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Chapter 1

Genetic Susceptibility to Graves' Ophthalmopathy

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Additional information is available at the end of the chapter

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1. Introduction

Graves' disease (GD) is an autoimmune thyroid disorder (AITD) with aberrant antibody production resulting in hyperthyroidism [1]. It is characterized by T cell and B cell reactivity to the thyrotropin (thyroid stimulating hormone; TSH) receptor (TSHR) located on the endothelial surface of thyroid follicular cells, and the presence of abundant serum antibodies against TSHR (TRAb) is used as a specific marker of GD. Follicular hyperplasia, intracellular colloid droplets, cell thinning and patchy T cell-predominant lymphocytic infiltrations can be observed in thyroid gland histology of GD patients. GD is considered primarily a T helper-2 (Th2) autoimmune disease, as TRAb stimulates TSHR as an agonist, resulting in the excessive production of thyroid hormones. The pathogenesis of GD has been studied for decades and several risk factors have been identified. Similar to other autoimmune diseases, GD is believed to develop because of a combination of genetic susceptibility and environmental triggers. Often there is a familial history of disease and it is prevalent in women [2]. These facts support a role for genetic susceptibility in the pathogenesis of GD. Environmental factors are also considered important for the susceptibility and onset of disease. Infections have been predicted to have a pivotal role in triggering autoimmune reactions and the breakdown of tolerance leading to GD, although evidence is scarce. Patients with GD frequently have a history of some type of psychological and/or physiological stress [3]. Recently, epigenetic factors have also been demonstrated to be involved in autoimmune pathogenesis [4]. Classical GD was described as a syndrome consisting of tachycardia, goiter and orbitopathy, called "Merseburg triad". Most GD patients develop tachycardia and goiter; however, GD patients with orbitopathy, named Graves' ophthalmopathy (GO), occur in up to 60% of all GD patients [5]. In particular, GO worsens the patients quality of life because of its intractable symptoms, including diplopia, proptosis, chemosis and retro-orbital pain. With severe GO patients may risk visual loss. Moreover, GO is also experienced in patients with Hashimoto's thyroiditis (HT) across ethnic backgrounds [6, 7]. HT is another common AITD, which is thought to develop from a combi-

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nation of genetic susceptibility and environmental factors. Many studies have investigated the genetic predisposition of HT, and suggest that GO patients may have partially different genetic backgrounds from GD patients and HT patients without GO.

In this review, we describe the pathogenesis and genetic predisposition of GD and HT first, followed by illustrating those of GO. Finally, we discuss the upcoming problems in future research.

2. The pathogenesis of Graves' disease

As described above, GD is considered a Th2 autoimmune disease. Generating TRAb is the essential for development of the disease, as TRAb signals through TSHR as an agonist, resulting in the overproduction of T4 that induces symptoms such as tachycardia, sweating and body weight loss (thyrotoxicosis) [8]. However, how TRAb is induced remains unknown.

GD is thought to have genetic predisposition. In 1967, Hall et al. published on the frequent familial occurrence of AITD, illustrating that a third of siblings of GD patients developed AITD and over half of asymptomatic children had thyroid antibodies in their blood [9]. Similar observations have been made for decades. Twin studies on GD have also provided persuasive evidence for a role of genetic susceptibility. Monozygotic (MZ) twins with completely identical genes would be expected to have full concordance in a monogenic disease. For diseases with more complex inheritance patterns, the concordance rate in MZ twins would be reduced, although still higher than for dizygotic (DZ) twins. Brix et al. conducted a twin cohort study and determined that the probandwise concordance rates of MZ pairs were much higher than for DZ pairs [10] and estimated that 79% of predisposition to the development of GD arose from genetic factors [11]. These results of family and twin studies demonstrated that GD had genetic predisposition(s) that were not due to a single gene, but rather to multiple interactions among genes [12]. Such genetic factors increase the susceptibility to GD and the development of GD may be triggered by individual environmental factors such as infection, iodine intake, psychological and/or physiological stress, smoking or pollution [13]. Iodine can induce thyroid autoimmunity by increasing the immunogenicity of thyroglobulin and/or releasing free oxygen radicals, resulting in immune attack against thyroid tissue [14]. Establishment of autoimmunity against the thyroid gland is mediated by dendritic cells (DCs), macrophages and/or B lymphocytes that present the antigen(s) to T lymphocytes through an immunological synapse. Furthermore, thyroid follicular cells can also present antigen by expressing major histocompatibility complex (MHC) class I and II molecules. Thus, autoimmune reactions against TSHR are established under such circumstances with the appropriate cytokine conditions. Once the stimulating anti-TSHR antibodies are produced, they continue to provide impetus to the thyroid follicular cells via TSHR to produce thyroid hormone uncontrollably. As will be discussed, many studies have been conducted in the development of GD over the last few decades, identifying numerous genes, of which some have proven to be significant genetic factors in GD pathogenesis. In the next section, we describe these susceptibility loci.

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3. Genetic susceptibility to Graves' disease

The establishment and development of immunological reactions specific to TSHR are hallmarks of GD. Therefore, GD susceptibility genes are likely to be involved in immune reactions, immunological regulation and thyroid specific proteins. The main methodological approaches for identification of susceptibility loci are based on linkage or association analysis, detecting single-nucleotide polymorphisms (SNPs). The majority of loci involved in the development of GD that have been identified confer only a low risk for disease, except one or two loci (odds ratio: ~1.2–1.5), suggesting gene-gene interactions among genes involved in GD and/or subset effects of GD should be further investigated. Recently, because of advances in high throughput genotyping technologies, it has become possible to conduct genome wide association studies (GWAS). However, only a few GWAS for GD have been conducted to date and published new findings from these are scarce. Currently, several groups are conducting GWAS studies for GD from various points of view.

Next, we will discuss the susceptibility loci for GD according to its pathogenesis, such as genes involved in immune reactions, immunological regulation and thyroid specific proteins.

3.1. Immunological synapse genes

The immunological synapse is the interface between T lymphocytes and antigen-presenting cells (APC) that is formed during peripheral T lymphocyte activation. It consists of a peptide antigen bound between human leukocyte antigen (HLA) class II molecules and the T-cell receptor (TCR), costimulatory molecules including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), B7 (CD80 and CD86), CD40 and other molecules [15]. Variations of molecules in the immunological synapse have been elucidated as genetic risk factors for GD. The MHC region, encoding the HLA glycoproteins, is a highly polymorphic genetic region [2]. HLA molecules play pivotal roles in the function of the immune system, binding fragments of antigens in the form of peptides and presenting them to T lymphocytes. HLA molecules are divided into HLA class I (HLA-A, B, C) and class II (HLA-DR, DQ, DP). HLA class I molecules interact with $CD8^+$ T lymphocytes which have cytotoxic effector functions. As host tissues are surveyed by $CD8^+$ T lymphocytes, HLA class I molecules are widely expressed throughout the body, including the thyroid follicular cells. HLA class II molecules, permanently expressed on the surface of cells involved in antigen presentation, present antigens to $CD4^+$ T lymphocytes, which initiate and regulate specific immune responses. Therefore, binding of an antigen fragment to HLA class II is an integrant of the development of immune responses. Apart from peripheral immunologic reactions, HLA molecules are necessary for ontogenesis of the immune system since they participate in the maturation and selection of lymphocytes in the thymus [15]. HLA genes and molecules display polymorphisms to ensure immunological diverseness. Such polymorphisms are particularly extensive in regions, known as pockets, which directly bind peptide residues and have extremely important functional significance because different HLA variants bind a distinctly different repertoire of peptides.

