

Genetic Insights into Heart Failure: A Study of HLA-DQ2 and HLA-DQ8 Haplotypes in Patients with Reduced Ejection Fraction

Uğur Küçük¹, Fatma Sılan², Emine Gazi¹, Öztürk Özdemir², Kadir Arslan¹,
Volkan Sönmez² and Ercan Akşit¹

¹Department of Cardiology, Faculty of Medicine, Canakkale Onsekiz Mart University, Canakkale, Turkey

²Department of Medical Genetics, Faculty of Medicine, Çanakkale Onsekiz Mart University, Çanakkale, Turkey

Received: 21 November 2024

Accepted: 30 April 2025

*Corresponding Author: drugurkucuk@hotmail.com

DOI 10.5001/omj.2025.98

Abstract

Objectives: Many factors play a role in the etiology of heart failure (HF). Genetics is one of these factors. The present study aimed to compare human leukocyte antigens (HLA)-DQ2 and HLA-DQ8 haplotypes between heart failure with reduced ejection fraction (HFrEF) and healthy control group.

Methods: Our study included 100 patients (50 in the HFrEF group and 50 in the healthy control group). The frequency and percentage of HLA-DQ2 and HLA-DQ8 were compared between the groups.

Results: HLA-DQ2 positivity was observed in 16% of the HFrEF group and 20% of the control group ($P = 0.795$), while HLA-DQ8 positivity was found in 24% and 26%, respectively. No statistically significant differences were observed between groups. Subgroup analyses also revealed no significant differences in haplotype distribution based on gender or HF etiology.

Conclusion: This study demonstrated that the HLA-DQ2 and HLA-DQ8 haplotypes are not significantly associated with HFrEF in the studied population. While these haplotypes are relatively common in the general population, their utility as standalone markers for early detection of HFrEF appears limited.

Keywords: Autoimmunity, heart failure, HLA-DQ2, HLA-DQ8

Introduction

Heart failure (HF) is characterized by shortness of breath, fatigue, and fluid retention wherein cardiac output does not meet the metabolic needs.¹ Despite the current successful management of cardiovascular diseases (CVD), there has been a parallel increase in HF prevalence due to the increase in the presence of additional comorbidities, such as diabetes mellitus (DM) or hypertension (HT), in the aging population.² Understanding the pathophysiology of HF is essential for formulating alternative treatment options for each patient and minimizing the cardiovascular risk factors to reduce HF risk.³

Evidence revealing that inflammatory mechanisms and autoimmune responses play an essential role in various CVD etiologies has been reported.^{4,5} Autoimmune diseases (ADs) can affect target organs and multiple systems.⁶ The association of HF with numerous ADs, such as systemic lupus

erythematosus, ankylosing spondylitis, Crohn's disease, and celiac disease (CD), has been reported in previous studies.⁷

Although human leukocyte antigens (HLA)-DQ2 and HLA-DQ8 are known to be pivotal risk factors for ADs, the possible roles of HLA-DQ2 and HLA-DQ8 positivity in other diseases and healthy individuals have not been fully investigated.⁸ HLA-DQ2 and HLA-DQ8 are useful diagnostic markers for CD and minimize the need for duodenal biopsy.⁹ There has been a report regarding the potential deterioration of cardiac functions in pediatric cases with a CD diagnosis.¹⁰ In another recent study, HLA-DQ2 and HLA-DQ8 positivity was associated with early vascular atherosclerosis.¹¹ Dilated cardiomyopathy (DCM) often appears to be caused by an unidentified viral infection, but in fact autoimmune mechanisms associated with HLA-DQ alleles play a primary role.¹² HLA alleles are not only associated with CD, but also with important cardiovascular problems such as HF, arrhythmia, and atherosclerosis. As a result of all this information, it seems that HLA-DQ2 and HLA-DQ8 haplotypes are associated with autoimmune disorders.

Their involvement in cardiovascular diseases with autoimmune or inflammatory components such as dilated cardiomyopathy and myocarditis is increasingly recognized. For example, an association between certain HLA genotypes, including HLA-DQ, and autoimmune responses in dilated cardiomyopathy has been shown, and a predisposition to immune-mediated myocardial damage has been demonstrated.¹³ Similarly, another study has highlighted the role of HLA-associated immune mechanisms in myocarditis, linking these haplotypes to inflammatory pathways and clinical outcomes.¹⁴ These findings suggest that HLA-DQ2 and HLA-DQ8 may contribute to the pathogenesis of heart failure via immune dysregulation and warrant further investigation in heart failure populations.

