REVIEW

IgG4-related Disease of the Thyroid Glands

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Abstract. Recent reports on Hashimoto's thyroiditis (HT) with increased numbers of IgG4-positive plasma cells suggest that this type of HT may have a close relationship to IgG4-related disease (IgG4-RD). This unique subgroup of HT is termed as IgG4 thyroiditis and reveals distinct clinical, serological, and sonographic features from the non-IgG4 thyroiditis group. On the basis of immunostaining for IgG4, HT was divided into an IgG4 thyroiditis group and a non-IgG4 thyroiditis group. Clinically, IgG4 thyroiditis was associated with younger age group, lower female-male ratio, higher levels of thyroid autoantibodies, diffuse low echogenicity, more rapid progress requiring surgical treatment and more subclinical hypothyroidism. Serum IgG4 concentrations elevated in IgG4 thyroiditis and decreased significantly after a thyroidectomy. Histopathologically, IgG4 thyroiditis showed a higher grade of stromal fibrosis, lymphoplasmacytic infiltration, and follicular cell degeneration than non-IgG4 thyroiditis. IgG4 thyroiditis may represent IgG4-RD of thyroid gland, because it shares common histopathological characteristics with IgG4-RD in other organs. The identification of IgG4-RD of the thyroid gland opens new insights not only for patient's treatment with HT but also for the development of new therapeutic approaches for this rapidly progressive destructive subtype of HT. This article mainly focuses on reviewing the unique histopathological, clinical, and serological features of IgG4 thyroiditis group of HT. The etiology and genetic changes of HT are also discussed.

Key words: IgG4, Thyroiditis, Autoimmune disease, Fibrosis, Pathology

IgG4-RD and the Thyroid Gland

The IgG4-related disease (IgG4-RD) is a new disease entity first proposed in relation to autoimmune pancreatitis (AIP) by Hamano *et al*. in 2001 [1]. Since then, IgG4-related lesions similar to AIP have been reported in various organs. These include retroperitoneal fibrosis [2], sclerosing cholangitis [3], hepatic inflammatory pseudotumor [4], lymphadenopathy [5, 6], lymphoid interstitial pneumonia [7], inflammatory pseudotumor of the lung [8], orbital pseudotumor [9], sclerosing sialoadenitis [10], tubulointerstitial nephritis [11], inflammatory aortic aneurysm [12], and pachymeningitis [13]. Each of these entities occurs in organ specific forms without AIP, in various combinations

and in systemic forms. Clinically, IgG4-RD is characterized by hypergammaglobulinemia with a predominant increase in IgG4 levels, and alleviation of symptoms after steroid therapy. Furthermore, irrespective of the organs affected, IgG4-related lesions also share similar pathologic features, including lymphoplasmacytic infiltration, fibrosis, obliterative phlebitis, and increased numbers of IgG4-positive plasma cells [6].

A high prevalence of hypothyroidism has been reported in patients with AIP [14], and this finding led us to investigate the relationship between HT and IgG4-RD. In 2009, it was reported by our group that on the basis of the immunohistochemistry of IgG4, HT can be divided into two groups, which were proposed as IgG4 thyroiditis (IgG4-positive plasma cell-rich group) and non-IgG4 thyroiditis (IgG4-positive plasma cell-poor group) [15]. The IgG4 thyroiditis group shows indistinguishable histological features and may have a close relationship with IgG4-RD in other organs. Furthermore, in 2010, it was demonstrated that IgG4 thyroiditis is clinically associated with a lower female-

Table 1 Clinical parameters of patients with IgG4 thyroiditis and non-IgG4 thyroiditis

	IgG4 thyroiditis (n=28)	Non-IgG4 thyroiditis (n=77)	*P* value
Age (years)*	52.39 ± 9.746	58.97 ± 10.02	0.0034
Sex (Male/Female)	7/21	3/74	0.0033
Disease duration (years)*	8.042 ± 7.915	15.07 ± 10.31	0.0028
TgAb (fold)*‡	1341 ± 1610	348.0 ± 633.2	0.0047
TPOAb (fold)*‡	377.1 ± 326.4	141.8 ± 152.1	0.0015
Thyroid functional status (subclinical hypo-/eu-/subclinical hyperthyroidism)‡	11/16/1	9/54/12	0.0041
Echogenicty (ultrasound) (diffuse low/ coarse)‡	19/9	19/52	0.0002

