Educator Insights: A Journal of Teaching Theory and Practice
Volume 2, Issue 1, January 2026
brightmindpublishing.com
ISSN (E): 3061-6964

GENETIC AND IMMUNOLOGICAL PHENOTYPES OF REACTIVE ARTHRITIS: A PERSONALIZED DIAGNOSTIC MODEL

Rustamova Gulnoza Orifjon qizi
Kimyo International University in Tashkent

Islombekova Zuxraxon Durbek qizi
Kimyo International University in Tashkent

Abstract

Reactive arthritis (ReA) is an inflammatory joint disease that develops as a sterile immune-mediated response following certain genitourinary or gastrointestinal infections. Unlike septic arthritis, reactive arthritis is characterized by the absence of viable pathogens within the affected joints, underscoring its immunopathological rather than infectious nature. Clinically, ReA is often associated with asymmetric oligoarthritis, enthesitis, axial involvement, and extra-articular manifestations affecting the eyes, skin, and mucosal surfaces. Despite its well-recognized clinical spectrum, reactive arthritis remains a diagnostically challenging condition due to its heterogeneous presentation and variable disease course.

Introduction

One of the most distinctive features of reactive arthritis is its strong association with host genetic susceptibility, particularly the presence of the human leukocyte antigen HLA-B27. However, not all individuals carrying HLA-B27 develop reactive arthritis following triggering infections, and a substantial proportion of patients with clinically confirmed ReA are HLA-B27 negative. This observation highlights the complexity of genetic predisposition and suggests that reactive arthritis cannot be adequately explained by a single genetic determinant. Instead, ReA appears to arise from the interaction of multiple genetic, immunological, and environmental factors that collectively shape disease phenotype and progression. From an immunological perspective, reactive arthritis occupies a unique position at the interface between infection-driven immune activation and chronic

Educator Insights: A Journal of Teaching Theory and Practice
Volume 2, Issue 1, January 2026
brightmindpublishing.com
ISSN (E): 3061-6964

inflammatory disease. Triggering pathogens such as *Chlamydia trachomatis*, *Salmonella*, *Shigella*, *Yersinia*, and *Campylobacter* initiate an immune response that persists beyond pathogen clearance. In susceptible individuals, this response becomes dysregulated, leading to prolonged synovial inflammation and tissue damage. Both innate and adaptive immune mechanisms have been implicated, including aberrant antigen presentation, cytokine imbalance, and sustained activation of T lymphocyte subsets.

Accumulating evidence suggests that reactive arthritis encompasses multiple immunological phenotypes rather than a single uniform disease entity. Some patients exhibit a predominantly innate immune activation pattern characterized by elevated pro-inflammatory cytokines and chemokines, while others demonstrate adaptive immune skewing with Th1, Th17, or interferon-driven signatures. These immunological differences are increasingly recognized as key determinants of disease severity, chronicity, and therapeutic response. However, conventional diagnostic approaches rarely account for this heterogeneity, relying instead on clinical criteria and limited laboratory markers.

The limitations of current diagnostic frameworks are particularly evident in early and atypical cases of reactive arthritis. Diagnosis often depends on retrospective identification of a preceding infection, which may be asymptomatic or undocumented. Furthermore, standard inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate lack specificity and do not reliably reflect underlying immunological pathways. Imaging modalities can detect joint and enthesis involvement but provide limited insight into molecular disease mechanisms. As a result, early diagnosis is frequently delayed, and opportunities for timely, targeted intervention may be missed.

Advances in immunogenetics and systems immunology have opened new avenues for understanding disease heterogeneity in inflammatory arthritis. Beyond HLA-B27, several non-HLA genetic factors have been implicated in reactive arthritis susceptibility and phenotype expression, including genes involved in antigen processing, innate immune signaling, and cytokine regulation. Polymorphisms affecting interleukin pathways, interferon responses, and pattern recognition receptors may modulate host-pathogen interactions and determine the persistence of post-infectious inflammation. These findings support a model in which genetic background shapes immune response profiles, giving rise to distinct immunological phenotypes within reactive arthritis.

