EUROPEAN ACADEMIC RESEARCH
Vol. XIII, Issue 8/ November 2025

Impact Factor: 3.4546 (UIF)
DRJI Value: 5.9 (B+)

ISSN 2286-4822
www.euacademic.org

Genetic Basis and Serum Biomarkers Association in the Progression of Rheumatoid Arthritis among Sudanese Patients

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Abstract

Background: *Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by persistent synovial inflammation, progressive joint destruction, and diverse extraarticular manifestations. Genetic factors, notably HLA Class II alleles such as HLA-DRB1 and HLA-DQB1, play a crucial role in RA susceptibility and severity. Emerging serum biomarkers—including angiotensinogen (AGT), serum amyloid A4 (SAA4), vitamin D-binding protein (VDBP), and retinol-binding protein 4 (RBP4) have recently shown promise in enhancing RA diagnosis and prognostication.*

Objective: *This study aimed to investigate the correlation between HLA Class II genotyping (specifically HLA-DRB1 and HLA-DQB1) and the serum levels of AGT, SAA4, VDBP, and RBP4 in Sudanese RA patients, with the goal of identifying predictive markers of disease progression.*

Methods: *In this cross-sectional study, 200 RA patients and 200 age- and sex-matched healthy controls were recruited. Serum biomarker levels were quantified using high-performance liquid chromatography (HPLC) coupled with liquid chromatography-mass spectrometry (LC-MS/MS). HLA typing for DRB1 and DQB1 alleles was performed via a PCR-based sequence-specific oligonucleotide probe (SSOP) method. Statistical analyses, including logistic regression and correlation analysis, were conducted to evaluate associations between genetic markers, serum biomarker levels, and the Disease Activity Score 28 (DAS28).*

Results: *Analysis revealed that elevated AGT levels were significantly associated with HLA-DRB1 positivity ($r = 0.32$, $P = 0.003$) and correlated with higher DAS28 scores, indicating more active disease. Additionally, SAA4 and RBP4 demonstrated strong correlations with RA progression. These findings underscore the potential of combining genetic and serum biomarker profiling to enhance early RA diagnosis and risk stratification.*

Conclusion: *Integrating HLA Class II genotyping with a panel of novel serum biomarkers offers a promising approach for improving the diagnostic accuracy and prognostic evaluation of RA, particularly in resource-limited settings such as Sudan. This comprehensive strategy may facilitate personalized treatment approaches and improve overall patient outcomes.*

Keywords: Rheumatoid arthritis, HLA-DRB1, HLA-DQB1, angiotensinogen, serum amyloid A4, vitamin D-binding protein, retinol-binding protein 4, Sudan

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1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, multifactorial autoimmune disorder characterized by persistent synovial inflammation, progressive joint destruction, and a spectrum of extra-articular manifestations that significantly impair patient quality of life (1,2). The disease arises from a complex interplay between genetic predisposition, environmental exposures, and aberrant immune responses. Although the precise etiology of RA remains incompletely understood, advances in immunogenetics have identified key genetic factors that predispose individuals to disease onset and influence their clinical course. Among the genetic risk factors, the strongest associations have consistently been mapped to the human leukocyte antigen (HLA) Class II region. Specific alleles of HLA-DRB1 and HLA-DQB1 are crucial in the presentation of antigenic peptides to T lymphocytes, thereby triggering autoreactive immune responses central to RA pathogenesis (3–5). The "shared epitope" hypothesis, first proposed in the late 1980s, suggests that a common amino acid motif within the third hypervariable region of the HLA-DRB1 molecule predisposes carriers to RA and is associated with more severe disease outcomes (3,4,36). However, genetic predisposition alone is insufficient to explain the heterogeneity observed in RA. Environmental factors such as cigarette smoking, microbial infections, and other yet unidentified triggers interact with these genetic elements to further modulate disease risk (10,11). In recent years, research has expanded beyond genetic susceptibility to explore the utility of serum biomarkers in enhancing the diagnosis and prognosis of RA. Novel biomarkers such as angiotensinogen (AGT), serum amyloid A4 (SAA4), vitamin D-binding protein (VDBP), and retinol-binding protein 4 (RBP4) have emerged as promising candidates that may provide additional insights into disease activity and progression (6,7,12). AGT, a precursor molecule in the renin-angiotensin system, has been implicated in vascular inflammation and immune modulation, suggesting its involvement in the pathological processes underlying RA beyond its classical role in blood pressure regulation (8,19). SAA4, an acute-phase reactant, can amplify inflammatory cytokine cascades, thereby potentially exacerbating synovial inflammation (9,25). Meanwhile, VDBP and RBP4, which are primarily involved in vitamin D transport and metabolic regulation respectively, may also influence immune responses and inflammatory pathways, contributing to disease severity (10,11). The integration of genetic markers with serum biomarker profiling holds promise for improving diagnostic accuracy, particularly in cases where traditional serological tests—such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide (ACCP)—are inconclusive (15,24). By comparing these novel biomarkers with conventional markers and correlating them with the Disease Activity Score 28 (DAS28), clinicians may gain a more comprehensive understanding of disease progression, facilitating early intervention and personalized treatment strategies (20,22,26). This study aims to elucidate the relationship between HLA Class II genotypes—specifically HLA-DRB1 and HLA-DQB1—and serum levels of AGT, SAA4, VDBP, and RBP4 in a cohort of Sudanese RA patients. Given the unique genetic background and environmental exposures in Sudan, there is a critical need to validate these biomarkers in this population. By integrating genetic and serum biomarker profiling, our approach seeks not only to improve early diagnosis and risk stratification

but also to tailor therapeutic interventions in resource-limited settings where RA remains underdiagnosed and undertreated (29,30).

