ORIGINAL ARTICLE

Genotypic and Allelic Association of HLA-DRB1 rs6457617 Gene Polymorphism in Rheumatoid Arthritis Patients with Concurrent Depression: A Case-Control Study

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ABSTRACT

Objective: To assess the genotypic and allelic association of the HLA-DRB1 rs6457617 gene polymorphism in rheumatoid arthritis patients with concomitant depression.

Study Design: Case-control study.

Place and Duration of Study: The study was conducted at the Multidisciplinary Laboratory, Department of Biochemistry, Islamic International Medical College Trust, Rawalpindi, in collaboration with Pakistan Railway Hospital, Rawalpindi, Pakistan, from October 2021 to September 2022.

Methods: A total of 264 individuals were recruited using non-probability convenience sampling. The study included 132 clinically diagnosed cases of rheumatoid arthritis and 132 age-, gender-, and ethnicity-matched controls. Among the cases, 66 individuals had rheumatoid arthritis with no symptoms of depression (Group 1), while 66 had rheumatoid arthritis with concurrent depression (Group 2). Depression severity was evaluated using validated psychometric tools (DSM-5 criteria for major depressive disorder). After obtaining approval from the Ethical Review Committee, venous blood samples were collected from the subjects. DNA extraction was performed using the Chelex method, followed by ARMS PCR using specific primers to assess genotypic and allelic frequencies from the collected samples.

Results: The genotypic frequencies of TT, TC, and CC genotypes in Group 1 were 30.3%, 48.5%, 21.2%, respectively. In Group 2, the corresponding frequencies were 22.7%, 53%, and 24.2%. The allelic frequencies of T and C genotypes were 54.5% and 45.5% in Group 1, compared to 49.2% and 50.8% in Group 2. Statistical analysis indicated a significant correlation between the *HLA-DRB1* TC genotype and cases of rheumatoid arthritis without depression, OR= 0.42 (0.21–0.86), *P*=0.02.

Conclusion: The TC genotype of HLA-DRB1 rs6457617 demonstrates a protective effect in patients with rheumatoid arthritis patients lacking concomitant depression. These findings suggest that targeted screening for this specific genetic variant could assist clinicians in earlier risk screening and the development of tailored therapy. Further large-scale, multi-center studies are recommended to validate these results.

Keywords: *Alleles, Arthritis Rheumatoid, Genetic, HLA-DRB1 Chains, Polymerase Chain Reaction, Polymorphism.*

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Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease that manifests as inflammatory polyarthritis with varying degrees of physical dysfunction, resulting in significant physical impairment and a decline in the quality of life.[1-3] Depression is the most frequent mood disorder worldwide, and one of the most prevalent comorbidities associated with RA.[4] Several factors, including biological, environmental, and

psychological, play a role in the development and progression of depression. The major symptoms include constant melancholy, feelings of guilt or worthlessness, hopelessness, loss of interest, changes in sleep and appetite, lack of energy, poor concentration, and/or active or passive suicidal ideation.[5] According to the World Health Organization (WHO) reported data, the prevalence of RA ranges from 0.3 to 1%, and that of depression concomitant with RA is 9.5% among females.[6,7]

The primary association between RA and depression is the activation of inflammatory pathways influenced by shared risk factors, such as biological, psychological, and environmental elements.[8] In RA, predisposed genes undergo genomic alteration due to interaction with environmental triggers.[1] The peptide-binding groove in the DR chain of the highly polymorphic MHC Class II, DR Beta 1 (HLA-DRB1) gene contains a common sequence of amino acids speculated to be involved in RA pathophysiology.[1] It accomplishes this by interfering with the T-cell receptors or by exposing the self-reactive T-cells to an exogenous microbial peptide or auto-antigenic endogenous peptides.[9] The correlation between particular HLA alleles and the development of RA varies amongst various human population subgroups, geographic and ethnic regions.[10] On the basis of this variation, the current study's objective is to assess the association between the HLA-DRB1 gene's single-nucleotide polymorphism (rs6457617) and susceptibility and protection to rheumatoid arthritis with or without depression.