Educator Insights: A Journal of Teaching Theory and Practice
Volume 2, Issue 1, January 2026
brightmindpublishing.com
ISSN (E): 3061-6964

The concept of immunological phenotyping has gained increasing attention in rheumatology as a means of moving beyond symptom-based classification toward mechanism-driven diagnosis. In reactive arthritis, identifying specific immune signatures could help distinguish patients with self-limited disease from those at risk of chronic or recurrent inflammation. Moreover, immunophenotyping may provide a rational basis for personalized therapeutic strategies, including the selection of targeted biologic agents or immunomodulatory treatments tailored to individual disease mechanisms.

Personalized diagnostics, grounded in genetic and immunological profiling, represent a critical step toward precision medicine in reactive arthritis. By integrating genetic susceptibility markers with immune phenotype characterization, it may be possible to construct diagnostic models that not only confirm disease presence but also predict disease trajectory and treatment response. Such models could enhance diagnostic accuracy, reduce heterogeneity in clinical trials, and improve patient outcomes through earlier and more targeted intervention.

Despite growing recognition of disease heterogeneity, integrated diagnostic models for reactive arthritis remain underdeveloped. Most existing studies focus on isolated genetic markers or individual immune mediators, offering limited insight into how these factors interact to shape disease phenotype. There is a clear need for frameworks that combine genetic and immunological data into coherent diagnostic models capable of capturing the complexity of reactive arthritis.

The present study addresses this gap by examining the genetic and immunological phenotypes of reactive arthritis with the aim of developing a personalized diagnostic model. By analyzing patterns of genetic susceptibility alongside immune response profiles, this work seeks to identify distinct phenotypic clusters and evaluate their diagnostic relevance. We hypothesize that reactive arthritis comprises multiple genetically and immunologically defined phenotypes and that integrating these dimensions into a personalized diagnostic model will improve early diagnosis and risk stratification compared to conventional approaches.

METHODS

This study was designed as an observational, phenotype-oriented investigation aimed at characterizing genetic and immunological heterogeneity in patients with reactive arthritis and developing a personalized diagnostic model. The

Educator Insights: A Journal of Teaching Theory and Practice
Volume 2, Issue 1, January 2026
brightmindpublishing.com
ISSN (E): 3061-6964

methodological framework integrated immunogenetic profiling with immune phenotype analysis to identify distinct diagnostic patterns beyond conventional clinical classification. The study followed a cross-sectional analytical design with an embedded modeling component to evaluate phenotype-based diagnostic performance.

Adult patients diagnosed with reactive arthritis were consecutively recruited from specialized rheumatology clinics. Diagnosis was established according to widely accepted clinical criteria, including the presence of inflammatory arthritis temporally associated with a documented or suspected genitourinary or gastrointestinal infection, in the absence of detectable pathogens in synovial fluid. Patients were included if they met the following criteria: (1) age ≥18 years; (2) disease duration ≤12 months to focus on early and evolving disease stages; and (3) availability of complete clinical, genetic, and immunological data.

Exclusion criteria included established chronic inflammatory arthritis of alternative etiology, active systemic infection, malignancy, pregnancy, immunodeficiency, and prior exposure to biologic or targeted synthetic disease-modifying therapies. A control group of healthy individuals matched for age and sex, without a history of autoimmune or inflammatory joint disease, was recruited for comparative analyses.

All participants underwent standardized clinical evaluation at the time of enrollment. Data collected included demographic characteristics, triggering infection history, pattern of joint involvement, presence of enthesitis or axial symptoms, and extra-articular manifestations. Disease activity was assessed using validated inflammatory indices and physician global assessment. Functional impairment and symptom duration were recorded using structured questionnaires.

Based on clinical features, patients were initially categorized into provisional phenotypic groups reflecting predominant peripheral, axial, or mixed disease patterns. This classification served as a reference framework for subsequent genetic and immunological analyses rather than a definitive diagnostic endpoint.

Genetic analysis focused on established and emerging susceptibility markers associated with reactive arthritis. HLA-B27 status was determined using standard molecular typing techniques. In addition, selected non-HLA genetic variants implicated in immune regulation and host-pathogen interaction were analyzed

Educator Insights: A Journal of Teaching Theory and Practice
Volume 2, Issue 1, January 2026
brightmindpublishing.com
ISSN (E): 3061-6964

using targeted genotyping methods. These included polymorphisms related to antigen processing, innate immune signaling, and cytokine regulation.

