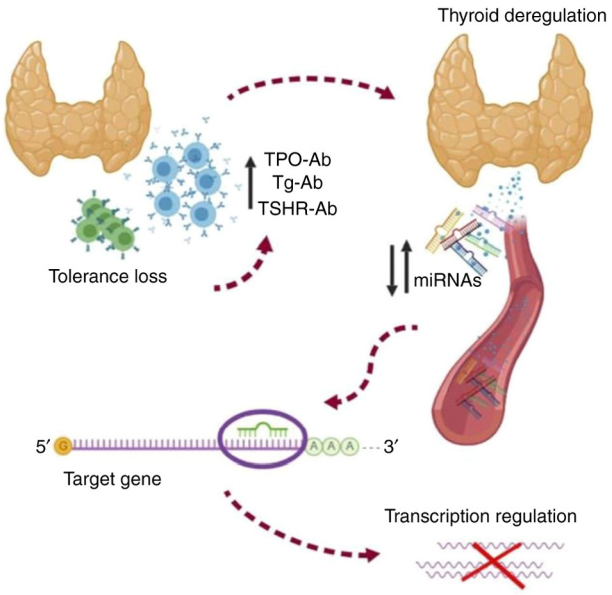

Figure 6. Image depicting the role of miRNAs in thyroid regulation (16). TPO-Ab, thyroid peroxidase antibody; Tg-Ab, thyroglobulin antibody; TSHR-Ab, thyroid-stimulating hormone receptor antibody.

components that underlie and provoke the disease (HT). Moreover, HT is an intricate autoimmune response manifested by immune-mediated inflammation, thyroid tissue destruction and ultimately, hypothyroidism (22,23).

Genetic predisposition. Individuals with a family history of autoimmune diseases, particularly HT are more than likely to suffer from the same condition. Specific gene variants, particularly in the HLA region and the genes outside the HLA, involved in immune function, can be traced back to be the genetic risk for HT (9).

Immune dysregulation. HT is marked by a particular type of immune-mediated inflammation that targets the thyroid. Predisposed subjects who encounter environmental triggers, such as viral infections or stressors have an altered response. The immune system attacks its own thyroid cells, mistaking them as foreign bodies. As a result, the process of autoreactive T-cell activation is triggered, and these cells begin penetrating the thyroid gland where they identify thyroid-specific antigens known as thyroglobulin and thyroid peroxidase (24).

Thyroid inflammation. The thyroid gland is one of the organs most affected by autoimmune processes; numerous patients with HT seek medical advice on lifestyle changes and dietary modifications in order to improve and maintain their thyroid function. In HT, T-cells stimulate B-cells to produce antinuclear antibodies, such as anti-thyroid peroxidase and anti-thyroglobulin antibodies. The autoantibodies, and the pro-inflammatory cytokines released by the activated immune cells induce secondary inflammation within the gland. Due to the infiltration of lymphocytes in the thyroid tissue, the formation of lymphoid follicles is generated, which in turn leads to the enhancement of the inflammatory response (25).

Thyroid damage. Disruptive inflammation and self-immune reactions against thyroid connective tissues lead to the continuous destruction of thyroid follicles, resulting in their inefficiency to perform their function of thyroid hormone synthesis. With thyrocyte cells being eliminated, thyroglobulin and thyroid peroxidase are released into the bloodstream, contributing to higher levels of the two thyroid autoantibodies in serum (26).

Hypothyroidism. Hypothyroidism is a common condition of thyroid hormone deficiency, which is readily diagnosed and managed; however, if left untreated, it can be potentially fatal in severe cases. The definition of hypothyroidism is based on statistical reference ranges of the relevant biochemical parameters and is increasingly a matter of debate. The clinical manifestations of hypothyroidism range from life threatening to no signs or symptoms. The most common symptoms in adults are fatigue, lethargy, cold intolerance, weight gain, constipation, a change in voice and dry skin, although the clinical presentation can differ with age and sex, among other factors, such as genetic factors, environmental factors, hormonal changes and nutritional status. The standard treatment is thyroid hormone replacement therapy with levothyroxine (23). HT is the most common cause of hypothyroidism in iodine-sufficient areas worldwide. An excessive iodine intake is associated with a higher prevalence of autoimmune thyroiditis; however, a lower prevalence of the condition is observed in iodine-deficient areas. For example, in China, autoimmune thyroiditis is observed in 0.3% of individuals in mildly iodine-deficient areas, while it is observed in 1.3% of individuals with excessive iodine intake (27).

