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Review Article

Graves' Disease and Hashimoto's Thyroiditis: Genetic and Non-genetic Perspective

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Abstract

In graves' disease genetic factors mainly plays a part in genesis of disorder. Although it is seen that infection and environmental factors due play a part as well. Graves disease is characterized by antibody response to the thyroid gland (characterized by lymphocytic infiltrations), thyroid stimulating hormone receptor (TSHR) and different thyroid antigens. Graves' disease is an autoimmune disorder in which host own immune system attacks self-antigens. The other autoimmune disorder of thyroid gland is Hashimoto disorder which also have a genetic basis.

Many gene are responsible for graves' disease like CD40, PTPN22 and thyroid-specific genes. CD40 gene is an essential immunomodulatory component for follicular cells in the thyroid gland. CD40, PTPN22 and thyroid-specific genes are immunomodulating genes for the TSH receptor and thyroglobulin molecule. CD40 used to be associated with Graves's disease as principal candidate on the basis of gene linkage study, connecting with 20q11 genome chromosomal region. The PTPN22 gene gives rise to a substantial risk of specific autoimmune and disease mechanisms.

Although genetic factor is principal mechanism but infections also have been implicated in the pathogenesis of Graves' disease that include microorganism like Coxsackie virus, Yersinia enterocolitica, Borrelia burgdorferi, Helicobacter pylori and retroviruses (HTLV-1, HFV, HIV and SV40). Infectious hepatitis C agents are also having affiliation with Auto Immune Thyroid Disease (viz graves diseases and Hashimoto disease). Some environmental triggers have also been reported like iodine, certain drugs, smoking and perhaps stress. Autoimmune disease-causing novel genes can be identified by recent molecular techniques involving gene expression studies namely, quantitative Real Time-PCR and microarray.

Keywords: Graves' Disease, Hashimoto's Thyroiditis, Genesis of Disorder

Introduction

Graves's disease (GD) is an autoimmune disease due to the action of Thyroid Autoantibodies (TRAb) that results in thyroxine overproduction leading to hyperthyroidism and features of thyrotoxicosis [1]. There are two autoimmune thyroid diseases (AITD) viz. GD and Hashimoto thyroiditis (HT), each pathologically characterized by thyroid infiltration of T and B cells due to autoimmune reaction to thyroid antigens and production of autoantibodies which clinically initiates abnormal thyroid features (hyperthyroidism in GD and hypothyroidism in HT) [2]. GD is characterized by combination of goitre, thyrotoxicosis due to increased release of thyroxine by thyroid stimulating hormone receptor (TSHR) antibody which stimulates the thyrocytes and features of ophthalmopathy. However, the traditional triad is not found in all patients and hyperthyroidism can also be the only current feature(1). Few cases of vertical transmission have been reported which shows that transplacental antibody transferred from mothers to children during pregnancy may induce neonatal hyperthyroidism [3].

Graves' disease is a multifactorial disorder caused by a complex interaction between genetic and environmental factors leading to loss of thyroid immune tolerance. Many autoimmune susceptibility genes that can be labelled into immune regulatory systems (HLA-DR, CTLA-4, CD40 and PTPN22) and thyroid specific genes (Thyroglobulin, TSHR) are responsible for the development of this disorder [4].

Among the non-genetic factor's infections line hepatitis C virus, Coxsackie virus, Yersinia enterocolitica, Borrelia burgdorferi, Helicobacter pylori and retroviruses (HTLV-1, HFV, HIV and SV40), excessive iodine intake, smoking and mental stress have a role, although there is no reliable and conclusive evidence is available [5]. The environment and genetics play an important role in the loss of tolerance and chance plays an important role, the combination of genetic predisposition and environment, the presence of self-reactive T cells and autoantibodies directed against auto-tissues suggests that adaptive immunity is necessary for pathogenesis and that the innate immune system can also play an important and critical role [6]. A recent twin study found that 79% of GD development is attributable to genetic factors. Therefore, about 20% development of GD is due to non-genetic factors, among the non-genetic factors postulated to precipitate AITD are iodine, drugs such as amiodarone and interferon alfa, infections, smoking and stress [5].