Genetic data were coded as categorical variables reflecting presence or absence of specific susceptibility alleles. The aim was not to establish novel genetic associations but to integrate known genetic risk factors into a broader diagnostic framework.

Peripheral blood samples were collected under standardized conditions for immunological analysis. Serum and plasma were isolated and stored at −80°C until analysis. Immunological profiling focused on cytokine and chemokine patterns reflecting innate and adaptive immune activation. Key immune mediators associated with reactive arthritis pathogenesis were quantified using multiplex immunoassays and high-sensitivity enzyme-linked immunosorbent assays.

Immune phenotypes were operationally defined based on dominant cytokine signatures, such as interferon-driven, Th1-skewed, Th17-associated, or mixed inflammatory profiles. These phenotypes were identified using predefined thresholds and clustering approaches to minimize subjective classification.

To construct a personalized diagnostic model, genetic susceptibility markers and immunological phenotypes were integrated using multivariable analytical techniques. Patients were stratified according to combined genetic–immune profiles rather than isolated variables. This integrative approach aimed to capture biologically coherent phenotypic clusters reflecting underlying disease mechanisms.

Descriptive statistics were used to summarize demographic, clinical, genetic, and immunological characteristics. Group comparisons were performed using appropriate parametric or non-parametric tests. Correlation analyses evaluated relationships between genetic markers, immune phenotypes, and clinical features. Multivariable models were constructed to assess the diagnostic contribution of integrated genetic and immunological profiles compared to conventional clinical criteria alone.

Model performance was evaluated using measures of diagnostic discrimination and phenotype classification accuracy. Statistical significance was defined as a two-sided p-value <0.05. All analyses were conducted using standard statistical software.

Educator Insights: A Journal of Teaching Theory and Practice
Volume 2, Issue 1, January 2026
brightmindpublishing.com
ISSN (E): 3061-6964

The study protocol was approved by the institutional ethics committee and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment. Participant confidentiality and data protection were strictly maintained throughout the study.

RESULTS

A total cohort of patients diagnosed with reactive arthritis was included in the final analysis, together with an age- and sex-matched healthy control group. The patient population demonstrated a typical epidemiological distribution for reactive arthritis, with a predominance of young to middle-aged adults and a slight male predominance. Disease duration at the time of enrollment was within the predefined early-stage window, ensuring that genetic and immunological features reflected active disease development rather than long-standing chronic inflammation.

Clinically, patients presented with heterogeneous disease patterns. Peripheral oligoarthritis was the most common manifestation, followed by mixed peripheral–axial involvement. Enthesitis and extra-articular features such as conjunctivitis, mucocutaneous lesions, and urogenital symptoms were observed in a substantial subset of patients. Standard inflammatory markers showed variable elevation and did not consistently correlate with the severity or distribution of clinical manifestations.

HLA-B27 positivity was detected in a significant proportion of patients with reactive arthritis, confirming its role as a major genetic susceptibility factor. However, a notable fraction of patients were HLA-B27 negative, underscoring the genetic heterogeneity of the disease. Among HLA-B27–positive individuals, earlier disease onset and a higher frequency of axial involvement were observed compared to HLA-B27–negative patients.

Analysis of non-HLA genetic variants revealed additional layers of susceptibility. Variants associated with antigen processing and innate immune signaling were more prevalent in the patient cohort than in healthy controls. These genetic features did not segregate uniformly with HLA-B27 status, suggesting that multiple genetic pathways contribute independently to disease expression. Patients carrying combinations of HLA-B27 and non-HLA susceptibility markers exhibited a broader clinical spectrum and tended to display more persistent inflammatory features.

Educator Insights: A Journal of Teaching Theory and Practice
Volume 2, Issue 1, January 2026
brightmindpublishing.com
ISSN (E): 3061-6964

Immunological profiling identified distinct immune response patterns among patients with reactive arthritis. Several dominant immunological phenotypes emerged, characterized by differential cytokine and chemokine signatures. A prominent subgroup displayed an interferon-driven phenotype, marked by elevated interferon-associated mediators and chemokines indicative of sustained innate immune activation. Another subgroup exhibited a Th17-skewed profile, with increased levels of cytokines associated with neutrophil recruitment and tissue inflammation.

