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The Relationship Between Human Leukocyte Antigen (HLA) and Autoimmune Diseases

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Abstract

Autoimmune disorders encompass a range of conditions that occur when the immune system fails to distinguish between self and non-components leading to a diverse array of symptoms based on the specific target affected by the immune response. This extensive and detrimental immune reaction can be either humoral or cell mediated affecting tissues or components, like hormones and neurotransmitters. The goal is to shed light on how genetic factors are linked to diseases and the potential impact of different alleles, on disease occurrence utilizing Auto Lipa (automatic line probe assay). This method relies on hybridization, for analysis. HLA genotyping was carried out using the PCR based SSO method The PCR based SSO kit, from Histo Type/DNA SSO Kits for both patients and healthy control groups. The presence of alleles, at varying frequencies is closely linked to the occurrence of the disease in question. Reinforces the genetic contribution to autoimmune conditions. There is a close relationship between autoimmune diseases and certain alleles, the frequency of which is considered to be factors associated with the onset of the disease. Conversely , the frequency of certain alleles in healthy people is completely resistant to the appearance of the disease.

Keywords: AD, MHC, HLA, T1D, SS, AS, RA, SLE, MS, CD, alleles.

Introduction

Autoimmune disorders (AD), a collection of conditions with complex mechanisms at play, can be categorized as targeting specific organs or affecting the entire system. They are distinguished by the activation of self-targeted immune responses involving B cells or T cells in the body's defense mechanism against itself. Despite the mystery surrounding their origins, ADs are recognized to be influenced by factors and a combination of genes that determine an individual's susceptibility or resistance to these conditions. Henceforth, the combined effect of factors shapes and defines autoimmune disorders. AD individuals exhibit a genetic inheritance pattern that deviates from the Mendelian model in various ways (1).

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Additionally, research conducted with fraternal twins has approximated the impact of genetic influences, as cited in (2). Key genetic elements frequently investigated in connection with disorders are genes situated within the Major Histocompatibility Complex (MHC) within regions of the Human Leukocyte Antigen (HLA) class I and class II. Various autoimmune disorders have been linked to forms of HLA genes belonging to class II (3). The MHC genetic mapping has discovered genes on chromosome number six's arm. Progress in methods using the sequence and structure of various HLA molecule epitopes and their encoding genes has allowed the progress of molecular and functional analysis. The collaboration of molecular epidemiology has enabled researchers to explore and propose the connections between HLA genetic variations and the underlying mechanisms of autoimmune diseases like rheumatoid arthritis (RA), lupus erythematosus (SLE), type 1 diabetes (T1D), multiple sclerosis (MS), celiac disease (CD), Sjögren's syndrome (SS) among others; or HLA gene variants and autoinflammatory conditions such, as ankylosing spondylitis (AS). The exact molecular processes linked to these conditions remain unresolved. The challenge lies in identifying genes that show secondary associations within the MHC region due to linkage disequilibrium (LD). It involves understanding how various molecules encoded by HLA (class I and class II) as non-HLA loci like TAP1 and TAP 12 in the MHC region contribute to susceptibility or protection(2,3). This also encompasses the roles of response functions in processing antigens and distinguishing between self and non-self to activate T cells (4,5). It has also been suggested that specific peptide sequences from organisms, like viruses or bacteria, could resemble peptides produced by the body itself. Possibly triggering an immune response known as molecular mimicry that showcases these self-proteins alongside HLA molecules despite their distinct sources (6).

Rheumatoid arthritis (RA)

The specific HLA genes that contribute to susceptibility to RA vary among groups. For Caucasians, the relevant genes are HLA\ DRBB\'04 \;01\' \' 04\;04\' and \ '04\;08\'; for Spaniards and Japanese, it is HLA\ DRBB\'04 \;05\'; Israelis are associated with HLA\ DRB\'01 \;01\' and \ '01\;02\'; some American populations like Pima and Yakima Indians show a connection with HLA\ DRB\'14 \;02\'; Greeks link to HLA\ DRB\'10 \;01\' (7) while HLA\ DRB\'01 \;01\' is significant, in understanding the susceptibility factors.

Multiple sclerosis (MS)

This medical condition is linked to a disorder where the body's immune cells react predominantly against proteins, like myelin essential protein (MB) (8). The HLA genetic markers DRB15 and DQB10602 are commonly found in Caucasians and Latin Americans with sclerosis (MS), indicating a risk. In a study by the International Multiple Sclerosis Genetics Consortium (IMSGC), it was found that the HLA gene variants HLA DQB3 *13 and HLA DQB4 *08 are linked with sclerosis at different odds ratios (OR), indicating associations with the disease risk level. In the region of Sardinia, Italy where multiple sclerosis is prevalent at rates higher than usual (9). There have been reports of associations with sclerosis for HLA genes such as HLA-DR and specific subtypes like *04,*03, and *13 (in addition to *15) (10)

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Systemic lupus erythematosus (SLE)

The human leukocyte antigen (HLA) has been identified as having a link to and impact on systemic lupus erythematosus among various autoimmune diseases studied so far. The primary genetic association was discovered in the HLA region known as HLA-DRBI. Research on HLA class I has consistently shown that the HLA-DR2 (*15; 01) HLA-DR3 (*03; 01) HLA-II DRBI *08; 01 alleles are commonly linked with this disease in European populations. Each allele is associated with an increased risk for systemic lupus erythematosus (11,12).