Methods

This case-control study was carried out over a one-year period from October 2021 to September 2022. It was conducted in collaboration with the Pakistan Railway Hospital, Rawalpindi, at the Multidisciplinary Laboratory in the Department of Biochemistry, Islamic International Medical College (IIMC) Trust, Rawalpindi, Pakistan. The Institutional Review Board (IRB) approval was obtained from the Institutional Review Board of Islamic International Medical College (IIMC) Trust, Riphah International University, Islamabad, Pakistan, vide letter no: Riphah/IIMC/IRC/21/67, dated 12th October 2021.

Data collection took place at The Pain Clinic in Rawalpindi and the General Medicine and Psychiatry Units of the Pakistan Railway Hospital in Rawalpindi. Laboratory genetic analyses were completed at the Multidisciplinary Laboratory, Department of Biochemistry, IIMC Trust, Rawalpindi.

A total of 264 participants were recruited in the study using non-probability convenience sampling. The study population comprised 132 cases and 132 age-, gender-, and ethnicity-matched controls. The cases were subdivided into two groups: Group 1 had 66 patients with RA but without depression, while Group 2 had 66 patients with RA and concurrent depression. (Figure 1).

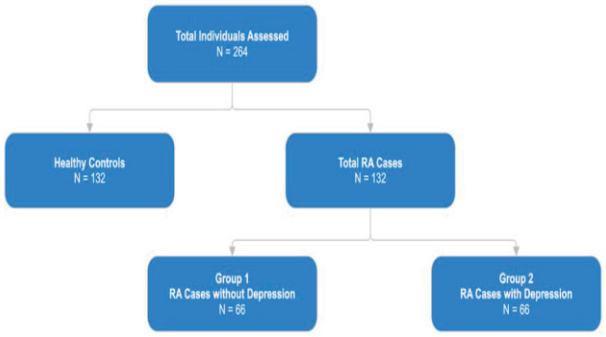

Fig.1: Flow Diagram of Participants Recruited for the Study

Inclusion and Exclusion Criteria

RA patients recruited for both groups 1 and 2 were diagnosed according to the American College of Rheumatology (ACR) 2010 updated criteria.[11] Additional inclusions for Group 2 were based on the concurrent diagnosis of depression according to the criteria outlined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[12] To minimize confounding factors, our study excluded patients with other autoimmune, psychiatric, or neurological conditions. Healthy controls were individuals with no medical history of RA, depression, or other chronic inflammatory conditions, matched appropriately with the cases.

Operational Definitions of Variables

To ensure transparency and reproducibility, the study's clinical, demographic, and genetic parameters were classified into quantitative and qualitative variables as follows:

Age was measured as a continuous numerical variable in years at the time of enrollment, utilized for descriptive baseline data and for group matching. Disease duration was recorded as a continuous numerical variable representing the length of time (in years) since the participant received a formal

clinical diagnosis of Rheumatoid Arthritis (RA.

For qualitative (categorical) variables, study group (phenotype allocation) was a nominal variable with three distinct categories: (1) Healthy Controls; (2) RA patients without concurrent depression (Group 1/RAC); and (3) RA patients with concurrent clinical depression (Group 2/ RAD).

HLA-DRB1 rs6457617 Genotype was a nominal genetic variable representing the inherited alleles at the specific locus of interest, categorized into three distinct genotypes: Homozygous TT, Heterozygous TC, and Homozygous CC. A dichotomous genetic variable tracking individual allele counts (T allele vs. C allele) within the cohorts. A dichotomous nominal variable (Male vs. Female) utilized for background descriptive tracking and cohort matching. A categorical nominal variable reflecting the cultural-geographic background of participants (e.g., Punjabi, Pathan, Kashmiri) used to control for population stratification.

Inflammatory Markers (ESR and CRP Status) were categorical nominal variables grouped qualitatively as either "Positive" or "Negative" based on clinical laboratory reference ranges to analyze phenotypic associations with the HLA-DRB1 polymorphism.

Serological Status (RF and ACPA Status) was taken as dichotomous qualitative classifications indicating whether patients were seropositive or seronegative according to standard clinical laboratory cut-offs.

Participants were recruited from the Pain Clinic, Rawalpindi, and the General Medicine and Psychiatry Units of the Pakistan Railway Hospital, Rawalpindi. A structured questionnaire approved by the IRB was used to collect demographic information and clinical history. Written informed consent was obtained from all participants prior to their recruitment in the study.