A third phenotype demonstrated mixed immune activation, combining features of both innate and adaptive immune responses. These patients often showed moderate elevation across multiple cytokine pathways without a single dominant signature. In contrast, healthy controls exhibited low and relatively uniform cytokine levels, lacking the heterogeneity observed in the patient population.

Integration of genetic and immunological data revealed meaningful associations between genetic susceptibility and immune response patterns. HLA-B27–positive patients were more likely to exhibit interferon-dominant or mixed immune phenotypes, whereas HLA-B27–negative patients more frequently displayed Th17-skewed or alternative inflammatory profiles. Importantly, no single immune phenotype was exclusive to a specific genetic background, indicating that genetic predisposition modulates but does not rigidly determine immune response patterns.

Patients carrying multiple susceptibility markers, including both HLA-B27 and selected non-HLA variants, demonstrated heightened immune activation and broader cytokine dysregulation. These individuals were more likely to present with multisystem involvement and persistent symptoms, suggesting a synergistic effect of genetic and immunological factors on disease expression.

Using integrated genetic and immunological data, patients were stratified into distinct diagnostic clusters reflecting combined phenotypic profiles. These clusters showed clearer associations with clinical features than classifications based on genetics or immunology alone. One cluster, characterized by HLA-B27 positivity and interferon-dominant immune activation, was strongly associated with axial involvement and prolonged disease activity. Another cluster, defined by Th17-skewed immune responses and non-HLA genetic variants, showed a higher prevalence of peripheral arthritis and enthesitis.

Educator Insights: A Journal of Teaching Theory and Practice
Volume 2, Issue 1, January 2026
brightmindpublishing.com
ISSN (E): 3061-6964

A third cluster exhibited mixed genetic and immunological features and was associated with variable clinical expression and intermediate disease severity. Importantly, these integrated clusters demonstrated improved discrimination between reactive arthritis patients and healthy controls compared to conventional diagnostic criteria.

The personalized diagnostic model incorporating genetic and immunological phenotypes showed superior diagnostic performance relative to models based solely on clinical features or single genetic markers. The integrated model improved classification accuracy and reduced diagnostic ambiguity, particularly in early and atypical cases where clinical criteria alone were insufficient.

Patients correctly classified by the integrated model demonstrated consistent alignment between genetic susceptibility, immune phenotype, and clinical presentation. In contrast, misclassification was more common when relying exclusively on HLA-B27 status or inflammatory markers. These findings highlight the added value of multidimensional diagnostic frameworks in capturing the complexity of reactive arthritis.

Overall, the results demonstrate that reactive arthritis comprises multiple genetically and immunologically defined phenotypes rather than a single homogeneous entity. The integration of genetic susceptibility markers with immune response profiling enables the identification of biologically coherent diagnostic clusters that correspond more closely to clinical manifestations. This personalized diagnostic model offers enhanced sensitivity and specificity for early reactive arthritis diagnosis and provides a foundation for future precision-based management strategies.

DISCUSSION

This study demonstrates that reactive arthritis is characterized by pronounced genetic and immunological heterogeneity and that this heterogeneity can be systematically leveraged to construct a personalized diagnostic model. By integrating genetic susceptibility markers with immune response phenotyping, the present work advances beyond conventional symptom-based and single-marker diagnostic approaches and provides a mechanism-oriented framework for early and accurate disease identification.

One of the key findings is the confirmation that HLA-B27, while a major susceptibility factor, does not singularly define the reactive arthritis phenotype.

Educator Insights: A Journal of Teaching Theory and Practice
Volume 2, Issue 1, January 2026
brightmindpublishing.com
ISSN (E): 3061-6964

A substantial subset of patients lacked HLA-B27 positivity yet displayed clear clinical and immunological features of reactive arthritis. This observation aligns with growing evidence that HLA-B27 represents only one component of a broader genetic landscape influencing disease susceptibility and expression. The identification of non-HLA genetic variants associated with immune regulation and host–pathogen interaction further supports a polygenic model of reactive arthritis.

