Genetics of Autoimmune Thyroid Diseases in Asians

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Abstract

Autoimmune thyroid diseases (AITDs), including Graves’ disease (GD) and Hashimoto’s thyroiditis (HT), are among the commonest autoimmune disorders, affecting approximately 2-5 % of the population. Epidemiological data support strong genetic influences on the development of AITD. The identification of genes placing individuals at an increased risk for the development of AITD has been a slow process. However, over the last 20 years real progress has been made with the mapping of novel loci, via a number of different approaches. The first AITD gene discovered, Human Leucocyte Antigen (HLA)/Major Histocompatibility Complex (MHC), is associated with both GD and HT. Non-MHC genes that confer susceptibility to AITD can be classified into two groups: (1) immune-regulatory genes (e.g. CD40, CTLA-4, and PTPN22); (2) thyroid-specific genes—thyroglobulin and TSH receptor genes. These genes interact with environmental factors, such as infection, likely through epigenetic mechanisms to trigger disease. In this review, we will summarize the latest findings on AITD susceptibility genes in Asians in comparison with Caucasians.

ABBREVIATIONS

AITDs: Autoimmune Thyroid Diseases; GD: Graves’ Disease; HT: Hashimoto’s Thyroiditis; HLA: Human Leucocyte Antigen; MHC: Major Histocompatibility Complex; TSHR:TSH receptor; DR1-Arg74:arginine at position 74 of the DR1 chain; CTLA-4: Cytotoxic T lymphocyte-Associated protein 4; PTPN22: Protein Tyrosine Phosphatase-22; Tg: Thyroglobulin; TRBS: Transcription factor-Binding Sites; ZFAT: Zinc-Finger gene

INTRODUCTION

Autoimmune thyroid diseases (AITDs) are common autoimmune endocrine diseases [1], and according to one study, AITD are the commonest autoimmune diseases in the USA [2]. Even though the hallmark of AITD is infiltration of the thyroid with thyroid reactive lymphocytes, the end result are two clinically opposing syndromes: Hashimoto’s thyroiditis (HT) manifesting by hypothyroidism and Graves’ disease (GD) manifesting by hyperthyroidism. In HT, the lymphocytic infiltration of the thyroid gland leads to apoptosis of thyroid cells and hypothyroidism [3]. In contrast, in GD, the lymphocytic infiltration of the thyroid leads to activation of TSH receptor (TSHR)-reactive B cells that secrete TSHR-stimulating antibodies causing hyperthyroidism [4]. GD and HT are complex diseases, and their etiology involves both genetic and environmental influences [1]. Up until 15 years ago, the only known gene for AITD was HLA-DR3 haplo type (DRB1*03-DQB1*02-DQA1*05:01) in Caucasians. However, with the advent of new genomic tools and the completion of the human genome and the Hap Map projects, new non-HLA genes have been identified and their functional effects on disease etiology started to be dissected as well.

In Caucasians, the first locus shown to be associated with AITDs was the HLA-DRB1 locus (reviewed in [5]). HLA-DR3 (DRB1*03) haplo type has been consistently shown to be associated with GD, with an odds ratio (OR) of 2.0–3.0 [6-8]. The literature regarding HT is less consistent with reports of associations with DR3 and DR4 in Caucasians, as well as a negative association with DR1 and 8, suggesting a protective role [9]. Recently, Zeitlin et al., [10] investigated DRB1-DQB1-DQA1 in the largest UK Caucasian HT case control cohort to date comprising 640 HT patients and 621 controls. A strong association between HT and DR4 haplo type (DRB1*04-DQB1*03-DQA1*03) was detected, and protective effects were detected for DR13 haplo type (DRB1*13-DQB1*06-DQA1*01) and DR7 [10]. It was recently shown that arginine at position 74 of the DR1 chain (DR1-Arg74) is important for the development of GD in a significant proportion of patients [11,12]. A study from England provided evidence of a primary association of HLA-C, and to a lesser extent HLA-B, with GD. Other genes have also been shown to influence the expression

of GD in Caucasians [13]. These include the genes for cytotoxic T lymphocyte-associated protein 4 (CTLA-4) [14,15], CD40 [16], protein tyrosine phosphatase-22 (PTPN22) [17], thyroglobulin (Tg) [18,19] and TSH receptor (TSHR) genes [20].