3.1.1. HLA class I

From the early reports of Farid et al. [16] and Grumet et al. [17], HLA class I antigens are thought to be primarily involved in the pathogenesis of GD. HLA-C*07 in particular was suggested to associate with GD susceptibility [18]. Simmonds et al. tested other loci and concluded that HLA-C and to a lesser extent HLA-B, were primarily associated with GD. However, the observed associations to HLA class I alleles could not be attributed to linkage disequilibrium (LD) within this haplotype. To date, many studies have evaluated other HLA class I alleles [19], and some demonstrated significant association to GD susceptibility. While the association between GD and HLA class I antigens has been evaluated, how they are involved in the pathology of GD is unclear. As cytotoxic pathogenesis is thought to be involved during the early stages of GD, they may alter immunological responses.

3.1.2. HLA class II

HLA-DR3 was the first candidate gene to be associated with AITD in Caucasians [20]. It has been identified as a major susceptibly gene for GD, although this is not the case for all ethnic populations. This association was originally demonstrated in a mixed Brazilian population, but the association was not observed in a Japanese population [19]. HLA-DR3 is also associated with the presence of GO and disease course of GD [2]. In other ethnic groups, different alleles were shown to associate with GD [19]. Recent studies on the variants of HLA class II antigens, especially HLA-DR3, focused on the binding pocket that interacts directly with antigenic peptides. Specifically, these studies concluded that the substitution of the neutral amino acids Ala or Gln for positively charged Arg at position 74 of the DR beta 1 chain (DRb1–Arg74) resulted in a structural change in the HLA-DR peptide binding pocket that conferred an increased risk for the development of GD [21]. Conversely, glutamine at this peptide binding pocket position was proven protective against GD. This change of amino acid at the pocket of the peptide binding cleft alters its three-dimensional structure that likely allows pathogenic peptides to bind to the HLA molecule so that subsequently auto-reactive T cells recognize the antigenic peptide and induce an autoimmune response.

3.1.3. CTLA-4

CTLA-4 is a major negative regulator of T cell activation [22]. While APCs activate T cells by interactions between HLA antigen and the TCR, CTLA-4 acts as an accessory molecule to the TCR and suppresses T cell activation to control normal T cell responses. Therefore, it is postulated that CTLA-4 polymorphisms reduce their own expression and/or function, resulting in increased predisposition to autoimmunity. Indeed, CTLA-4 polymorphisms have been identified in various autoimmune conditions [23] including both GD [24] and HT [19], across ethnic and geographic groups. CTLA-4 loci are shown to regulate T cell activation in a complicated manner. Vieland et al. recently showed CTLA-4 played a role in the susceptibility to high levels of thyroid specific antibodies (TAb), and clinical AITD when interacting with other loci [25]. They also demonstrated that both the G allele and the A allele of the A/G49 SNP of CTLA-4 might predispose to AITD when interacting with different loci. At present, three main variants of CTLA-4 have been evaluated: an AT-repeat microsatellite at the 3'UTR of the

CTLA-4 gene; an A/G SNP at position 49 in the signal peptide resulting in an alanine/threonine substitution (A/G49); and an A/G SNP located downstream and outside of the 30UTR of the CTLA-4 gene (designated CT60) [19]. To identify which is the causative variant for AITD including GD, many functional studies are currently being conducted.

3.1.4. CD40

CD40 expressed primarily on B cells and other APCs, plays a crucial role in B cell activation and antibody secretion as a co-stimulatory molecule [26]. It is associated with GD as a positional candidate on the basis of a genome-wide linkage study [27, 28]. Further sequencing studies of the CD40 gene have shown a C/T SNP in the CD40 gene, likely to be the causative variant in Caucasian, Korean and Japanese populations [19]. The CC genotype of this SNP was demonstrated to associate with development of GD in many ethnic populations [29]. The CC genotype, located in the Kozak sequence of CD40, can alter CD40 translation and expression [28]. The C-allele of the SNP was shown to increase the translation of CD40 mRNA transcripts by 20–30% compared to the T-allele [28, 30]. CD40 is expressed on B cells [26] and on thyroid follicular cells [31], and so the C-allele-induced increase in CD40 expression on B cells and/or thyrocytes may predispose to the disease. Increased expression of CD40 on B cells may result in the enhanced production of anti-TSHR-stimulating antibodies, whereas increased expression of CD40 on thyrocytes can trigger an autoimmune response to the thyroid.

3.1.5. The protein tyrosine phosphatase-22 (PTPN-22) gene

Lymphoid tyrosine phosphatase, encoded by the protein tyrosine phosphatase-22 (PTPN22) gene, is shown to be a negative regulator of T cell activation [32]. The PTPN22 gene is associated with AITD, including both GD and HT. Differences in the ethnic contribution of the PTPN22 SNP have also been identified [19, 33]. PTPN22 is involved in limiting the adaptive immune response to antigen by dephosphorylating and inactivating TCR-associated kinases and their substrates. The best documented association of PTPN22 variants to autoimmune disorders including GD is rs2476601 (C1858T). This C1858T SNP, encoding an Arg to Trp substitution at residue 620 (R620W), is located in the P1 proline-rich motif of PTPN22, which binds with high affinity to the Src homology 3 (SH3) domain of Csk [34]. This disease-associated variant is a gain-of-function variant, resulting in suppression of TCR signaling more efficiently than wild type protein. *In vitro* experiments have shown hyper-responsiveness of T cells expressing the W620 allele, indicating that carriers of this allele may be prone to autoimmunity [35]. While many experiments have been conducted to evaluate the immunological pathway of PTPN-22 polymorphisms, they are still controversial. Many complicated immunological pathways concerning T cell activation are expected to be involved. Further studies are required to elucidate the role of PTPN-22 polymorphisms in susceptibility to disease.

3.2. T cell regulation

Natural regulatory T (Treg) cells are an important subset of T cells that regulate T cell activation [36]. They play a pivotal role in peripheral tolerance to self-antigens. In murine studies, up-regulation of Treg cells suppressed experimental autoimmune thyroiditis [37], while depletion

of Tregs increased their susceptibility to experimental GD [38]. Treg cells are characterized by constitutively expressing CD25, CTLA-4, and glucocorticoid-induced tumor necrosis factor receptor. Their development is regulated by a master gene, FOXP3 [36]. Interestingly, both FOXP3 and CD25 are associated with AITD [19, 39].

3.2.1. FOXP3

Ban Y. et al. tested the FOXP3 gene in two cohorts of AITD patients, including U.S. Caucasians and Japanese. They demonstrated an association of a microsatellite in the FOXP3 gene with AITD in Caucasians but not in the Japanese, suggesting ethnic differences in disease susceptibility [39]. The estimated pathogenesis of the FOXP3 variant is thought to mediate pathogenesis by weakening suppression of autoimmune effector T cell activity.