Hashimoto's encephalopathy. Hashimoto's encephalopathy or encephalitis is a very rare complication of HT. Neurological complications are sometimes associated with thyroid dysfunction, although patients with this type of encephalopathy are usually euthyroid. It is treatable, steroid-responsive, progressive or relapsing encephalopathy associated with an elevation in the levels of of thyroid-specific autoantibodies (28).

Hashimoto's ophthalmopathy. Thyroid-associated orbitopathy usually occurs in Graves's disease with hyperthyroidism, and sometimes, in euthyroid and hypothyroid patients. Since the majority of euthyroid and hypothyroid patients with orbitopathy are thyrotropin receptor antibody (TRAb)-positive, they are diagnosed as having euthyroid Graves' disease or hypothyroid Graves' disease. When euthyroid and hypothyroid patients with orbitopathy are TRAb-negative, but have HT, Hashimoto's ophthalmopathy may be considered. As patients with HT test negative for TRAb, other autoantibodies against an eye muscle antigen, such as calsequestrin, flavoprotein, or G2s are considered to be involved (29).

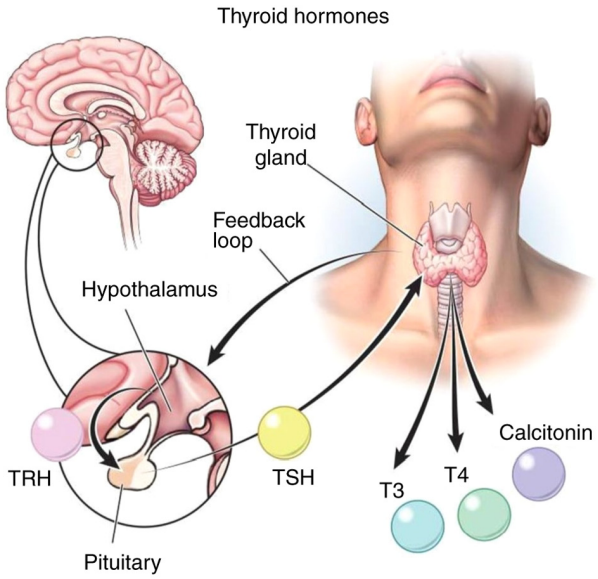

Figure 7. Illustration of the thyroid gland depicting the hormones it produces (26). TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

6. Diagnosis of Hashimoto's thyroiditis

The diagnosis of HT often results from a synthesis of a clinical examination, the examination of TSH levels and the assay of anti-thyroid auto-antibodies (8). A description of the diagnostic measures used for HT is presented below:

Clinical evaluation. Although the diagnosis of HT usually begins with a comprehensive medical history and physical examination by a health care provider, sometimes, other imaging and laboratory tests are performed to help confirm diagnosis. The appearance of certain symptoms of hypothyroidism, such as exhaustion, weight gain, cold intolerance, constipation, dry skin and irregular menstruation in women, may trigger more attacks, which will increase the likelihood of further investigations (8).

Thyroid function tests. The most fundamental investigation is thyroid function tests used to assess the levels of hormones (Fig. 7) produced by the thyroid and are used in the discovery of the thyroid disorder (27). The most commonly performed tests are the following:

TSH. TSH is considered to be the most sensitive and specific indicator of thyroid function as compared to other available thyroid tests. High TSH levels will most likely occur due to HT, the hereditary form of thyroid disease (30).

Free thyroxine (FT4). T4 is referred to as FT4 and represents the amounts of thyroxine, the primary hormone that the thyroid gland secretes. In the case of HT, the FT4 level tends to be abnormal or low, depending on the stage of the disease (30).

