

Autoimmune thyroid diseases and genetic factors

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Abstract

The autoimmune thyroid condition with the highest prevalence is Hashimoto's thyroiditis (HT). Autoimmune thyroid diseases (AITD), including Graves' disease (GD) and Hashimoto's thyroiditis, arise due to complex interactions between environmental and genetic factors. Each is presenting with distinct clinical features. Significant progress has been made in our understanding of the mechanisms leading to AITD. Because of the complex nature of AITD, caused by their polygenic nature and a complex mode of inheritance, there are still more questions to be answered than answers that can be given, especially about the nature of Hashimoto's thyroiditis. One of the cornerstones to understanding illness pathophysiology and creating better treatments is figuring out the genetic component of AITD. Common HT and GD genes have been identified, as well as genes that are characteristic of only one of those diseases.

Keywords: Autoimmune thyroid diseases; Genetic factors; Graves' disease; Hashimoto's thyroiditis

1. Introduction

Hashimoto's thyroiditis (HT), the most prevalent autoimmune thyroid disease (AITD), is becoming more and more commonplace in recent years [1,2]. Since the entity of Hashimoto's thyroiditis (HT) was described by Hashimoto in 1912, it has evolved as the most common etiology of acquired hypothyroidism in adolescents and children [3,4]. Additionally, it is referred to as autoimmune thyroiditis or chronic lymphocytic thyroiditis. HT is primarily a disease of adult and senior women between 45-65 years. When compared to men it has 10 to 20 times more female sex predilection [4,5]. HT in children rarely occurs before four years of age with a peak age of incidence around adolescence (10-12 years) [3]. Goiter associated with hypothyroidism characterizes HT, loss of thyroid follicular cells, circulating autoantibodies to thyroid-specific antigens: thyroid peroxidase (TPO) and thyroglobulin (Tg); infiltration of the thyroid by T and B cells reactive with these thyroid antigens [3]. The presence of autoantibodies against Tg and TPO is a hallmark of the early stages of HT [3], and the lymphocytic infiltration of the thyroid gland leads to apoptosis of thyrocytes and hypothyroidism [6]. Hashimoto's thyroiditis cases have been increasing noticeably during the last few years [2]. The progressive degeneration of the thyroid gland that occurs after intrathyroidal lymphocytic infiltration may cause subclinical or overt hypothyroidism [1]. Three phases make up the traditional clinical picture of HT: initial hyperthyroidism (overt, subclinical), euthyroidism, and permanent hypothyroidism with or without goiter. The duration of these phases is neither discrete nor sequential in a given individual varying from weeks to months. Years later after the diagnosis long euthyroid period ended up in hypothyroidism. The diagnosis of HT based on seropositivity of elevated anti-TPO antibody titer along with thyroid dysfunction with or without goiter. Additional confirmatory criteria include radiological ultrasonography criteria for diffuse hyperechogenicity [1,3] and pathological FNAC features for lymphocytic infiltration, fibrosis, Hurthle cells, plasma cells, and thyrocyte destruction [5,7].

