ISSN: 3005-8449
IRABCS https://irabcs.com INNOVATIVE RESEARCH IN APPLIED, BIOLOGICAL AND CHEMICAL SCIENCES

Research Article

IRABCS, vol. 2, issue 2, pp. 181-185, 2024
Received: September 9, 2024
Revised: December 04, 2024
Accepted: December 23, 2024
https://doi.org/10.62497/IRABCS.2024.69

Investigating the Role of Genetic Predisposition in Developing Rheumatoid Arthritis

Nishwa-Tul-Eman[1], Sandal Rafiq[1], Aqsa Hayat[2]*, Natasha Imtiaz[1], Sabir Hussain[1] and Mansoor Ahmad[1]

1. *Abbottabad International Medical Institute, Abbottabad, Pakistan*
2. *Jinnah Medical College, Peshawar, Pakistan*
3. *E-mail any correspondence to: aqsamcm11@gmail.com*

How to cite: Eman NT, Rafiq S, Hayat A, Imtiaz N, Hussain S, Ahmad M. Investigating the Role of Genetic Predisposition in Developing Rheumatoid Arthritis. IRABCS. 2024. vol. 2, issue 2, pp. 181-185. DOI: https://doi.org/10.62497/IRABCS.2024.69. Available from: https://irabcs.com/ojs/article/view/69

Abstract

Background: A chronic autoimmune disease called rheumatoid arthritis (RA) is impacted by both environmental and genetic factors. This work explores the impact of genetic predisposition in the development of RA, focusing on the HLA-DRB1 common epitope, PTPN22, and STAT4 gene variations.

Objectives: In a cohort from Hayatabad Medical Complex (HMC), the research sought to evaluate the relationship between important genetic markers and RA susceptibility as well as investigate the interplay between genetic predisposition and environmental variables, such as smoking.

Methods: 132 RA patients participated in a cross-sectional research that ended in August 2024. To determine the existence of HLA-DRB1, PTPN22, and STAT4 gene variations, genetic analysis was done. The strength of relationships was determined by calculating odds ratios, or ORs. Analysis was also done on the relationship between smoking and the common epitope of HLA-DRB1. At $p < 0.05$, statistical significance was established.

Results: The common epitope between HLA-DRB1 and RA was substantially correlated (OR = 3.45, $p < 0.001$). While STAT4 did not exhibit a significant correlation with RA (OR = 1.29, $p = 0.365$), PTPN22 was likewise associated with RA (OR = 2.15, $p = 0.009$). Compared to non-smokers (OR = 2.18, $p = 0.021$), smokers with the HLA-DRB1 allele had a significantly higher risk of RA (OR = 5.87, $p < 0.001$).

Conclusions: The main genetic indicators for RA susceptibility are HLA-DRB1 and PTPN22, and smoking greatly increases the risk in those who are genetically susceptible to the condition. These results emphasize the value of lifestyle changes and customized risk assessment in the prevention of RA.

Keywords: rheumatoid arthritis, HLA-DRB1, PTPN22, STAT4, genetic predisposition, smoking, autoimmune disease, risk factors, epigenomics

Introduction

A systemic autoimmune disease that mostly affects the synovial joints, rheumatoid arthritis (RA) causes pain, swelling, stiffness, and eventual joint destruction. In addition to affecting joints, RA may also impact other organ systems such as the heart, lungs, and blood vessels, which can lead to a more extensive systemic burden for those who are impacted [1]. About 1% of people worldwide suffer with RA, with women being disproportionately impacted. Significant impairment, a worse quality of life, and a higher death rate are often brought on by the illness. Although the precise cause of RA is still unknown, it is known to be complex and to result from the interaction of immunological, environmental, and genetic variables [2, 3].

Over the last few decades, a great deal of study has been conducted on the role that genetic predisposition plays in the development of RA. Research indicates that around 60% of the risk for RA may be ascribed to genetic factors; the greatest correlation was discovered in the human leukocyte antigen (HLA) area, namely the HLA-DRB1 locus [4,5]. This locus is linked to the "shared epitope" theory, which states that certain amino acid sequences in HLA-DRB1 alleles increase the chance of developing RA. Moreover, a number of non-HLA loci, including PTPN22, STAT4, and TNFAIP3, which are involved in immune regulation and add to the genetic architecture of RA, have been found by genome-wide association studies (GWAS) [6-8].