*Data are mean ± SD. ‡Not all of the patients had complete clinical data.
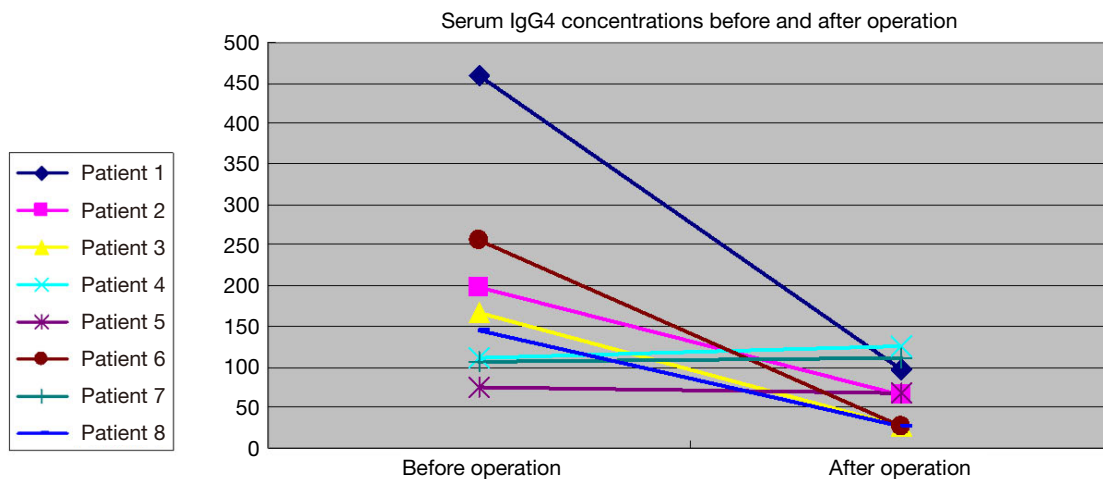
Fig. 1 Changes of preoperative and postoperative serum IgG4 concentrations of eight patients with IgG4 thyroiditis. After total thyroidectomy, a significant reduction of IgG4 level in the serum can be identified.

to-male ratio, more rapid progress, subclinical hypothyroidism, diffuse low echogenicity, and a higher level of circulating thyroid autoantibodies than non-IgG4 thyroiditis as shown in the Table 1 [16]. This is the first report which disclosed HT is still a heterogenous autoimmune disease and that the morphological characteristics with IgG4 immunohistochemistry can successfully elucidate patients with aggressive (rapidly progressive) type of HT who develop more subclinical hypothyroidism [16].

Riedel thyroiditis (RT) is another candidate for IgG4-RD. It is a rare form of chronic thyroiditis, characterized by inflammatory proliferative fibrosis which involves the thyroid parenchyma and surrounding tissue structures [17, 18]. In 2010, Dahlgren *et al.* reported that IgG4-RD was the underlying condition in a part of the cases of RT [19]. They also demonstrated that multifocal fibrosclerosis was actually IgG4-RD in one patient, who had lacrimal gland, pulmonary, and biliary tract involvement as well as thyroid disease. It was the first report establishing RT as a member of the IgG4-RD spectrum [19]. We postulated that when IgG4-RD occurs in a systemic pattern, the thyroid involvement may present as RT rather than HT. Different from RT, the IgG4 thyroiditis group of HT proposed by our group may be an organ-specific form of IgG4-RD, because none of the cases we examined in the IgG4 thyroiditis group showed systemic involvement of IgG4-RD in other organs. Moreover, the serological examination supported this hypothesis because, after total thyroidectomy, the serum IgG4 concentration in our patients with IgG4 thyroiditis showed a significant reduction and returned to the normal value (Fig. 1), which indicated that the major source of elevated serum IgG4 was the thyroid gland in these patients [16]. In addition to this observation, the majority of the patients with IgG4-RD