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2. Pathogenesis

Significant progress is made in our understanding of the mechanisms leading to AITD. The intricate interactions between environmental and genetic factors are the cause of AITD, which includes Graves' disease and Hashimoto's thyroiditis [8,9]. Each is exhibiting unique clinical characteristics [10]. However, due to the polygenic character of AITD and their complex way of inheritance, there are still more questions than answers that can be given, particularly about the nature of Hashimoto's thyroiditis [2]. The exact mechanisms responsible for the disease development are still not completely understood despite a very high HT prevalence. Significant advances in the knowledge of the causes and pathogenesis of autoimmune thyroid disease which most frequently occurs in the form of Graves' disease (GD) or HT [1]. Hashimoto's thyroiditis is the result of multistep, complex pathophysiology that is influenced by several genetic, environmental, and immunological variables. When individuals genetically predisposed are exposed to the above-mentioned ecological factors, the initial inflammatory changes in the disease process are triggered. The major histocompatibility complex (MHC) class 2 antigen-presenting cells, which include dendritic cells and macrophages, invade the thyroid gland after the initial inflammatory process. These cells present the autoantigen components of the thyroid gland to the immune system for processing. Within the myriad of potential auto-antigens, thyroglobulin is believed to play a central role in the pathogenesis of this disease [3]. Thyroglobulin was reported to have nearly 40 different types of epitopes, which play an essential role in the aetiopathogenesis of the disease [3]. The epitope recognition pattern of the antibodies in autoimmune thyroid disease is changed, activating inflammatory and immunological processes, in contrast to the epitope recognition pattern of healthy persons [3]. Thyroid peroxidase, an enzyme that catalyzes the oxidation of iodine, also plays a significant role as an autoantigen in disease pathogenesis. Moreover, 180 different types of thyroid peroxidase antibodies are identified, thus far. The formation of autoreactive cells directed against the thyroid gland is considered a significant step in the pathogenesis which could result from defects in central tolerance or errors in peripheral tolerance. Loss of immune tolerance is associated with genetically determined immune abnormalities or with the lack of regulatory T-cells which forces the suppressive function [3]. The previous process is followed by the formation, clonal extension, and maturation of self-reactive T-lymphocytes and B-lymphocytes in the draining lymph nodes. Then, this step is followed by a central phase of autoimmunity, characterized by the unconscious production of autoantibodies and self-reactive cells in response to the presented antigens. This process primarily takes place in the lymph nodes but as the disease continues the production process shifts to the thyroid gland where the evolution of lymphoid tissue follows. Stimulated B-lymphocytes produce anti-thyroid peroxidase (ATPO) antibodies and antithyroglobulin (TGAB) which are directed toward thyroid cells. The autoreactive T-cells infiltrate the thyroid gland and mediate destruction through cytotoxicity with the help of CD+8 cells. The macrophages which are stimulated in this process produce numerous cytokines which, along with antibodies, initiate the process of tissue destruction through apoptosis [11].

Caspases, which are self-activated through proteolytic cleavage, induce enzymes that are directly involved in the destruction of the thyroid gland. In the normal thyroid gland, the production of new cells and the removal of old cells are dynamically adjusted so that a constant proportion of functioning cells is always present. During the disease, the control over the destruction of cells in the thyroid gland is lost. Etiopatho-genetically, HT has been held as an organ-specific immunological disease, later evidence and a surge of molecular researchers suggest that both genetic and environmental factors influence its genesis [12,13].

Genetic Factors Monogenic Autoimmune Thyroiditis. The relevance of thymic tolerance and regulatory T cells in preventing thyroid autoimmunity from developing spontaneously is best illustrated by two uncommon monogenic diseases. Mutations in the autoimmune regulator AIRE gene cause autoimmunity polyglandular syndrome type 1. Many other autoimmune disorders, including hypothyroidism, emerge in these patients in addition to the cardinal childhood signs of autoimmune hypoparathyroidism, Addison's disease, and chronic mucocutaneous candidiasis, albeit not in all populations [20]. AIRE is produced in thymic medullary epithelial cells and is essential for exposing young T cells to a wide variety of ectopically expressed self-antigens that cause their deletion. There are at least 60 known AIRE mutations, and in individuals with these mutations, an improper presentation of self-antigen in the thymus results in loss of self-tolerance. The formation of neutralizing autoantibodies against type 1 interferons and T helper cell cytokines related to interleukin-17 is most likely the cause of the chronic candidiasis component of the illness [18]. Emerging models suggest that the abnormal thymic microenvironment in this syndrome may lead to the production of cytokine autoantibodies as an initiating step, which in turn may permit less-well tolerized T cells to emerge, with a greater susceptibility to activation by autoantigens in the periphery. IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome, the second of these monogenic syndromes, is characterized by the deadly neonatal start of autoimmune diseases, including thyroiditis. These patients have mutations in the FOXP3 gene, which is responsible for the normal functioning of regulatory T cells [21]. These two monogenic illnesses highlight how either abnormal thymic development or the breakdown of peripheral tolerance can lead to autoimmunity. They are rare, and polymorphisms of the genes involved are not known to play a role in more common forms of autoimmune thyroiditis.