2. MATERIALS AND METHODS

A descriptive cross-sectional study was conducted between 2022 and 2024 in Khartoum, Sudan, involving 200 patients diagnosed with rheumatoid arthritis (RA) according to the 2010 ACR/EULAR criteria (15) and 200 age- and sex-matched healthy controls. Ethical approval was obtained from Karary University and the Sudan Ministry of Health Research Ethics Committee, and informed consent was secured from all participants. Peripheral blood samples were collected from each subject; genomic DNA was extracted using standard protocols, and HLA-DRB1 and HLA-DQB1 alleles were determined via polymerase chain reaction (PCR)-based sequence-specific oligonucleotide probe (SSOP) methods (13). In parallel, serum levels of angiotensinogen (AGT), serum amyloid A4 (SAA4), vitamin D-binding protein (VDBP), and retinol-binding protein 4 (RBP4) were quantified using high-performance liquid chromatography (HPLC) coupled with liquid chromatography-mass spectrometry (LC-MS/MS) (14). Conventional serological markers were also assessed, with rheumatoid factor (RF) measured by nephelometry and anti-cyclic citrullinated peptide (ACCP) antibodies determined via enzyme-linked immunosorbent assay (ELISA). RA disease activity was evaluated using the Disease Activity Score 28 (DAS28) (15). Data were analyzed using SPSS version 26 (IBM Inc.). Normality was assessed by the Shapiro-Wilks test and histograms; normally distributed data were expressed as mean ± standard deviation (SD) and compared using the unpaired Student's t-test, whereas non-parametric data were presented as median with interquartile range (IQR) and analyzed using the Mann-Whitney test. Categorical variables were expressed as frequencies and percentages, and group comparisons were performed using the Chi-square or Fisher's exact test as appropriate. Associations between continuous variables were evaluated using Pearson or Spearman correlation analyses, and univariate and multivariate logistic regression models were applied to identify independent predictors of RA. The diagnostic performance of serum biomarkers was further assessed using Receiver Operating Characteristic (ROC) curve analysis, with the area under the curve (AUC) serving as the measure of overall test performance; a two-tailed P value <0.05 was considered statistically significant.

3. RESULTS

A total of 200 rheumatoid arthritis (RA) patients (mean age 50.9 ± 17.07 years, median 51; 102 males [51%] and 98 females [49%]) and 200 age- and sex-matched healthy controls were enrolled.

Table 1. Demographic and Clinical Characteristics

Parameter	RA Patients (n=200)	Controls (n=200)
Age (years)	Mean: 50.9 ± 17.07 Range: 18–79 Median: 51	Age-matched distribution
Sex	Male: 102 (51%) Female: 98 (49%)	Approximately 50% male/female
DAS28 (RA only)	Mean: 3.9 ± 1.47 Range: 1.53–6.43 Median: 3.97	N/A

Purpose: Provides an overview of the study population and highlights demographic differences between RA patients and controls.

Table 2. Serological and HLA Typing Results

Marker	RA Patients (n=200)	Controls (n=200)*
RF Test	Positive: 145 (72.5%) Negative: 55 (27.5%)	Significantly lower positivity
ACCP Test	Positive: 140 (70%) Negative: 60 (30%)	Significantly lower positivity
HLA-DRB1 Typing	Positive: 130 (65%) Negative: 70 (35%)	Significantly lower prevalence
HLA-DQB1 Typing	Positive: 115 (57.5%) Negative: 85 (42.5%)	Significantly lower prevalence

Purpose: Demonstrates the association of conventional serological markers and genetic predisposition with RA.

Table 3. Serum Biomarker Levels

Biomarker	RA Patients	Controls	P-value
AGT (ng/mL)	Mean: 3.09 ± 1.19 Median: 3.1 Range: 0.51–4.96	Mean: 2.59 ± 1.24 Median: 2.5 Range: 0.55–4.99	0.004*
SAA4 (ng/mL)	Mean: 31.04 ± 11.17 Median: 31 Range: 10.21–49.41	Mean: 28.50 ± 10.50 Median: 28 Range: 9.50–48.00	0.010*
VDBP (ng/mL)	Mean: 62.19 ± 24.70 Median: 63.5 Range: 20.1–99.71	Mean: 58.00 ± 23.00 Median: 59 Range: 19.0–95.00	0.015*
RBP4 (ng/mL)	Mean: 15.42 ± 5.18 Median: 16 Range: 5.29–24.84	Mean: 13.90 ± 5.00 Median: 13.5 Range: 5.18–23.50	0.020*

*Significant at $P < 0.05$.

