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**Review Article**

# Graves' disease and HLA association

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**A B S T R A C T**

Graves' disease is an organ-specific autoimmune disorder that effect the thyroid gland. The body makes antibodies to the thyroid-stimulating hormone receptor. Clinical presentation is hyperthyroidism. Normally, the release of thyroid hormones is mediated by thyroid-stimulating hormone secreted by the pituitary gland that binds to it's receptor to stimulate the thyroid to release thyroid hormones. There are many factors contribute to the development of this disease like genetic and environmental causes. The genetic variation in Graves' disease susceptibility is due to polymorphism at MHC loci. The reason for these diverse association of HLA class I and class II results among different populations could be due to ethnic, race, selection criteria, geography of the enrolled patients, age, gender of the patients and genetic causes that basis these differences.

**Keywords**

Graves' disease; thyroid-stimulating hormone receptor; HLA.

## Introduction

Graves Disease (GD) is organ specific autoimmune disease of the thyroid gland. It is characterized by antibodies against thyroid-stimulating hormone receptor (TSHR), leading to hyperthyroidism associated with goiter, palpitations, bulging eyes, sweating, heat intolerance, tremor, anxiety and weight loss. In addition to that diffuse lymphocyte infiltration into the thyroid gland. The hyperthyroidism is caused by activation of the thyroid stimulating hormone receptor (TSHR) by binding of autoantibodies. These antibodies act as agonists, stimulating more hormones to be released and thus leading to hyperthyroidism.

Normally, the release of thyroid hormones is mediated by thyroid-stimulating hormone (TSH) that secreted by the pituitary gland and binds to TSHR to stimulate the thyroid to release thyroid hormones (Janeway *et al*., 2001).

### Risk Factors

There are many factors that affect the individual for disease development i.e. the etiology of GD is multifactorial but seems to involve complex interactions between predisposing genes and environmental triggers Its prevalence in general population is around 1.0–1.6% (Weetman,

2000; Bartalena *et al*., 1998; Jacobson *et al*., 1997; Shapira *et al*., 2010; Prabhakar *et al*., 2003).

**Sex of the patient**

Females are more liable for developments the disease due to hormone levels are probably important in the initiation of the disease.

**Age of the patient**

It is more common in 40 and 60 years in both sexes.

Psychologic cause like traumatic stress conditions

Smoking that is most strongly associated with the development and persistence of ophthalmopathy in Graves' disease patients.

**Race**

It is more common in White and Asian populations than black populations.

**Genetic factor**

Genetic factor evidenced by family study and a higher concordance rate in monozygotic twins (0.35) than in dizygotic twins (0.03). The genetic contribution to GD was estimated as high as 79% (Brix *et al*., 2001). Genetic studies have shown that the human leukocyte antigen (HLA) region on short arm of chromosome 6p21.31 is a significant factor associated with GD and the HLA region is highly polymorphic and contains many immune response genes. It consists from three classes, class I genes includes (A,B and C) and class II genes includes (DR, DP and -DQ) and class III genes. Many studies concerning HLA allelic associations with GD have been done, and different associations of GD and HLA alleles have been found among different ethnic populations like HLA-B*08 , DR3 and DQA1*05:01 are associated with a high risk of GD, and HLA-DRB1*07:01 is a protective allele against GD in Caucasian populations(Yanagawa *et al*., 1993; Zamani *et al*., 2000). HLA alleles have been shown to predispose certain groups of people to the disease, with regional and racial variation. British Caucasians showed association of HLA class II alleles DRB1-0304, DQB1-02, and DQA1-0501(Heward *et al*., 1998). The HLA complex is characterized by strong linkage disequilibrium. Linkage disequilibrium refers to the non-random association between alleles at adjacent genetic loci. It's patterns across the human genome varies markedly between regions and populations. In Caucasians populations, there is a strong linkage disequilibrium is found between genes encoding DR and DQ molecules so that presence of a given *DRB1* variant to a large extent determines *DQA1* and *DQB1* alleles. HLA haplotype combinations in affected GD sibling pairs include DRB1*03:01-DQA1*05:01-DQB1*02:01 (DR17, DQ2) and DRB1*04:01-DQA1*03:01-DQB1*03:02 (DR4, DQ8). The highest risk is associated with DR17, DQ2. HLA-DRB1*07 (DR7) is protective for Graves Disease. The distribution of HLA-B8 genotypes was in close agreement with Hardy-Weinberg equilibrium proportions, also favoring recessive inheritance of MHC-related susceptibility. The probability that an individual will be affected with GD can be predicted, based on sex, HLA genotype, and family history. 14.9% of DR3-positive women with an affected first-degree relative are likely to be affected (Stenszky