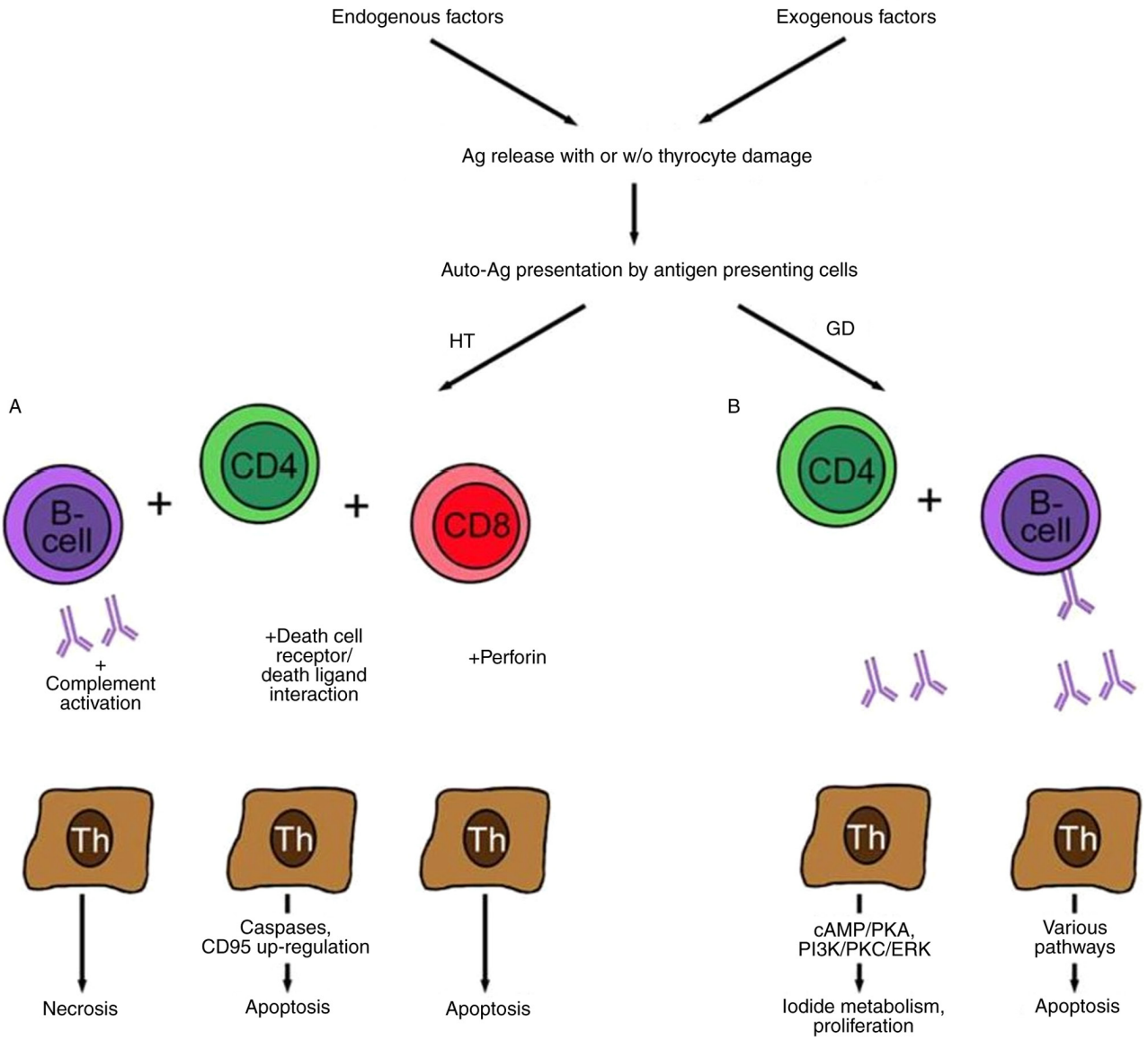

Figure 8. Illustration of thyroid antibodies (30). (A) Hashimoto's thyroiditis and (B) Graves' disease.

Triiodothyronine (T3). The T3 levels may be screened as well; however, as it is frequently found that the T3 levels are usually within the normal range in patients with hyperthyroidism (30).

Autoimmune thyroid antibodies. The evaluation of autoimmune thyroid antibodies (Fig. 8) is a strategy used to identify the factors that have triggered HT attacks and rule out other causes of hypothyroidism. The following antibodies are usually assessed (31).

Anti-thyroid peroxidase antibodies. Thyroid peroxidase bound antibodies (TPO Ab) can be found in >90% of individuals with HT, and it has now been proven that their existence defines the disease (32).

Anti-thyroglobulin antibodies. HT may, to a certain extent, also be related to the presence of a thyroglobulin antibody, although these are generally less specific than TPO antibodies (32).

Thyroid-stimulating immunoglobulins (TSI). The ability to differentiate HT from Graves' disease, another autoimmune thyroid condition, is aided by the presence of TSI antibodies. Similar to patients with HT, individuals with Graves' disease also experience hypothyroidism (33).