The processes by which these genetic markers contribute to the pathophysiology of RA are still unclear and

complicated, even after their detection. The knowledge of the genesis of RA is further complicated by the recognized interactions between genetic variables and environmental triggers, including smoking, infections, and hormone changes. For instance, it has been shown that smoking cigarettes interacts with HLA-DRB1 alleles, greatly raising the risk of RA in those who are genetically susceptible to the disease. Histone alterations and other epigenetic changes have also been proposed as possible mediators of gene-environment interactions in RA [9, 10. Determining who is at high risk and creating individualized treatment plans need an understanding of the genetic foundation of RA.

By enabling earlier identification and more focused preventative measures, genetic screening may be able to change the course of the illness before substantial joint damage happens. Additionally, by clarifying the molecular mechanisms linked to hereditary vulnerability, new pharmaceutical strategies targeting immune system modulation and RA prevention may be developed. With an emphasis on finding important genetic markers and comprehending how they interact with environmental circumstances, this research attempts to explore the role of genetic predisposition in the development of RA. This study aims to give a thorough knowledge of the genesis of RA by investigating its genetic foundations and to open new directions for early identification, prevention, and treatment approaches.

Materials and methods

Study Design

The purpose of this cross-sectional research, which is conducted at a hospital, is to find genetic predispositions linked to RA. It lasted for a year, ending in August 2024, in the Hayatabad Medical Complex (HMC), Peshawar. Prior to data collection, ethical permission was acquired from HMC's institutional review board.

Study Population

Based on the 2010 categorization criteria established by the American College of Rheumatology (ACR), 132 participants with rheumatoid arthritis were included in the research [11]. Patients were chosen from the HMC Department of Rheumatology. Patients had to be 18 years of age or older, have a verified diagnosis of RA, and provide their informed permission in order to be eligible for participation. The research excluded patients with insufficient medical data or concomitant autoimmune disorders.

Sample Size Calculation

32 was the sample size determined by using the cross-sectional study formula. A minimal sample size of 130 was established, assuming a 95% confidence interval, a 5% margin of error, and an estimated 30% prevalence of genetic markers linked to RA. The ultimate sample size was raised to 132 in order to take into consideration any dropouts or missing data.

Data Collection

Genetic tests and a study of medical records were used to evaluate the patients. For genotyping, blood samples were taken from each participant. The main targets of genetic testing were known RA-associated markers, such as the HLA-DRB1 alleles and non-HLA locations like STAT4 and PTPN22. Demographic and clinical information was also documented, such as age, gender, length of illness, and lifestyle choices (such as history of smoking). A standardized questionnaire was used to gather data on possible exposures to the environment. Additional variables, including obesity, dietary habits, and occupational exposure, were also analyzed to assess their potential influence on RA risk. Data on body mass index (BMI), dietary patterns (e.g., frequency of processed food consumption, fruit and vegetable intake), and type and duration of occupational activities (e.g., exposure to physical labor or chemicals) were collected through detailed interviews and medical record reviews.

Statistical Analysis

The clinical features and patient demographics were compiled using descriptive statistics. Chi-square testing and logistic regression were used to evaluate the relationship between genetic markers and RA. To assess the strength of connections, adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were computed. At $p < 0.05$, statistical significance was established. SPSS version 25 was used for all analyses.

Results

The research included 132 individuals with a diagnosis of RA. The average age of the participants was 48.3 ± 12.5 years, and 72.7% of the patients were female (n = 96). This indicates that women are more likely than males to have RA. There was a broad range of illness severities and an average disease duration from diagnosis of 6.8 ± 4.1 years. A significant environmental risk factor for RA was found in 38.6% (n = 51) of the patients who had smoked in the past. In addition, 22.7% (n = 30) of the participants mentioned having autoimmune illness in their family, suggesting that RA development may have a genetic component, as seen in table 1.

Table 1: Demographic and Clinical Characteristics of RA Patients.