To clarify the similarities and differences in the contribution of those genes to AITD susceptibility between Asian and Caucasian populations, this review will summarize the association of those genes with AITD in Asians, especially Japanese, in comparison with Caucasians (Tables 1,2). Since most of the studies were performed in relatively small size samples recruited from Asians, the results have been some limitations.

**HLA GENES IN ASIANS**

Located on chromosome 6p21 is the major histocompatibility complex region that encodes for HLA glycoproteins. The HLA region is a highly polymorphic region that contains many immune response genes and has been found to be associated with various autoimmune disorders. The HLA molecule binds a peptide antigen (auto antigen in the cause of autoimmunity). It presents the antigen for recognition by the T cell and as such the T cell then determines if the antigen is self (and no immune response is mounted) or non-self and an immune response is mounted [21].

The HLA associations are with different alleles in Asians in comparison with Caucasians. In previous studies, HLA-B35 is associated with GD and HLA-DRw53 with HT in the Japanese population (reviewed in [22]). HLA-Bw46 is associated with GD and HLA-DR9 with HT in the Chinese population (reviewed in [22]). The European GD-associated HLA haplo type (HLA-B*08-DRB1*03-DQA1*05:01-DQB1*02) is virtually absent in Japanese [23]. Dong et al., previously reported that HLA-A*02 and DPB1*05:01 are associated with Japanese GD [24]. Recently, they also demonstrated that HLA-A’02 and DPB1’02:02 showed association with thyroid-stimulating hormone-binding inhibitory immunoglobulins (TBI)-negative GD, indicating that TBI-negative GD may be genetically distinct from TBI-positive GD [25]. In addition, Wan et al. reported that HLA-A’02 and DPB4’01:01 are associated with Japanese HT [26]. Nakabayashi et al., conducted a two-stage genome-wide association study (GWAS) using 1119 Japanese individuals with GD and 2718 unrelated controls, and a subsequent replication study using 432 GD cases and 1157 controls [27]. They identified 34 SNPs to be significantly associated with GD in the GWAS phase, and twenty-two out of 34 SNPs remained positive in the replication study [27]. All 22 SNPs were located within the HLA locus on chromosome 6p21. Multivariate stepwise logistic regression analysis selected seven out of 22 SNPs, as markers for independent risk loci for GD, although causal variants remain to be identified [27].

Most recently, same group from Japan identified 4 and 2 susceptible HLA molecules primarily associated with GD and HT, respectively, HLA-B*35:01, HLA-B*46:01, HLA-DRB1*14:03 and HLA-DPB1*05:01 for GD and HLA-A*02:07 and HLA-DRB4 for HT [28]. In a direct comparison between GD and HT, They identified GD specific susceptible class II molecules, HLA-

### Table 1: A summary of genes investigated for association with AITD in Asians.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Genes</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune regulatory genes</td>
<td>HLA</td>
<td>Ueda*, Chu40</td>
</tr>
<tr>
<td></td>
<td>CTLA-4</td>
<td>Furugaki*, Ban5, Weng5, Zhao5, Chu6</td>
</tr>
<tr>
<td></td>
<td>CD40</td>
<td>Kim5, Mukai7, Ban5, Yang63</td>
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<tr>
<td></td>
<td>PTPN22</td>
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<td>ZFAT</td>
<td>Shirasawa52</td>
</tr>
<tr>
<td></td>
<td>FCRL3</td>
<td>Kochi5, Chu80</td>
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<td>FOXP3</td>
<td>Inoue10</td>
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**Thyroid-specific genes**

<table>
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<tr>
<th>Genes</th>
<th>Authors</th>
</tr>
</thead>
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<tr>
<td>Thyroglobulin</td>
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</tr>
<tr>
<td>TSHR</td>
<td>Hiratani73, Chu80</td>
</tr>
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</table>

**Abbreviations:** AITD: Auto Immune Thyroid Disease.

### Table 2: Association of candidate genes for AITD in Japanese and Caucasian populations.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Association with GD</th>
<th>Association with HT</th>
</tr>
</thead>
</table>
| Causative SNPs associated with AITD are different between the two populations.