This article will summarize our current understanding about genetic factors as a risk factor for the development of a grave's disease and our understanding of the aetiology of the disease and future research on issues related to these diseases.

1. Autoimmune thyroid diseases (AITD)

Autoimmune thyroid diseases encompass two disorders namely, GD and Hashimoto's thyroiditis (HT). GD is an autoimmune disease that leads to a generalized over activity of the entire thyroid gland (hyperthyroidism). GD is four times greater in females and the incidence in Europe is approximately 20 per 100,000 person years [7]. It usually influences younger ladies from 20 to 40 years; however, it can occur at any age. GD occurs in 1 in 500 pregnancies and raises specific management problems. Hyperthyroidism in pregnancy is difficult to diagnose because signs of normal pregnancy overlap that of GD. GD during pregnancy require quick treatment with anti-thyroid drugs and should closely monitored for signs of foetal and maternal hyperthyroidism and hypothyroidism. Untreated GD causes adverse pregnancy outcome, because

maternal TRAb and anti-thyroid medication can pass the placenta resulting in foetal/neonatal thyrotoxicosis and hypothyroidism [8]. These symptoms are due to self-reactive thyroid CD4+ T cells that infiltrate the thyroid and activate B cells. This is characterized through the infiltration of the thyroid with inflammatory cells, hyperplasia and hypertrophy of the thyroid follicles and the formation of the resulting goitre [9]. The variable presence of thyroid stimulating and destructive autoantibodies may additionally explain the unique pathogenesis of GD. Twin babies' studies and family clustering of GD with massive investigations have verified a greater concordance of the GD rate in monozygotic than in dizygotic twins [10].

Hashimoto's thyroiditis (HT) on the other hand is the most common autoimmune disorder in humans which often leads to hypothyroidism or continual lymphocytic thyroiditis, characterized by infiltration of the thyroid gland of inflammatory cells, resulting in degeneration of the thyroid tissue resulting in hypoactivity [11]. HT is defined as a tissue-specific destructive autoimmune disorder with detectable anti-thyroglobulin (Tg) and anti-thyroid peroxidase (TPO) antibodies. HT is seen more frequently in people who suffer from other several autoimmune diseases such as type 1 diabetes (T1D) or rheumatoid arthritis [12]. HT forms eventually evolve into hypothyroidism, although patients may be euthyroid or even hyperthyroid at the time of presentation. HT is characterized by a cellular immune response with lymphatic infiltration of the thyroid gland of T and B cells, as well as through a main humoral immune response to the production of unique antibodies [13].

There is a Th1 model of immune response reported in HT and a predominance of T-helper cell 2 cytokines in GD, indicating a humoral immune response sample for the GD [14]. T cells, through their T Cell Receptor (TCR), CD3 complex collectively with CD4, and a co-receptor of this TCR-CD3 complex, binds to the autogenic peptide located in the binding pocket of a HLA class II molecule on the surface of APC [15]. The T cell now requires extra co-stimulation to proliferate and secretes cytokines. In GD, both Th1 mediation of cell mediated immunity and Th2 mediation humoral immunity is found [14]. The active inflammatory section of GD is associated with a prevalent Th1 mediated immune response that modify to a Th2 phenotype in long standing GD. The regulation of these auto reactive B cells are also possibly to be affected through GD with defects in central and peripheral B cells. B cell surviving factors such as B cell activating component and B cells acting as APCs are needed to generate a repertoire of exclusive T cells, as well as the improvement of memory T cells [16]. Apoptosis is regulated during the course of GD through Th2 cytokines. This may additionally increase anti apoptotic molecules, which includes Bcl-2 and thyrocytes in affected individuals and suffer from low apoptosis levels compared to normal. These thyrocytes shows subnormal levels of fast and excessive levels of Bcl2 (anti-apoptotic protein) [17].