They could be categorized as single-order disasters. The Swiss-cheese model of disaster describes how the typical autoimmune thyroiditis develops when several minor hereditary (and non-genetic) events line up like the holes in slices of Swiss cheese to allow the undesirable event to happen. Numerous Autoimmune Thyroiditis The major histocompatibility complex [MHC; in humans, this is the well-known human leukocyte antigen (HLA) system] was quickly shown to be important in the predisposition of animals to this disorder through observations in the early models of experimental autoimmune thyroiditis, and the influence of additional non-MHC genes was quickly recognized [19]. At the same time, family studies in humans, such as those by my mentor Reg Hall and colleagues in Newcastle-upon-Tyne [18] confirmed that there was a genetic component to Hashimoto thyroiditis. More recently, Brix et al. [20] have used extensive twin studies in Denmark to identify the importance of genetic factors in Hashimoto thyroiditis and thyroid autoantibody formation. The last two decades have seen the application of increasingly sophisticated molecular genetics approaches to identify the genes responsible for this predisposition [18]. The most enlightening claim made by Davies [18] is that there aren't any genes that are significant for autoimmune thyroid disease. In other words, there isn't a dominant gene for substantial Hashimoto thyroiditis susceptibility, and the HLA system's role in susceptibility is less clear than it is in conditions like type 1 diabetes and celiac disease. As with many other autoimmune conditions, four distinct genetic influences have been found in autoimmune thyroid disease. It must be emphasized that Hashimoto thyroiditis and Graves disease have received less attention in genetic studies than those on the former. In some studies, these two conditions are included under the umbrella term "autoimmune thyroid disease," which has questionable nosological validity. As just one example, disease associations with these two disorders, which are very likely to have a genetic basis, are rather distinct [22]. In the most recent discoveries of genetic polymorphisms associated with Hashimoto thyroiditis, there is a focus on possible genetic heterogeneity across different ethnic groups, which compounds the difficulty of interpretation. For instance, single nucleotide polymorphisms (SNPs) in the PTPN22 gene have been associated with several autoimmune disorders in discrete ethnic groups. In Caucasians, there is evidence of a relationship with Graves disease, whereas, in Koreans, the association seems to be with Hashimoto thyroiditis but not the latter [23]. These two autoimmune thyroid disorders in Koreans are related differently to SNPs of the STAT4 gene, which is implicated in interleukin signaling [24]. There may also be sex differences in the influence of genetic polymorphisms. A common polymorphism in the IL12B gene's coding area was found to be differently related to Graves disease and Hashimoto thyroiditis in a recent investigation of SNPs in this gene, but only in men [25]. In all 3 of these studies, relatively small populations were studied, albeit with replication in the last. Identification of new risk loci by genome-wide association methods typically requires enormous populations: the recognition of new loci at 6q27 and 4p14 in Graves disease recently required an initial set of 1,516 patients, with replication in a further 3,994 along with similar numbers of controls [26]. This does not work for the faint-hearted or inadequately funded. To date, there have been no similar mammoth undertakings in Hashimoto thyroiditis. Genome-wide approaches cannot readily identify the rare alleles (< 5% of the population) that associate with the disease and the loci found are often located in regions that affect gene expression, which in turn makes interpretation of the underlying mechanism of disease very difficult, although this is essential to understanding how environmental factors interact with genetic susceptibility [18]. Copy number variation is also likely to contribute to susceptibility to autoimmune disease and thus add even greater complexity [18]. As of yet, we have no real idea of the number of genetic loci which contribute to the development of Hashimoto thyroiditis, but an insight into this may be gleaned from studies of vitiligo. This disorder of skin pigmentation is well known to be associated with autoimmune thyroid diseases and other autoimmune disorders, based on the sharing of genetic susceptibility [27]. An international consortium has recently published two genome-wide association studies with a meta-analysis, and this has revealed the existence of 27 separate susceptibility loci, an unexpectedly large number when it is noted that these loci account in total for less than 20% of the heritability of vitiligo [28, 29]. The majority of these loci encode genes that can be classified as broadly immunoregulatory or that code for proteins found in melanocytes; many of the former have characteristics with other autoimmune diseases, such as thyroiditis. In conclusion, we now understand that, despite certain genetic susceptibility being shared by Graves disease, Hashimoto thyroiditis, and other associated disorders (HLA-DR3 allele and CTLA4), there are immunoregulatory genetic variations that contribute to autoimmune thyroid disease. The precise illness outcome from an underlying thyroid-centered autoimmune diathesis in which thyroglobulin and thyroid peroxidase autoantibody production features may be determined by thyroid-specific genes, such as TSHR [18]. Similar to vitiligo, it is likely that an absurdly large number of genetic loci, some of which are ethnically distinct, dictate heredity. These loci, in turn, may interact with one another and environmental factors in ways that may be specific to extremely small cohorts of patients. The complexity of the pathogenesis of autoimmune thyroid disorders is badly underestimated, and this is where we are right now [30].