Based on this information, the etiology of HF is complex and may be a trigger in this process with autoimmune diseases. The presence of HLA in HF patients has not been adequately studied. The purpose of this study was to investigate the relationship between HLA-DQ2 and HLA-DQ8 and heart failure with reduced ejection fraction (HFrEF).

Methods

Our study followed a case-controlled cross-sectional design and was carried out at a tertiary healthcare center over the period from August 2021 to August 2022. Our study patients consisted of patients who had physical examination findings such as dyspnoea, swelling of the feet and rapid fatigue suspicious for HF in our cardiology unit and were hospitalized for further diagnosis and treatment. The study included 50 patients with HFrEF and 50 age- and sex-matched healthy volunteers. HFrEF group includes patients with left ventricular ejection fraction (LVEF) less than 40%. HFrEF patients were classified into two subgroups as ischaemic (n=27) and non-ischaemic (n=23) groups. The ischaemic group consisted of patients who had beforehand undergone percutaneous coronary intervention (n=18) or coronary artery bypass surgery (n=9) for coronary artery disease. The control group included patients with an LVEF of $\geq 40\%$ and with no any modifiable cardiovascular risk factors and active. The control group was selected to match the HFrEF group by age and sex. In addition to the absence of modifiable cardiovascular risk factors, all control participants were clinically assessed to ensure they had no active cardiovascular disease or any significant clinical comorbidities. While we acknowledge that subclinical cardiovascular conditions might still exist in some individuals, we selected participants who were considered to have no overt or subclinical cardiovascular diseases, ensuring that they represented a generally healthy population without significant risk factors or underlying cardiac conditions. This careful selection criterion aimed to minimize confounding factors when comparing the HFrEF group with healthy controls. The non-ischaemic group consisted of patients without severe coronary artery disease (coronary lumen diameter stenosis $\leq 30\%$) revealed by coronary angiography.

Patients with acute or chronic liver disease, severe renal failures (eGFR <30 ml/kg/1.73 m²), hepatitis B or C, moderate to severe heart valve disease, inflammatory and hematological diseases, CD, active thyroid disease, cancer, autoimmune thyroiditis, genetic cardiomyopathy (such as hypertrophic cardiomyopathy, left ventricular noncompaction and restrictive cardiomyopathy), structural heart disease, collagen tissue diseases, toxin-induced cardiomyopathy, suspected

pregnancy, or peripartum cardiomyopathy and patients who did not want to participate in the study and younger than 18 years of age were excluded from the study. Certain exclusion criteria were applied to avoid confounding effects. For example, CD was specifically excluded from the study due to the well-established relationship between HLA-DQ2/DQ8 haplotypes and CD. While it is true that these haplotypes can be present in individuals without biopsy-confirmed CD, we chose to exclude individuals diagnosed with CD to avoid potential overlap of autoimmune mechanisms that could confound the interpretation of HLA-DQ2/DQ8's role in HF.

Ethics Committee approval was obtained for this study (Date: 03/11/2021; No. 2021-08). Written informed consent was obtained from all participating patients. This study is designed in line with the principles of the Helsinki Declaration.

All patients underwent echocardiographic examinations using a Vivid 7 Pro device (GE, Vingmed, Horten, Norway). Two experienced cardiologists blinded to the study assessed LVEF. LVEF was calculated using the modified Simpson method.¹⁵

Samples of blood were taken from peripheral veins via venipuncture and placed in EDTA tubes. Following DNA extraction from peripheral blood using QIAamp DNA Blood Mini Kit, real time PCR was performed with geneMAP Celiac detection kit and Qiagen Rotor-Gene Q protocol. After the completion of the run, data were analyzed using melting curve software (QIAgen Rotor-Gene Q series Software) to detect the HLA haplotypes. The positive and negative values for HLA-DQ2 and HLA-DQ8 are shown in Figure 1.