in the literature who developed hypothyroidism have not been reported to have RT in their thyroid. As the majority of IgG4-RDs in the other organs show both an organ specific inflammation (which is confined within the primary organ) and an invasive type inflammation (which extends beyond its capsule and is destructive to the surrounding structures) therefore the distinction between organ confined (HT) type and invasive (RT) type may not be an essential or important parameter in the other IgG4-RDs. It is our impression that RT type IgG4 thyroiditis may be rare or exceptional, because our experience on a few cases of RT and the other forms of thyroiditis did not show increased IgG4 positive plasma cells immunohistochemically [15, 20].

Gross Findings of IgG4 Thyroiditis and its Differences from RT

The thyroid gland from a patient with IgG4 thyroiditis is usually elastic soft in consistency and ivory white in color on cut surface as shown in Fig. 2. The thyroid lobe is clearly demarcated with capsule that was non-adherent and could be easily separated from the surrounding tissue structures surgically. Therefore, the diagnosis of RT or extra-thyroid extension of malignant disease beyond capsule could be ruled out macroscopically. The majority of thyroid glands showed diffuse symmetric enlargement without a dominant mass, which may reflect diffuse low echogenicity.

Histological Evaluation and Diagnostic Criteria for IgG4 Thyroiditis

The diagnosis of HT was clinically based on the Guidelines of the Japanese Thyroid Society [16], and was further confirmed by histological examination of thyroid glands. The essential histologic features of HT include lymphoplasmacytic infiltration and germinal center formation. Histologically, as we previously suggested, the IgG4 thyroiditis group showed a significantly higher grade of lymphoplasmacytic infiltration and stromal fibrosis than the non-IgG4 thyroiditis group [15, 16]. The detail histopathologic examinations obtained from the 105 cases of HT including 28 cases of IgG4 thyroiditis were under preparation [21]. As to the IgG4 thyroiditis group, 23 of 28 lesions (82.14%) showed marked stromal fibrosis (Fig. 3), while remaining five cases showed only mild to moderate fibrosis. In the non-IgG4 thyroiditis group
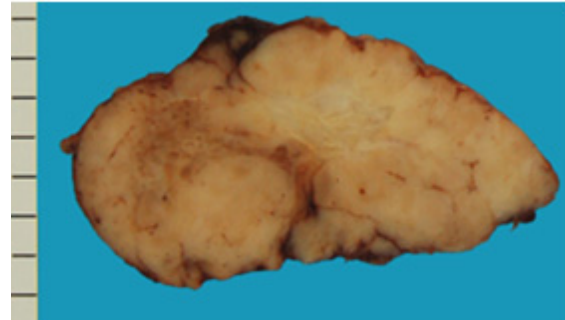
Fig. 2 Gross appearance of IgG4 thyroiditis. It is well demarcated with sharp border from the surrounding tissue structure. On cut section it is ivory-white in color with lobulation, which indicates replacement of the thyroid parenchyma by fibrous tissue and inflammatory cell infiltration.