Characteristic	Value
Mean Age (years)	48.3 ± 12.5
Female Patients	72.7% (n = 96)
Mean Disease Duration (years)	6.8 ± 4.1
Smoking History	38.6% (n = 51)
Family History of Autoimmune Disease	22.7% (n = 30)
Obesity (BMI > 30)	31.8% (n = 42)
High Processed Food Intake	45.4% (n = 60)
Occupational Exposure to Chemicals	18.2% (n = 24)

The genetic research focused on a number of markers, such as HLA-DRB1, PTPN22, and STAT4, that have been connected to RA. The HLA-DRB1 common epitope was shown to be strongly associated with higher vulnerability to RA. 48.5% (n = 64) of the group as a whole tested positive for the HLA-DRB1 allele linked to RA, and those who had this variant had a markedly increased chance of

getting the illness. The odds ratio (OR) of 3.45 (95% CI: 1.92–6.20, p < 0.001) indicated that HLA-DRB1 plays a crucial role in the pathophysiology of RA. Apart from the common epitope between HLA and DRB1, non-HLA loci were also analyzed. Of the patients, 32.6% (n = 43) had the PTPN22 risk allele. A statistically significant correlation was observed between this allele and RA, with an OR of 2.15 (95% CI: 1.20–3.85, p = 0.009). These results support the role of PTPN22 in immune modulation and its association with an increased risk of RA.

Despite being found in 28.0% (n = 37) of the cohort, the STAT4 gene variation did not show a statistically significant correlation with RA in this group. The OR for STAT4 was 1.29 (95% CI: 0.74–2.25, p = 0.365), indicating that while STAT4 could be important in other populations, it might not have a significant impact on the research sample in question, as shown by Table 2.

Table 2: Association of Genetic Markers with RA Susceptibility.

Genetic Marker	(n) %	OR (95% CI)	p-value
HLA-DRB1 (Shared Epitope)	(64) 48.5%	3.45 (1.92–6.20)	< 0.001
PTPN22	(43) 32.6%	2.15 (1.20–3.85)	0.009
STAT4	(37) 28.0%	1.29 (0.74–2.25)	0.365

n: Frequency in RA Patients, OR: Odds Ratio

To evaluate the relationship between the common epitope of HLA-DRB1 and smoking, a known environmental risk factor, further investigation was done. In comparison to non-smokers with the same genetic propensity, the risk of getting RA was considerably higher among the people who had a history of smoking and tested positive for the HLA-DRB1 allele. The substantial correlation between smoking and genetic vulnerability was seen in the OR of 5.87 (95% CI: 2.45–10.52, p < 0.001) among smokers who carried the common epitope. The HLA-DRB1 allele, on the other hand, was associated with a decreased but statistically significant risk of RA among non-smokers (OR of 2.18 (95% CI: 1.12–4.31, p = 0.021). This result (Figure 1) highlights the role that both environmental and genetic variables play in the pathophysiology of RA and implies that lifestyle changes, like quitting smoking, may be especially helpful for those who are genetically predisposed to the disease.

This work validates the important contribution of genetic predisposition to the development of RA, namely the PTPN22 gene and the HLA-DRB1 common epitope. The relationship between smoking and HLA-DRB1 emphasizes how crucial environmental variables are in influencing genetic risk. In this group of patients, the STAT4 gene did not significantly correlate with RA, despite being present in a portion of them. These results imply that genetic and lifestyle variables may influence tailored approaches to RA prevention and therapy, especially in genetically predisposed patients.

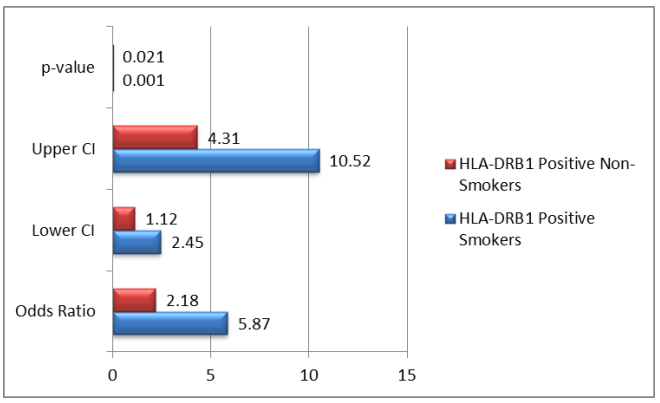

Figure 1: Interaction between Smoking and HLA-DRB1 in RA Susceptibility.

Discussion

The results of this investigation validate the documented involvement of genetic susceptibility in the onset of rheumatoid arthritis (RA), specifically with regard to the common epitope of HLA-DRB1 and the PTPN22 gene. These findings are in line with other studies that have repeatedly shown these genetic markers to be important risk factors for RA [12]. The work adds to our knowledge of RA etiology by highlighting the intricate interactions between hereditary variables and environmental ones like smoking. This study's substantial correlation (OR = 3.45, p < 0.001) between the common epitope of HLA-DRB1 and RA is consistent with earlier results [13]. Research has repeatedly shown that the HLA-DRB1 alleles are the most important genetic risk factors for RA, and that they are associated with both the severity and course of the illness. The prominent function of this genetic marker is further validated by the near match between the odds ratio computed in this cohort and what has been reported in other populations.