3.2.2. CD25

Treg cells are characterized by the constitutive expression of high levels of CD25, the alpha chain of the IL-2 receptor [36]. Similar to FOXP3, recent studies have found an association between the CD25 gene and GD [19]. While the variant of CD25 is thought to alter the suppressive effects on self-reactive T cells, the detailed mechanisms are still unclear.

3.3. Thyroid specific genes

As GD is a thyroid specific autoimmune disease, it is highly likely that polymorphisms of genes coding for thyroid-specific proteins affect the susceptibility to GD, similar to other AITD such as HT.

3.3.1. Thyroglobulin

Thyroglobulin (Tg) is a main target of the immune response in AITD [40]. A whole-genome linkage study identified the Tg gene as a major AITD susceptibility gene [41]. Moreover, several groups also have reported similar findings for Tg gene predisposition to AITD in Caucasian, Japanese and Taiwanese populations [19]. Tg variants may predispose to GD by altering Tg degeneration in endosomes with slight changes in amino-acid sequences. This may result in the production of a pathogenic Tg peptide repertoire that interacts with HLA-DRb1-Arg74 and leads to a high prevalence of GD [42]. Recently, a newly identified TG promoter SNP (-1623A/G) was found to associate with AITD in another pathway [43]. The disease-associated G allele in -1623A/G SNP confers increased promoter activity through the binding of the interferon regulatory factor-1 (IRF-1), a major interferon-induced transcription factor. Murine studies indicated that IRF-1 was associated with AITD [44]. These results suggest that variants of Tg itself possibly alter the reactivity of cytokines through IRF-1.

3.3.2. TSH receptor

Regarding the pathology of GD, it is not surprising that TSHR gene variants predispose to GD. Indeed, TSHR was the first gene after HLA to be tested for association with GD. Early studies tested three non-synonymous SNPs in the TSHR gene for association with GD, D36H and P52T

that are located in the extracellular domain and D727E which in present in the intracellular domain [19]. However, conflicting results on the association of SNPs in the TSHR gene to GD were reported. This encouraged increasing research for susceptibility loci to non-coding sequences within the TSHR gene. Japanese large scale analyses of SNPs showed evidence for three haplotypes within TSHR intron 7 that were strongly associated with GD. In contrast, a Caucasian study showed evidence for a SNP (rs2268458) located in intron 1 associated with GD. Moreover, Brand et al. investigated a combined panel of 98 SNPs in intron 1 of TSHR [45], showing 2 SNPs associated with GD. Functional analyses suggested that SNPs in the intron region could be associated with reduced expression of full length TSHR mRNA and in turn lead to increased shedding of the A-subunit of the TSHR receptor, which is an important molecule for the induction of autoantibodies against TSHR [46]. Recently, a non-synonymous SNP in the distal part of the gene, rs3783941, was indicated to be associated with GD in a large GWAS study of non-synonymous variants among 4500 subjects [47]. However, this might represent a false positive because this association was not replicated. However, there remains the possibility that the lack of replication was due to insufficient power.

3.4. Other genes

Many other genes, apart from the three categories described above, have been associated with the development of GD. Fc receptor-like 3 (FCRL3) is a receptor of unknown function with structural homology to immunoglobulin constant chains (Fc receptors). Allele C of rs7528684 located at position –169 in the promoter region was demonstrated to associate with GD in the Japanese [48] and UK population [47]. In contrast, a negative association between GD and FCRL3 was also reported [49]. FCRL3 is expressed in lymphoid tissues especially on the surface of B cells and a subset of Treg cells [50]. This suggested a function of FCRL3 in the regulation of autoimmunity, although its functions remain unknown. Variants of the promoter of the Secretoglobin 3A2 (SCGB3A2) gene encoding secretory Uteroglobin-Related Protein 1 (UGRP1) have been reported to associate with GD in an extensive study of 2500 patients and controls from the Chinese population [51]. This finding was confirmed in a UK population and Russian population study [19]. UGRP1 is a ligand for macrophage scavenger receptor with collagenous structure, which is predominantly expressed in the lung, although low-level expression is also present in the thyroid [52]. While SNPs in SCGB3A2 were found to reduce promoter activity by 24% [53], their function in the pathogenesis of GD is unclear. The variant rs1990760 present as A946T in the interferon-induced helicase C domain 1 (IFIH1) C domain was demonstrated to associate with GD in a UK population [54]. However, no statistically significant association was found in subsequent German [55], Chinese [56] and Japanese studies [57]. IFIH1 is part of a family of intracellular proteins involved in innate immunity through recognition of viral RNA [58], although it is unknown how polymorphisms in IFIH1 affect the pathogenesis of GD. The variant rs763361, which is a non-synonymous SNP in the intracellular tail of the CD226 molecule, was also reported to be associated with GD [54]. This variant possibly alters splicing of the CD226 transcript, suggesting an association with GD. There are also a number of other genes reported to be associated with GD, such as vitamin D receptor (VDR), type II iodothyronine deiodinase, IL23 receptor (IL23R), estrogen receptor beta (ESR2) and a promoter variant of a gene encoding nuclear factor-kappaB (NF-κB) [19, 59]. To

examine the significance of these polymorphisms on the predisposition of GD, further studies with significant power and a variety of ethnic groups are required.

4. Genetic susceptibility to Hashimoto's thyroiditis (HT)

Although HT is less commonly involved in GO patients, it is the most prevalent autoimmune thyroid disorder. Lymphocytic infiltration within the thyroid gland is often followed by a gradual destruction and fibrous replacement of the thyroid parenchymal tissue. The principal biochemical characteristic of the disease is the presence in the patients' sera of autoantibodies against two major thyroid antigens (TAbs), thyroid peroxidase (TPO) and Tg. Antibodies against TPO (TPOAbs) and Tg (TgAbs) cause damage to thyroid cells because of antibody dependent cell-mediated cytotoxicity [60]. TPOAbs are prevalent in nearly all patients and TgAbs are present in approximately 80% of HT patients. TSHR antibodies are the principal biochemical characteristics of GD, and generally do not exist among HT patients. While TSHR antibodies are of primary importance in developing GO, it is unclear how GO develops in certain HT patients who do not have TSHR antibodies. With increasing knowledge of the etiology and pathology of AITD, including HT and GD, HT has been shown to develop in genetically susceptible individuals triggered by environmental cues similar to patients with GD [61]. In the following section, we shall discuss the genetic predisposition of HT. The genetic susceptibility of HT is similar to that of GD described above. Despite the disease outcomes being opposite, hypothyroidism and hyperthyroidism, respectively, the immunopathology and genetic predisposition are shown to be common. Indeed, a report describes monozygotic twins where one developed HT and the other GD, indicating commonality between the genetic factors of HT and GD [62]. On the basis of familial and twin studies, a strong genetic predisposition to AITD has been identified. Familial clustering of AITD including HT and GD has been confirmed [61]. The sibling risk ratio for AITD was calculated as 28, which indicated the highly significant contribution of genetic factors to disease development [63].

4.1. HLA genes

In HT, aberrant expression of HLA class II molecules on thyrocytes has been demonstrated. Presumably, thyrocytes may act as APCs capable of presenting thyroid autoantigens and initiating autoimmune thyroid disease [64]. In Caucasians, associations between HT and various HLA alleles, including DR3, DR5, DQ7, DQB1*03, DQw7 or DRB1*04-DQB1*0301 haplotype were reported. In Japanese, associations with DRB4*0101, HLA-A2 and DRw53 were demonstrated, while in Chinese patients association with DRw9 was observed [61].