27 cases revealed almost negligible fibrosis, whereas 38 of the remaining 50 cases with various degrees of fibrosis [21]. Obliterative phlebitis is one of the characteristic features of IgG4-RD reported in other organs, but this type of vasculitis has not been reported in any variants of HT; this feature was confirmed in our 105 cases of HT including both IgG4 thyroiditis group and non-IgG4 thyroiditis group, which is consistent with textbook descriptions on HT [21]. It should be one of the most important observations reported in our series of HT patients and we believe it does not conflict with our conclusion that IgG4-RD in the thyroid is IgG4 thyroiditis of HT type, whereas obliterative phlebitis is often reported as a histopathologic characteristic of IgG4-RD in the other organs. It is of note that RT has been reported to have obliterative phlebitis in addition to fibrosclerotic change histopathologically [18], and this is the reason why many researchers speculated that RT may be one of the thyroid manifestations involved by systemic form of IgG4-RD, although most of them including us could not confirm it. We further assumed that there may be a significant link between obliterative phlebitis and extracapsular fibrosis, because both of them made it possible to differentiate the fibrosclerotic thyroid disease into two distinctive forms, HT and RT type. There should also be an etiological link between obliterative phlebitis and extracapsular fibrosis, and we assumed that the presence of obliterate phlebitis must be essential to develop systemic involvements beyond the primary organ through involved vascular network. In conclusion, the IgG4 thyroiditis of HT type revealed distinct histological features (Fig. 3), such as increased IgG4 positive plasma cells and more fibrotic changes,
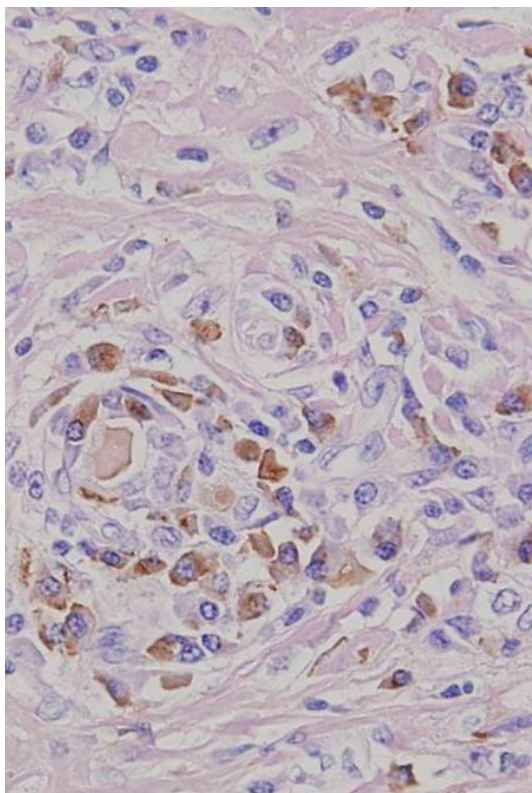
Fig. 3 IgG4 thyroiditis demonstrates numerous IgG4 positive plasma cells in the fibrotic thyroid parenchyma. Brown color indicates cytoplasm of plasma cells containing IgG4, deep blue shows their nuclei. Note collagenous fibrosis in interfollicular pattern and atrophic small follicles contain pink colloid. (immunoperoxidase stain for IgG4 with hematoxylin eosin counter stain, X10)

from the non-IgG4 thyroiditis. All fibroinflammatory changes of IgG4 thyroiditis were limited within the thyroid capsule and no vascular change was observed. As a result, the differential diagnosis from Riedel thyroiditis was confirmed.

Immunohistochemistry and Diagnostic Threshold of IgG4 Thyroiditis

On the basis of the immunostaining of IgG4 and IgG, and the cutoff value of >20/HPF IgG4-positive plasma cells and >30% IgG4/IgG ratio, the patients with HT were successfully subclassified into IgG4 thyroiditis group (Fig. 3) and non-IgG4 thyroiditis group as proposed in our previous report [15, 16]. Immunohistochemically, the IgG4 thyroiditis group showed diffuse or nodular dense infiltration of IgG4-positive plasma cells with a high ratio of IgG4/IgG-

positive plasma cells. In contrast, in the non-IgG4 thyroiditis group, although many IgG-positive plasma cells were found in the stroma, only a few of them were demonstrated to be IgG4-positive.