It was discovered that there was a substantial correlation between RA and the immune regulation-related PTPN22 gene (OR = 2.15, p = 0.009). This result is consistent with previous studies that showed PTPN22 mutations increase the risk of autoimmune disorders, including RA [14]. The somewhat lower odds ratio (OR) in this research, however, shows population-specific variances in contrast to several other studies that found greater ORs for PTPN22 [15]. This variance demonstrates how important it is for genetic study to take geography and ethnicity into account. The STAT4 gene variation did not significantly correlate with RA in this study (OR = 1.29, p = 0.365), which is in contrast to other studies that found STAT4 to be a factor in RA susceptibility in different populations [16]. The lack of a significant correlation in this case can be due to sample size constraints or ethnic variations, underscoring the need of researching a variety of groups to completely comprehend the genetic makeup of RA.

The study's key discovery is the substantial correlation between smoking and the common HLA-DRB1 epitope. While non-smokers with the same genetic marker had a decreased, but still substantial, risk of RA (OR = 2.18, p = 0.021), smokers who had the common epitope had an elevated risk (OR = 5.87, p < 0.001). The hypothesis that environmental influences, including smoking, might increase genetic risk is supported by this interaction. The

fundamental process might be smoking-induced citrullination of proteins, which in genetically predisposed people sets off autoimmune reactions [17]. These results highlight the significance of changing one's lifestyle, such as giving up smoking, especially for those who are predisposed to certain diseases. This work adds to our expanding knowledge of the genetic risk factors for RA. Yet, differences in the impact of genetic markers such as STAT4 across groups imply that the genetic foundations of RA may vary by region and ethnicity [18]. While previous research on European populations has shown higher relationships with some markers, this cohort from Hayatabad Medical Complex showed distinct patterns [19, 20].

These results have important ramifications for the creation of RA tailored treatment approaches. Managing environmental factors like smoking in addition to genetic screening for RA-associated markers like HLA-DRB1 and PTPN22 may help identify high-risk people early. This strategy may result in more potent prophylactic measures or customized therapies to postpone or stop the beginning of RA, particularly in communities where these genetic markers are very prevalent.

Conclusion

This research demonstrates the important role that the PTPN22 gene and the HLA-DRB1 common epitope play in raising the risk of developing rheumatoid arthritis, as well as the noteworthy interplay between smoking and genetic predisposition. In this group, the STAT4 gene variation did not exhibit any meaningful connection. These results underscore the significance of both environmental and genetic variables in the development of RA and the possibility of customized risk assessments and preventative measures, especially in genetically predisposed people. Ethical considerations must be central to any application of genetic testing for RA predisposition.

Conflict of interest

The authors state no conflict of interest.

Author Contributions

All authors contributed equally, reviewed the final version to be published and agreed to be accountable for all aspects of the work.

References

1. Barton A, Ollier W. Genetic approaches to the investigation of rheumatoid arthritis. Current opinion in rheumatology. 2002 May 1;14(3):260-9. https://journals.lww.com/co-rheumatology/abstract/2002/05000/genetic_approaches_to_the_investigation_of.12.aspx

2. Deane KD, Demoruelle MK, Kelmenson LB, Kuhn KA, Norris JM, Holers VM. Genetic and environmental risk factors for rheumatoid arthritis. Best practice & research Clinical rheumatology. 2017 Feb 1;31(1):3-18.

3. Yarwood A, Huizinga TW, Worthington J. The genetics of rheumatoid arthritis: risk and protection in different stages of the evolution of RA. Rheumatology. 2016 Feb 1;55(2):199-209. https://doi.org/10.1016/j.berh.2017.08.003

4. Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis. Arthritis research & therapy. 2002 Jul;4:1-8. https://doi.org/10.1186/ar578

5. Viatte S, Plant D, Raychaudhuri S. Genetics and epigenetics of rheumatoid arthritis. Nature Reviews Rheumatology. 2013 Mar;9(3):141-53. https://doi.org/10.1038/nrrheum.2012.237

6. Vetchinkina EA, Mikhaylenko DS, Kuznetsova EB, Deryagina TA, Alekseeva EA, Bure IV, Zamyatnin Jr AA, Nemtsova MV. Genetic factors of predisposition and clinical characteristics of rheumatoid arthritis in Russian patients. Journal of personalized medicine. 2021 May 25;11(6):469. https://doi.org/10.3390/jpm11060469