Under aseptic conditions, three milliliters of venous blood were drawn from each participant and placed in EDTA-containing vials. The samples were transported to the Multidisciplinary Laboratory at IIMC and stored at -70°C until further analysis.

Genomic DNA was extracted from 200L whole blood using the Chelex-100 resin technique.[13] Samples were lysed with distilled water and centrifuged for 2 minutes at 5000 rpm, before being washed repeatedly to obtain white blood cell pellets. The pellets were resuspended in 200L of 7% Chelex solution, heated at 95 °C for 20 minutes, and centrifuged at 1300 rpm for 2 minutes. The supernatant containing DNA was collected and stored at -70°C until Polymerase Chain Reaction (PCR) amplification.

The HLA-DRB1 rs6457617 polymorphism was detected using Amplification Refractory Mutation System (ARMS) PCR with specific primers supplied by Macrogen Inc. (Korea).[14] ARMS PCR reactions were performed in 25L total volume containing 8.5L PCR water, 12.5L ThermoScientific Master Mix, 1L primer mix, and 3L template DNA.

PCR products were analyzed on 2% agarose gel with ethidium bromide using a 100 bp DNA ladder. Electrophoresis was performed for 45 minutes at 100 volts, and gels were visualized under UV transillumination. Genotypes (TT, TC, CC) were determined from specific banding patterns and documented (Figure 2).

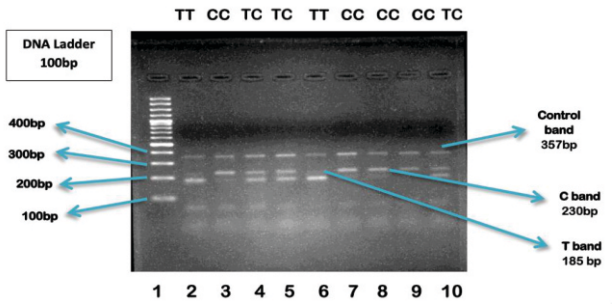

Fig.2: HLA-DRB1 gene polymorphism (rs6457617) amplified PCR products with a 100 bp DNA marker shown in an electrophoretogram on a 2% agarose gel

For quality control of the genetic data, stringent thresholds were applied to ensure the fidelity of the ARMS PCR assays. The genotype call rate for the HLA-DRB1 rs6457617 polymorphism was maintained at 100%, with all 264 recruited samples yielding unambiguous banding patterns during agarose gel electrophoresis and UV transillumination.

Statistical analysis was carried out using SPSS version 21.0 on Microsoft Windows. Both cases and controls were tested for the Hardy-Weinberg equilibrium. The genotypic and allelic frequencies were calculated and compared using Fisher's exact test or the chi-squared test, as appropriate. VassarStats software was used to calculate the odds ratio (OR) and 95% confidence interval (CI). A *P*-value of ≤ 0.05 would correspond to a statistically significant difference.

Because this research was conducted as an observational candidate-gene association pilot, our analysis relied on bivariate odds ratios (ORs), 95% confidence intervals (CIs), and Chi-square tests to evaluate raw allelic and genotypic frequencies across categorical phenotypic groups. Multivariable regression modeling to adjust for dynamic clinical variables was not performed due to power constraints inherent in our subgroup sample sizes (N=66 per RA subgroup).

Results

The genotypic and allelic distribution of HLA-DRB1 rs6457617 polymorphism is presented in Table 1. In Group 1 (RA without depression), the frequencies of TT, TC, and CC genotypes were 30.3%, 48.5%, and 21.2%, respectively. Among Group 2 (RA with depression), the corresponding frequencies were 22.7%, 53%, and 24.2%. In the control group, the frequencies of the genotypes TT, TC, and CC were 18.9%, 72%, and 9.1%, respectively. Across all study groups, the heterozygous TC genotype was the most prevalent.

Allelic frequencies of the T and C alleles were 54.5% and 45.5% in Group 1, and 49.2% and 50.8% in Group 2. The corresponding T and C allele frequencies in the control group were 54.9% and 45.1%, respectively. This shows that the T allele is the major/wild allele and the C allele is the minor/variant allele in our study population.

For the HLA-DRB1 rs6457617 polymorphism, both the case and control groups were in Hardy-Weinberg equilibrium, confirming that our genetic analysis was not affected by deviations from expected genotypic frequencies.