Clinical, Laboratory and Sonographic Findings of IgG4 Thyroiditis

Clinical, laboratory and sonographic findings of the patients were reported in our previous publication and the comparison between the two subgroups are summarized in Table 1 [15, 16, 21]. Patients in the IgG4 thyroiditis group were significantly younger than those in the non-IgG4 thyroiditis group. Although generally the female-to-male ratio is about 8-9:1 for HT, the IgG4 thyroiditis group was demonstrated to be associated with a lower sex ratio ($P = 0.0033$). In addition, patients in the IgG4 thyroiditis group had significantly shorter disease duration of HT than non-IgG4 thyroiditis before they underwent total thyroidectomy. In terms of routine laboratory examinations, circulating thyroid autoantibodies, both thyroid peroxidase (TPO-Ab) and thyroglobulin (Tg-Ab) levels were significantly higher in the IgG4 thyroiditis subgroup than in the non-IgG4 thyroiditis subgroup. Under thyroid hormone treatment, the patients revealed different types of thyroid functional status: subclinical hypothyroidism, euthyroidism, and subclinical hyperthyroidism. Their distribution significantly differed between the two groups, and the IgG4 thyroiditis subtype was demonstrated to be associated more with subclinical hypothyroidism. Furthermore, sonographic examinations revealed that the IgG4 thyroiditis group was significantly correlated with diffuse low echogenicity (Fig. 4), whereas non-
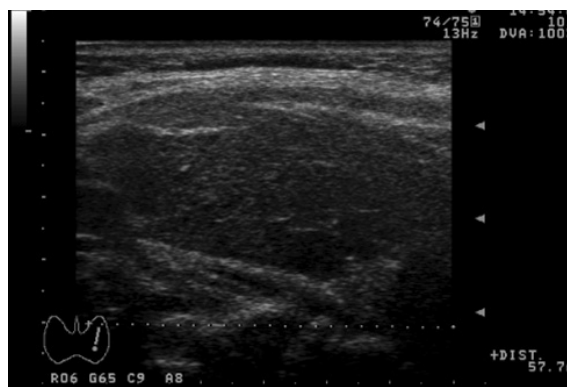
Fig. 4 Ultrtasonographic profiles of IgG4 thyroiditis. Note diffuse low echo pattern in the entire thyroid gland.

IgG4 thyroiditis showed an association with diffuse coarse echogenicity. Interestingly, previous investigators have reported several sonographic patterns in HT [22-26]. They have found also a relation between the sonographic findings and the degree of thyroid function impairment suggesting the degree of disease severity [24, 26]. Hayashi *et al.* firstly proposed to classify HT according to the echogenicity of the thyroid. In their study, 53 untreated patients with histologically confirmed HT were divided into two groups by comparing the thyroid image with that of the adjacent muscles. Their 25 cases in which the echogenicity of the thyroid was almost equal to or less than that of the adjacent muscles were classified as group A. The cases in their group A had abnormally low T4 and abnormally high TSH more frequently than those in the other group. Furthermore, histopathologically in all cases of group A, there was severe degeneration and disappearance of thyroid follicles. Based on the above findings, the authors indicated that low echogenicity of the thyroid may be a sign suggestive of hypothyroidism and severe follicular degeneration similar to those observed in our IgG4 thyroiditis.

Serum IgG4 and its Thyroid Origin

The preoperative and postoperative serum concentrations from eight patients of the IgG4 thyroiditis group are shown in Fig. 1. Before thyroidectomy, serum IgG4 concentrations were elevated beyond the normal range. Serum concentrations of IgG4 from the IgG4 thyroiditis group were significantly higher in the IgG4 thyroiditis group than the non-IgG4 thyroiditis group. However, the serum levels of IgG1, IgG2, and IgG3 did not differ between the two groups [16]. Importantly, as we expected, serum IgG4 concentrations were significantly reduced after total thyroidectomy, which indicated that the origin of serum IgG4 must be from the thyroid glands. Marked reductions of more than twofold were detected in 5 cases (5/8) of IgG4 thyroiditis. One patient with a normal preoperative serum IgG4 concentration showed a relatively stable value. The remaining two cases of IgG4 thyroiditis showed a slight elevation after surgery. In these 3 cases, the thyroid glands could not have been the major origin of serum IgG4 and there should be the other organs which secreted IgG4 to the serum. Review of these 3 patients failed to identify any systemic involvements of IgG4-RD in the other organs, and no reasonable explanations for the source of IgG4 in these patients could be made.

Thyroiditis and Variants of HT

Classification of thyroiditis includes acute suppurative thyroiditis, mycotic thyroiditis, palpation thyroiditis, subacute thyroiditis, silent thyroiditis, Hashimoto's thyroiditis (HT), and Riedel's thyroiditis (RT) [27]. It is about 100 years since the publication of the original description of the disorder now termed as Hashimoto's thyroiditis or Hashimoto's disease. Hashimoto's thyroiditis is the most common cause of goitrous hypothyroidism in the world where dietary iodine is sufficient [27]. It is a spectrum of autoimmune thyroid diseases, which also including Grave's disease. Characteristic autoimmune features include the presence of circulating antibodies, TPO-Ab and Tg-Ab.