Purpose: Highlights the significant elevation of novel serum biomarkers in RA patients compared to controls.

Additional analyses (including laboratory technique comparisons, DAS28 scores, correlations, and logistic regression analyses) were performed in our extended dataset. However, for this paper, we focus on the three selected tables above to elucidate the key findings.

4. DISCUSSION

Our study confirms a complex interplay between genetic predisposition and serum biomarker expression in the progression of rheumatoid arthritis (RA) among Sudanese patients. Regarding the demographic and clinical characteristics, RA patients had a mean age of 50.9 ± 17.07 years with a nearly equal gender distribution (51% male, 49% female) (Table 1). This finding is particularly notable because global RA data typically demonstrate a female predominance. The near-equal distribution in our cohort suggests

that regional environmental exposures, occupational factors—such as the higher prevalence of manual labor—and sociocultural influences may significantly modulate RA susceptibility in Sudan. Such factors could alter immune responses or trigger inflammatory pathways differently than observed in other populations, emphasizing the need for locally tailored diagnostic criteria and management strategies (2,11). In our serological and HLA typing analyses (Table 2), conventional markers such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide (ACCP) antibodies were positive in 72.5% and 70% of RA patients, respectively. In parallel, HLA-DRB1 and HLA-DQB1 alleles were significantly more prevalent in the RA group compared to controls. These results lend strong support to the "shared epitope" hypothesis, which posits that specific HLA-DRB1 sequences facilitate the presentation of citrullinated peptides to autoreactive T cells, thereby driving the autoimmune cascade characteristic of RA (3,4,36). Moreover, logistic regression analyses identified these alleles as independent predictors of RA, reinforcing their value in risk stratification and indicating that genetic screening could play a vital role in early identification of at-risk individuals (24,27). Our evaluation of serum biomarker levels (Table 3) further illuminates the molecular underpinnings of RA in this population. All four novel biomarkers angiotensinogen (AGT), serum amyloid A4 (SAA4), vitamin D-binding protein (VDBP), and retinol-binding protein 4 (RBP4)—were significantly elevated in RA patients compared to controls. Notably, AGT demonstrated the most marked elevation ($P = 0.004$) and achieved an area under the curve (AUC) of 0.76 in ROC analysis, highlighting its strong diagnostic potential. This finding supports the hypothesis that the renin-angiotensin system, with AGT as a key component, is intricately involved in inflammatory processes and synovial remodeling in RA (8,19). In addition, the increased levels of SAA4 and RBP4 suggest that both inflammatory and metabolic dysregulations are integral to RA pathogenesis in this cohort (9,10,25). Although vitamin D-binding protein (VDBP) was also elevated, its lower diagnostic performance implies that it may be most useful when combined with other biomarkers in a composite panel rather than as a stand-alone indicator (12). The integration of HLA Class II genotyping with serum biomarker profiling offers a multifaceted diagnostic approach. The combination of genetic markers (HLA-DRB1 and HLA-DQB1) with a panel of serum biomarkers (especially AGT, SAA4, and RBP4) enhances diagnostic accuracy and provides valuable prognostic information. This integrated strategy is particularly advantageous in cases where conventional markers (RF and ACCP) yield inconclusive results, and it is especially promising in resource-limited settings like Sudan, where access to advanced imaging modalities is often constrained (14,16,20). Furthermore, the observed correlations between serum biomarker levels and disease activity—as measured by the Disease Activity Score 28 (DAS28)—suggest that these biomarkers can serve not only as diagnostic tools but also as indicators for monitoring disease progression and therapeutic response. The high internal consistency among the biomarkers, evidenced by a Cronbach's alpha of 0.912, underlines the reliability of this multi-marker panel and supports its potential for routine clinical application (15,33,56). Future research should focus on longitudinal studies to validate the prognostic utility of these biomarkers over time and to explore their mechanistic roles in RA pathogenesis. Expanding the study cohort to include a more diverse population would help refine diagnostic thresholds and enhance the generalizability of

our findings (24,27,30,34,40,46,52,57,65,66). Ultimately, the integration of genetic and serum biomarker profiling may pave the way for personalized treatment strategies that improve patient outcomes by allowing clinicians to tailor interventions based on an individual's molecular profile.

5. CONCLUSION

This study demonstrates that RA in Sudanese patients is strongly associated with HLA-DRB1 and HLA-DQB1 alleles and that serum biomarkers—particularly AGT, SAA4, and RBP4—are significantly elevated and correlate with disease activity. Integrating HLA Class II genotyping with a multi-analyte biomarker panel offers a promising strategy for improving early diagnosis, risk stratification, and personalized management of RA, especially in resource-limited settings.

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