4.2. CTLA-4

Several polymorphisms of the CTLA-4 gene in HT patients have been studied. The initially reported (AT)n microsatellite CTLA-4 polymorphism in the 3′ untranslated region (UTR) was found to be associated with HT in Caucasian and Japanese patients, but not in an Italian population [61]. The exon 1 located 49A/G SNP results in a threonine to alanine substitution

and is associated with HT [65]. The exact mechanism conferring susceptibility to HT has not been elucidated yet and further studies are needed to find out which CTLA-4 polymorphism is causative.

4.3. PTPN22

As is for GD, the C1858T SNP of the PTPN22 gene was also demonstrated to be a risk factor for HT [66]. However, the mechanism is not clear. This observation was not confirmed in German, Tunisian or Japanese population studies [61].

4.4. Vitamin D receptor (VDR) gene

Vitamin D, which acts via VDR, is classically involved in the metabolism of calcium. However, recent studies have revealed that it possesses immunomodulatory properties and its deficiency is implicated in the development of autoimmune diseases [67]. Many immune cells, particularly DCs, express VDR, whose stimulation has been shown to enhance tolerogenicity. Tolerogenic DCs promote the development of Treg cells, inducing peripheral tolerance. Therefore, modulation of VDR may affect the ability of DCs to alter the induction ability of Treg cells. To date the association between VDR-FokI SNP in exon 2 and HT has been identified in Japanese and Taiwanese populations [61]. In a Croatian study, the VDR gene 3' region polymorphisms were related to HT [68], possibly by affecting VDR mRNA expression.

4.5. Thyroglobulin genes

Considering the pathogenesis of HT, it is reasonable that Tg gene polymorphisms genetically predispose individuals to HT. As described in the previous section, there have been reported many genetic regions related to AITD [69]. The association of HT with Tgms2, a microsatellite marker in intron 27 of the Tg gene was confirmed in Japanese and Caucasian populations [61]. However, these observations were not confirmed in a larger data set of UK Caucasian patients or in a Chinese population.

4.6. TPO genes

TPO is also considered an important gene in the pathogenesis of HT, because antibodies against TPO are characteristic of HT. To date, the T1936C, T2229C and A2257C TPO gene polymorphisms have been tested for association with TPOAb levels [61].

4.7. Cytokine genes, immune related genes and others

According to recent advances in the understanding of immune cell subsets and cytokines, several genes encoding different inflammatory cytokines have been studied in HT, and some have shown the ability to influence the severity of disease. As HT is thought to be a cytotoxic T cell-mediated autoimmune disease, cytokines produced by T-helper type 1 (Th1) cells, including interferon (IFN)-γ, have been well studied among HT patients. The T allele of the +874A/T IFN-γ SNP, which causes an increased production of IFN-γ, was reported to be associated with the severity of hypothyroidism in HT patients [70]. However, a higher

frequency of severe hypothyroidism was also observed in Japanese patients with a CC genotype of -590C/T interleukin (IL)-4 SNP [71]. IL-4 is a key Th2 cytokine that can suppress cell-mediated autoimmunity, and this polymorphism was thought to lead to reduced IL-4 production. These studies demonstrated the complexity of HT pathogenesis. Gene polymorphisms of transforming growth factor (TGF)-β, an inhibitor of cytokine production, were also associated with HT [72]. The T allele of +369T/C SNP causes reduced secretion of TGF-β, and was more frequent in severe hypothyroidism than in mild hypothyroidism. SNPs of the gene encoding FOXP3, an essential regulatory factor for Treg cell development, was shown to associate with a severe form of HT [61]. The C allele of tumor necrosis factor (TNF)-α, 1031T/C SNP, was shown to associate with the development of HT by an over-production of TNF-α [61].

5. Genetic susceptibility to Graves' ophthalmopathy

In the previous sections we described genetic susceptibility to GD and HT because GO develops in GD and occasionally in HT patients. While GD and HT patients in the previously described studies included those with and without GO, the research described in this section will focus on the genetic factors of GO compared to the possession rate of the polymorphism among normal controls, GD without GO patients and GD with GO patients.

5.1. The pathogenesis of GO

GO is an orbital manifestation of AITDs, mainly GD, and develops in 25-50% of GD patents and up to 5% of HT patients. The pathogenesis of GO has been studied for several decades, but remains controversial. At present, it is presumed to occur through the same underlying immune processes as GD, such as the involvement of TRAbs [73]. TSHR was expressed in the orbital tissues, especially on fibroblasts. When TRAbs interact with TSHR, inflammatory immune cells and cytokines become activated and cause inflammation in the retrobulbar tissues. Inflammation in the muscles that direct eyeball movement upsets the coordination of their movements, resulting in enlargement of the involved muscles and double vision. Inflammation in retro-orbital fat tissue enlarges its volume, leading to protrusion of the eyeball (proptosis). Some patients develop inflammation of the eyelids and/or lachrymal gland. However, such pathways are unable to expound why GO can develop in some HT patients who do not possess TRAbs. Moreover, the level of TSHR expression in the orbital tissue, including fibroblasts and eye muscles, is so low that it is unlikely to induce sufficient inflammation to affect tissues such that they lose function. One hypothesis suggests that the thyroid and orbital tissues share antigens, and that when autoantibodies are induced during autoimmune thyroid disease, concurrent inflammation in the orbit(s) may also occur [74]. Potential shared antigens include Fp, G2S, calsequestrin (CSQ) 1 and 2 and collagen XIII [74]. However these results have not been confirmed. Although it is difficult to regard such antigens as primary antigens for GO because Fp, G2s, and CSQ1 and 2 are proteins located inside the cell, they may emerge as a consequence of destruction of the thyroid gland and/or orbit tissuesal through autoimmune or other immune reactions. TRAb titers were positively correlated with

clinical features of GO, whereas thyroid stimulating immunoglobulin (TSI) and TPO antibody were not [75]. Recently a new TSI testing method showed a significant correlation between TSI and the clinical features of GO [76].

5.2. The genetics of GO

While the pathogenesis of GO is thought to share similar genetic factors with GD and HT, it is unknown what divides GD patients with GO from GD patients without GO. Much research has focused on inflammatory factors because the inflammation present in orbital tissues in GO patients is believed to be disease-specific. In the following section, we provide a detailed review of the immunogenetic associations of GO. A summary of the relevant studies is provided in Table 1.

Categories		GD including GO	GO	HT
Immunological	HLA class I	HLA-C*07		
synapse genes		HLA-B*08		HLA-A2
	HLA class II	HLA-DR3	HLA-DPB 2.1/8	HLA-DR3
			HLA-DR4	HLA-DR5
			HLA-DR7	HLA-DR7
			HLA-DRB1	HLA-DQB1*03
			HLA-DRB3	HLA-DQw7
				HLA-DRB1*04
				HLA-DQB1*0301
				HLA-DRB4*0101
				HLA-DRw53
				HLA-DRw9
		CTLA-4	CTLA-4	CTLA-4
		PTPN22		PTPN22
			PTPN12	
		CD40		
T cell regulation		FOXP3		FOXP3
		CD25		
Thyroid specific		Thyroglobulin		Thyroglobulin
genes		DIO 2		
		TSHR		

Categories	GD including GO	GO	HT
Cytokines or		TNF-α	TNF-α
Cytokine receptors		IL-1α	IL-4
		IL-1β	TGF-β
		IL-1RA	
		IFN-©	IFN-γ
	IL-23R		
Other immunological	NF-κB	NF-κB	
molecules	CD226	ICAM-1	
	FCRL3	TLR-9	
	SCGB3A2	CD86	
	IFIH1	CD103	
Others	VDR	GR	VDR
	ESR2		

Each genetic locus is referenced in the body of the manuscript.