3. Genetic Susceptibility

One of the factors that play an essential role in the deregulation of the natural destructive mechanisms in the thyroid gland is genetic susceptibility. The genetic analysis of HT shows two types of susceptibility genes-immune regulatory and thyroid-specific genes [14,15]. Thyroid-specific genes act on inter- and intracellular milieu responsible for normal hormone synthesis. The thyroid auto-immunity is controlled by immunomodulatory genes such HLA-DR, CTLA-4, and

PTPN22 [1]. Thyroid-specific genes such as Top, NIS, Duox2, thyroglobulin, TSH receptor have also implicated in pathogenesis and thyroid dysfunction [5]. Also, the exact genotype-phenotypic correlations and risk categorisation of hypothyroid phenotypes resulting from these known mutations are mainly speculative [15]. The autoimmune response to thyroid antigens in AITD is hypothesized to be triggered by genetic susceptibility in conjunction with environmental variables (such as dietary iodine) [16]. Although some replicated, genetic associations are emerging, providing insights into the underlying disease mechanisms, a significant component of the genetic association to AITD remains unknown [3]. AITDs (GD and HT) are complex genetic diseases that most likely have more than 20 genes contributing to the clinical phenotypes [1, 17]. One of the keys to understanding illness pathophysiology and creating better treatments will be to unlock the genetic contribution to AITD [3]. Common HT and GD genes are identified, as well as genes that are characteristic of only one of those diseases [2]. It has been demonstrated that seven genes play a role in the etiology of AITD. GD and HT both contribute to the first AITD gene found in HLA-DR3. The immune-modifying genes (such as HLA and CTLA-4) and thyroid-specific genes make up the probable GD and HT susceptibility genes (e.g. HLA, CTLA-4) and thyroid-specific genes (e.g. TSHR, Tg) and it is likely that the final disease phenotype is a result of an interaction between these loci, as well as environmental influences [16]. Candidate gene analysis, whole-genome linkage screening, genome-wide association studies, the whole-genome sequencing are the major technologies that have advanced this field that lead to the identification of at least seven genes whose variants are associated with AITD. One of the major ones is the HLA-DR gene locus [9]. Nine potential novel regions of association with GD were discovered in a recent association scan employing a genome-wide set of nonsynonymous coding single-nucleotide polymorphisms (nsSNPs) in four illnesses, including GD [3]. The genes that are known to be involved can be divided into two groups: thyroid-specific genes (TG and TSHR) and immune regulatory genes (HLA, CTLA4, PTPN22, CD40, CD25, and FCRL3). Genetic predisposition although the heredity of thyroid autoantibodies is something we are aware of, precise estimations for HT have only lately been determined. Probandwise concordance rates for HT in sizable Swedish twin research were 0.29 and 0.1 for monozygotic and dizygotic twins, respectively, yielding an estimated heritability of 0.64 [32]. This underlines the significance of both genetic and environmental variables in determining vulnerability. In the same population, this was lower than for type 1 diabetes mellitus (0.81) and Addison's disease (0.97) In contrast to what would have been anticipated, familial co-aggregation of the other autoimmune illnesses with HT was less frequent, but the higher concordance in monozygotic twins provided further evidence that this disease sharing was based on shared genes. Most attempts to look at the genes which predispose to autoimmune thyroid disease have recently focussed on Graves' disease rather than HT but an attempt has been to look at how much the established or tentative polymorphisms associated with HT contribute. In a relatively small series of 142 Polish cases, only seven polymorphisms could be confirmed as being associated, due to the small sample size, only 5.5% of the total variability and none of the typical environmental factors appeared to be linked to susceptibility [33]. Another study from Croatia of 405 patients, with a confirmation cohort of a further 303, identified three novel variants