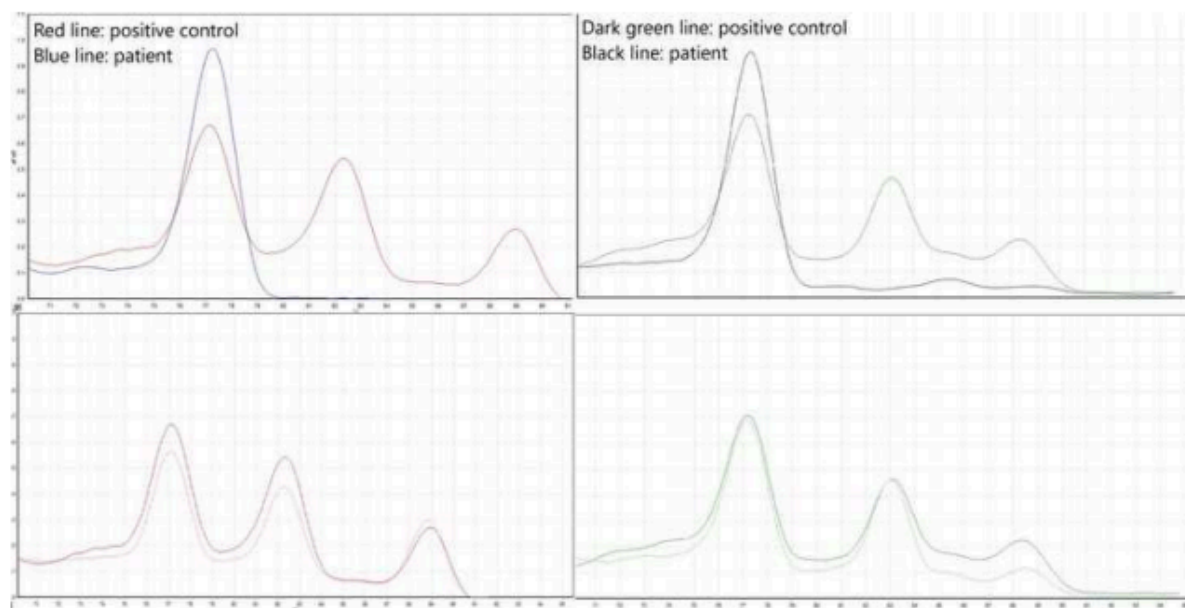


Figure 1: Positive and negative value diagram for HLA-DQ2 and HLA-DQ8

DQ2 Negative: The red line represents the positive control, and the blue line represents the patient. As the patient's pattern does not match the positive control's, and only a single peak was observed, the result is negative. (top left)

DQ2 Positive: The red line represents the positive control, and the pink line represents the patient's data. The patient's data follows the positive control's pattern and displays three peaks, indicating a positive result. (top right)

DQ8 Negative: The dark green line represents the positive control, and the black line represents the patient. As the patient's pattern does not follow the positive control and shows only a single peak, the result is negative. (bottom left)

DQ8 Positive: The dark green line represents the positive control, and the light green line represents the patient. The patient's data follows the positive control's pattern with three peaks, confirming a positive result. (bottom right).

All data analyses were applied using SPSS software version 19.0 (SPSS Inc., Chicago, IL, USA). The distribution of the continuous variables was analyzed using Kolmogorov–Smirnov test. Data were expressed as mean $\pm$ SD. Parameters showing normal distribution were compared using the Student's t-test. The categorical variables were reported as percentages and numbers. Chi-square or Fisher's exact tests were used to compare the probability ratios of the categorical variables. $P < 0.05$ was considered statistically significant in all the analyses.

Results

In total, 100 patients were included in the HFrEF (36 males, 14 females) and control (28 males, 22 females) groups. The mean age of the patients in the HFrEF group was 62.22 ± 15.06 years and that of the control group was 59.66 ± 13.63 years. The HFrEF and control groups had 8 (16%) and 10 (20%) HLA-DQ2–positive patients ($P = 0.795$), respectively, and 12 (24%) and 13 (26%) patients with HLA-DQ8–positive patients ($P > 0.99$) [Table 1].

Table: Demographic findings of heart failure patients and control group.

	HF (n=50)	Control (n=50)	p-value
Age (years)	62.22 ± 15.06	59.66 ± 13.63	0.375
Gender			0.145
Male	36	28	
Female	14	22	
Smoking n (%)	8 (16)	-	
DM n (%)	8 (16)	-	
HT n (%)	9 (18)	-	
LVEF (%)	28.34 ± 7.95	57.68 ± 5.46	<0.001
BMI (kg/m^2)	25.34 ± 3.83	25.20 ± 1.44	0.810
Heart rate	83.44 ± 12.18	81.24 ± 11.84	0.362
SBP (mmHg)	119.44 ± 20.54	125.60 ± 12.94	0.076
DBP (mmHg)	72.44 ± 8.15	72.78 ± 8.32	0.837
HLA-DQ2 n (%)	8 (16)	10 (20)	0.795
HLA-DQ8 n (%)	12 (24)	13 (26)	>0.99

HF: Heart Failure; DM: Diabetes mellitus; HT: Hypertension; LVEF: left ventricular ejection fraction; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HLA: Human leukocyte antigens

HLA-DQ2 positivity was observed in two female and six male patients in the HFrEF group ($p > 0.99$) and in four female and six male patients in the control group ($P > 0.99$) based on gender differences. HLA-DQ8 was positive in four female and eight male patients in the HFrEF group ($P = 0.718$) and in four female and nine male patients in the control group ($P = 0.339$) [Table 2]. There was no significant difference between patients with HFrEF who were classified as ischaemic or non-ischemic [Table 2].