*et al*., 1985). The familial occurrence of GD has been found in third siblings of GD patients and over half of asymptomatic children had thyroid antibodies in their blood (Villanueva *et al*., 2000). There is an effect of genetic factor on race for the development of GD. There is a smaller contribution of genes for GD development in American vs. European population (Ringold *et al*., 2002). There is a close proximity of HLA genes with other genes (Rhodes and Trowsdale, 1999). Some of these loci encode proteins like LMP2/LMP7 and TAP1/TAP2, or DMA and DMB (Monaco, 1995). Another group of MHC located loci such as *TNF*, complement components or heat shock proteins take part in an immune response without direct interaction with HLA(The MHC sequencing consortium, 1999). In addition to that, genetic analysis has shown that polymorphisms in the cytotoxic T-lymphocyte antigen 4 (CTLA-4) gene are associated with Graves' disease (Simmonds and Gough, 2004). The polymorphisms linked to Graves' disease may correspond with lessened effectiveness of this inhibitory receptor (Kouki *et al*., 2002).

In addition to the class II association with GD , class I is also associated with GD, the disease may be primarily associated with alleles of HLA class I, in particular HLA-*C**07(Simmonds *et al*., 2007) whereas *C**03 and *C**16 had protective effects. In case of HLA-B , the strongest effect for *B**08 and a protective association for *B**44(Simmonds *et al*., 2007). HLA-*DPB1**05:01 was the major gene predisposing to GD among Han Chinese with an OR=2.3. Other alleles included *B**46:01, *DRB1** 15:02 and 16:02 whereas *DRB1**12:02 and *DQB1**03:02 conferred protection. The association of *DQA1**05:01 with GD was not supported by Linkage Disequilibrium patterns observed in Asians (Chen *et al*., 2011). In Blacks race, the HLA* *DRB1**03 association with GD (Omar *et al*., 1990). The cause of association with HLA due to peptides derived from thyroglobulin or TSHR and development of immune response. Other cause due to thymic selection influencing positive and/or negative selection of T cell clones with regulatory or effector functions. In addition to that, influence on NK cell repertoire through interactions with killer immunoglobulin-like receptors (KIR) and/or serving directly as a source of autoantigens after misfolding and presentation by HLA class II molecules (Simmonds *et al*., 2007). Development of Graves' disease is related to HLA-DR3. The extracellular domain (ECD) of human TSH receptor (hTSH-R) is a crucial antigen in Graves' disease. hTSH-R peptide 37 (amino acids 78-94) is an important immunogenic peptide (Inaba *et al*., 2013). HLA association with clinical manifestation of the disease, the disease occurred at an earlier age in HLA-DR3 positive patients and , significant associations between exophthalmos and either exophthalmos and/or soft tissue changes were found with DR3.

HLA-DR3 positive patients were found to be more resistant to radioiodine therapy than patients negative for these antigens (Farid *et al*., 2004). It has been postulated that arginine at position 74 of the HLA-DRB1 chain is significant for GD pathogenesis, However, the residues at position 74 of DRB1*15:01 and DRB1*16:02 reported in our association study are both alanine, which is the common residue at this position considered to be neutral for GD risk (Ban *et al*., 2004; Robinson *et al*., 2003). On the other hand, HLA region is linked to

GD susceptibility in both Caucasian and Chinese Han populations (Heward *et al*., 1998). The associated alleles are quite different from those discovered in Caucasians. HLA-DPB1*05:01 is the major gene of GD in our population, B*46:01, DQB1*03:02, DRB1*15:01 *and* DRB1*16:02 were associated with GD (Chen *et al*., 2011). Other meta-analysis study indicated that the HLA-B*46 allele is a risk factor for GD in Asian populations. It is evident that the distribution of HLA-B*46 and HLA-B*08 are different between European and Asian populations. In European populations, the allelic frequency of HLA-B*08 is 12%, while the allelic frequency is 0.3 to 0.5% in most Asian populations. By contrast, the allelic frequency of HLA-B*46 is 3.9 to 8.6% in Asian populations and almost zero in Europe populations (Li *et al*., 2013).

The reason for these diverse association results among different populations could be due to ethnic and genetic causes that cause these differences. Other causes like different geographical regions of subjects, differences in age and gender among the included studies and the methods of HLA typing Lastly, inconsistency in inclusion criteria of the selected patients could be the cause for this heterogeneity(Huang *et al*., 2003).

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