Type 1 diabetes mellitus (T1D)

Some specific genes, like HLA DQB 03/02 and 02/01, have been linked to an increased risk of Type 2 Diabetes (T2) (13,14). People with both genes are more likely to develop the disease than the population. Many DRB104 genes linked with HLA DQB 03/02 can also influence the risk of developing the disease. The connection between HLA genes and T2 Diabetes is intricate and multifaceted. Initially, it was thought that patients with this condition had HLA B8, HLA B18, and HLA B15 (known as B62) (15). On with the advancement of tests, the link was found to extend to HLA DR3 alleles such as HLA DRBI *03; 01 HL A. DR 4 (HL et al. B 104) HLA DQB 10201 and HLADQB10302. The number of alleles linked to TID in the DR and DQ loci is considerable. However, it is uncertain which specific locus or loci are responsible for vulnerability/protection since they exhibit impact compared to the recognized susceptibility combinations for TID. This could be attributed to the array of alleles within the HLA system's changes in the population demographics, such as susceptibility and protection of alleles like HLA. DRBI * 15; 01 and/or HLA. DQB 7 * 06; 02 are inherited (16,17).

Sjögren's syndrome (SS)

SS is a condition where the body's immune system mistakenly attacks the tear glands with lymphocytes and plasma cell infiltration, causing eye and mouth dryness due to the production of self-targeting antibodies that affect saliva production and eye moisture levels, according to recent research gathering data from various global studies linking HLA Class II genes with SS across different populations totaling 1, 166 cases and 6 470 controls, from 23 studies. At the level of DQA, genetic variants showed associations with disease risk and protection. DQA variants 05 to 01 and DQB variants 02 to 01 were linked with increased risk, while DQA 02 to 01 and DQB variants 05 to 01 were identified as factors(18).

Celiac disease (CD)

Celiac disease affects the intestine because the body's immune system reacts to wheat gluten improperly ingested by individuals with this disorder (19). The influence of genetics on disease is evident, with a high level of agreement among identical twins, at almost 90%, while only about 10 percent is seen in first-degree relatives. A substantial portion of the disease susceptibility is attributed to HLA genes. HLAD Q2, which is produced by a combination of HLA DQA *05;*01 and HLA DQB *02;*01 or HLA DQL produced by DQA *03;*01 and DQB *03;*02 are found in around 30% 35 % of

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populations, with a prevalence of disease (CD) but only 2% 5 % of those carrying the genes develop CD suggesting that other genetic and environmental factors play a role, in the development of CD (20).

Ankylosing spondylitis (AS)

AD association with type I HLA alleles is uncommon except in the case of spondylitis (AS), which is classified as an auto condition rather than an autoimmune disease. HLA B *27 has been found in 96 percent of individuals with AS; however, not all B *27 alleles are linked to the disease's progression (21).

Methodology

This study was approved by the ethical research committee / College of Veterinary Medicine/ Al Muthanna University (No.123587) on 22 August 2024. All participants signed the consent form before enrollment in the study. Thirty-three individuals diagnosed with type I diabetes mellitus (DM) systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Crohn's disease (CD), within the age range of 20 to 50 years were included in this study along with 20 participants for comparison purposes of age groups across both patient and control groups. These individuals were selected from patients visiting hospital outpatient clinics as private clinics at AL Kadhimiya Teaching Hospital and Baghdad Medical City Teaching Hospital between April 2022 and December 2023. Consultants confirmed the diagnosis of each condition based on assessments and diagnostic imaging such as X-rays and ultrasound examinations. Each individual had three milliliters of blood extracted using a method and placed in an EDTA tube for HLA class I and II genotyping; afterward, stored at 20°C before undergoing DNA extraction with the Qiagen Genome DNA extraction kit from Germany; all DNA samples were then frozen at 20°C until further testing was conducted. HLA genotyping was performed using the PCR-based SSO method, following the manufacturer's instructions. The PCR-based SSO kit was utilized from Histo Type/DNA SSO Kits Inno Genetics Line Probe Assay in Belgium. Additionally, this approach relies on hybridization.
Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS version 14). The relationship between alleles and disease progression was determined by calculating adjusted odds ratios and 95% confidence intervals using the Chi test method. To explore the variations in values across study groups deeper, the Mann-Witney test was employed to ascertain significance levels. Results with a P value below 0.05 were deemed significant by the researchers.

Result

The results suggest that having an occurrence of HLA DQB 01;01 and 02;01 alleles could increase the likelihood of developing type 2 diabetes; on the hand having a lower frequency of HLA A *33;01,B *08;26 DR B *07;01,*11;01 and HLA DQB 06;04 could potentially offer some protection against the condition.