Imaging studies. Two-dimensional (2D) imaging may be done with the aid of a thyroid ultrasound to analyze the size and shape of the thyroid gland. In HT, the ultrasound may demonstrate either diffuse or heterogeneous echogenicity of the thyroid gland, bilateral thyroid enlarge (goiter) or presence of thyroid nodules (2).

Fine-needle aspiration (FNA) biopsy (if indicated). During an ultrasound examination of thyroid nodules, a biopsy procedure is often administered to diagnose thyroid abnormality if deemed necessary (Fig. 9) (2).

Clinical criteria. Clinical factors, such as goiter (Fig. 10) or the family history of a patient are also crucial, as they may be useful to assist to diagnose HT as well, although they are not very specific to this disease (28).

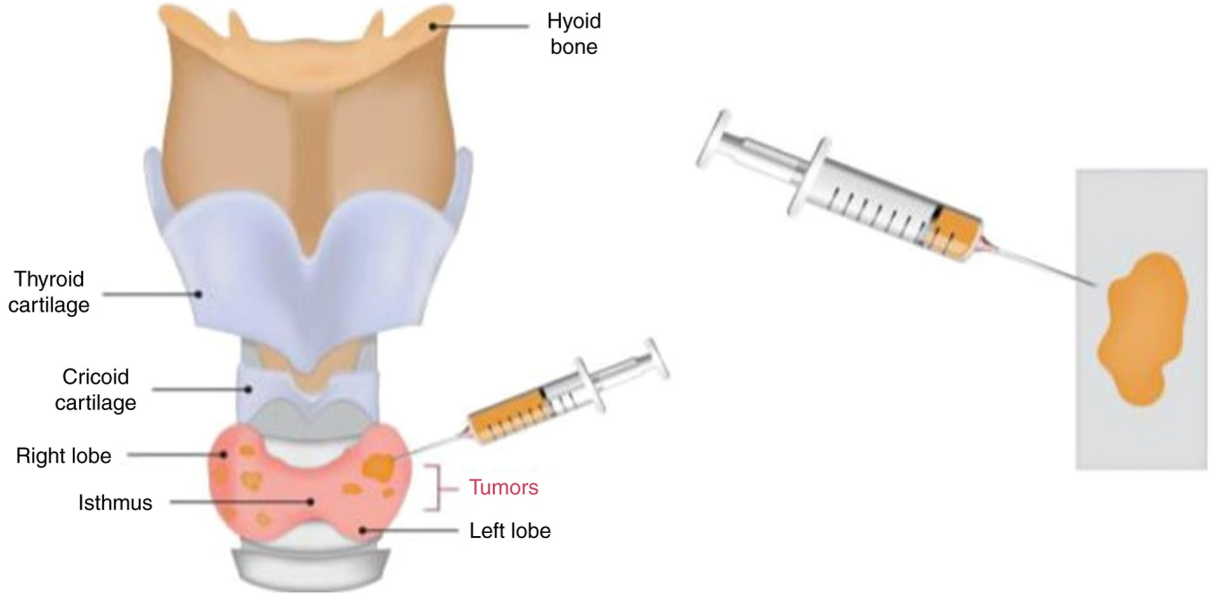

Figure 9. Image depicting needle aspiration biopsy (2).

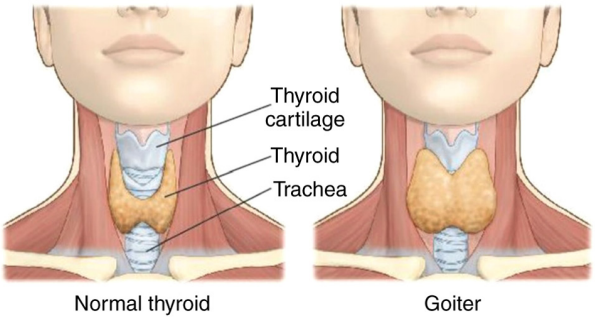

Figure 10. Image depicting the thyroid gland in both normal and abnormal states.

7. Treatment of Hashimoto's thyroiditis

The management of HT involves medication for thyroid hormone replacement to control hypothyroidism, lifestyle changes, keen regular monitoring and appropriate management for symptom relief and improvement in the life quality. With appropriate treatment, related complications and risk factors can be reduced. Collaborative treatment requires various healthcare professionals, and patients and their care team have to work together to successfully manage HT (27,34).