Table 2: Prevalence of HLA-DQ2 and HLA-DQ8 Haplotypes in Heart Failure, Ischemic and Non-Ischemic Subgroups: A Gender-Based Comparison.

Group	HLA-DQ2 Present	HLA-DQ2 Absent	p-value	HLA-DQ8 Present	HLA-DQ8 Absent	p-value
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Heart Failure (Total)						
Male	6	30	>0.99	8	28	0.718
Female	2	12	>0.99	4	10	0.339
Control group (Total)						
Male	6	22	>0.99	9	19	0.339
Female	4	18	>0.99	4	18	0.339
Ischemic heart Failure						
Male	4	19	>0.99	4	19	>0.99
Female	0	4	>0.99	1	3	>0.99
Non-Ischemic heart Failure						
Male	2	11	>0.99	4	9	>0.99
Female	2	8	>0.99	3	7	>0.99

DISCUSSION

Our study revealed that HLA-DQ2 and HLA-DQ8 haplotype frequencies may be similar in patients with HFrEF and healthy individuals regardless of gender. In addition, similar results may be observed between ischaemic and non-ischaemic HFrEF patients in terms of HLA-DQ2 and HLA-DQ8 haplotype frequencies.

Despite increased CVD management in developed countries, age-independent HF incidences appear to be decreasing, but overall HF incidences have increased as a result of aging.¹⁶ The true prevalence of HF may be even higher because the current studies include previously diagnosed as well as newly diagnosed patients. In addition, even patients with mild symptoms are at risk for hospitalization and death.¹⁷ Therefore, it is important to diagnose HF and determine its etiology in the early period.

HF is caused by different aetiologies geographically, but coronary artery disease and hypertension are the two major risk factors in developed countries. As well as valvular heart disease, arrhythmias, congenital heart disease, pericardial, infiltrative (such as sarcoidosis and amyloidosis), and metabolic (such as endocrine disorders and Alzheimer's) diseases, there are also some specific causes of HF.¹⁸

HLA-DQ2 and HLA-DQ8 have been reported to be associated with ADs, particularly CD.¹⁹ However, the frequency and prevalence of HLA-DQ2 and HLA-DQ8 haplotypes exhibit differences between populations, which affects the diagnostic value of these genes.^{20,21} In pediatric patients with CD, the aortic strain and stiffness parameters were found to be similar to that of healthy individuals. Currently, there is no information regarding HLA-DQ2 and HLA-DQ8 positivity in this patient group.²² Ogata et al.²³ examined HLA positivity in patients with abdominal aortic aneurysm (AAA) and reported that especially HLA-DQA1 may play a role as a genetic risk factor for AAA. In a case report, a possible relationship was demonstrated between CD and HF, and the LVEF values of the patient improved after following a gluten-free diet.²⁴ However, severe anemia was initially observed in this case, which may have complicated the cause-effect relationship. Particularly in this abovementioned case, there may be certain changes in the carnitine metabolism secondary to CD-related malabsorption, and HF may have developed as a result of carnitine deficiency, as reported in a previous study.²⁵ In another study conducted with approximately 29,000 patients, the risk of idiopathic dilated HF was reported to potentially increase in patients with CD; however, it was reported as a statistically insignificant risk.²⁶

Although this study did not directly investigate the mechanisms by which HLA-DQ2 and HLA-DQ8 may influence cardiovascular outcomes, existing literature suggests potential pathways involving immune-mediated processes. HLA haplotypes, including DQ2 and DQ8, have been associated with autoimmune diseases, where they may modulate antigen presentation and T-cell activation.²⁷ Such mechanisms could theoretically contribute to chronic inflammation or autoimmune myocarditis, both of which are implicated in heart failure pathophysiology. For instance, studies have shown that HLA-DQ haplotypes are linked to altered cytokine profiles and increased levels of inflammatory markers, such as T cell stimulation and interleukin-6 (IL-6), which are known to exacerbate myocardial remodeling

and dysfunction.^{28,29} Furthermore, these haplotypes may predispose individuals to immune dysregulation, potentially triggering pathways that impair cardiac function. Future studies should explore these mechanisms through larger cohorts and experimental models to determine how HLA-DQ2 and HLA-DQ8 haplotypes may contribute to the development and progression of HFrEF. Investigating the role of these haplotypes in inflammatory and autoimmune processes could provide novel insights into personalized therapeutic strategies.

