Cell. Mol. Biol. (ISSN: 1165-158X)

Journal Homepage: www.cellmolbiol.org

Cellular and Molecular Biology

Original Article

Relationships between genetic polymorphisms of IL-1β and rheumatoid arthritis

Nawres Adnan Abdulameer*

Technical Institute of Al-Diwaniyah, Al-Furat Al-Awsat Technical University (ATU), Iraq

Article Info

Article history:

Received: July 22, 2024
Accepted: November 01, 2024
Published: December 31, 2024

Use your device to scan and read the article online

Abstract

This study aimed to investigate the association between the interleukin-1 beta (IL-1β) gene polymorphism (rs2853550) and the risk of rheumatoid arthritis (RA) in a sample of the Iraqi population. The study included 100 RA patients and 100 healthy controls. Demographic characteristics, including age and gender, were collected and compared between the two groups. The IL-1β (rs2853550) polymorphism was genotyped using the ARMS-PCR method. The distribution of genotypes and alleles of the IL-1β (rs2853550) polymorphism was significantly different between RA patients and healthy controls. The frequency of the heterozygous AG genotype was significantly higher in the patient group compared to the control group (33% vs. 25%, p=0.001). The odds ratio for RA in individuals with the AG genotype was 1.5038 (95% CI: 0.7274-3.1086), indicating that it may be a potential risk factor. Additionally, the frequency of the G allele was significantly higher in RA patients compared to controls (129 vs. 109, p=0.0021), with an odds ratio of 1.5169 (95% CI: 1.0151-2.2667). The present study demonstrates that the IL-1β (rs2853550) polymorphism is associated with an increased risk of rheumatoid arthritis in the Iraqi population. The AG genotype and the G allele of this polymorphism may serve as genetic markers for susceptibility to RA.

Keywords: IL1B (rs2853550), Rheumatoid Arthritis, SNPs

1. Introduction

Rheumatoid arthritis, a chronic autoimmune illness marked by joint inflammation, is one such disease that has received a lot of attention, Rheumatoid arthritis (RA) is a chronic, autoimmune inflammatory disorder that primarily affects the synovial joints, leading to progressive joint destruction and disability [1]. The pathogenesis of RA is complex and multifactorial, involving the interplay of genetic, environmental, and immunological factors [2]. Some genetic variants may put people at a higher risk of developing rheumatoid arthritis, and the interleukin-1 beta (IL-1β) gene is a crucial factor in this disease's development. The possibility exists to enhance patient outcomes and transform therapy approaches by comprehending the connection between IL-1β genetic variants and rheumatoid arthritis [3]. A growing body of evidence suggests that proinflammatory cytokines, such as interleukin-1 beta (IL-1β), play a crucial role in the development and progression of RA [4]. IL-1β, a key pro-inflammatory cytokine, is known to drive the inflammatory cascade in RA by promoting the production of other inflammatory mediators, enhancing matrix metalloproteinase activity, and inducing osteoclast differentiation [4]. Genetic variations in the IL1B gene, which encodes the IL-1β protein, have been implicated in the susceptibility and severity of various inflammatory and autoimmune diseases, including RA [4]. Several studies have investigated the association between IL1B polymorphisms and the risk of RA, with inconsistent results reported across different populations [4;5]. The rs2853550 polymorphism, a single nucleotide polymorphism (SNP) in the promoter region of the IL1B gene, has been of particular interest due to its potential impact on IL-1β production and subsequent inflammation [5]. Understanding the genetic factors that influence susceptibility to RA is crucial for identifying individuals at risk, providing personalized treatment strategies, and developing targeted therapeutic interventions. Therefore, the present study aimed to investigate the relationship between the IL1B (rs2853550) polymorphism and the risk of rheumatoid arthritis in an Iraqi population.

2. Materials and Methods

2.1. Consent Patient

100 patients with RA and 100 healthy controls from Iraq's Education Al-Dewaniyah Hospital were informed consent and provided by a health care about the risks, benefits, and alternatives of a given procedure or intervention.

2.2. Samples collection

At Iraq's Education Al-Dewaniyah Hospital, there were 100 patients with RA and 100 healthy controls. All patients were found to have RA after a physician performed a pathology diagnosis. The individuals in the control group were

* Corresponding author.
E-mail address: dw.noras@atu.edu.iq (N. A. Abdulameer).
Doi: http://dx.doi.org/10.14715/cmb/2024.70.12.13

all in good health, with no history of inflammatory bone and joint problems, and they were of similar age and sex.