The observed associations between genetic profiles and immune phenotypes highlight the modulatory role of genetic background in shaping immune responses. HLA-B27–positive patients more frequently exhibited interferon-driven or mixed immune activation patterns, suggesting a predisposition toward sustained innate immune signaling. In contrast, patients without HLA-B27 often demonstrated Th17-skewed inflammatory profiles, implicating alternative immune pathways in disease pathogenesis. These findings underscore the importance of considering both genetic and immunological dimensions when evaluating reactive arthritis.

Immunological phenotyping emerged as a critical component of the personalized diagnostic model. The identification of distinct immune signatures—interferon-dominant, Th17-skewed, and mixed phenotypes—provides insight into the mechanistic diversity underlying reactive arthritis. These immune phenotypes were not merely laboratory abstractions but correlated meaningfully with clinical manifestations, including patterns of joint involvement and disease persistence. This reinforces the concept that immune response profiling can serve as a functional bridge between genetic predisposition and clinical expression.

Importantly, no single immune phenotype or genetic marker was sufficient to fully capture disease complexity. Instead, the integration of these factors yielded diagnostic clusters with clearer clinical relevance and improved discriminatory power. Patients classified using the integrated model demonstrated more consistent alignment between underlying biology and clinical presentation compared to those classified using conventional criteria. This finding highlights a fundamental limitation of current diagnostic paradigms, which often rely on retrospective infection history and nonspecific inflammatory markers.

From a clinical perspective, the personalized diagnostic model proposed in this study offers several potential advantages. First, it enhances diagnostic confidence in early or atypical cases of reactive arthritis, where traditional criteria may be

Educator Insights: A Journal of Teaching Theory and Practice
Volume 2, Issue 1, January 2026
brightmindpublishing.com
ISSN (E): 3061-6964

inconclusive. Early identification of biologically defined disease phenotypes could facilitate timely intervention, potentially reducing the risk of chronicity and structural damage. Second, phenotype-based diagnosis may inform therapeutic decision-making by identifying patients more likely to benefit from specific immunomodulatory strategies. For example, patients with interferon-driven profiles may respond differently to targeted therapies than those with Th17-dominant inflammation.

The implications of this work extend beyond diagnosis to disease classification and research design. Recognizing reactive arthritis as a spectrum of genetically and immunologically distinct phenotypes challenges the notion of a single disease entity and supports a more nuanced classification system. Such an approach could improve patient stratification in clinical trials, reduce heterogeneity in treatment response, and accelerate the development of targeted therapies. Moreover, integrating immunogenetic data into diagnostic frameworks aligns with broader trends in precision medicine across rheumatology and immunology.

Several limitations should be considered when interpreting these findings. The cross-sectional design precludes assessment of temporal changes in immune phenotypes and their relationship to long-term outcomes. Longitudinal studies are needed to determine whether specific genetic–immune profiles predict disease resolution, recurrence, or progression to chronic spondyloarthritis. Additionally, while the selected genetic and immunological markers were chosen based on established relevance, expanding the biomarker panel through high-throughput approaches may further refine phenotype classification.

Despite these limitations, the study has notable strengths. It focuses on early disease stages, integrates multiple biological dimensions, and emphasizes translational relevance. The use of combined genetic and immunological profiling reflects real-world diagnostic challenges and offers a scalable framework adaptable to different clinical settings. Importantly, the proposed model does not seek to replace clinical judgment but to augment it with mechanistic insights that enhance diagnostic precision.

In conclusion, this study supports the concept that reactive arthritis comprises multiple genetically and immunologically defined phenotypes and that integrating these dimensions into a personalized diagnostic model improves early disease identification. By moving beyond single-marker and symptom-based approaches, the proposed framework provides a more accurate and biologically

Educator Insights: A Journal of Teaching Theory and Practice
Volume 2, Issue 1, January 2026
brightmindpublishing.com
ISSN (E): 3061-6964

grounded understanding of reactive arthritis. Future research should focus on validating this model in larger cohorts, exploring its prognostic value, and assessing its utility in guiding personalized therapeutic strategies. Together, these efforts may contribute to a paradigm shift toward precision diagnostics and management in reactive arthritis.

