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ARTICLE

Human Leukocytes Antigen HLA-DQB1 Determine Susceptibility to Thyroid Disease

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Abstract

Background: Thyroid disease is a common disease in women of the reproductive age. This disease arises due to complex interactions between environmental and genetic factors. However, the interactions between genes and environment are yet well defined. Among the main susceptibility genes that have been identified is the HLA-DQB1 gene locus. The major environmental factors include iodine, medications, infection, smoking, and possibly stress. **Aim of study:** To ascertain the association between HLA-DQB1 alleles and goitrous thyroid disease in a sample of Iraqi Arab Muslims. **Patients and methods:** A cross sectional case-control comparative study was carried out. Patients with thyroid disorders who attended this hospital in the period from September 2013 to June 2014 for thyroidectomy were studied. HLA-DQB1genotyping was done using a panel of sequence-specific oligonucleotide probes (SSOP) using HLA-DQB1 amplification and hybridization kits (SSO HLA type DQB1 plus and Mastermix for HLA type DQB1 Amp plus) using automated method by AutoLipa-48. **Results:** There was an increased frequency of HLADQB1*03:01and 0601 in control group compared with patients group (P=0.005, Odds ratio=0.0164, 95% CI: 0.0009-0.2926) and (P=0.01, Odd ratio=0.1667, 95% CI: 0.0412 to 0.6750) respectively. Other alleles like HLA-DQB1* 0202, 03:02, 0501 and 06:02 were detected in the patients' group but not in controls. **Conclusions:** HLA alleles have an effect on development thyroid disease. HLADQB1* 0301 and 0601 is a protective in Iraqi Arab Muslims individuals.

Key words: HLA, thyroid, genetics.

Introduction

Goiters whether diffuse or nodular is a common problem in the general population. A goiter can be associated with euthyroidism, hyperthyroidism, or hypothyroidism (1). Goiters are multifactorial in their origin. They develop in iodine deficiency in genetically susceptible individuals with other risk factors such as cigarette smoking, pregnancy, Selenium or Zinc deficiency, exposure to goitrogens and even emotional stress (2).

Pathogenesis of nodular goiters induced by iodine deficiency with mutagenic environmental factors in genetically predispose person that leads to cellular proliferation and formation of free radicals that promotes the appearance of somatic mutations in thyrocytes (3). Therefore, the etiology of this disease seems to involve complex interactions between predisposing genes and environmental factors.

Four genetic loci were associated with thyroid volume and two of which are independent loci that located upstream of and within CAPZB, which encodes the beta subunit of the barbed-end F-actin binding protein that modulates actin polymerization. The third locus marks FGF7, which encodes fibroblast growth factor 7. The fourth locus represents a ''gene desert'' on chromosome 16q23, located directly downstream of the predicted coding sequence LOC440389 (4).

Other genetic studies have shown that the human leukocyte antigen (HLA) region on chromosome 6p21.31 is an important factor associated with thyroid disease, as the HLA region is highly polymorphic region and contains many immune response genes. This region encodes genes that are grouped into three classes, first is class I genes (HLA-A, HLA-B and HLA-C), second is class II genes (HLA-DR, HLA-DP and HLA-DQ) and last one is class III genes(5).

Many studies regarding HLA allelic associations with thyroid disease have been performed, and different associations with HLA alleles have been reported among diverse ethnic populations. Due to the crucial role played by HLA class II molecules in antigenic peptide presentation to T helper cells in both the blood periphery and during thymic selection and education, components of the HLA class II region (DRB1 and DQB1) have been associated with thyroid disease. For example, predisposing or positive effect (increased risk of disease) for DRB1*03-DQB1*02-DQA1*05 (DR3) and a protective or negative effect (decreased risk of disease) for DRB1*07-DQB1*02- DQA1*02 (DR7) have been consistently reported (6,7).

In the current study, we studied the association between HLA-DQB1 alleles and goitrous thyroid disease in a sample of Iraqi Arab Muslims.

Patients and methods

Setting and protocol

A cross sectional case-control comparative study was carried out in Al-Kindy Teaching Hospital (Baghdad-Iraq). All patients with thyroid disease who attended this hospital in the period from September 2013 to June 2014 for thyroidectomy were included in the study. The study was approved by the Al-Kindy College of Medicine's Ethical Committee and all patients gave an informed written consent.

Study population

The population consisted of 30 Iraqi Arab Muslims patients who had been clinically diagnosed to have a goiter (nodular, multinodular and diffuse) and by laboratory tests diagnosed as hypothyroidism (symptoms & low levels of T4 and T3 with high level of TSH), hyperthyroidism (symptoms & high levels of T4 and T3 with low level of TSH) or Euthyroid (symptoms due to pressure effects & normal levels of T4, T3 and TSH)**.** 24 of the patients were females, 6 were males. The mean age of the patients was 35.5 years (range 20-61 years). The control group consisted from 30 healthy individuals ethnically matched with patients group. They do not have any past history of thyroid disease. 15 of them were males and the rest was females, with ratio 3:1 males to females. The mean age of the controls was 36.5 years (range 23-60 years).

