HLA-DRB1*04 and HLA-DQB1*0201 Association with Chronic Autoimmune Thyroiditis in a Turkish Population

*Türk Toplumunda Kronik Otoimmün Tiroidit ile HLA-DQB1*0201 İlişkisi*

Reyhan Ersoy, İlhan Yetkin*, Sevim Gönen**,
Oğuz Söylemezoğlu**, Esen Akbay***, Metin Arslan*

Ankara Ataturk Education and Research Hospital, Department of Endocrinology and Metabolism,, Ankara, Turkey
*Gazi University Faculty of Medicine, Department of Endocrinology and Metabolism, Ankara, Turkey
**Gazi University Faculty of Medicine, Department of Pediatric Nephrology, Ankara, Turkey
***Mersin University Faculty of Medicine, Department of Endocrinology and Metabolism, Mersin, Turkey

Abstract

Objective: We aimed to determine the human leukocyte antigen (HLA) haplotypes of patients with autoimmune thyroiditis (AIT) and HLA group frequencies in clinical subgroups of disease and thus, investigate their role in the etiology of the disease.

Material and Method: One hundred patients with the diagnosis of AIT and 150 healthy controls with no known diseases were included in the study.

Results: HLA-DRB1*04 allele was significantly higher in the whole patient population, patients with hypothyroidism and/or atrophic thyroid gland compared to the control group, whereas there was no significant difference between patients with goitrous thyroiditis and clinically euthyroid compared to the control group. HLA-DQB1*0201 allele was significantly higher in the whole patient population and subgroups compared to the control group. HLA-DRB1*08 allele was defined as a protective locus due to its high positively rate in the control group compared to the whole patient population, and the presence of HLA-DRB1*12 allele was a protective factor, particularly for atrophic thyroiditis (AT). Evaluations of patients with hypothyroidism and AT showed that the development of hypothyroidism in clinical course of the disease was delayed in the presence of HLA-DQB1*02 allele.

Conclusion: The presence of HLA-DRB1*04 and HLA-DQB1*0201 alleles pose as risk factors for the development of AIT and especially of AT, where as the presence of HLA-DRB1*12 and HLA-DQB1*02 have protective roles, particularly in the development of AT, in our country. *Turk Jem 2007; 11: 29-33*

Key words: Autoimmunity, Thyroiditis, Human leukocyte antigen

Özet

Amaç: Çalışmamızda kronik otoimmün tiroiditli (OİT) hastalarda İnsan Lökosit Antijenlerine (HLA) ait haplotipleri belirlemeyi ve hastalığın klinik olarak alt gruplarında HLA gruplarının sıklığını ve etyolojideki rolünü araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmaya kronik OİT tanısı almış olan 100 olgu ve herhangi bir hastalığı olmayan 150 sağlıklı olgu alındı.

Bulgular: Çalışmamızda tüm hasta grubunda, hipotiroidi ve/veya tiroid bezinde atrofi gelişmiş olgularda HLA-DRB1*04 allelinin bulunma oranının kontrol grubuna göre anlamlı olarak fazla olduğunu, guatröz tiroiditli ve klinik olarak ötiroidik olgularda ise kontrol grubuna göre anlamlı fark olmadığını saptadık. HLA-DQB1 doku antijeni haplotipleri arasında HLA-DQB1*0201 alleli, tüm hasta grubunda ve hastalığın alt gruplarında (ötiroid, hipotiroid ve atrofik tiroiditli hastalarda) kontrol grubuna göre anlamlı olarak yüksek olarak saptandı. Tüm hasta grubu değerlendirildiğinde HLA-DRB1*08 alleli kontrol grubundaki yüksek pozitiflik oranı ile koruyucu bir lokus olarak tanımlandı. Çalışmamız, özellikle AT için koruyucu bir faktörün de HLA-DRB1*12 allel varlığı olduğunu gösterdi. Hipotiroidik ve Atrofik tiroiditli hasta gruplarındaki değerlendirmeler sonucu HLADQB1*02 allel varlığının, hastalığın seyri sırasında hipotiroidi gelişimini zorlaştıran bir faktör olduğu belirlendi.