**Abbreviations:** AITD: Auto Immune Thyroid Disease; GD: Graves’ Disease; HT: Hashimoto’s Thyroiditis; N/A: Not Applicable; SNP: Single Nucleotide Polymorphism.
DPB1 (HLA-DPB1*05:01; Pc=1.0X10^4) and HLA-DR14 (HLA-DRB1*14:03; Pc=0.0018) [28]. In contrast, HLA components on 3 common haplo types in Japanese showed significant protective effects against the development of GD and HT (HLA-A*24:02-C*12:02-B*52:01-DRB1*15:02-DQB1*06:01-DBB1*09:01 and HLA-A*24:02-C*07:02-B*07:02-DRB1*01:01-DQB1*05:01-DBPB1*04:02 haplotypes for GD and HLA-A*33:03-C*14:03-B*44:03-DRB1*13:02-DQB1*04:04 haplo type for GD and HT) [28] (Table 2). Interestingly, the representative protective HLA, HLA-DR13 (HLA-DRB1*13:02), was epistatic to susceptible HLA-DPS in controlling the development of GD [28]. Moreover, the HLA-DRB1*03:01 and HLA-DQA1*05:01 alleles are associated with GD in the Brazilian population representing the gene contribution from several ethnic backgrounds [29].

HLA gene are associated with other autoimmune diseases in Asians, including type 1 diabetes (T1D) [30], rheumatoid arthritis (RA) [31], systemic lupus erythematosus (SLE) [32], multiple sclerosis (MS) [33]. HLA-DR (DRB1*04:05-DQB1*04:01) and HLA-DR9 (DRB1*09:01-DQB1*03:03) haplo types are associated with T1D in Japanese [30]. HLA-DR9*08:03, DRB1*09:01, DRB1*14:06, DRB1*15:01, and DRB1*15:02 are associated with RA in Japanese [31]. Interestingly, Amino acid position 74 in HLA-DRB1 is strongly associated with anti-citrullinated protein antibodies (ACPA) levels in ACPA-positive RA, as well as with RA susceptibility [34]. An association between SLE susceptibility and HLA-DR2 (or HLA-DRB1*15:01 or HLA-DRB1*16) was found in Korean, Chinese, and Malaysian populations [32]. HLA-DR3 (or HLA-DRB1*0301 or HLA-DR17) also showed associations with SLE in Korean and Chinese populations [32]. There is a line of evidence showing that conventional MS (CMS) is associated with HLA-DRB1*15:01, and that optic neuropathy (OSMS) is associated with HLA-DRB1*05:01 [33].

NON-HLA IMMUNE-REGULATORY GENES IN ASIANS

The CTLA-4 Gene

The cytotoxic T lymphocyte-associated protein 4, CTLA-4, gene is located on chromosome 2q. It is a highly polymorphic gene that was first discovered to be associated with risk for AITD by the candidate gene approach. Under normal circumstances, the CTLA-4 protein acts to suppress T cell activation during normal immune response in order to prevent T cell over-activity [35]. CD4+CD25-T cells only express CTLA-4 on their surface after the T cell receptor is activated, and its engagement with its ligand suppresses the ongoing immune response. Decreased or absent CTLA-4 activity permits uninhibited T cell activity and a prolonged, unregulated immune response [36], making CTLA-4 an attractive candidate gene for autoimmunity. Indeed, the CTLA-4 gene has been found to be associated with many other autoimmune diseases.

A microsatellite in 3'UTR of CTLA-4 has been linked to AITD in Caucasians (reviewed in [35]); the longer the AT repeats at this site, the less inhibitory activity CTLA-4 has. It has also been associated with AITD in Japanese [38] and Koreans [39]. However, CTLA-4 +49A>G SNP is not associated with GD in the Brazilian population representing the gene contribution from several ethnic backgrounds [40]. Recently, an A/G SNP downstream from the 3'UTR, designated CT60, was found to be associated with GD in Caucasians and has been suggested as the causative variant, albeit this has not been conclusively demonstrated [15]. It was also found to be associated with AITD in Japanese [41,42] and Taiwanese populations [43] (Table 2). Interestingly, Other SNP (rs231779) is more likely the susceptibility variant for GD in Chinese Han population, suggesting the susceptibility variants of the CTLA-4 gene varied between the different geographic populations with GD [44]. Additionally, most recent stratification analyses suggested a possible synergistic interaction of CTLA-4 CT60 with HLA-A*02 and -DPB1*0501 in the susceptibility to TBI-positive GD [45].