Sampling and analysis

Ten ml of venous blood were collected by venipuncture from all the study patients and controls. Five ml was put into plain containers, which was used for thyroid function test (TSH, T4, T3). The other five ml was placed in in EDTA containers for DNA extraction by QIAmp DNA blood Mini Kit, (Qiagen Inc. Germany).

DNA product was verified by electrophoresis in a 2% agarose gel containing ethidium bromide and was visualized under UV light. Locus- and allele-specific amplification of genomic DNA was performed for DQB1. Amplification and hybridization was performed using a panel of sequence-specific oligonucleotide probes (SSOP) using HLA-DQB1amplification and hybridization kits (SSO HLA type DQB1 plus and Mastermix for HLA type DQB1 Amp plus kits (Innogenetics, Belgium) using automated method by AutoLipa-48 (Innogenetics-Belgium). The results were interpreted using LiRas version-5.0 software (Innogenetics, Belgium).

Statistics analysis

Statistical analysis was done using MiniTab version 3.0. The distribution of HLA alleles in patients and controls were compared using Chi-square or Fisher's exact test as necessary. In each comparison, the Odds ratio (OR) along with the 95% confidence interval (95% CI) was used. P-value less than 0.05 were considered statistically significant.

Table1. Human leukocytes antigens (HLA-DQB1) alleles frequencies in patients with thyroid disease and in healthy control groups

HLA-DQB1* alleles	Thyroid Patients Group (No = 30)		Healthy Control Group (No = 30)		Odd Ratio (95% confidence interval)	P value
	Number	Percentage	Number	Percentage		
02:01	15	25	12	20	1.5 (0.5395 - 4.1707)	0.43
02:02	9	15	0	0	NA	NA
03:01	15	25	30	50	0.0164 (0.0009-0.2926)	0.005
03:02	3	5	0	0	NA	NA
05:01	6	10	0	0	NA	NA
06:01	3	5	12	20	0.1667 (0.0412 - 0.6750)	0.01
06:02	6	10	0	0	NA	Na
06:04	0	0	6	10	NA	NA

NA = Not applicable

Results

Allele's frequencies of HLA-DQB1for thyroid patients and control group are shown in Table 1. There was an increased frequency of HLADQB1*03:01and 0601 in control group compared with patients group (P=0.005, Odds ratio=0.0164, 95% (CI:0.0009-0.2926) and (P=0.01, Odd ratio=0.1667, 95% CI: 0.0412 to 0.6750) respectively. Other alleles like HLA-DQB1* 0202, 03:02, 0501 and 06:02 were detected in patients group and not in control group.

Discussion

Genetic factors are important causative agents of thyroid disease. HLA alleles are one of the predisposition or protective against this disease. Many studies were conducted in this field regarding the association of thyroid disease and HLA typing. Grumet et al. first showed this association with alleles of MHC class I HLA-B8 (8). Farid et al. (9) were the first to use a case control based method to show a strong association with HLA-DR3 in Canadian Caucasians and strong linkage disequilibrium with HLA-B8.

Our study found that a greater frequency of HLADQB1*03:01 and 0601 in the control group compared with patients group (P=0.005, Odds ratio=0.0164, 95% CI: 0.0009-0.2926) and (P=0.01, Odd ratio=0.1667, 95% CI: 0.0412 to 0.6750) respectively. This means that DQB1*03:01 and 06:01 is protective against development of thyroid disease. Other study demonstrated HLADRB1*0301 and HLA-DQB1*0201 considered to be a risk candidates for developing disease, while DQB1*0601 is a protective allele in Sudanese population (10). In Romanian population, HLA-DRB1*03 and DRB1*11 may be the primary susceptibility to thyroid disease whereas HLA-DRB1*01 and DRB1*15 seem to be protective (11). In other races like nonwhite South African blacks populations, has been found the associated of HLA-DR1 and DR3 (12).

MHC haplotype association with thyroid disease was reported in many studies. Heward et al. have confirmed the association of HLA DRB1*0304-DQB1*02-DQA1*0501 haplotype (13). This is in agreement with our study, HLA-DQB1*02 was detected in patients group and not in control group. The other linkage disequilibrium is DRB3*020/DQA1*0501 haplotype in African Americans population (14).

Other haplotypes in Hong Kong Chinese individuals are associated with thyroid disease are B46, DR9, DRB1*303, and DQB1*0303 (15). This discrepancy in the results may be attributed to many factors such as race of the population, religion, criteria of sample selection, size of sample under study, and the method being used in testing either serology or molecular.

In conclusion, HLA alleles has an effect on development of thyroid disease. HLADQB1* 0301 and 0601 is a protective in Iraqi Arab Muslims individuals.

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