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THE HLA GENE COMPLEX IN THYROID AUTOIMMUNITY: FROM EPIDEMIOLOGY TO ETIOLOGY

Eric M. Jacobson, PhD, Amanda Huber, Bsc, and Yaron Tomer, MD, FACP*

Division of Endocrinology, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Abstract

The autoimmune thyroid diseases (AITD) comprise a cadre of complex diseases whose underlying pathoetiology stems from a genetic-environmental interaction, between susceptibility genes (e.g. CTLA-4, HLA-DR, thyroglobulin) and environmental triggers, (e.g. dietary iodine) that orchestrates the initiation of an autoimmune response to thyroid antigens, leading to the onset of disease. Abundant epidemiological data, including family and twin studies, point to a strong genetic influence on the development of AITD. Several AITD susceptibility genes have been identified, with HLA genes, in particular, appearing to be of major importance. Early studies showed association of HLA-DR3 with Graves' disease (GD) in Caucasians. More recently, the importance of an amino acid substitution at position 74 of the DR beta 1 chain of HLA-DR3 (DRb1-Arg74), in susceptibility to Graves' disease, has been shown. Furthermore, there is increasing evidence for a genetic interaction between thyroglobulin variants and DRb1-Arg74 in conferring risk for GD. Mechanistically, the presence of an arginine at position 74 elicits a significant structural change in the peptide binding pocket of HLA-DR, potentially affecting the binding of pathogenic thyroidal peptides. Future therapeutic interventions may attempt to exploit this new bolus of knowledge by endeavoring to block or modulate pathogenic peptide presentation by HLA-DR.

Keywords

Gene; Thyroid; Graves' disease; Hashimoto's thyroiditis; HLA; Linkage; Association

BACKGROUND

The autoimmune thyroid diseases (AITD) encompass a number of conditions, the most classical of which include Graves' disease (GD) and Hashimoto's thyroiditis (HT). AITD share a commonality in their underlying cellular and a humoral immune responses that are targeted at the thyroid gland, resulting in infiltration of the thyroid by T and B lymphocytes reactive to thyroid antigens and the production of thyroid autoantibodies, leading to the clinical manifestations of hyperthyroidism in GD and hypothyroidism in HT (1;2). While the exact etiology of the immune response to the thyroid remains unknown, there exists solid evidence for a major genetic influence on the development of AITD (reviewed in (3)). Hence, the currently accepted paradigm is that AITD are complex diseases in which susceptibility genes, in combination with environmental triggers, initiate the autoimmune response to the thyroid. Recently, several AITD susceptibility genes have been identified (3), and it is clear that, from

Address for correspondence: Yaron Tomer, MD, Division of Endocrinology, University of Cincinnati College of Medicine, 3125 Eden Ave, Cincinnati, OH 45267, Voice: 513-558-1774, Fax: 513-558-8581, E-mail: Yaron.Tomer@uc.edu.

*Cincinnati VA Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA

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the battery of candidate susceptibility genes, HLA genes play a major role in the susceptibility to AITD (4). Therefore, in this review, we will focus on the association of HLA genes with AITD and the functional implications of this association.

THE AUTOIMMUNE THYROID DISEASES ARE FAMILIAL

The familial occurrence of AITD has been reported by investigators for many years. Studies have shown that 33% of siblings of GD or HT patients developed AITD themselves, and 56% of siblings of AITD patients produced thyroid autoantibodies (TAbs) (reviewed in (4)). A metric known as the sibling risk ratio, which is the ratio of the prevalence of the disease in siblings of affected individuals compared to the prevalence of the disease in the general population, serves as a good estimate of disease heritability, with a ratio of > 5 considered significant. Recently, we have calculated the sibling risk ratio for AITD in our own patient population, and our results showed a ratio of 16.9. This high sibling risk ratio supports a strong genetic influence on the development of AITD.