Sonuç: Ülkemizde HLA-DRB1*04 ve HLA-DQB1*0201 allel pozitifliğinin OİT özellikle de AT oluşumunda risk faktörü teşkil ettiğini bunun yanında HLA-DRB1*08 allelinin OİT, HLA-DRB1*12 ve HLADQB1*02 allel pozitifliğinin ise özellikle AT gelişimine karşı koruyucu etki gösterdiğini düşünmekteyiz. *Turk Jem 2007; 11: 29-33*

Anahtar kelimeler: Otoimmünite, tiroidit, insan lökosit antijenleri

Introduction

Autoimmune thyroiditis (AIT) is one of the main causes of hypothyroidism and goiter in regions with sufficient dietary iodine intake (1). AIT has two clinical forms; called Hashimoto's thyroiditis (HT) when goiter is present or atrophic thyroiditis (AT) when the gland is atrophic. Both are characterized by the presence of auto- antibodies in serum and variable degrees of thyroid dysfunction (2).

AIT develops as a result of the immune system's response to the antigenic structures of thyroid. Immune response against the anti-

Address for Correspondence: Reyhan Ersoy, MD, Ankara Ataturk Education and Research Hospital, Department of Endocrinology and Metabolism, Ankara, Turkey
Phone: +90 312 291 25 25 E-mail: roersoy@tnn.net

genic structures of thyroid cells develops on the grounds of genetic factors with the contribution of environmental factors and results in tissue damage. Human Leukocyte Antigens (HLA) plays a major role in genetic contribution (3).

In AIT pathogenesis, HLA presents thyroid antigens to lymphocytes for initiation of immune response. Lymphocytes secrete cytokines and express intracellular adhesion and Fas molecules, which have important roles in intercellular interactions and apoptosis, respectively. The expression of HLA class II molecules on thyroid cells was first observed by Bottaza et al., who proposed viral infections in thyroid as initiation events for AIT that leads to stimulation of T lymphocytes and secretion of interferon-γ (IFN-γ) by the activated T lymphocytes, which in turn induce HLA class II expression (3). These events are currently believed to occur as a result of immune response rather than inducing immune response. Nevertheless, observations made by Bottaza and colleagues attracted attention onto the relationship between AIT and HLA class II molecules. HLA played important roles in the development of the disease in animal models. In mice, genes corresponding to human HLA loci were shown to be involved in the response of helper and suppressive T lymphocytes against certain antigens. HLA gene loci also regulate response of helper and suppressive T lymphocytes against certain antigens in humans and suppressive T lymphocytes for thyroid antigens were shown to be dysfunctional in individuals with certain genotypes. Hence, a genetically determined HLA-dependent antigen-specific suppressive T lymphocyte dysfunction was proposed as the main initiator of AIT in humans (4, 5).

HLA typing and nomenclature were modified within years and different phenotypes were defined in several studies. Genetic constitution of the populations under study was modified by migration, consanguinity and environmental factors. HLA studies are influenced by these factors (4).

Although studies on chronic AIT susceptibility determined by HLA class II genes were conducted in many populations, studies done in our country investigating the relationship between genetic factors and chronic AIT are scarce and small-scale (6, 7). In this study, we aimed to determine HLA class II haplotypes in chronic AIT patients and investigate an etiological role by studying the HLA group frequencies in clinical subgroups of disease.

Materials and Method

In this study, 100 patients with the diagnosis of chronic AIT based on clinical, laboratory, ultrasonographic and scintigraphic findings were included. As the control group, 150 healthy individuals (renal transplant donors) with no known diseases were included. The diagnosis of AIT was mainly ascertained by the detection of high levels of auto- antibodies in serum. The patient population was either hypothyroid or euthyroid based on the results of thyroid function tests done at the time of diagnosis. Ultrasonographic findings such as irregular appearance of thyroid gland decrease in gland size with concomitant increase in fibrosis or increase in gland size with widespread hypoechogenic appearance supported the diagnosis made by the presence of auto- antibodies. The heterogeneous distribution of radioactive material in thyroid scintigraphy and/or low uptake of radioactive material, irregular outline of thyroid gland, low uptake levels in patients undergoing radioactive iodine uptake test further supported the diagnosis.