GD: Graves' disease; GO: Graves' ophthalmopathy; HT: Hashimoto's thyroiditis; HLA: Human leukocyte antigen; CTLA: Cytotoxic T-lymphocyte-associated protein; CD: Cluster of Differentiation; PTPN: Protein tyrosine phosphatase; FOXP: forkhead box P; TSHR: Thyroid stimulating hormone receptor; FCRL: Fc receptor-like; SCGB3A2: Secretoglobin 3A2; IFIH1: Interferon-induced helicase C domain 1; VDR: Vitamin D receptor; GR: Glucocorticoid receptor; DIO 2: Type II iodothyronine deiodinase; IL: Interleukin; ESR2: Estrogen receptor 2; NF-κb: Nuclear factor-kappa B; IFN: Interferon; TGF: Transforming growth factor; TPO: Thyroid peroxidase; TNF: Tumor necrosis factor; ICAM: Intercellular Adhesion Molecule; TLR: Toll-like receptor.

Table 1. Genetic predisposition to Graves' disease, Graves' ophthalmopathy and Hashimoto's thyroiditis

5.3. Cytokines

Similar to GD, disease in GO is thought to involve an imbalance between the production of pro- and anti-inflammatory cytokines [77]. Therefore, SNPs in cytokine related genes that participate in the GO pathogenesis could promote or protect from its development. As shown in Table 1, the association between various pro- and anti-inflammatory cytokine gene polymorphisms in GO have been identified. Cytokines released mainly by leukocytes infiltrating into the retro-orbital tissues are likely to play key roles in the cascade of autoimmune reactions in the orbit [78]. Although several significant associations between genetic polymorphisms of cytokine genes and GO have been reported, the immediate consequences of cytokine gene polymorphisms are not well studied. Thus, how polymorphisms of cytokine genes relate to biological changes such as serum and local tissue concentration and functional activity are unknown. Moreover, publication of polymorphisms suggested to have a positive correlation with GO provokes many unpublished and/or published contradictory reports performed by other research groups. This might reflect the presence of different genetic patterns of suscept-

ibility among different ethnic groups, or might be an outcome of the product of chance. Among cytokines studied, the association of genetic susceptibility to GO with cytokine gene polymorphisms from the family of IL-1 and TNF-α-related cytokines seems to be the strongest. Recently a specific TNF-α inhibitor, Infliximab, was demonstrated to be effective for treatment of severe GO [79]. Several groups showed positive associations between the development of GO and TNF-α polymorphisms, including -863C/A region in Japanese and Chinese, -238G/A in Polish and -1031T/C in Japanese populations [80]. As regards the IL-1 superfamily, IL-1α and-β are pro-inflammatory cytokines, and the IL-1receptor antagonist (RA) competes for receptor binding with IL-1α and-β [81]. Retro-orbital fibroblasts derived from GO patients expressed and secreted significantly reduced levels of intracellular and soluble IL-1RA [82]. Thus, an imbalance between IL-1 and IL-1RA may play an important role in the pathogenesis of GO and gene polymorphisms in IL-1α, -1β and/or IL-1RA may have a causal relationship with such an imbalance. IL-1 is a key cytokine in many inflammatory reactions. It stimulates retro-orbital fibroblasts to proliferate, synthesize glycosaminoglycans and express immunomodulatory molecules [83] including adhesion molecules, cytokines, complement regulatory proteins and stress proteins. Reports on polymorphisms of IL-1α and -β genes are conflicting, with some showing positive [84] and negative [85] associations.

IFN-γ is a type II interferon involved in Th1 immune responses and can regulate Th2 immune reactions. We studied IFN-γ gene polymorphisms in Japanese GD patients and 2 out of 8 polymorphisms were associated with GO [86]. An Iranian group also demonstrated a significant association between GO and an IFN-γ polymorphism at UTR 5644A/T [87].

5.4. CTLA-4

As shown in previous sections, CTLA-4 gene polymorphisms, especially the A/G49 SNP of CTLA-4, are strongly associated with GD and HT. A UK study showed the A/G49 SNP of CTLA-4 was associated with an increased risk of GO [88] and was confirmed by an Iranian group [80]. However, the association between the CTLA-4 gene polymorphism and the development of GO is still controversial [89]. First, the same polymorphism was shown to be associated with HT and GD with or without GO. Second, many follow-up studies have been performed, and while some studies confirmed such an association the others did not [80].

5.5. HLA

As GD is believed to be a Th2 related disease, HLA class II is thought to have an association with GD. GO is one of many symptoms of GD, and thus it is justifiable to regard GO as a Th2 related disease. However, this is still controversial because no antibodies have been confirmed to have a causal association with GO except TSHR antibodies. Moreover, not all GD patients develop GO; the prevalence of GO among GD patients is only 25-50%. Thus, there is a limitation in studying autoimmune associations of different HLA alleles because of the strong LD between HLA alleles and alleles of undefined neighboring loci, which may exert primary effects [90]. Therefore, functional studies of the biological effects of different HLA alleles are needed to determine the true effects of these potential genetic associates of GO. Several studies support a role for HLA-DRB1, which has a critical role in antigen presentation, in the devel-

opment of GO [80]. However, contradictory reports also exist [80, 90]. HLA-DR7 alleles are also reported to have an association with the development of GO [91], and several isolated studies have shown a weak association between HLA-DR4, HLA-DPB 2.1/8 and HLA-DRB3 alleles and GO [80, 92]. However, the opposite outcome has also been shown for HLA-DR3, -DR4 and -DR7 alleles [89]. Several HLA class I and class II lesions were shown to be genetic susceptibility genes for GO [80], although they are still controversial because of a lack of confirmation of the results.

5.6. Other genes

GO has reported to be associated with several genes involved in immunopathogenesis. Polymorphisms in intracellular adhesion molecule (ICAM)-1, which is a pivotal molecule in leukocyte migration and circulation, was recently reported to be a predisposition for GO [93]. Interactions between CD40 and CD40 ligand were demonstrated to induce the expression of ICAM-1 on the surface of retro-orbital fibroblasts [94]. Thus, the polymorphism of ICAM-1 could alter its expression levels resulting in the modification of leukocyte migration to the orbits. Similar to GD and HT, PTPN22 is a candidate genetic factor for GO [95], although the connection between PTPN22 and GO has not been confirmed. However, a polymorphism in PTPN12, an important regulator of T cell receptor signal transduction other than PTPN22, was demonstrated to have an association with the presence of mild to moderate GO in a Caucasian population through interactions with TSHR [80]. NF-κB, toll-like receptor (TLR)-9, glucocorticoid receptor, CD86 and CD103 have also been reported to be associated with the clinical course of GO [59, 80]. While TSHR gene polymorphisms are major genetic factors of GD, they have been demonstrated to play a role in the development of GO among GD patients.