Thyroid hormone replacement therapy. The treatment of HT-induced hypothyroidism requires three steps: First, the establishment of a correct diagnosis by measuring thyroid hormone and thyrotropin levels should be carried out. Second, the replacement of insufficient thyroid hormones is required. The patients are treated with synthetic T4 medications, such as levothyroxine (35).

In the majority of cases, levothyroxine is received by mouth once per day, the majority of which have been prescribed to be taken in the morning on an empty stomach to produce optimum absorption levels (35). It is necessary to adjust the levothyroxine dose based on personal factors, including age, weight, severity and other health disorders (35). Periodic blood examinations that include TSH stability are necessary to control levothyroxine dosing, and to ensure that thyroid hormone levels are within the target range (35).

Lifestyle modifications. Patients with HT can benefit by adopting a healthy lifestyle, which should include a balanced diet, regular exercise, stress management and getting a sufficient amount of sleep. Diet-related factors can encompass sufficient iodine supply (if deficient), avoiding excess supplementation, and consuming minimal amounts of goitrogenic foods which can aggravate the condition (e.g., cruciferous vegetables). Smoking cessation is necessary due to the fact that it may aggravate autoimmune thyroid diseases, as well as the passage of thyroid hormones through the metabolism process.

Monitoring and follow-up. The dose of the medication will be adjusted as per the TSH levels, and patients should be monitored regularly for their TSH levels. Depending on the result, the dose of levothyroxine is adjusted accordingly (36). A follow-up appointment with an endocrinologist at 8-12 weeks following the start of treatment should be scheduled, and patients can monitor their symptoms and TSH levels by frequently visiting their physician. Patients and physicians should work together to ensure the successful management of the disease and to maintain the patient's health (36).

Management of symptoms. In addition to thyroid hormone replacement therapy, symptomatic management may be required to reduce other diseased aspects (fatigue, weight gain, over-dried and cold-intolerant skin, and constipation) (36). When patients also have symptoms of depression and mood disturbances, mental health services are recommended (36).

Complications. In patients with HT, tests for complications and comorbidities that are associated with hypothyroidism may be

considered, such as hyperlipidemia, cardiovascular diseases and osteoporosis. The therapy of these diseases may require other tactics, such as consuming fewer fat foods or tailoring cardiovascular risk components, as well as taking calcium/vitamin D supplements (37).

Patient education and support. Making patients aware of the nature of HT, the importance of adhering to medication, and the need for a considerable amount of follow-up is critical. Patient advocacy groups and online help sources can share knowledge, inspiration and help patients with HT bear these challenges (38).

8. Conclusion and future perspectives

In conclusion, the study of the genetic and epigenetic markers of HT helps to understand the disease mechanisms and enhances the diversity of diagnostic and treatment options. Through gene investigations, some exclusive variants in genes such as HLA and non-HLA gene variants have been identified, thus highlighting how genetics is a precursor to the development of the disease and its interactive role with immunity, thyroid functions and cytokine signaling. Of note, epigenetic mechanisms, such as DNA methylation, histone modifications and miRNAs play a critical role in gene expression and the regulation of the immune system. The dysregulation of epigenetic processes, and their role in the development of HT is becoming clearer, which paves the way for treatment by way of intervention. The combination of genetic and epigenetic data could provide a novel strategy for the health management of patients, including diagnostic, prognostic and treatment approaches that are tailored to individual patients. Furthermore, by tracing how genes, the environment and epigenetics interact, doctors are better able to account for the challenges associated with HT and can thus develop more specific and effective strategies for controlling HT in individuals. Nevertheless, further studies are required to understand, confirm and enhance the conciseness of the previously identified genetic and epigenetic markers, explore their functional significance and search for more possible treatments. Strategic alliance between basic scientists, clinicians and bioinformaticians is mandatory in order to translate these outcomes to clinical practice and develop the necessary tools that can be used improve the quality of lives of patients with HT. In brief, researching genetic and epigenetic markers of HT is an encouraging direction which can be used to advance both the knowledge of a complex autoimmune diseases and improve the quality of care for patients.

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Authors' contributions

All authors (SSA, HOS and AFS) conceptualized the study. SSA wrote the original draft of the manuscript. HOS and AFS provided critical revisions. All authors contributed to manuscript revision and have read and approved the final version of manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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