Thyroid function tests

Thyroid hormone levels [free T3 (FT3), free T4 (FT4) and TSH)] were measured by Abbott- Architect machine using chemiluminescence's method. Serum Thyroglobulin (Tg), thyroid peroxidase antibody (Anti-TPO Ab) and Thyroglobulin antibody (Anti-Tg Ab) levels were measured by commercial kits using radioimmunoassay method.

Ultrasonography of thyroid

Siemens Sonoline SL-1 with 7.5 MHz linear probe was used for ultrasonographic evaluation of thyroid. Width, depth and height of each lobe were measured. Thyroid volumes were also calculated. Volume for each lobe was calculated using the following formula (8);

Volume (mL) = p/6 x width x height x depth.

Total volume was determined by summation of lobe volumes.

Thyroid scintigraphy

Thyroid scintigraphy was taken using pinhole collimator gamma camera 20-40 minutes after intravenous injection of 5 mCi Tc 99m pertechnetate to the patients.

Method for tissue typing of HLA class II molecules

DNA isolation

Five mL blood from patients and healthy controls were collected in tubes with EDTA and centrifuged for 5 minutes at 1500 rpm. Genomic DNA from patient and control bloods was isolated using the denaturation- precipitation method with ammonium bromide salts. Isolated genomic DNAs were subjected to polymerase chain reaction (PCR) with commercially available primers (Olerup- SSP). Perkin-Elmer 9600 PCR machine was used. After PCR amplification, samples were separated on 2% agarose gel electrophoresis, stained with ethidium bromide and evaluated under UV light. DNA samples were typed as HLA-DRB1 and DQB1 after evaluation.

Statistics

SPSS Windows 10.0 package was used for statistical tests in the study. Student t test for independent samples was used to compare group averages. Data were expressed as mean ± standard error. p values with less than 0.05 were considered significant. Chi-square test or if needed, Fisher's exact chi-square test, were used to test the significance of differences in ratios between patient and control groups having certain tissue phenotypes. Odds ratio (OR) and 95% confidence interval for OR were calculated to determine the risk posed by having certain HLA tissue types.

Results

Ninety-one percent (91%) of patients were women and 9% were men with 43 ± 1.2 (range = 16-75) years of age at the time of diagnosis. Thirty-nine percent (39%) of the cases were euthyroid, while 61% were hypothyroid at the time of diagnosis. Fifty-one percent (51%) of the cases were goitrous, while 49% were non-goitrous thyroiditis. The comparative data of patients based on thyroid function tests and thyroid gland size are shown in Table 1 and 2.

HLA-DRB1*04 allele in HLA-DR tissue group was detected with highest frequency (35%) in patients with AIT. This allele was detectable in 22.6% of controls. There was a significant difference between patients and controls with regard to HLA-DRB1*04 allele positivity (p = 0.034). According to the odds ratio, the probability of contracting the disease by individuals with this allele was 1.837

times higher than by the individuals without this allele. HLA-DRB1*08 allele was detected in 3% of the patients while 12% of the controls was positive for this allele; this difference was statistically significant (p = 0.02).

DQB1*03 allele in HLA-DQ tissue group was the most frequent group with a rate of 53% in AIT patients. This group was positive in 50.6% of the controls and the difference between patient and control group was not statistically significant (p = 0.718). While DQB1*0201 allele was detectable in 6% of the patients, control group was negative for this allele. The difference between patient and control groups was statistically significant (p = 0.009).

When HLA-DR tissue group was examined in the clinically euthyroid patient population, the most frequent allele was again HLA-DRB1*04 with 33.3%. However, when patient and control groups were compared for HLA-DRB1*04 positivity, the difference was not statistically significant (p = 0.173). When HLA-DQB1 tissue group positivity was examined, DQB1*0201 allele was determined at a frequency of 5.1% in the patient population. The difference between groups in terms of DQB1*0201 positivity was statistically significant (p = 0.042).

When HLA-DR tissue group was examined in patients with clinical hypothyroidism, HLA-DRB1*04 allele was the most frequent with 36.1% positivity. The difference between patient and control groups was statistically significant for this allele (p = 0.047). HLA-DRB1*08 allele was detected in 3.3% of patients with hypothyroidism. The difference between patient and control groups was not statistically significant (p = 0.068). HLA-DQB1*02 allele among HLA-DQ tissue group was detected in 13.1% and 26.6% of patient and control groups, respectively. The difference between groups in terms of HLA-DQB1*02 positivity was statistically significant (p = 0.037). The most significant finding for correlation between HLA and hypothyroid AIT was the positivity of HLA-DQB1*0201 allele in 6.5% of the patients while controls were completely negative (p = 0.007).