Twin data have confirmed, with remarkable clarity, the presence of a substantial inherited susceptibility to AITD. Several large twin studies have reported a higher concordance rate of AITD in monozygotic (MZ) twins compared to dizygotic (DZ) twins (reviewed in (4)). Concordance rates were 35% in MZ twins and 3% in DZ twins for GD, and 55% in MZ twins and 0% in DZ twins for HT.

HLA CLASS II GENES ARE ASSOCIATED WITH AITD

The Major histocompatibility complex (MHC)

The MHC region, encoding the HLA glycoproteins, consists of a complex of genes located on chromosome 6p21. The MHC locus encodes genes which are grouped into 3, distinct classes: (1) Class I genes include the HLA antigens A, B, and C, (2) Class II genes include the heterodimeric HLA-DR, DP, and DQ genes, and (3) Class 3 genes include complement components (e.g. C4), tumor necrosis factor alpha, heat shock protein 70, and several other genes (for a review see (5)). Since the HLA region contains many immune response genes, and has been shown to be highly polymorphic, it logically became the first candidate genetic region to be studied for association with AITD, as well as for association with other autoimmune diseases.

Association of HLA with Graves' disease

Early studies of HLA in Graves' disease (GD) have found that HLA-B8 was associated with GD with relative risks for GD ranging from 1.5 to 3.5 (6). Subsequent research, however, found that GD was more strongly associated with HLA-DR3, which is now known to be in linkage disequilibrium with HLA-B8 (reviewed in (7)). The frequency of DR3 in GD patients was generally 40–55% in GD patients, and ~ 15–30% in the general population, resulting in a relative risk for people with HLA-DR3 of 3–4 (6)). Confirming the results of the case control studies was a family-based association study from the UK, using the transmission disequilibrium test (TDT) (8). Additionally, among Caucasians, HLA-DQA1*0501 was also shown to be associated with GD (9;10), but recent studies have suggested that the primary susceptibility allele in GD is indeed HLA-DR3 (HLA-DRB1*03) (11).

The role of HLA polymorphisms on the clinical expression of GD has also been explored. Intriguingly, some groups reported an association between the likelihood of relapse of GD and HLA-DR3, but most other investigators were unable to confirm this observation (reviewed in (4)). Additionally, studies of HLA associations in Graves' ophthalmopathy have also produced conflicting results with some reporting increased frequency of HLA-DR3 in patients with Graves' ophthalmopathy, and others reporting no difference in the distribution of HLA-DR

alleles between GD patients with and without ophthalmopathy (4). For the case of Graves' disease patients with and without pretibial myxedema, no difference in the DR3 frequency was observed (6).

Association of HLA with Hashimoto's thyroiditis

Data on HLA haplotypes in Hashimoto's thyroiditis (HT) have been less definitive than in GD. A general methodological problem has been disease definition. HT encompasses a spectrum of manifestations, ranging from the simple presence of thyroid autoantibodies to the presence of goitrous or atrophic thyroiditis, characterized by gross thyroid failure (12). In terms of genetics, there are reports of an association of HT with HLA-DR3 (13), and HLA-DR4 (14) in Caucasians. Interestingly, we recently have shown the HLA-DR3 was the primary HLA class II allele responsible for the joint susceptibility for type 1 diabetes and AITD in families in which both diseases cluster (15). Furthermore, the association of HLA-DR3 with HT is further bolstered by studies in mice, where it was found that mice harboring a DR3 transgene were susceptible to severe experimental autoimmune thyroiditis (EAT), while mice with a DR2 transgene were resistant to EAT (16). Finally, an association between HT and HLA-DQw7 (DQB1*0301) has also been reported in Caucasians (17).

THE EFFECT OF ETHNICITY ON THE ASSOCIATION OF HLA WITH AITD

The HLA genes have been shown to be associated with GD in non-Caucasian populations as well, although the associated alleles were different from those observed in Caucasian groups. Studies in the Japanese population have shown associations of GD with HLA-B35 (18). In addition, other HLA alleles have also been reported to be increased in Japanese GD patients (19;20). In the Chinese population, an increased frequency of HLA-Bw46 has been reported (21;22), and in African-Americans an increased frequency of HLA-DRB3*0202 was reported (23). Interestingly, one study of a mixed population in Brazil showed association with HLA-DR3 implying that this allele may confer susceptibility in other ethnic groups and not just Caucasians (24). Alternatively, this Brazilian population may have been comprised mostly of European ancestry.