The evaluation of genetic predisposition to GO is complicated. As described above, studies on the association of GO and cytokines or CTLA-4 are still controversial. The polymorphisms of HLA genes have unsolved problems because they tend to be in LD with neighboring genes. Unfortunately, functional analysis of candidate genes is not performed often enough, and so the genetic predisposition to GO is often not validated. Despite many studies, there is often a bias towards certain ethnic groups, whereas for example those containing African populations are scant. The clinical features of GO between ethnic groups can be different. For example, the severity and activity of GO in Asian populations tend to be milder than in Caucasian patients [96]. This suggests that genetic factor(s) are important in the development of GO severity. Moreover, the ratio of females/males with GO is lower than that of GD without GO and HT [1, 97], suggesting that GO is less dependent on the X chromosome. Thus, it is reasonable to regard GO as a disease that has genetic predispositions. On the contrary, Yin et al. recently showed that there was no association between both the development of GO and the severity GO and genetic polymorphisms of HLA-DR3, CTLA-4, TSHR and IL-23R, which are well-established GD susceptibility genes [98]. They also showed that any combination of genetic polymorphisms among these four genes did not contribute to GO, suggesting an absence of distinct genetic predisposition to GO. Indeed, the strongest influencing factor in the development of GO is smoking, which is a typical environmental factor [97]. Does this mean then that the effects of different ethnic backgrounds and sex ratio on the clinical phenotype of GO can

be explained by environmental factors only? This is a fundamental issue that should be resolved.

	Class	Grade
0	**N**o physical signs or symptoms	
I	**O**nly signs, no symptoms (lid retraction, lid lag)	Lid retraction **a**:<2mm **b**: 2-5mm **c**: "/>5mm
II	**S**oft tissue involvement (sandy sensation, lacrimation, photophobia, lid fullness, conjunctival injection, chemsis, lid edema)	**0**: Absent **a**: Mild **b**: Moderate **c**: Marked
III	**P**roptosis	**0**: < 17mm **a**: 17 - 18mm **b**: 18 - 21mm **c**: "/>21mm
IV	**E**xtraocular muscle involvement	**0**: Absent **a**: Limitation of motion in extremes of gaze **b**: Evident restriction of motion **c**: Fixation of a globe or globes
V	**C**orneal involvement	**0**: Absent **a**: Stippling of the cornea **b**: Ulceration **c**: Clouding, necrosis, perforation
VI	**S**ight loss (optic nerve involvement)	**0**: Absent **a**: Visual acuity 0.63-0.5 **b**: 0.4-0.1 **c**: <0.1 - no light perception

Table 2. Modified "NOSPECS" classification. Grades a, b and c within class I, class II, class III and class IV are largely undefined. Severity should be scored by skillful experts in GO. The classification score should be expressed as the largest each class and the subclass, e.g. class II_a, III_b, IV_b.

5.7. Subtypes of Graves' ophthalmopathy

The most important issue is the definition of GO. Currently, ophthalmopathy related to AITD is described as GO, although there is no evidence to suggest that GO accompanied by GD and GO with HT are the same disease despite, having almost the same clinical phenotype. Moreover, GO has diverse symptoms and clinical features. For example, some lesions are unilateral, others are bilateral, and some effects are observed in the extra-ocular muscle and others in the retro-orbital fat tissue without any lesions in the extra-ocular muscles. Observations in patients with GO indicate the presence of subtypes, although there have been few descriptions published to date.

For half a century, clinicians have sorted GO patients for treatment by clinical grade. Werner SC has classified GO into 7 classes as shown in Table 2 [99]. This classification is termed "NOSPECS" classification and has been adopted as the "official" classification of the American

Thyroid Association. Clinicians use this as a clinical stratification of GO. Indeed, the prognosis of eye function of the patient tends to worsen in the order of this classification. Intriguingly, there exist many GO patients who develop a certain class of symptoms do not develop symptoms that belong to a lower class. For instance, it is not rare for a patient with GO who has an extra-ocular muscle symptom (class VI) to have no symptoms of proptosis (class III). This suggests that there are several symptoms involved in GO, which could progress independently each other. Although these facts have encouraged researchers to analyze the clinical course and patterns of affected lesions in GO patients, such reports are scarce. El-Kaissi et al. classified the clinical features of GO into three subtypes [100] containing: 1) congestive ophthalmopathy that mainly affects the retro-orbital fat tissue; 2) myopathic ophthalmopathy affecting the extra-ocular muscle(s); and 3) mixed congestive and myopathic ophthalmopathy. From the clinical point of view, this classification is useful because eye muscle involvement is a key factor for the aggressive treatment for GO that consists of intravenous glucocorticoid therapy and/or irradiation of the retro-orbital lesion. Furthermore, there are also other symptoms of GO including inflammation of the lachrymal glands and/or eyelids and eyelid retraction. To identify and diagnose extra-ocular muscle lesions precisely and accurately, magnet resonance imaging (MRI) of the retro-orbital area is an efficient tool for clinicians. It is useful to make detailed graphics to measure the volume of extra-ocular muscles and the grade of proptosis, and to discriminate the affected lesion inside the orbit from normal tissue. MRI can be used to obtain a variety of subtracted images useful for making decisions on the condition of GO [101, 102]. While MRI has several undesirable aspects (i.e. time-consuming, expensive, difficulty in comparison of images taken at different times and/or by different machines), it is still the most useful device for the evaluation of GO. The progress of MRI technology has contributed to the treatment of GO.

Examples of MRI for GO are shown. Figure 1 shows an 83-year-old male affected with GO. MRI imaging indicates the enlargement of all bilateral extra-ocular muscles with compression of the optic nerves. This patient has a rapidly progressing disorder in bilateral visual function. However, he has no proptosis. This case is NOSPECS class I_b, II_a, III_0, IV_b, V_0, VI_b and "myopathic ophthalmopathy" type. With bilateral lower eyelid retraction and mild lid edema, this can be sorted as "mixed ophthalmopathy" type. Figure 2 shows a 42-year-old female with bilateral proptosis. She has right lid retraction in primary gaze (Darylmple's sign) and lid edema. MRI imaging indicates her disease does not affect extra-ocular muscles. This case is NOSPECS class is I_a, II_a, III_b, IV_0, V_0, VI_0 and "congestive ophthalmopathy." Figure 3 shows a 51-year-old female with GD. She has bilateral eyelids swelling without proptosis or diplopia. MRI shows the prominent swelling of upper eyelid and slight enlargement of the superior levator muscles. There is no enlargement of the rectus muscles nor retro-orbital fat expansion. This case is classified as NOSPECS class I_0, II_c, III_0, IV_0, V_0, VI_0. With examining without MRI, this case is regarded as "congestive ophthalmopathy." However the findings on MRI images suggest it is "mixed congestive and myopathic ophthalmopathy." Figure 4 shows a 65-year-old male with HT. While he has no TRAb, he has evident proptosis (left side > right side) and deviation of the left eyeball. MRI imaging shows marked enlargement of the inferior and medial rectus muscles of the left eye. The MRI STIR imaging suggests intense inflammation in

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these muscles. This case is classified as NOSPECS class I_0, II_a, III_a, IV_c, V_0, VI_0 and "mixed congestive and myopathic ophthalmopathy."