There was no statistical difference between controls and patients with goitrous AIT for allelic frequencies of HLA-DR and DQ. However, when groups were compared for HLA-DRB1*08 and HLA-DQB1*02 alleles, which were previously found to be probable protective factors, they were not significant statistically (p = 0.065 and p = 0.063, respectively).

When HLA- DR tissue group was examined between AIT patients with normal sized or atrophic thyroid glands and controls, HLA-DRB1*04 was the most frequent allele in the patient population with a rate of 42.8%. The difference was statistically significant when compared to the control group (p = 0.007), while OR was calculated as 2.559.

Another interesting finding in this group was the complete absence of DRB1*12 allele of HLA-DR group in the patient population, while 11.3% of the controls were positive for this allele. The difference between groups was statistically significant (p = 0.008).

When HLA-DQ antigens were examined, HLA-DQB1*03 allele was found positive in 49% of the patients. However, 50.6% of the controls were also positive for this allele and the difference was not statistically significant (p = 0.838). On the other hand, DQB1*0201 allele was positive in 8.1% of the patients while none of the controls were positive for this allele. The differences between groups were highly significant (p = 0.003).

A general evaluation of the results showed that a correlation exists between HLA histocompatibility antigens and AIT, particularly of those with hypothyroidism or atrophy in clinical course. For this reason, we generated a new group consisting of patients with clinical hypothyroidism and with less-than-normal sized thyroid glands (i.e. primary myxedema, atrophic thyroiditis). In this group, there were 41 patients with 3 men and 38 women. The age at the time of diagnosis was 47.58 ± 1.93 (range = 18-75 years). The average thyroid gland volume of the patients was 9.53 ± 0.68 mL. TSH, anti-TPO Ab and anti-Tg Ab were determined as 47.25 ± 12.72 mIU/mL, 2219.63 ± 402.62 U/mL and 839.01 ± 246.43 IU/mL (mean ± standard error), respectively. The allelic distribution fre-

Table 1. Comparative data of patient population based on thyroid functions

	Euthyroid	Hypothyroid	p
N (%)	39 (39.0)	61 (61.0)	
Age (years)	38.05 ± 1.67	46.11 ± 1.66	0.002
TSH (mIU/ml)	1.63 ± 0.20	41.17 ± 9.14	0.000
Anti-TPO Ab (U/ml)	2016.63 ± 369.76	2159.80 ± 324.69	0.776
Anti- Tg Ab (IU/ml)	741.82 ± 257.47	784.15 ± 183.64	0.891
Thyroid volume	20.48 ± 1.80	13.54 ± 1.26	0.002

Table 2. Comparative data of patient population based on thyroid gland size

	Goitrous	Non-goitrous	p
N (%)	51 (51.0)	49 (49.0)	
Age (years)	40.07 ± 1.69	45.97 ± 1.80	0.019
TSH (mIU/ml)	12.15 ± 4.18	39.9 ± 10.89	0.018
Anti-TPO Ab (U/ml)	2243.71 ± 344.31	1958.51 ± 347.86	0.562
Anti- Tg Ab (IU/ml)	799.84 ± 215.95	734.13 ± 208.96	0.828
Thyroid volume (ml)	22.59 ± 1.63	9.64 ± 0.58	0.000

quencies of tissue histocompatibility antigens were compared with the control group. HLA-DRB1*04 was the most frequent tissue group allele in the patient population with a positivity rate of 41.4%. The difference was statistically significant when compared with the control group (p = 0.018). OR was calculated as 2.417.

When the whole patient population was evaluated, HLA-DRB1*08 allele emerged as a protective factor (p = 0.02). While this allele was positive in 4.8% of patients with atrophic thyroiditis, control group had 12% positivity rate, but this difference was not statistically significant (p = 0.202).