GD & HT diagnosis is currently established through a series of symptoms, the presence of serum antibodies against thyroid antigens (TSH receptor, thyroid oxidase and thyroglobulin) and the appearance on the thyroid ultrasound. Thyroid absorption of radioactive iodine and cytological examination of the thyroid aspirate are used less frequently these days [18].

The AITD susceptibility to candidate genes can be classified into two large groups. (1) **Immune modulating genes** (2) **Specific thyroid genes**. The first group consists of genes CD40, CTLA-4 and PTPN22, while the second group includes thyroglobulin (Tg) and TSH Receptor genotypes [19]. (Table 1)

Aberrant expression of IGF-1 receptors on T cells and B cells has also been recently implicated for development of graves' disease. IGF-1R helps the growth of reminiscence T cells in the blood and

fibroblasts of orbital tissue in GD and IGF-1 receptor antagonists can work synergistically with TSH-R antibodies to activate thyrocyte [20]. Copy number variants (CNVs) which are large duplications or deletions of DNA sequence, have also been reported to be related with autoimmune disorders [21].

Table 1: Genes related with autoimmune thyroid disease

Genes associated	Functions or associated diseases
CTLA 4	Member of immunological superfamily
PTPN22	Involved in T cell signal transduction
CD 40	TNF-receptor superfamily member 5
TG	Associated with Thyroid Dyshormonogenesis 3 and Familial Thyroid Dyshormonogenesis
TSHR	Diseases associated with congenital hypothyroidism nongoitrous 1 and familial gestational hyperthyroidism
HLA I	key role in presenting endogenous antigen, such a virally derived antigen, for recognition by CD8+ T Cells
HLA II	key role in presenting exogenous antigen for recognition by CD4+ T helper cells
IL2RA	Immune tolerance
FCRL3	Associated with rheumatoid arthritis and autoimmune thyroid disease

2. Cluster of differentiation 40 (CD40) gene

CD40 is mainly expressed on B cells and different antigen-presenting cells (APCs) and performs a key role in B cell activation, B cell proliferation, antibody class switch, immunoglobulin secretion and generation of memory cells [22]. CD40 is a most important APC and B cell co-stimulatory molecule. CD40 as an essential susceptibility gene for GD [23] and the sequencing of complete CD40 gene resulted in the identification of a C/T polymorphism in the 5′-Untranslated region of CD40, with the genotype CC of this single nucleotide polymorphism (SNP) strongly associated with GD [24]. It has been reported that a SNP at a position of the Kozak sequence of the CD40 gene is related with the improvement of GD [25]. The affiliation of the C/T polymorphism in the 5′UTR of CD40 gene with GD has been mentioned in Caucasian and Koreans [26]. The interaction of CD40 with its ligand induces T helper (Th) 2 immune response, leading to thyroid autoimmunity in the direction of GD and could affect the production of TSH antibody in GD and clinical manifestation.

Blocking CD40/CD40L interactions in murine models have shown to suppress thyroiditis [27]. Also, CD40 Kozak SNP of C allele was strongly related with high ranges of IgE in asthma [28].

3. Protein Tyrosine Phosphatase-22 (PTPN22) gene

The lymphoid tyrosine phosphatase (LYP), encoded by protein tyrosine Phosphatase-22 (PTPN22) gene, CTLA-4 is an effective cell activation inhibitor [29]. Crystal structure of protein tyrosine phosphatase 22 reveals

Protein tyrosine phosphatases (PTPs) play a critical role in regulating cellular functions by selectively dephosphorylating their substrates. The structural comparison identified four different conformational loops which had catalytic activity.