The pathology of HT was formerly considered to be uniform, but currently it is more and more seen as varying [28]. HT is a multifaceted disease including various subtypes which exhibit distinct clinicopathological characteristics [16]. It appears that different types of immunopathogenetic mechanisms may be at work in its disease processes in addition to autoimmune inflammation. Several subclassification schemes of HT have been introduced [29-31]. For example, a morphological subclassification proposed by Mizukami *et al.* divides HT into four groups: oxyphilic group, mixed group, hyperplastic group and focal group, and correlates the morphological features with different thyroid function status [32]. Fibrous variant of HT was first reported by Katz and Vickery as a variant of HT and some regarded it as end stage of HT [33]. In our previous study, we concluded that the IgG4 thyroiditis may overlap the so-called fibrous variant of HT to a large extent because of the close histologic similarities [15]. However five of 28 cases (17.86%) of IgG4 thyroiditis demonstrated less stromal fibrosis and they belonged to neither fibrous variant of HT nor RT. Therefore, in our conclusion, fibrous variant of HT or RT is not overlapped completely with IgG4 thyroiditis. We further speculate that IgG4 thyroiditis may be a wider disease entity than fibrous variant HT and RT, and the IgG4 thyroiditis may cover their early phase of thyroid inflammation in addition to full blooming fibrous variant HT and RT, because the degree of fibrosis likely varies according to disease duration and other factors (Fig. 5).
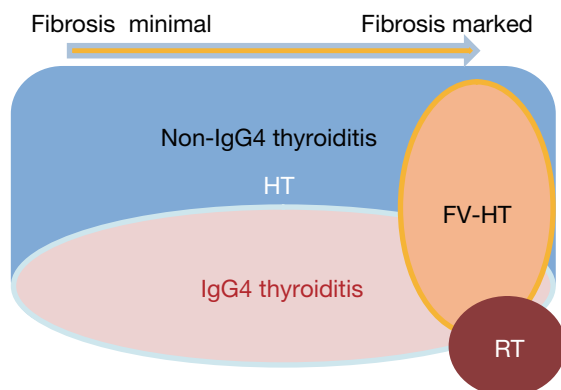
Fig. 5 Differential diagnosis of thyroiditis according to IgG4 immunostaining, degree of stromal fibrosis and invasive fibrosis beyond thyroid capsule. HT: Hashimoto's thyroiditis, FV-HT: fibrous variant of Hashimoto's thyroiditis, RT: Riedel thyroiditis.

Etiology and Genetics of HT

Etiologically, HT is a complex disease caused by the combined effect of multiple susceptibility genes and environmental factors. In the past decade, significant progress has been made in our understanding of the genetic and environmental triggers contributing to HT. The major histocompatibility complex (MHC) region, encoding the HLA glycoproteins, consists of a complex of genes located on chromosome 6p21 [34]. Because the HLA region is highly polymorphic and contains many immune response genes, it was the first candidate for a genetic region to be studied for association with HT [35]. Earlier studies showed an association of goitrous HT with HLA-DR5 and of atrophic HT with HLA-DR3 [36, 37]. Later studies have reported association of HT with HLA-DR3, HLA-DR4, or HLA-DR5 in Caucasian patients [38-42]. However, a recent study has shown that a molecular signature of HLA-DR pocket, determined by specific amino acids, confers a significant risk for the development of HT across HLA-DR alleles [35, 43]. In these studies, the presence of the HLA-DR amino acids Tyr-26, Tyr-30, Gln-70, and Lys-71 in the pocket was demonstrated to be strongly associated with HT. This pocket amino acid signature resulted in a unique pocket structure that is likely to influence pathogenic peptides (e.g., TPO-derived peptides) binding and presentation to T-cells.