As seen in AIT patients with normal sized or atrophic thyroid glands, HLA-DRB1*12 allele was also negative in patients with atrophic thyroid glands and hypothyroidism, while the positivity rate of this allele in the control group was 11.3%. This difference between groups was statistically significant (p = 0.013).

While there was no difference for HLA-DQB1*02 frequency between AIT patients with normal sized or atrophic thyroid glands and the control group, it was important not to find this allele in patients with atrophic thyroiditis in spite of the fact that this allele was know as another protective factor in patients with hypothyroidism. The difference between patient and control groups was also significant (p = 0.03).

While 7.3% of the patient population was positive for DQB1*0201 allele of HLA-DQB1 group, the control group was negative. The difference between groups was statistically significant (p = 0.009).

Discussion

Although there are no strong epidemiological indications for the contribution of genetic factors to AIT etiopathogenesis, a few hereditary factors have been described by investigating clues at hand. The most widely studied factors on this subject are tissue histocompatibility antigens (4). We have investigated the haplotypes of HLA class II in patients with chronic AIT diagnosis. The frequency of HLA-DRB1*04 allele was significantly higher in the whole patient population and patients with hypothyroidism or atrophic thyroid glands compared to the controls. There was not a significant difference between clinically euthyroid patients with goitrous thyroiditis and the control group. Accordingly, HLA-DRB1*04 allele could be proposed as an effective locus in the etiology of AIT in Turkey.

Moreover, HLA-DQB1*0201 allele among HLA-DQB1 tissue antigen haplotypes was found significantly higher in the subgroups of disease (euthyroid, hypothyroid and atrophic thyroiditis patients) compared to the control group. Our data supports the notion that in the presence of this allele the development of AIT, particularly of those progressing to hypothyroidism or atrophy is facilitated.

When the whole patient population was evaluated, HLA-DRB1*08 allele was defined as a protective locus due to its high positivity rate in the control group. Although the evaluations in subgroups suggested that in the presence of this allele the development of AIT, particularly of those with goitrous or hypothyroid course was less likely; however, this notion was not supported statistically.

Our study showed that another protective factor from AIT was the presence of HLA-DRB1*12 allele. Hence, the negativity of HLA-DRB1*12 allele might be rendering AIT development more likely in our country. Based on evaluations made in subgroups (patient populations with hypothyroidism and AIT), the presence of HLA-DQB1*02 allele was determined as a restrictive factor for development of hypothyroidism in the course of disease (Table 3).

HLA nomenclature and typing has been modified since its discovery. Different AIT phenotypes have been defined in various studies. Different phenotypes might emerge because of the complexity in the genetic make up of the population under study. There have been some inconsistencies in the correlation studies due to such problems in basics.

Initial studies examining white race showed correlations between HLA-B8/HLA-DR3 and atrophic form of AIT, and also between HLA-DR5 and HT (9-11). Different results were obtained by latter studies and studies done on subgroups of the disease. Mones et al. detected HLA-DR3 positivity in AIT patients significantly higher than in controls (11). Stenszky et al. reported a correlation between goitrous Hungarian HT patients and HLA-DR3 (OR = 3.3) (12).

Studies with more comprehensive HLA typing revealed HLA-DQ7 allele with an OR of 4.7 as the strongest correlate (13). HLA-DR4 was reported to correlate with HT in other studies conducted in white race (14-17). In a meta-analysis based on HLA series data from English population, OR was found low -2.3 and 1.6 for HLA-DR3 and HLA-DR4, respectively-, and no correlation was evident between DR/DQ alleles and disease (18). In a study conducted on Japanese population, a correlation was detected between the disease and HLA-B46/HLA-DR9 alleles (19). In another study conducted on Japanese population, HLA-DRw53 allele was also found to correlate with HT (20).