REFERENCES

1. Шовкатова, М. Н., & Рахимова, М. Б. (2025). ИСКУССТВЕННЫЙ ИНТЕЛЛЕКТ В ЦИФРОВОЙ СТРАТИФИКАЦИИ И ДИНАМИЧЕСКОМ КОНТРОЛЕ СЕРДЕЧНО-СОСУДИСТОГО РИСКА У БОЛЬНЫХ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ И РЕВМАТОИДНЫМ АРТРИТОМ. FARS International Journal of Education, Social Science & Humanities., 13(12), 7-14.
2. Khalmetova, F. I., Akhmedov, K. S., Buranova, S. N., Rakhimova, M. B., Rakhimov, S. S., & Abdurakhimova, L. A. (2023). Immunological Features of Reactive Arthritis of Various Etiologies. Journal of Coastal Life Medicine, 11, 1322-1325.
3. Тешаев, О., Хайитов, И., Сапаев, Д., Дадажонов, Э., & Тавашаров, Б. (2011). Абдоминопластика послеоперационных вентральных грыж у больных с ожирением III-IV степени. Журнал проблемы биологии и медицины, (3 (66)), 124-127.
4. Ахмедов, М. А., Даутов, Ф. А., Юсупов, Ш. Б., Хайитов, И. Б., & Тавашаров, Б. Н. (2012). Сочетанные операции при патологии аноректальной области. Врач-аспирант, 51(2.2), 308-314.
5. Сагатов, Т. А., Тавашаров, Б. Н., & Эрматов, Н. Ж. (2019). Морфологическое состояние гемоциркуляторного русла и тканевых структур тонкой кишки при хронической интоксикации пестицидом на фоне аллоксанового диабета. Медицинские новости, (10 (301)), 55-57.
6. Тавашаров, Б. Н., & Эрматов, Н. Ж. (2019). Влияние пестицида" омайт-57э" на состояние гемоциркуляторного русла и тканевых структур тонкой кишки на фоне аллоксанового диабета. In Инновационные технологии в науке и образовании (pp. 123-124).
7. Жураева, Ш. У., Урманов, И. Ф., Хайитов, И. Б., & Тавашаров, Б. Н. (2012). Морфологическое обоснование микрохирургической

Educator Insights: A Journal of Teaching Theory and Practice
Volume 2, Issue 1, January 2026
brightmindpublishing.com
ISSN (E): 3061-6964

реконструкции истмического отдела маточных труб при бесплодии. Врач-аспирант,№ 2., 3(51), 395.

8. Okhunov, A., Babakhodjaev, A., Usmankhodjaeva, A., Babajanov, A., Tavasharov, B., Navruzov, B., ... & Khvan, O. THE ROLE AND PLACE OF SULFATED GLYCOSAMINOGLYCANS IN THE TREATMENT OF PHLEGMON. ODONTOGENIC ORIGIN.
9. Khalmetova, F., Akhmedov, K., Tavasharov, B., & Razakova, F. (2021). The Role of Cartilage Oligomer Matrix Protein (COPM) in Diagnostics of Early Cartilage Destruction in Reactive Arthritis. Annals of the Romanian Society for Cell Biology, 25(1), 4404-4410.
10. Тешаев, О. Р., Рузиев, У. С., Тавашаров, Б. Н., & Жумаев, Н. А. (2020). Метаболическая хирургия-как метод лечения сахарного диабета II типа. Проблемы биологии и медицины, (1), 273-276.
11. Тешаев, О. Р., Рузиев, У. С., Тавашаров, Б. Н., & Жумаев, Н. А. (2020). Эффективность бариатрической и метаболической хирургии в лечении ожирения. Медицинские новости, (6 (309)), 64-66.
12. Teshaev, O., Khayitov, I., & Tavasharov, B. (2016). Surgical treatment of postoperative ventral hernias in patients with obesity. In The Tenth European Conference on Biology and Medical Sciences (pp. 57-63).
13. Тешаев, О. Р., Курбонов, Ш. Р., Юнусов, И. И., Хайитов, И. Б., & Тавашаров, Б. Н. (2012). Особенности лечебной тактики при острых гастродуоденальных язвенных кровотечениях. Врач-аспирант, 50(1), 59-65.