Enzymatic assays revealed large differences in the catalytic activity of PTP and identified PTPD1, PTPD2 and HDPTP as catalytically inert phosphatases [30].

It has been observed that substitution of tryptophan/ arginine codon 620 (R620W) in PTPN22 used to be related with AITD which includes both GD and HT and different autoimmune illnesses [31]. The disease related tryptophan variant makes the LYP protein to be an even stronger T cell inhibitor leading to a tendency for self-reactive T cells to escape thymic deletion and thus remain in the periphery and cause autoimmunity. Mechanism of PTPN22 action is via regulation of TRAF3 ubiquitination and dephosphorylation of signalling intermediates in T cells and myeloid cells. PTPN22 associates with the TLR activated signalling molecule TRAF3 to help its activation via K63-linked ubiquitination and therefore activation of downstream IRF and IFN creation [32].

4. CTLA-4(Cytotoxic T-lymphocyte protein 4) gene

CTLA-4 also known as CD152 (Cluster of differentiation 152), is a protein receptor that, functioning as an immune checkpoint, downregulates immune responses [33]. CTLA-4 is a surface protein of T lymphocytes that plays a necessary role in reducing the immune response [34]. Several variants of the gene have been implicated in GD, of which a polymorphism in position 60 is the most appropriate candidate [35]. It is believed that the useful significance of this polymorphism is due to a reduced expression of the mRNA that encodes the soluble structure of the molecule.

5. Thyroglobulin (Tg) gene

Thyroglobulin (Tg) represents one of the fundamental auto-antigens of AITD, which include both GD and HT. However, in GD the essential auto-antigen is TSHR and antibodies in opposition to TSHR (TRAb) are present in nearly all patients with Graves' associated hyperthyroidism. Thyroglobulin Gene producing thyroglobulin (Tg) protein is the essential antigen of thyroid protein and is a precursor to thyroid hormones [36]. Tg is additionally a key antigen in AITD, as evidenced by the fact that anti-thyroglobulin antibodies is detected in 75% of auto-immune disease patients. Multiple SNP in intron 41 of thyroglobulin gene is implicated in GD [37]. Tg is the precursor of thyroid hormones and a necessary auto-antigen concerned in the pathogenesis of AITD and possibly contributing to the pathogenesis of graves ophthalmopathy (GO). Extensive genomic trying out has proven a link between a locus on chromosome 8q24, the place the Tg gene is located and AITD.

6. TSH receptor (TSHR) gene

The TSHR gene is located on chromosome 14q [38]. It used to be observed with GD both through the candidate gene strategy and by using the complete genome linkage studies. The TSHR gene is a predominant candidate gene for GD, considering that GD is triggered through autoantibodies that bind to and stimulate the TSH receptor [39]. GD is seen associated with polymorphisms in the intron 1 gene region of TSHR.

7. Other genes

7.1 Human leukocyte antigen (HLA)

The HLA complex is located on the short arm of chromosome six and includes sequences encoding genes concerned in the regulation of the immune response. HLA genes are labelled into three essential classes: (1) Class I, including histocompatibility genes expressed on the surface of most cells (HLA-A, HLA-B and HLA-C) (2) Class II, including histocompatibility genes expressed completely on leukocytes and immune competent cells (HLA-DR) (3) Class III, including a heterogeneous group of genes that encode molecules concerned in the immune response and others that are no longer truly related to immunity [40].

Graves' disease (GD) is associated with human leukocyte antigen (HLA)-DR3 and DQA1*0501 in Caucasians [41].

7.2 Fc Receptor-like-3 (FCRL3) gene

The FCRL gene family encodes a number of proteins involved control B cell signalling [42]. Association of SNPs of FCRL3 has been seen in GD patients of Asian population as well as Caucasian descent [43].