HLA-Bw46 was detected frequently in Chinese patients from Shanghai having goitrous HT (21). In another study conducted on southern Chinese, a correlation was detected between HT and

Table 3. HLA Class II markers and risk or protective factors for AIT

	Risk factors		Protective factors	
	HLA- DR	HLA- DQ	HLA- DR	HLA- DQ
All patients	DRB1*04	DQB1*0201	DRB1*08	None
Euthyroid	None	DQB1*0201	None	None
Hypothyroid	DRB1*04	DQB1*0201	None	DQB1*02
Goitrous	None	None	None	None
Non-goitrous	DRB1*04	DQB1*0201	DRB1*12	None
Atrophic AIT	DRB1*04	DQB1*0201	DRB1*12	DQB1*02

HLA-DRw9 (22). A correlation was detected between HT and HLA-DR4 in patients who had migrated from East Asia and been residing in England (23). In a study conducted in Korea, a strong correlation was detected between atrophic AIT patients with TSH-R blocking antibody positivity and HLA-alleles DR8 (OR = 5.7) and DQB1*0302. Specific DR and/or DQ alleles could not be detected in patients who were negative for TSH-R blocking antibody or had goitrous AIT (24).

In a study conducted in Brazil, DRB1*04 allele was shown to correlate with autoimmune thyroiditis (25). There were strong correlations between the atrophic form of disease and DRB1*04/DQB1*03 alleles.

There have been two studies investigating the correlation between chronic AIT and HLA in Turkish population (6, 7). Ozbey et al. examined HLA class I and II antigens by serologic methods in 28 patients with atrophic thyroiditis and 306 healthy controls. The frequency of HLA-A2 (RR = 2.25), B16 (RR = 4.89) and DR4 (RR = 3.02) antigens were found significantly higher in patients compared to controls, whereas HLA-DR2 (RR = 0.20) and DRw52 (RR = 0.43) antigens were found significantly lower. HLA-DR4 antigen was proposed as a risk factor for developing Grave's disease in Turkish population and also as a predisposing locus for development of autoimmune thyroid diseases in our country (6).

Yetkin et al. determined MHC class II histocompatibility antigens (DR, DQ) by serologic methods in 27 HT patients and compared the results to 100 controls. There was no difference between patient and control groups in terms of HLA antigens. Nevertheless, HLA-DQw3 antigen was detected higher in the healthy control group than HT patients (HLA-DQw3 frequency and OR in control and patient groups were 64% and 11.1% (p = 0.07), respectively). As a result, HLA-DQw3 allele was reported as a protective factor for the disease (7).

Not only our study is the most comprehensive one ever conducted on Turkish population, but also the first one for using DNA analysis technique. Our results support the correlation between AIT and HLA-DR4 that were detected by Ozbey et al. using serologic techniques.

Our study indicated that the positivity HLA-DRB1*04 and HLA-DQB1*0201 alleles pose as risk factors for the development of AIT, especially AT. Moreover, the positivity of HLA-DRB1*08 allele acts as a protective factor for AIT, while HLA-DRB1*12 and HLA-DQB1*02 alleles have protective roles from AT development in particular.

We did not detect any specific locus that increased or decreased the susceptibility risk for contracting goitrous AIT. Considering the existence of an endemic goiter region in our country, the iodine prophylaxis may also have contributed to the disease development process, thus these cases may have been influenced by the environmental factors for disease development.

HLA system constitutes only a small fraction of genetic factors in AIT etiology. Besides, even in groups with same ethnic backgrounds, alleles might be effecting differentially due to environmental factors stemming from settlements in different populations and geography. We believe that the studies investigating correlations between AIT and HLA should continue in parallel to the advances made in molecular biology and in the light of new discoveries regarding human genome.