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Table. 1: Alleles frequency in Diabetic patients and Healthy control groups alleles frequency

HLA-allele	DM Patients (N=33)	%	Control ((N=20	%	OR	EF	PF	P-Value
DQB1*0201	2	6.67%	7	35.00 %	0.158	-10.6	0.91	.020
DRB1 *0701	9	30.00%	0	0.000 %	18.116	8.50	1.13	.007

OR=Odd ratio**, EF=** Etiological factor**, PF**=Preventive factor

For LE disease the patients group most frequent allele was DQA1 and DRB1 whereas the A*0302 and A*0503 are the most frequent in healthy groups.

Table.2: Alleles frequency in .lupus erythematosus patients

HLA- allele	SLE Patients(N=33)	%	Control (N=20	%	OR	EF	PF	P-Value
*DQA1*0201	9	30.00%	0	0.00%	18.116	8.50	1.13	-007
*DRB1*0321	6	20.00%	0	0.00%	6.962	3.43	1.41	0.05
A*0302	1	3.33%	6	30.00%	0.158	1.87	2.25	0.20
A*0503	0	0.000	4	20.00%	16.636	0.00	0.00	0.21

In Rheumatoid arthritis patients the most frequent region was HLA-DRB1*0202 and HLA-DRB1*0303

Table.3: Alleles frequency in Rheumatoid arthritis and control groups

HLA-Allele	RA Patients(N=33)	%	Control((N=20	%	OR	EF	PF	P-Value
*HLA-DRB1*0202*	0	0.00%	4	20.00%	0.060	0.00	0.00	0.21
*HLA-DRB1*0303*	4	13.33%	0	0.00%	6.962	3.43	1.41	NS
*0302	5	16.67%	2	10.00%	1.596	1.87	2.25	NS
*0503	2	6.67%	0	0.000%	3.596	1.44	3.25	NS

For the Celiac disease patients group an increased frequency in the DQA and DQB region revealed a significant role in disease occurrence.

Table.4: Differences between Celiac disease and control groups allele frequency

HLA-A allele	CD Patients (N=33)	%	Control ((N=20	%	OR	EF	PF	P-Value
DQA*0201	9	30.00%	0	0.00%	18.116	8.50	1.13	0.007
DQB*0321	4	13.33%	0	0.00%	6.962	3.43	1.41	NS
A*0302	5	16.67%	2	10.00%	1.596	1.87	2.25	NS
A*0503	2	6.67%	0	0.000%	3.596	1.44	3.25	NS

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Discussion

In their investigation, the researchers used type methods to determine the HLA alleles at the DNA level, focusing on genotyping HLA class I and II using PCR-based SSO and studying its potential link to TIDM (Type 1 diabetes mellitus). Their findings showed that the prevalence of the HLA A*The 3301 allele was greater in the group of individuals than in those with the condition. The findings in this study contradict those of Noble et al. (22), Who identified B * 5701, B * 3906, A * 2402, and A * 0201 alleles associated with T1DM (considered protective factors). They also noted a decrease in the presence of A * 1101 A * 3201 A * 6601 B * 07002 B * 44003 B * 35002 C *16001 and C *04001 among patients. The study found that specific alleles, like DRBI * 070I and DQB * 010I, were common in TIDM patients, while the frequency of DRBI * 0304 and DRBI * 0404 alleles did not show significance. This aligns with findings from studies in Iraq (23) and other ethnic groups (24,25), where these alleles are considered risk genes for TIDM in patients compared to those in Asian populations (26).
In individuals with Celiac disease, a higher frequency of variations in the DQA and DQB regions has been found to play a role in the development of the disease by influencing enzymes such as prolyl endopeptidase and cysteine proteases that can break down gluten peptides resistant to human digestion. In this scenario, the system's malfunction leads to an attack on the tissue and consequent damage. The immune system targets tissues in systemic lupus erythematosus. This condition can impact various parts of the body, such as the skin, joints, kidneys, brain, and other organs. It may be associated with elements including genetics, environmental factors, hormonal influences, and specific medications. The higher occurrence of alleles in a group of patients might be seen as a predisposing factor, while an increased frequency in a group could be viewed as a protective factor.
Patients with arthritis have shown the occurrence of specific genetic markers in both the DRBI and the region of the DNA sequences known as the DQB gene locus group, indicating a genetic influence on the development of this condition, which is categorized among immune-mediated diseases, where the body's defense system targets the healthy tissues surrounding joints.

Conclusion

A variety of significant groups for many Autoimmune diseases were reported, both as prophylactic alleles and disease-associated predisposing alleles, ensuring the genetic role in the incidence of the autoimmune disease.

DECLARATION

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Competing interests statement

The authors have declared no conflict of interest.

Ethics statement

The author approved that this research follows the journal's Attach Ethic Approval guidelines as appeared on the journal's author guidelines page. And the study was performed in line with the principles of the declaration of Helsinki. Approval was granted by the veterinary Medicine College of Ethical Approval committee (Approval No. 123587) .

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