contributing 4.8% of the genetic variance in HT, but due to limited power, the authors could not confirm associations already established by conventional association studies [34]. Much larger studies are needed but these will be difficult to organize and fund, given the perception that HT is less important than Graves' and other diseases. At this stage, we can see that there must be dozens of genes at least, each contributing a tiny fraction to the overall complex picture. Its prevalence and heredity are comparable to those of HT, making vitiligo a useful comparison. Genome-wide screening has been more successful in vitiligo than in HT and other autoimmune illnesses because about 60 common genetic variations account for almost two-thirds of the heritability of the condition overall and have larger impact sizes than other complex diseases [35]. It has also been possible to impute that there is no 'missing heritability' (for instance due to epistasis or epigenetic effects) in vitiligo, whereas this remains an assumption for most other autoimmune diseases. Nonetheless identifying the myriad of rare and private genetic variants that account for 29% of the genetic risk in vitiligo will take huge populations or a fresh approach; this challenge will be far greater still in HT were rare variants seem to predominate. The description of a previously unreported splice site variant in the thyroglobulin gene (TG c. 1076- 1G >C), associated with exon skipping and resulting in a variant transcript of TG, was found in affected members of an autosomal dominant HT family, as well as one unaffected child (who may yet develop HT or represent incomplete penetrance) [36]. Certain TG polymorphisms have already been linked to HT and Graves disease, although only at very low risk. It is unclear whether the unique variant encodes a thyroglobulin protein that injures thyroid cells, causing autoimmunity, or elicits an immune response via alternative pathways, but it is worth noting that affected members exhibited autoantibodies to both thyroglobulin and thyroid peroxidase (TPO). Another autosomal dominant HT family with a mutation leading to haploinsufficiency of the gene-producing tumor necrosis factor- α -induced protein 3, also known as A20 [37] has been found. It is already known that A20 haploinsufficiency may result in inflammatory and autoimmune disorders, presumably through the role of A20 in regulating T helper 17 (Th17) cells and other immune responses, and another such patient with HT in association with Behçet's syndrome and vitiligo has been reported recently [31]. In a study of 298 Jordanian HT patients compared to healthy controls, consanguinity was associated with an increased relative risk of 3.3 for HT [31]. Such unions lead to increased expression of autosomal recessive but not autosomal dominant or X-linked disorders, and further studies of such examples may be fruitful. More traditional candidate gene association studies have continued to add prospective candidates to those already found, although they are frequently modest in size and have yet to be

repeated. The tumor necrosis factor superfamily member 4 gene, which encodes OX40 ligand (CD252), a co-stimulatory signal expressed by many antigen-presenting cells, is one potentially significant example. Polymorphisms in this gene have been linked to autoimmune rheumatological disorders, and a weak link to HT in young Han Chinese patients has since been discovered [31]. The same group examined five ubiquitin gene variants, perhaps utilizing overlapping patient cohorts, and found no relationship with Graves' illness but reported one weak unconfirmed association with HT [31].

4. Conclusion

Graves' disease and Hashimoto's thyroiditis are autoimmune thyroid diseases caused by complex interactions between environmental and genetic factors. There is strong evidence from epidemiological, family, and twin studies that there is a strong genetic influence on the development of AITD. In this review, we summarize new findings on genetic susceptibility to AITD, with a focus on emerging susceptibility mechanisms.

Compliance with ethical standards

Disclosure of conflict of interest

There is no conflict of interest.

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