7.3 Secretoglobin 3A2 (SCGB3A2) gene

Variants in the promoter of the SCGB3A2 gene encoding secretory Uteroglobin related protein 1 (UGRP1) have been related with GD in a significant study of a total of ∼2500 patients and controls in Chinese population [44]. The -112G>A polymorphism of the secretoglobin 3A2 (SCGB3A2) gene increases risk for the development of Graves' disease in subsets of patients with elevated levels of immunoglobulin E [45].

Several other genes involved in the immune response in thyroid autoimmunity have been studied over the years, for example interleukin- 1 (IL-1), IL-1 receptor antagonist, interleukin-2 receptor alpha (IL-2), tumor necrosis factor receptor 2 (TNFR-2) and interferon-γ (IFN- γ) [46], most of which confirmed no significant associations with GD.

8. Role of non-genetic factors in autoimmunity diseases

8.1 Role of infections in autoimmunity diseases

Infectious hepatitis C agents are confirmed to be associated with AITD [47]. The incidence of autoimmune thyroid disease in patients with HCV differs from patients with hepatitis B virus (HBV). The incidence is actually much higher in women and at the start of therapy, thyroid autoimmunity may be a cytokine-induced disease in susceptible patients [48]. The prevalence of abnormally high levels of thyroid antibodies varies greatly of patients with chronic hepatitis C [49]. The mutable biological dissemination has also been established. In general, the individual role of the virus itself or of antiviral behaviour remains to be simplified. Defects in thyroid function could be a part of HCV syndrome and patients should be screened for thyroid dysfunction discovery occasionally to identify patients necessitating action.

Data regarding the role of the spirochete, Borrelia burgdorferi and Enterobacter, Yersinia enterocolitica triggering thyroid autoimmunity remain unfinished [50]. The molecular mimicry could provide an explanation for an association between both pathogens and AITD and strong association between AITD and Hepatitis C Virus (HCV) [51]. Infections have been occupied in the pathogenesis of AITD comprising Coxsackie virus, Helicobacter pylori, Y. enterocolitica, Borrelia burgdorferi and retroviruses. A trigger virus can be eliminated from the body without any virological trace, except for the presence of specific antibodies. It is important to look for viral agents in the tissues where they can persevere without systemic display. Direct sign of the presence of viruses or their organ mechanisms are available for retroviruses and mumps in subacute thyroiditis, by retroviruses (HTLV-1, HFV, HIV and SV40) in GD and enterovirus, rubella, herpes simplex virus (HSV), Epstein- Barr Virus (EBV), mumps virus and the parvovirus in HT [52]. It remains to be determined if they are responsible for thyroid diseases and that viral disease is the result of an interaction between a virus and the host, in which the genetic background definitely plays a role. Although most infected people do not show any signs of disease and it is not inconceivable that a virus has a role in disease pathogenesis. The relationship between viruses and thyroid diseases has to be established in order to develop new strategies for their prevention and treatment.

8.2 Environmental toxins

Many environmental contaminants, consisting of polyaromatic hydrocarbons, perfluorinated chemicals, phthalates and bisphenol etc. which are widely used in various industrial and consumer products may additionally have thyroid disorder properties [53]. Polyaromatic hydrocarbons, polychlorinated biphenyls (PCBs) and polyhalogenated biphenyls (PBBs) are organic compounds produced through coal and which are in air, water can cause thyroiditis [54].

8.3 Iodine

A large quantity of epidemiological statistics suggest that iodine provided in the diet performs an essential function in generating GD in genetically predisposed individuals [55]. Overall, GD is a relatively common disorder, the most common cause of thyrotoxicosis, at least in countries with sufficient iodine [56].

8.4 Psychological stress

Psychological stress is related with accelerated secretion of adrenocorticotropic hormone (ACTH) and cortisol, which in turn can lead to immune suppression [57]. Immune suppression may also additionally be caused by way of other ACTH associated phenomena. The restoration of such immune suppression, immune rebound, may additionally be related with immune hyperactivity, which theoretically could precipitate autoimmunity [58].