7. Olsson LM, Lindqvist AK, Källberg H, Padyukov L, Burkhardt H, Alfredsson L, Klareskog L, Holmdahl R. A case-control study of rheumatoid arthritis identifies an associated single nucleotide polymorphism in the NCF4 gene, supporting a role for the NADPH-oxidase complex in autoimmunity. Arthritis research & therapy. 2007 Oct;9:1-1. https://doi.org/10.3390/jpm11060469

8. Plant D, Thomson W, Lunt M, Flynn E, Martin P, Eyre S, Farragher T, Bunn D, Worthington J, Symmons D, Barton A. The role of rheumatoid arthritis genetic susceptibility markers in the prediction of erosive disease in patients with early inflammatory polyarthritis: results from the Norfolk Arthritis Register. Rheumatology. 2011 Jan 1;50(1):78-84. https://doi.org/10.1093/rheumatology/keq032

9. Scherer HU, Häupl T, Burmester GR. The etiology of rheumatoid arthritis. Journal of autoimmunity. 2020 Jun 1;110:102400. https://doi.org/10.1016/j.jaut.2019.102400

10. Kurkó J, Besenyei T, Laki J, Glant TT, Mikecz K, Szekanecz Z. Genetics of rheumatoid arthritis—a comprehensive review. Clinical reviews in allergy & immunology. 2013 Oct;45:170-9. Doi: https://doi.org/10.1007/s12016-012-8346-7

11. Maurits MP, Wouters F, Niemantsverdriet E, Huizinga TW, van den Akker EB, Le Cessie S, van der Helm-van Mil AH, Knevel R. The Role of Genetics in Clinically Suspect Arthralgia and Rheumatoid Arthritis Development: A Large Cross-Sectional Study. Arthritis & Rheumatology. 2023 Feb;75(2):178-86. https://doi.org/10.1002/art.42323

12. Jiang X, Alfredsson L. Modifiable environmental exposure and risk of rheumatoid arthritis—current evidence from genetic studies. Arthritis

research & therapy. 2020 Jun 22;22(1):154. https://doi.org/10.1186/s13075-020-02253-5

13. Seldin MF, Amos CI, Ward R, Gregersen PK. The genetics revolution and the assault on rheumatoid arthritis. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 1999 Jun;42(6):1071-9.

14. Ollier WE, MacGregor A. Genetic epidemiology of rheumatoid disease. British Medical Bulletin. 1995 Apr 1;51(2):267-85. https://doi.org/10.1093/oxfordjournals.bmb.a072960

15. Ebrahimiyan H, Mostafaei S, Aslani S, Jamshidi A, Mahmoudi M. Studying the association between STAT4 gene polymorphism and susceptibility to rheumatoid arthritis disease: An updated meta-analysis. Iranian Journal of Immunology. 2019 Mar 1;16(1):71-83. https://iji.sums.ac.ir/article_44701_1834bfad7d73e9908f4791491ad21e54.pdf

16. Jawaheer D, Gregersen PK. Rheumatoid arthritis: the genetic components. Rheumatic Disease Clinics. 2002 Feb 1;28(1):1-5. https://www.rheumatic.theclinics.com/article/S0889-857X(03)00066-8/abstract

17. Kronzer VL, Davis JM. Etiologies of rheumatoid arthritis: update on mucosal, genetic, and cellular pathogenesis. Current rheumatology reports. 2021 Apr;23:1-0. https://doi.org/10.1007/s11926-021-00993-0

18. Schulz S, Pütz N, Jurianz E, Schaller HG, Reichert S. Are There Any Common Genetic Risk Markers for Rheumatoid Arthritis and Periodontal Diseases? A Case-Control Study. Mediators of inflammation. 2019;2019(1):2907062. https://doi.org/10.1155/2019/2907062

19. Orozco G, Barton A. Update on the genetic risk factor s for rheumatoid arthritis. Expert Review of Clinical Immunology. 2010 Jan 1;6(1):61-75. https://doi.org/abs/10.1586/eci.09.72

20. Wysocki T, Olesińska M, Paradowska-Gorycka A. Current understanding of an emerging role of HLA-DRB1 gene in rheumatoid arthritis–from research to clinical practice. Cells. 2020 May 2;9(5):1127. https://doi.org/10.3390/cells9051127