Table 1: Association between Gene Polymorphism of *HLA–DRB1* and Rheumatoid Arthritis Cases and Controls (N=132)

Parameter	Cases (N = 132)		Controls (N = 132)	Odds Ratio (95% CI) *P-Value*
	Group 1 (N=66)	Group 2 (N=66)		
Genotypes				
				Ref 1
TT	20 (30.3%)	15 (22.7%)	25 (18.9%)	0.68 (0.30 – 1.56) 0.37[a]
				0.66 (0.25 – 1.75) 0.39[a]
				0.42 (0.21– 0.86) 0.02[b]
TC	32 (48.5%)	35 (53.0%)	95 (72.0%)	1.46 (0.55 – 3.84) 0.45[b]
				0.61 (0.29 – 1.30) 0.20[c]
CC	14 (21.2%)	16 (24.2%)	12 (9.1%)	2.22 (0.83 - 5.95) 1.11[c]
Alleles				
T	72 (54.5%)	65 (49.2%)	145 (54.9%)	Ref 1
				0.81 (0.49 – 1.31) 0.39[a]
C	60 (45.5%)	67 (50.8%)	119 (45.1%)	1.01 (0.67 – 1.54) 0.92[b]
				1.26 (0.83 – 1.91) 0.29[c]

Group 1: Rheumatoid arthritis but no depression, Group 2: Rheumatoid arthritis along with depression
a: Genotypic / Allelic association of Groups 1 and 2, b: Genotypic/Allelic association of Group 1 and Controls, c: Genotypic / Allelic association of Group 2 and Controls

Our results show that TT, being the homozygous dominant, is the wild genotype. TC is the heterozygous genotype, whereas CC, the homozygous recessive, is the mutant genotype. A significant association was observed between the HLA-DRB1 TC genotype and RA cases without depression (Group 1) compared to controls (OR = 0.42, 95% CI: 0.21-0.86, *P* = 0.02). This odds ratio < 1.0 indicates a protective effect of the TC genotype against RA in the absence of depression.[15] No significant associations were found between other genotypes and disease susceptibility, nor between any genotype and RA patients with concurrent depression (Group 2). Allelic comparison of the groups suggests that the heterozygous genotype likely imparts the protective effect, rather than individual alleles.

Discussion

The HLA-DRB1 gene is the most commonly implicated gene in the pathogenesis of RA. This gene displays a high degree of polymorphism, which makes it an important area of research concerning RA. Several studies have been conducted globally to establish the link between HLA-DRB1 rs6457617 and RA, with a focus on disease susceptibility and protective effects. The single nucleotide polymorphism (SNP) that has been worked on in our study has previously been studied in various countries, but only in the context of RA alone, not RA with concurrent depression. These studies were conducted on the American, British, Chinese, Tunisian, Korean and Indian populations.[14-18]

Two genome-wide association studies (GWAS) have been performed in Pakistan, which have revealed the sharing of RA risk loci (HLA-DRB1 rs660895) among different population groups, in which 31 different SNPs were analyzed, including rs660895 and rs6910071. However, no study has been conducted in Pakistan to determine the association of rs6457617 with Rheumatoid Arthritis.[18,19]

In the US, various SNPs were analyzed, amongst which the rs6457617 has been found to be significantly associated with anti-citrullinated antibody (ACPA) positive RA, in terms of increased disease susceptibility, a finding that is incongruent with our results.[16] In the Han Chinese population, the homozygous CC variant genotype carried a lower risk for RA, compared to the homozygous TT wild genotype, whereas the heterozygous TC carriers were at a greater risk compared to CC.[16]

This is incongruent with our findings, since in our population the wild-type is TT, the variant is CC, and the heterozygous is C, which do not confer a risk of RA susceptibility.

In the Korean population, the TT genotype showed a 4.77-fold increase in risk, versus the CC genotype.[18] Certain GWAS conducted in the Spanish and Indian populations also found a significant association between RA and rs6457617; however, this was not explored further.[20,21] The Tunisian population showed a significant association between the wild type genotype, TT, and RA susceptibility, compared to the CC and TC genotypes.[15]

Our results are generally consistent with the Indian population. A study conducted in Northern India revealed that rs6457617 was associated with a decreased susceptibility to RA.[14] Similarly, in our study, the heterozygous TC genotype did not confer an increase in the risk or severity of RA in either subgroup (Groups 1 and 2). Instead, it was associated with a protective effect, demonstrating a 0.42-fold decreased risk in patients who had RA without depression (Group 1).