8.5 Vitamin D and selenium

In patients with GD there was reduced serum vitamin D and they were consequently related with a high rate of hyperthyroidism after removal of anti-thyroid drugs, though the mechanisms underlying these associations remain unsolved [59]. Selenium deficiency is reported in patients with GD, which should be explained by means of the antioxidant action of selenium. Therefore, oxidative stress could lead to pathogenesis of thyroid autoimmunity. Also selenium has been found to be beneficial in patients with mild GO [60].

8.6 Smoking

Many studies have shown that tobacco smoking may result in development of thyroid auto-immunity particularly graves induced hyperthyroidism and graves orbitopathy (GO), although the role of smoking is not well established for HT. Also smoking increases the multinodular goitre incidence. Suggested mechanisms for graves orbitopathy include tissue hypoxia, modulation of circulating pro- and anti-inflammatory cytokines and accentuation of fibroblast HLA-DR expression [61].

Discussion

GD and HT are an autoimmune organ specific disorder characterized by widespread goitre and excess thyroid hormone secretion resulting from the stimulation of the TSHR antibody. Although the aetiology of the autoimmune diseases remains unclear, it is believed to be brought on by a complex interaction between infection, genetic and environmental factors. Recent genome wide surveys provided evidence for GD linkage of loci on more than one chromosome, which include the 20q loci chromosomes in specified GD in Caucasian populations. Evidence suggests that environmental factors, infections, drugs, smoking and iodine on the background of AITD trigger genetic predisposition. Immune system regulators that predispose AITD (CD40 and PTPN22 among different emerging immune modulatory genes) play essential components in the improvement of an immune response together with self-tolerance, cell mediated and humoral immunity. The proliferation of T-cells enhanced memory space should additionally notice that PTPN22 is broadly expressed in hematopoietic cells,

modifications in a quantity of immune parameters and the mechanism for susceptibility disease can also extend beyond T cells. Knowledge of many enzymes phosphatases in combination with population's genetic data, T cell regulation circuits may additionally ultimately enable researchers to identify necessary pathogenic mechanisms involved in AITD and several autoimmune diseases.

Gene expression study of autoimmunity diseases by microarray and quantitative real-time PCR shows various cytokines, a group of molecules composed of interleukins (IL) and Chemokines signalling, are involved in the development of many autoimmune diseases, including GD and HT. Genetic polymorphisms or abnormal expression of different cytokines may confer a risk not only for the development of GD, but also influence the severity or prognosis. Cytokine protein microarray, a new molecular biological method, is capable of simultaneously detecting multiple cytokines in a single sample, have been used to compare the profile of cytokines in GD and GD relapsed into different remission and miRNA expression in peripheral blood mononuclear cells (PBMC) of GD patients and healthy individuals and examine their direct responses to T3 treatment. The importance of miRNAs in GD and HT has been recently studied and compared with miRNA expression patterns in PBMCs of healthy individuals for e.g., DNA methylation in PBMC have been seen in both HT and GD [62]. Histone tail modifications like global reduction of histone 4 acetylation have been observed in GD [63]. These techniques also help to identify the new miRNAs as biomarkers of GD and HT, further provide potential targets for the treatment of autoimmune diseases.

The immunomodulation of both T cells and B cells can assist to get an autoimmune disease into remission. Anecdotal efficacy of these drugs, however, provides beneficial information on the pathogenesis of GD and HT. In the future, with the creation of new and effective biological product, it may also be possible to treat GD and HT by using direct immunomodulation.

The overall conclusion of this study, is to identifying new genes involved and defining the extent to which infection, non-genetic factors, genetic factor, environmental issue, iodine, stress, sex and smoking are involved in development of AITD. Future research will focus on the genetic versions of AITD essential for the improvement of new specific and preventive therapies and the environmental causes of the variants which are critical for the improvement of new targeted and preventive treatment for the autoimmune diseases.

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