HLA association studies in HT also have not shown consistency across non-Caucasian ethnic groups, e.g. HLA-DRw53 in Japanese (25), and HLA-DR9 in Chinese (26).

SEQUENCING OF THE HLA-DR IN GRAVES' DISEASE

The MHC class II molecules are a highly polymorphic group, with HLA-DR3 alone having over 25 subtypes with distinct sequence variants. However, until recently, the exact amino-acid sequence in the DRb1 chain conferring susceptibility to GD was unknown. In other autoimmune diseases, including Type 1 diabetes (T1D) (27), there is compelling evidence that disease is associated with specific amino-acid sequences of the DRB1 and DQ genes. Therefore, we sequenced the HLA-DRB1 locus in a population of GD patients and controls. Our sequencing endeavors led to the identification of an arginine residue, at position 74 of the HLA-DRb1 chain (DRb1-Arg74), as the critical DR amino acid conferring susceptibility to GD (28). These data have since been replicated in an independent dataset (29). Except for arginine, the other most common amino acids occupying position 74 of the DRb1 chain are either alanine or glutamine; therefore, the presence of DRb1-Ala74 or DRb1-Gln74 could, theoretically, afford protection against GD. Indeed, further analysis has shown that the presence of Glutamine at position 74 was protective for GD (28). This suggested that position 74 of the DRb1 chain is critical for GD pathoetiology.

MECHANISMS BY WHICH HLA ALLELES CAN PREDISPOSE TO AITD

The mechanisms through which HLA molecules confer susceptibility to autoimmune diseases are now beginning to be understood. T cells recognize and respond to an antigen by interacting with a complex composed of an antigenic peptide, presented by an HLA molecule (reviewed in (30)). It is thought that different HLA alleles have different affinities for peptides from autoantigens (e.g. thyroid antigens). Hence, a distinct HLA allele would be capable of binding a distinct peptidic repertoire. Once bound, peptides are then presented to and recognized by T cell receptors on cells that have escaped tolerance (5). Ultimately, in terms of relevance to autoimmunity, specific HLA-DR alleles may permit an autoantigenic peptide to fit into their peptide binding pockets and to be recognized by the T-cell receptor, while other HLA-DR alleles would not be able to bind the same autoantigenic peptide (31). Thus, we hypothesize that the molecular linchpin, of a burgeoning thyroid autoimmune response, is the presence of an HLA-DR allele with the appropriate amino acids, in its peptide binding cleft, that would enable the binding of an autoantigenic thyroidal peptide.

Studies on the structure of HLA polymorphisms associated with Type 1 DM provided strong evidence in support of this hypothesis. Sequencing of the HLA-DQ genes showed that an aspartic residue at position 57 of the DQ beta chain played a key role in the genetic susceptibility to Type 1 diabetes (32). Individuals who did not have Asp57 on both of their DR alleles were at high risk for Type 1 diabetes (relative risk > 50) (33). The lack of aspartic acid at position 57 permits immunogenic insulin peptides to fit into the antigen binding groove of the HLA molecule and to be recognized by the T-cell receptor (34). In contrast, the presence of aspartic acid at position 57 of the DQ beta chain prevented insulin peptides from fitting, and hence prevented autoantigen presentation to the T-cell receptor (31). Moreover, it has also been shown that an aspartic acid at position 57 on the DQ beta chain dictates the antigen binding properties of an HLA-DQ alpha-beta heterodimer (32).