Allele analysis in our study population was consistent with findings from Korean and Chinese studies, in which the C allele was the minor allele.[17,18] In contrast, the British WTCCC study reported the T allele as the minor and risk allele.[18] No significant association was found in our study population between the T and C alleles, similar to the results from the Tunisian population.[15] These inter-population differences in allelic frequencies and their associations with RA point toward the possible population-specific risk/protective effect of the rs6457617 locus, reflecting genetic heterogeneity across different ethnic groups.

Using the Hardy-Weinberg equation, the Hardy-Weinberg equilibrium was tested for both case and control groups. The SNP rs6457617 did not deviate from equilibrium in either group, indicating that the genotyping data were reliable. The findings of this study are consistent with prior studies on the rs6457617 polymorphism.

The HLA-DRB1 region directly dictates the structural architecture of the peptide-binding groove on MHC Class II molecules, orchestrating antigen

presentation and peripheral cytokine cascades. Because comorbid depression in chronic autoimmune diseases like RA is heavily driven by neuroinflammatory pathways secondary to peripheral cytokine translocation across the blood-brain barrier, it is highly plausible that specific variants, such as the rs6457617 TC genotype, modulate baseline systemic inflammatory thresholds. Consequently, this polymorphism may serve as a shared genetic bridge that determines both the severity of articular inflammation and susceptibility to neuroinflammation-mediated mood disorders.

Ultimately, large-scale multicenter replication studies and functional genomic analyses across diverse cohorts will be essential to validate these findings, firmly establishing whether the rs6457617 polymorphism can serve as a robust, clinically actionable predictive biomarker for psychiatric vulnerability in autoimmune patient populations.

Several limitations must be acknowledged when interpreting the findings of this study.

First, the use of a non-probability convenience sampling technique at a single regional medical center in Pakistan introduces a risk of selection bias and constrains the generalizability of our findings to ethnically and geographically diverse populations.

Second, while the overall sample size (N = 264) was sufficient for broad case-control comparisons, the resulting sub-allocations into specific clinical arms (66 RA cases with depression and 66 RA cases without depression) reduced the statistical power needed to detect minor, subgroup-specific genetic variants.

Third, the retrospective case-control design inherently limits our ability to establish direct causal relationships or temporal pathways between the HLA-DRB1 rs6457617 polymorphism and the onset of psychiatric symptoms.

Fourth, despite adjusting for core demographic variables, potential residual confounding may remain due to unmeasured clinical factors, such as longitudinal disease activity index (DAS28) scores and precise histories of corticosteroid or immunomodulatory therapy, and systemic inflammation and mood trajectories. Future studies with larger, prospectively tracked cohorts are necessary to perform multivariable logistic regression modeling to adjust for these dynamic clinical covariates.

Finally, our focus on a single candidate single-nucleotide polymorphism (SNP) inherently overlooks the polygenic architecture and epistatic networks that typically drive complex autoimmune and neuropsychiatric phenotypes.

Conclusion

In conclusion, our study identifies HLA-DRB1 rs6457617 as a protective gene locus against RA without depression, while no such association was observed in RA with concurrent depression. Further studies with larger Pakistani cohorts are necessary, given the genetic heterogeneity, the high prevalence of depression, and the highly polymorphic nature of the HLA-DRB1 gene. Replication analyses of this gene and the other GWAS-associated risk SNPs in RA will help establish risk profiles specific to our population and its diversity, which might be an important variable in future genetic polymorphism studies. Ultimately, gene association studies such as ours can inform earlier risk screening and the development of tailored therapy through gene expression profiling.

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Conflict of Interest: The authors declare no conflict of interest

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Author Contributions

IA: Conception, design of the work, and approval for final submission
AR: Revising, editing, supervising for intellectual content, and approval for final submission
MA: Data acquisition, curation, statistical analysis, and approval for final submission
SN: Manuscript writing for methodology design, investigation, and approval for final submission
TSH: Validation of data, interpretation, write-up of results, and approval for final submission
AA: Writing the original draft, proofreading, and approval for final submission
IA is the nominated guarantor and takes full responsibility for the overall content and integrity of the work