The CD40 Gene

The CD40 molecule, located on chromosome 20q, is crucial to both the innate adaptive immune responses. It is present on the surface of antigen presenting cells (APCs) including B cells. The T cell-APC interaction results in activation of CD40 as a co-stimulatory molecule. CD40 also plays a critical role in activating B lymphocytes allowing them to terminally differentiate and secrete antibodies (reviewed in [46]). It is no surprise that the CD40 gene has been linked to many autoimmune disorders. Whole genome linkage scanning has identified strong linkage of CD40 to GD. The causative variant predisposing to GD is a C/T polymorphism in the Kozak sequence (dbSNP accession number rs1883832), a nucleotide sequence that is essential for the initiation of translation of the CD40 molecule. Specifically, the CC genotype has been identified in Caucasians to be associated with GD [16]. Indeed, functional studies demonstrated that the C-allele of this SNP increased CD40 mRNA translation by ~20-30% when compared with the protective T allele [35]. We and others have also confirmed an association between the rs1883832 and GD in Koreans [47], Japanese [48,49] and Chinese Han populations [50] (Table 2).

The PTPN22 Gene

The protein tyrosine phosphatase-22 (PTPN22) gene encodes for the lymphoid tyrosine phosphatase (LYP), a molecule that, similar to CTLA-4, functions to inhibit T cell activation [51]. An non-synonymous SNP in the PTPN22 gene, R620W (dbSNP accession number rs2476601), was found to be associated with GD, as well as other autoimmune diseases [Table 2]. This substitution results in a functional change in the LYP protein resulting in activation of T cell, but the mechanism is unclear [46]. Indeed, this association seems specific for Caucasians and was not found in the Japanese GD population [52].

Recently, the rs2488457 SNP in the promoter region was reported to be associated with acute onset T1D in a Japanese population [53]. However, there was no association of theirsrs2488457 SNP with GD [54]. Furthermore, the rs3789604SNP of the PTPN22 gene was found to be associated with RA, independently of rs2476601 [55]. The rs3789604 SNP lies 1496 bases downstream of PTPN22 at the 50 end of the round spermatid basic protein 1 gene (RSBN1), where it...
encodes either a silent mutation or putative transcription factor-binding sites (TRBS), depending on the transcript. Recently, the AA-genotype and A-allele frequencies of the rs3789604 were significantly higher in GD patients than in control subjects [54], suggesting that the rs3789604 or a gene with linkage disequilibrium may be relevant to susceptibility to GD in Japanese populations. Therefore, we further analyzed five other SNPs including rs12760457, rs2797415, rs1310182, rs2476599, and rs3789604, to clarify whether a susceptibility locus for AITD exists at another location within the PTPN22 gene. Our results showed no association with disease of any of the individual SNPs [56] (Table 2).

Because of the strong LD between five variants, haplo type analysis was undertaken using the computer program SNPAlalyze version 7.0. Five haplo types were identified, three of which (haplo types 1, 2, and 4) were correlated with haplo types 1, 4, and 5 identified in the report by Carlton et al., (Table 3) [55]. Four haplo types (haplo types 1-4) were relatively common and 1 haplo type was rare. Distribution of the haplo type is significantly different between AITD and control by permutation procedure (p=0.0036) [56]. A novel protective effect of a haplo type containing five SNPs was observed (P<0.0001 for AITD, P<0.0001 for GD, and P<0.0001 for HT, respectively) (Table 3) [56].

The zinc-Finger gene in the AITD Susceptibility region (Zfat)

Shirasawa et al., [57] identified a novel zinc-finger gene, designated ZFAT, as one of the AITD susceptibility genes in 8q23-q24 through an initial association analysis using the probands in their previous linkage analysis [58]. The distance between thyroglobulin and ZFAT genes is about 1.8 M bp. The human ZFAT gene encodes a 1,243-amino acid residue protein containing one AT-hook and 18 C2H2 zinc-finger domains. ZFAT human ZFAT gene encodes a 1,243-amino acid residue protein between thyroglobulin and ZFAT genes is about 1.8 M bp. The probands in their previous linkage analysis [58]. The distance between thyroglobulin and ZFAT genes is about 1.8 M bp. The human ZFAT gene encodes a 1,243-amino acid residue protein containing one AT-hook and 18 C2H2 zinc-finger domains. ZFAT is also highly conserved among species from fish to human [57]. The ZFAT protein is expressed in the B and T lymphocytes in mice, and ZFAT regulates the genes involved in immune responses [59]. Furthermore, ZFAT is an anti-apoptotic molecule that is critical for cell survival in human leukemic MOLT-4 cells [60].