The current study found no significant differences in HLA-DQ2 or HLA-DQ8 positivity between healthy individuals and patients with HFrEF. Furthermore, HLA-DQ2 and HLA-DQ8 haplotype frequencies did not differ significantly between ischemic and nonischemic individuals with HFrEF. Based on these results, considering the characteristics of our study population, we can say that HLA haplotypes do not have a potential role in HFrEF patients, and in addition, HLA cannot be used alone as a sufficient marker for early detection of HFrEF. This study specifically focused on the HLA-DQ2 and HLA-DQ8 haplotypes due to their well-documented associations with immunological mechanisms and inflammatory responses, which are relevant to the pathophysiology of HFrEF. HLA-DQA1 or other alleles were not included in the analysis, as the primary aim was to explore the potential associations of these specific haplotypes with HFrEF. While this represents a limitation, it also underscores the need for future studies to expand the genetic scope and investigate additional alleles, including HLA-DQA1, to gain a more comprehensive understanding of the genetic basis of HFrEF.

First, one limitation of this study is its single-center design, which may limit the generalizability of our findings to broader populations. Additionally, the lack of functional data prevents us from directly linking the presence of HLA-DQ2 and HLA-DQ8 haplotypes to specific biological pathways involved in heart failure. Future research, particularly through large, multi-center studies, would provide a more comprehensive understanding of the genetic factors associated with heart failure. Furthermore, genome-wide association studies (GWAS) could offer valuable insights into other genetic variants that contribute to the development of heart failure, helping to validate and expand upon our findings.³⁰ In this study, no statistically significant differences were found in the association of HLA-DQ2 and HLA-DQ8 haplotypes with HFrEF. However, it is important to interpret these findings in light of the study's limited sample size, which may reduce the ability to detect subtle genetic variations. For instance, the prevalence of HLA-DQ2 was 16% in the HFrEF group and 20% in the control group, but this difference did not reach statistical significance ($p = 0.795$). This outcome may reflect a limitation of the sample size rather than a true absence of association. Larger, multicenter studies are warranted to explore these genetic relationships in greater detail. Second, although HLA-DQ2 and HLA-DQ8 haplotypes are strongly associated with CD, none of the participants underwent a biopsy for CD. However, previously diagnosed patients with CD were excluded from the current study. Although biopsy was not performed, the fact that HLA genotypes did not differ between the male and female participants or in the ischemic and nonischemic patients with HF strengthens the results of this study. Third, In our study, while making comparisons between the subgroups of ischemic and non-ischemic HFrEF groups, necessary analyses were performed to evaluate the effect of potential confounding factors. However, statistical adjustments such as complex regression analyses or multivariate methods were not performed in our study. This was a preference due to the limited sample size and our initial focus on the prevalence of genetic haplotypes. In our future studies, multivariate analyses with larger samples will allow for more detailed control of potential confounding factors. In addition, it should be noted that the statistical differences encountered in the subgroup analyses may have been affected by the limited sample size. Finally, cardiac magnetic resonance imaging was not performed in all the patients; however, imaging was performed in the patients who were clinically suspected of having infiltrative diseases.

Conclusion

The pathogenesis of HF is a complex clinical syndrome. HF is associated with various ADs. This is the first study to show that there is not always a potential role between HLA-DQ2 and HLA-DQ8 haplotypes and HFrEF. This study highlights the potential role of HLA-DQ2 and HLA-DQ8 haplotypes in HFrEF. However, several limitations must be considered when interpreting these findings. The relatively small sample size, consisting of 50 patients and 50 controls, reduces the statistical power of the study and may have influenced the robustness and generalizability of the results. HF is a complex

condition with heterogeneous etiologies, including autoimmune processes, which could potentially interact with genetic factors like HLA-DQ2 and HLA-DQ8. Future studies should aim to incorporate larger sample sizes, multi-center designs, and a more comprehensive evaluation of confounding factors to better understand the relationship between HLA haplotypes and heart failure. Moreover, exploring additional genetic markers and their interactions with environmental and clinical factors will help clarify the broader implications of these findings in both the diagnosis and management of heart failure. While our findings offer valuable insights into the immunological mechanisms underlying heart failure, further investigation is necessary to validate these results and determine their clinical relevance. Larger, more robust studies will provide the necessary data to better understand the genetic predisposition to heart failure and may guide future therapeutic approaches.

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