As discussed above, sequencing the DR beta chain has revealed a strong association between the presence of arginine at position 74 of the DR beta chain and GD in Caucasians. Position 74 of the DRb1 chain is strategically located in pocket 4 (P4) of the DR peptide binding cleft (figure 1). It is then possible that an arginine at position 74 alters the structure of the pocket in a way that would influence peptide binding and presentation to T-cells, much like the case in Type 1 DM and Asp57. Indeed, structural modeling analysis, performed by us, demonstrated that the change at position 74, from the common neutral amino acids (Ala or Gln) to a positively charged hydrophilic amino acid (Arg), significantly modified the three dimensional structure of the P4 peptide-binding pocket, and thus would be expected to modify the interaction of the DR peptide binding pocket with antigenic peptides during presentation to T-cells (28). Very few studies, to date, have examined the binding and presentation of thyroidal autoantigens to T-cells by different HLA-DR subtypes. One study has shown a higher affinity of HLA-DR3 to TSHR immunodominant peptides than to TSHR non-immunodominant peptides, suggesting that certain DR sequences influence the binding and presentation of TSHR peptides (35), and this may afford a mechanism through which DRb1-Arg74 can influence susceptibility to GD. Interestingly, we have found evidence for interaction, at the genetic level, between a thyroglobulin gene variant and DRb1-Arg74 in predisposing to GD resulting in an odds ratio of more than 16 (36). This result may suggest that the thyroglobulin/DRb1-Arg74 genetic interaction is mirrored by a biochemical interaction, in which Arg74 influences the presentation of thyroglobulin peptides in the initiation phase of GD.

For thyroid autoantigens to be presented by HLA molecules to T-cells, a mechanism of autoantigen presentation must exist within the thyroid gland or the draining lymph nodes of the gland. One potential intrathyroidal mechanism not utilizing professional antigen presenting cells (APC's) may be through aberrant expression of HLA class II molecules on thyrocytes

(37). Unlike in thyroids from normal individuals, thyroid epithelial cells from patients with GD and HT have been shown to express HLA class II antigen molecules similar to those normally expressed on APC's such as macrophages and dendritic cells (38). The aberrant expression of HLA class II molecules on thyroid cells may initiate thyroid autoimmunity via direct thyroid autoantigen presentation (38), where the thyroid cells serve as facultative APC's. However, in order for thyrocytes to fully stimulate T-cells, a co-stimulatory signal from the thyrocyte to the T-cell is needed, in addition to the stimulus provided by the presented peptide, alone. Hence, thyrocytes need to express requisite co-stimulatory molecules that can stimulate the T-cells, during antigen presentation within the HLA-DR peptide binding pockets. In terms of candidate co-stimulatory molecules, recent data from our lab suggest that CD40 may be one of the co-stimulatory molecules, expressed on thyrocytes, which helps trigger Graves' disease (39). This paper is part of the Mosaic of Autoimmunity special issue and we note other papers on this theme as well as several related papers on the genetics of both thyroid and other autoimmune diseases (40–58).

CONCLUSIONS AND FUTURE DIRECTIONS

The AITD are complex diseases believed to be caused by the combined effects of multiple susceptibility genes and environmental triggers. There are sufficient epidemiologic data to support an important genetic contribution to the development of AITD, and, in the past few years, several loci and genes have shown evidence for linkage and/or association with AITD. It is now clear that the HLA-DR genes play a major role in the etiology of Graves' disease in Caucasians, and possibly in other ethnic groups, as well. Recent data point to the importance of arginine at position 74 of the DRb1 chain in the pathogenesis of GD. We postulate that DRb1-Arg74 increases the risk for GD by allowing pathogenic TSHR and/or thyroglobulin peptides to be presented to T-cells. If this mechanism is confirmed, it will pave the way for possible therapeutic interventions by blocking presentation of pathogenic peptides to T-cells.

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Figure 1.

The HLA-DR3 molecule, shown in ribbon diagram format. The alpha chain (yellow) and the beta chain (turquoise) assemble to form a functional heterodimeric MHC II molecule. The peptide binding cleft is flanked by alpha helices, while anti-parallel beta pleated sheets make up its floor. It is estimated that any given MHC II binding cleft can bind anywhere from 650 to 2000 different peptides (the peptidic repertoire), ranging in size from 13 residues to 18 residues. Arg74, due to its strategic location, would be expected to exert an influence on the character of the peptidic repertoire.