References

1. Weetman AP, McGregor AM. Autoimmune thyroid disease: Further development in our understanding. Endocr Rev 1994; 15: 788-830.
2. Weetman AP. Chronic autoimmune thyroiditis. In: Braverman LE, Utiger RD, editors. Werner and Ingbar's The Thyroid, 8th ed. Philadelphia, New York: Lippincott-Raven Publishers 2000; 721-32.
3. Bottazzo GF, Pujol-Borell R, Hanafusa T, et al. Role of aberrant HLA_DR expression and antigen presentation in induction of endocrine autoimmunity. Lancet. 2: 1983; 1115-9.
4. Barbesino G, Chiovato L. The genetics of Hashimoto's disease. Endocrinol Metab Clin North Am 2000; 29: 357-74.
5. Strakosch CR, Wenzel BE, Row VV, et al. Immunology of autoimmune thyroid diseases. N Engl J Med 1982; 307: 1499.
6. Ozbey N, Orhan Y, Çarın M. Primer miksödem ile HLA grupları arasındaki ilişki. Ulusal Endokrinoloji Dergisi 1996; 6: 175-83.
7. Yetkin İ, Ayvaz G, Tülek N, et al. Association between Hashimoto's thyroiditis and human leukocyte antigens. Turkish J Clin Res 1997; 15: 29-31.
8. Hegedus L. Thyroid size determined by ultrasound. Influence of physiological factors and non- thyroidal disease. Dan Med Bull 1990; 37: 249.
9. Farid NR, Sampson L, Moens H, et al. The association of goitrous autoimmune thyroiditis with HLA-DR5. Tissue Antigens 1981; 17: 265-8.
10. Irvine WJ, Gray RS, Morris PJ. HLA in primary atrophic hypothyroidism and Hashimoto goiter. J Clin Lab Immunol 1978; 1: 193-5.
11. Moens H, Barnard JM, Bear J, et al. The association of HLA-B8 with atrophic thyroiditis. Tissue Antigens 1983; 13: 342-48.
12. Stenszky V, Balanzs C, Kraszits E, et al. Association of goitrous autoimmune thyroiditis with HLA-DR3 in eastern Hungary. J Immunogenet 1987; 14: 143-8.
13. Badenhoop K, Schwartz G, Walfish PG, et al. Susceptibility to thyroid autoimmune disease: Molecular analysis of HLA-D region genes identifies new markers for goitrous Hashimoto's thyroiditis. J Clin Endocrinol Metab 1990; 71: 1131-7.
14. Farid N R, Thompson C. HLA and Autoimmune endocrine disease. Mol Biol Med 1986; 3: 85-97.
15. Shi Y, Zou M, Robb D, et al. Typing for MHC complex Class II antigens in thyroid tissue blocks: Associations of Hashimoto's thyroiditis with HLA-DQA0301 and DQB0201 alleles. J Clin Endocrinol Metab 1992; 5: 943-6.
16. Thompson C, Farid NR. Postpartum thyroiditis and goitrous Hashimoto's thyroiditis are associated with HLA-DR4. Immunol Lett 1985; 11: 301-3.
17. Vargas MT, Gladman D, Walfish PG. Antithyroid microsomal autoantibodies and HLA-DR5 are associated with postpartum thyroid dysfunction: Evidence supporting an autoimmune pathogenesis. J Clin Endocrinol Meta 1998; 67: 327-33.
18. Jenkins D, Penny MA, Fletcher JA, et al. HLA class II gene polymorphism contributes little to Hashimoto's thyroiditis. Clin Endocrinol 1992; 37: 141-5.
19. Ito M, Tanimoto M, Kamura H. Association of HLA antigen and restriction fragment length polymorphism of T cell receptor beta-chain gene with Grave's disease and Hashimoto's thyroiditis. J Clin Endocrinol Metab 1989; 69: 100-4.
20. Honda K, Tamai H, Morita T, et al. Hashimoto's thyroiditis and HLA in Japanese. J Clin Endocrinol Metab 1989; 69: 1268-73.
21. Wang WF, Yu ZQ, Xy JJ. HLA and hypertrophic Hashimoto's thyroiditis in Shanghai Chinese. Tissue Antigens 1988; 32: 235-6.
22. Hawkins BR, Lam KSL, Ma JTC, et al. Strong associations between HLA DRw9 and Hashimoto's thyroiditis in Southern Chinese. Acta Endocrinol 1987; 114: 543-6.
23. Tandon N, Zhang L, Weetman AP. HLA associations with Hashimoto's thyroiditis. Clin Endocrinol (Oxf) 1991; 34: 383-6.
24. Cho BY, Chung JH, Shong YK, et al. A strong association between thyrotropin receptor-blocking antibody-positive atrophic autoimmune thyroiditis and HLA-DR8 and HLA-DQB1*0302 in Koreans. J Clin Endocrinol Metab 1993; 77: 611-5.
25. Zantut-Wittmann DE, Persoli L, Tambascia MA, et al. HLA_DRB1*04 and HLA_DQB1*03 association with the atrophic but not with goitrous form of chronic autoimmune thyroiditis in a Brazilian population. Hormon Metab Res 2004; 36: 492-500.