Meanwhile, polymorphisms of non-MHC genes including CTLA-4 and PTPN22 genes were also proved to be linked with HT. Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) is a major negative reg-ulator of T-cell responses [44]. Yanagawa *et al.* were the first to show an association between CTLA-4 and autoimmunity [45]. Since this original publication, several CTLA-4 polymorphisms have been identified and shown to be linked with HT and GD. The most consistent associations were found with three variants: an AT-repeat microsatellite at the 3' untranslated region (3'UTR) of the CTLA-4 gene, (AT)n; an A/G SNP at position 49 in the signal peptide resulting in an ala-nine/threonine substitution, (A/G49); and an A/G SNP located downstream and outside of the 3'UTR of the CTLA-4 gene [45-52]. However, it is still not known which variant is the causative type and by what mecha-nism it confers susceptibility to autoimmunity [35].

Another recently described genetic determinant of susceptibility to HT is a functional polymorphism in protein tyrosine phophatase-22 (PTPN22) gene that encodes a lymphoid tyrosine phosphatase, which is also thought to inhibit T-cell function. A tryptophan/argin-ine substitution at codon 620 (R620W) of PTPN22 was found to be associated with HT [53]. Nevertheless, The PTPN22 gene shows significant ethnic differences in association. In Japanese population, the tryptophan variant of the PTPN22 gene is very rare, and it is con-jectured that PTPN22 may not contribute to autoim-munity in Japanese patients [54]. The gain-of function tryptophan variant makes the protein an even stron-ger inhibitor of T-cells, which might be involved in the pathogenesis of HT.

It is likely that the mechanism of immune-regulatory genes interacting with autoantigen-specific genes, may be a more general mechanism for the development of organ-specific autoimmune disease [55]. Indeed, this mechanism has been shown to play a major role in the etiology of Type 1 diabetes [56]. Thyroglobulin (Tg) gene is the first thyroid-autoantigen gene to be shown to confer susceptibility for AITD [57-59]. Similar to results reported in Caucasian population, a signifi-cant association between the 330bp/352bp genotype of Tgms2 and HT was found in a large cohort of Japanese AITD patients [55]. Therefore, it is possible that the Tg gene may predispose to AITD across populations of different ethnic backgrounds.

Akin to other autoimmune diseases, HT has a strong genetic component, which is supported by a higher concordance of disease in monozygotic twins than dizygotic twins [60]. However, even with iden-tical twins the concordance rate was only about 50%, emphasizing that other important factors such as envi-

ronment play a significant role in disease pathogenesis. The major environmental triggers of HT include iodine, medications, infections, smoking, and possibly stress [35]. Among these non-genetic factors, the best established environmental trigger promoting the development of HT is excess dietary iodine. The highest prevalence of HT is reported in countries with the highest intake of iodine, such as United States and Japan [61]. However, there is little information about how such agent works in developing HT. For exploring the influence of iodine, a unique animal model, the NOD. H2h4 mouse was utilized recently. It is a spontaneous animal model of autoimmune thyroiditis that closely resembles human HT [62]. By studying this well-defined mouse model, Bonita *et al*. found that the constitutive expression of intracellular adhesion molecule-1 (ICAM-1) on thyrocytes was upregulated upon excess iodine ingestion. This work suggests that iodine itself could increase ICAM-1 in the thyrocytes. Furthermore, as we well known, intercellular adhesion molecule (ICAM)-1 is a single-chain cell surface glycoprotein

that plays a role in inflammatory processes and in the T-cell mediated host defense system. It functions as a co-stimulatory molecule on antigen-presenting cells to activate MHC class II restricted T-cells, and on other cell types in association with MHC class I to activate cytotoxic T-cells [63]. Therefore, excess iodine intake may have multiple significant roles in the pathogenesis of HT, one of which is to increase thyroglobulin immunogenicity while another is to increase local expression of ICAM-1.

Although the above studies describe more knowledge about the etiology and genetic changes of HT, the PubMed literature survey on thyroiditis and IgG4 in September, 2011 provided no publication that dealt with genetic analysis or molecular data on IgG4 thyroiditis of HT type. Further analysis with recent molecular methods on this old autoimmune disease will hopefully provide better understanding of and new therapeutic approaches to this unique new entity of IgG4 thyroiditis.

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