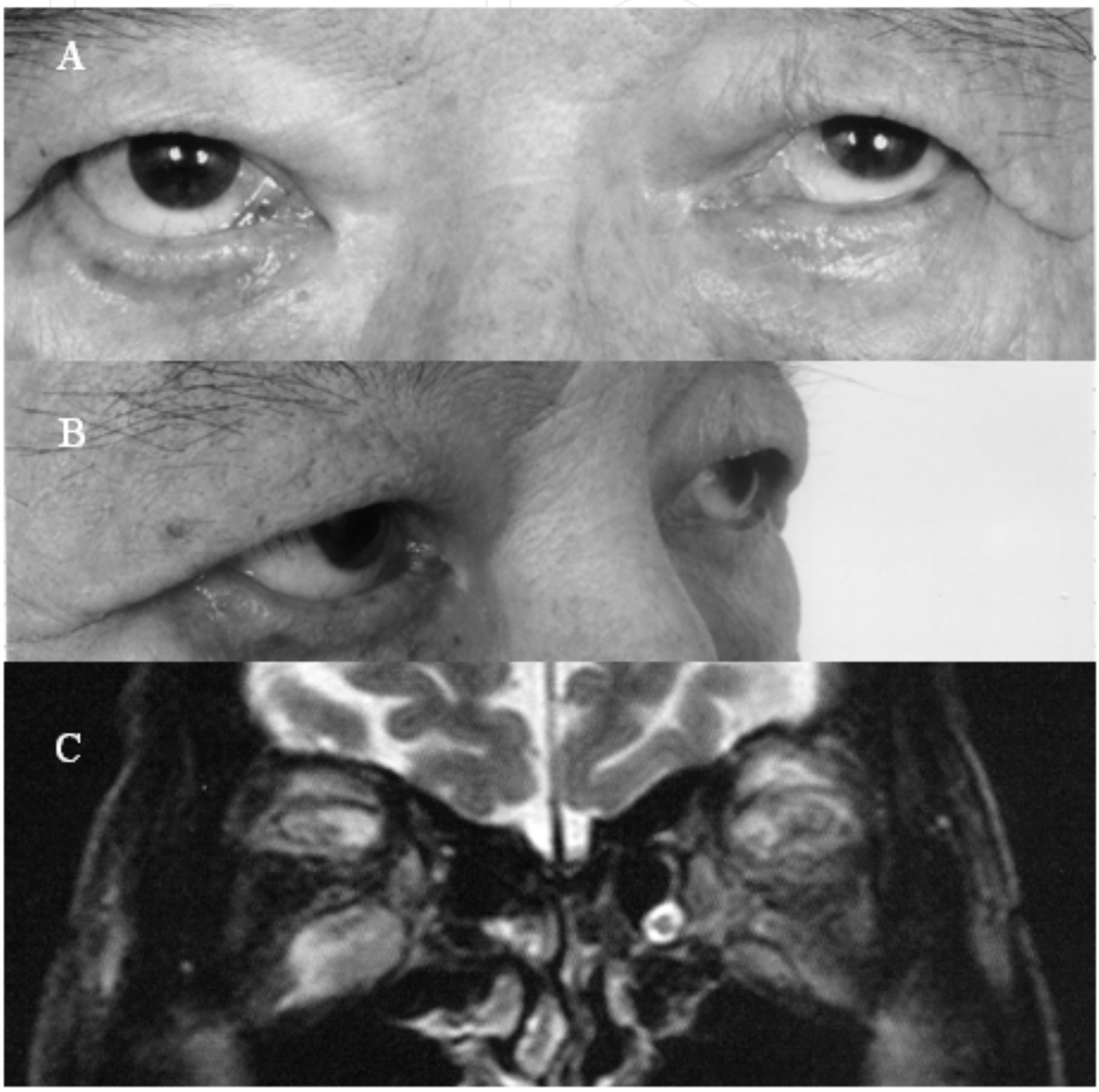


Figure 1. An 83-year-old male with GD. A) He has bilateral lower eyelid retraction and mild lid edema. B) He has no proptosis suggesting NOSPECS class III_0. C) MRI imaging indicates the enlargement of all bilateral extra-ocular muscles with compression of the optic nerves. The STIR (Short TI Inversion Recovery) imaging, which suppresses the signal from fat, shows high intensity inside the bilateral eye muscles indicating the inflammation of eye muscles. This case is NOSPECS class I_b, II_a, III_0, IV_b, V_0, VI_b.

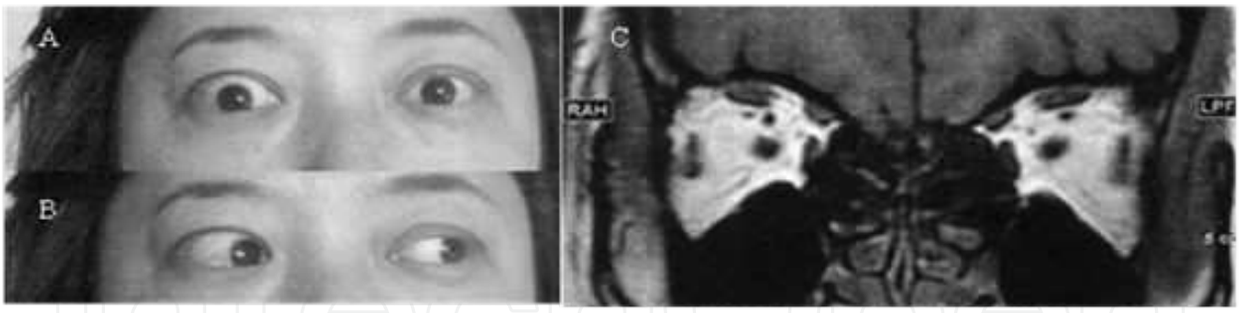


Figure 2. A 42-year-old female with bilateral proptosis. A). She has right lid retraction in primary gaze (Darylmple's sign) and lid edema. B) However her eye movement was normal. C) MRI imaging shows all her extraocular muscles are intact. This case is NOSPECS class is I_a, II_a, III_b, IV_0, V_0, VI_0.