The FCRL Genes

Fc receptor-like 3 (FCRL3) is one of five FCRL genes that are preferentially expressed on B-lymphocytes and have a highly structural homology with Fc receptors [61]. The 1p21-23 cytoband, in which the FCRL family resides, has been identified as a candidate locus for multiple autoimmune disorders in both human and murine models [62]. Koji et al., [63] identified a strong association of SNPs in this region with GD-susceptibility in Japanese and concluded that the origin of the association was a regulatory SNP in the promoter region of FCRL3. This susceptibility gene of GD was first identified from Japanese population. This SNP (-169C/T) (dbSNP accession number rs7522061) alters the binding affinity of NFκB and regulates gene expression, and high FCRL3 expression on B-lymphocytes is observed in individuals with the disease-susceptible genotype. The SNP rs7522061 in the FCRL3 gene was also reported to be associated with AITD in Caucasians [64] and two other autoimmune diseases, RA and SLE [63] (Table 2). More recently, SNP rs3761959, which tags rs7522061 and rs7528684 (previously associated with RA and GD), was associated with GD in the extended cohort, confirming the original result. In total, three of the seven FCRL3 SNPs showed some evidence for association (P <0.05), with SNP rs11264798 showing the strongest association of the tag SNPs (P=4.0X10-3) [61]. SNPs rs6667109 in FCRL5, which tagged SNPs rs6427384, rs2012199 and rs66679793, all found to be weakly associated in the original study, showed little evidence of association in the extended cohort [65].

The FOXP3 Gene

Two whole genome scans for linkage in GD have shown evidence for linkage at putative X-chromosome loci, Xq21 [66] and Xp11 [67], and these loci have also been identified in localized linkage scans of the X-chromosome, Xq21 [66] and Xp11 [68], although one of the two genome wide screen increased their numbers and performed an enlarged genome wide screen and no evidence for Xp21 as a region of linkage to GD [69]. In terms of broader relevancy to autoimmunity in general, Xp11 has also been linked to other autoimmune disorders, T1D, MS, and RA, thus suggesting the presence of common susceptibility polymorphism(s) [70-72]. The FOXP3 gene is located at Xp11.23 within this area of autoimmune disease linkage, and is therefore an excellent positional candidate gene for autoimmunity at this locus. Indeed, Bassuny et al., [73] reported an association between a functional microsatellite polymorphism, (GT)n, located in the promoter/enhancer region of FOXP3, and T1D in a Japanese population. However, a subsequent study could not confirm the FOXP3 association with T1D in an Italian population [74]. A recent study from the UK tested several FOXP3 polymorphisms for associations with GD, and found no robust evidence that those polymorphisms contributes to the susceptibility to GD [75].

Table 3: PTPN22 haplo type structure and frequencies.

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>AITD</th>
<th>GD</th>
<th>HT</th>
<th>Controls</th>
<th>AITD vs Controls P-value</th>
<th>GD vs Controls P-value</th>
<th>HT vs Controls P-value</th>
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<td>T</td>
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<tr>
<td>5</td>
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<td>0.051</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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</table>

*The program, SNPAlalyze ver. 7.0, Standard, was used to estimate common (frequencies >0.01) haplo types for the five SNPs genotyped.
*Each haplo type was compared with the other haplo types combined.

**Abbreviations:** SNP: Single Nucleotide Polymorphism; AITD: Autoimmune Thyroid Disease; GD: Graves’ Disease; HT: Hashimoto’s Thyroiditis.
tested the FOXP3 gene locus for associations withAITDs in two
cohorts of US Caucasians and Japanese AITD patients [76]. Our
study demonstrated a weak association between polymorphisms
of the FOXP3 gene and AITD in US Caucasians but not in the
Japanese. However, One group from Japanese reported that the
-3279A/C SNP of the FOXP3 gene is related to the development
and intractability of GD and the -2383CC genotype to the severity
of HT [77] (Table 2). These results, if replicated, may suggest that
inherited abnormalities of Treg function may contribute to the
etiology of AITD.

THYROID–SPECIFIC GENES IN ASIANS

The Thyroglobulin Gene

The thyroglobulin (Tg) protein is the major thyroidal protein
antigen and is a precursor to thyroid hormones. Tg is also a key
antigen in AITD as evidenced by the fact HT is characterized
by anti-thyroglobulin antibodies which are detected in 75% of
patients [46]. Whole genome linkage studies identified a locus
on chromosome 8q24 that was linked with AITD; this locus
contained the Tg gene [69]. Sequencing of the Tg gene identified
several non-synonymous SNPs that were associated with AITD
[78]. Haplo type analysis of those four SNPs revealed that the
G-C-A-C haplo type was significantly associated with HT (P <
0.01, Odds ratio [OR] = 3.06) and with serum anti-Tg antibody
concentrations in HT patients [46]. Whole genome linkage studies
identified a locus
intron 7 of TSHR gene were associated with GD [86] (Table 2).