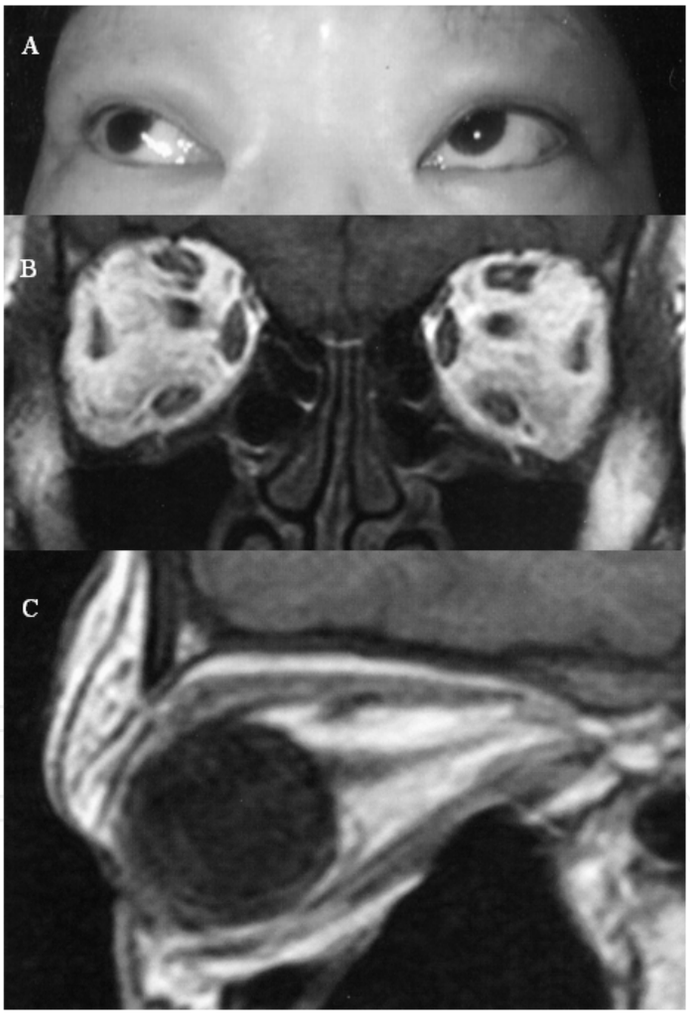


Figure 3. A 51-year-old female with GD. A) She has bilateral eyelids swelling without proptosis or diplopia. B, C) MRI shows the prominent swelling of upper eyelid and the enlargement of the superior levator palpebrae muscle. There is no enlargement of the rectus muscles or retro-orbital fat expansion. This case is classified as NOSPECS class I_0, II_c, III_0, IV_0, V_0, VI_0.

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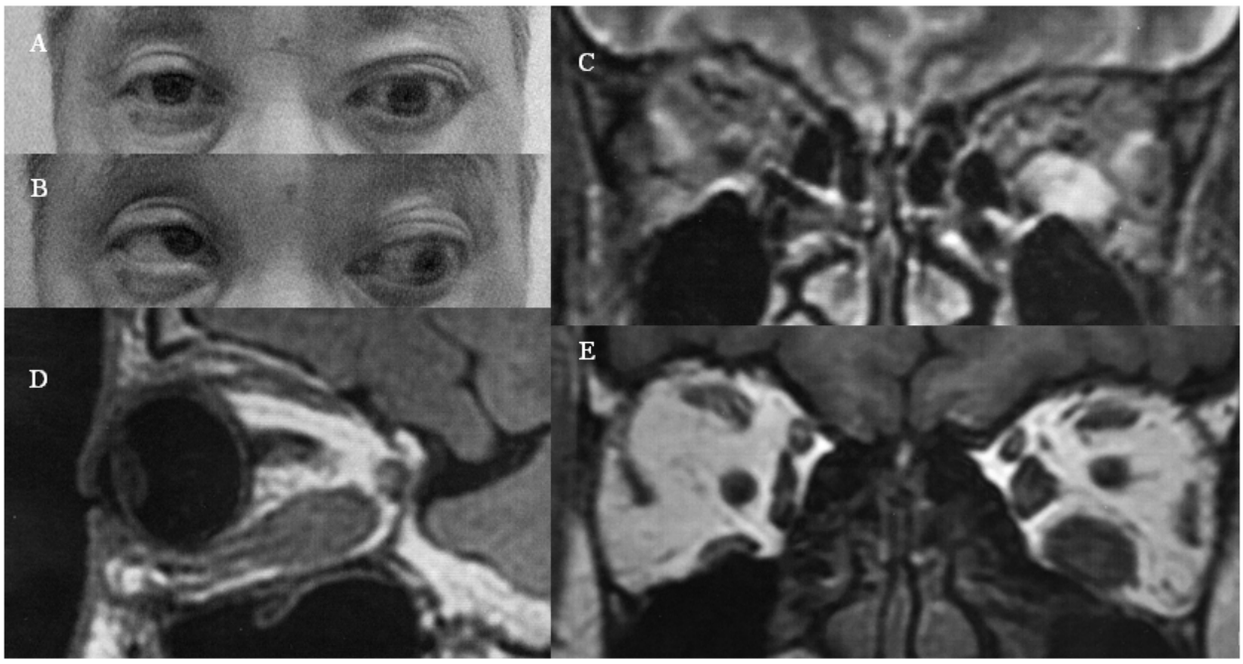


Figure 4. A 65-year-old male with HT. He has hypothyroidism and needs thyroid hormone replacement therapy. His eye symptoms, which are mainly diplopia, commenced when he had a traffic accident. They worsened in a few months and came to see us. A) He has evident proptosis (left side > right side) and deviation of the left eye ball. B) His left eye movement is seriously impaired when gazing in left to upward direction. His left inferior and medial rectus muscles are shown to be enlarged in the MRI imaging (C, D, E). The MRI STIR imaging shows intense inflammation in muscles involved (C). This case is classified as NOSPECS class I_0, II_a, III_a, IV_c, V_0, VI_0.

Recent progress in imaging inspection including MRI introduces a new concept of the disease. Volpe et al. demonstrated that 55% of GD patients without clinical evidence of GO were diagnosed with GO by ocular echography [103]. They named this type of GO as "occult thyroid eye disease." If MRI is performed for all GD patients, a large number of patients with "occult thyroid eye disease" would likely be diagnosed. Thus, we have to consider such GO patients for further evaluation of the pathogenesis and immunogenetics of GO. Furthermore, we could sort GO phenotypes in order of timing of development of disease (simultaneous onset with GD, later onset and earlier onset than GD). Thus, further investigation and discussions by experts are needed to establish more accurate definitions of the subtypes of GO.

6. Conclusion

GO is a manifestation related to AITD, although the immunogenetic component of disease susceptibility is still controversial. The strongest factor which affects the presence and/or severity of GO is smoking, a common environmental factor. From these studies and/or experimental data, some researchers have concluded that there is no genetic susceptibility component in GO. In contrast, many studies investigating the effects of ethnic background on the presence and severity of GO and differences in the male/female ratio between GO patients and GD without GO patients suggest the possibility of a genetic predisposition to GO. To solve

such discrepancies, there should be an emphasis on reconsideration of the determination of GO. The disease we all recognize as GO might not be a single disease. At present, GO has many manifestations during the course of the disease, including associated diseases (GD, HT and sometimes thyroid cancer), differences in onset timing, MRI findings and location of lesions. Therefore, reclassification of GO into several patterns using MRI will be of great help. Using state-of-the-art imaging equipment and immunological and biological technology, we should classify GO into more ideal and probable subtypes, which might help research focused on the pathogenesis and/or genetics of GO. To date, several studies have tested genetic susceptibility from the view point of NOSPECS severity classification, resulting in a failure to establish evidence for genetic factors of GO. High quality research should be conducted by experts of GO, allowing discussion on the probable and appropriate genetic susceptibility of GO. Moreover, ongoing GWAS studies and genetic mapping of SNPs studies on GD and HT will accumulate evidence and new findings on genetic susceptibility to the diseases, contributing to the establishment of genetic predispositions to GO, which can be appropriately classified into subtypes. Further studies are required for this purpose.

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