New Genome-Wide Association Studies in AITD in Asians

Recently, the first genome wide association study (GWAS) was
reported in GD. In this large study from China 1,536 GD patients
and 1,516 controls were genotyped for approximately 660,000
SNPs [87]. In addition, to confirming previously identified GD
loci the investigators mapped two new GD loci, on chromosomes
6q27 and 4p14. Both of these loci contain several genes and it is
currently unclear which genes in these loci are associated with GD
[87]. We replicated an association between GD and the G allele of
rs9355610 (Table 5) [88]. Furthermore, there was an association
in the Polish population between 4p14 (rs6832151) and GD but
only a trend for 6q27 (rs9355610) [89]. These findings show that
rs9355610 contribute to GD pathogenesis in Japanese.

Another recent study from Japan used a two-stage genome
wide comparison between HT and GD [90]. A genome-wide
direct comparison between HT and GD revealed an SNP at the
VAV3 locus with genome-wide significant association signals
(rs7537605: P=3.90X10-8; OR =1.77) [90]. An association
analysis using healthy controls showed that rs7537605 is

<table>
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<th>SNP Name</th>
<th>Allele/Genotype</th>
<th>Control (n=221)</th>
<th>AITD (n=458)</th>
<th>P value</th>
<th>GD (n=287)</th>
<th>P value</th>
<th>HT (n=171)</th>
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<td>0.70</td>
</tr>
</tbody>
</table>

Values given are the number of subjects, with the percentage in parentheses.

Abbreviations: SNP: Single Nucleotide Polymorphism; AITD: Autoimmune Thyroid Disease; GD: Graves’Disease; HT: Hashimoto’s Thyroiditis.

singly associated with HT (P=1.24X10^{-5}; OR =1.60) but not with GD (P=0.50), suggesting that the variants specifically affects susceptibility to HT [90]. Considering physiological roles of VAV3 at 1p13, such as a guanine nucleotide exchange factor, their finding provides new insight into the molecular mechanism of HT [90].

Susceptibility Genes of Graves’ ophthalmopathy in Asians

Graves’ ophthalmopathy (GO), an inflammatory process in the orbital region, is the most common extra thyroidal feature of GD and is clinically present in 25–50% of individuals with GD [91-94]. Clinical manifestations of GO include periorbital oedema, proptosis, lid retraction, diplopia and optical nerve compression. Despite many findings favoring a genetic contribution to the development of GO in Asians [95-100], the role of genetic factors in GO remains controversial, and the mechanisms underlying the development of GO still need to be elucidated.

CONCLUSIONS

Through the genetic studies undertaken to date, we now know that substantial ethnic differences exist in AITD genetic predispositions between populations of Caucasian and Japanese ancestries. Beside the HLA-DRB1 alleles as described, the most evident ethnic difference is seen in the non-synonymous coding polymorphism of the PTPN22 gene in Caucasian populations. This polymorphism is rarely found in Japanese population [52], and thus specifically contributes to AITD in populations of Caucasian descent. The absence of a disease-risk allele in a population, as in the case of PTPN22, can easily explain the genetic heterogeneity between populations [101]. However, the situation is more complex in cases where the disease-risk allele is shared among different populations, and the results of association tests are not. This could occur when: (1) a positive association in the primary report represents a false-positive due to sampling biases; (2) a negative association observed in a replication study is a false-negative due to a lack of statistical power; or (3) true genetic heterogeneity exists (genetic contribution of the gene polymorphisms is zero in a population, or lower than that of the population originally reported) [101].

Genetic analyses undertaken in the last decade have revealed a completely new picture of AITD pathogenesis and made us aware of heterogeneity among individuals and populations. Our final goal is to establish new treatments for AITD, based on the pathogenesis and prognosis of individuals, which could lead to the development of tailor-made therapies for AITD. To reach this goal, we should continue to uncover unknown genetic predispositions and clarify differences in roles among ethnicities. Upcoming genome-wide scans for additional populations worldwide and the meta-analysis of these studies may elucidate the complete picture of AITD.

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