2.3. SNP genotyping

We chose IL1B polymorphisms (rs2853550) based on data from the USCS database and other research. Both patients and healthy controls had their blood samples (5 mL) collected and kept in tubes coated with EDTA. Genomic DNA was isolated from peripheral blood and preserved at -80 °C until the experiment. (F: CCATGTCCACCCAAGTCTCT, R: TGCTGGGCGGTAAAATTTCC); Product Size: 235).

2.4. Statistical analysis

We used Fisher's exact test as a control to check if each SNP was in Hardy-Weinberg equilibrium. The statistical studies were performed with SPSS 20.0, based in Chicago, IL, USA. When we adjusted for age and sex, we utilized odds ratios (OR) and 95% confidence intervals (CI) to assess the association between IL1B polymorphisms and the risk of RA.

3. Results

3.1. Demoghraphic Characteristics

One hundred sick and one hundred healthy individuals participated in the current research. Table 1 displays the demographic information of both the patients and the control participants. There was no significant difference in the mean age between the control subjects and patients (P = 0.277), with the control subjects' mean age being (46.04±13.77) years and the patients' mean age being (49.31±7.89) years. The age distribution of patients and control participants did not differ significantly from one another (P = 0.598). There was no significant difference in the frequency distribution of patients and control individuals according to gender (P = 0.299). The patients' group consisted of 58 (58.00%) males and 42 (42.00%) females, while the control group had 56 (56.00%) males and 44 (44.00%) females. The outcomes above have guaranteed the necessary statistical matching of the patient and control groups concerning age and gender for this type of case-control study.

3.2. Detection of *IL1B (rs2853550)* Polymorphism

The ARMS-PCR method was used to identify the IL1B (rs2853550) polymorphism distribution. This locus has three genotypes: AG, GG, and AA. Only the A allele was amplified at a product size of 235 bp in the wild-type homozygote genotype. Only the G allele was amplified at a product size of 235 kb in the mutant-type homozygote genotype. On the other hand, the G and A alleles were amplified at 235 bp product sizes, respectively, in the case of the heterozygote genotype, as shown in Figure (1).

3.3. Genotypic analysis for studied genes in Patients and Control groups

Table (2) shows the relationship between the risk of rheumatoid arthritis and the IL1B polymorphisms (rs2853550), which is an A < G POLY gene polymorphism. There was a statistically significant increase in the frequency of the heterozygous genotype AG in the sick group (33 cases versus 25 in the control group; p=0.001). The odds ratio for rheumatoid arthritis was 1.5038 (95% CI: 0.7274-3.1086), suggesting that genotype AG was a risk factor.

The correlation between the risk of rheumatoid arthritis and the IL1B polymorphisms (rs2853550) A < G poly allele polymorphism is displayed in Table (3). The patients' group had 129 instances of allele G compared to the control group's 109, which was statistically significant (P = 0.001). Consequently, there was a 1.5169 odds ratio (95% CI 11.0151-2.2667) for rheumatoid arthritis associated with genotype G.

4. Discussion

Examining the links between IL-1B gene polymorphisms and RA vulnerability was the driving force behind this study. Based on our results, rs2853550 of IL-1B polymorphisms may have a strong association with RA vulnerability. As cellular signaling molecules, cytokines are essential for immune response, inflammation, and

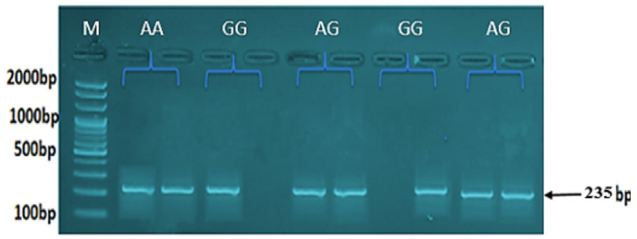

Fig. 1. Agarose gel electrophoresis image that showed the ARMS-PCR product analysis of ILIB polymorphisms (rs2853550) A < G gene polymorphism. Where M: marker (2000-100bp). The presence of A or G allele were observed at 235 bp product size.

Table 1. General characteristics of the subjects in this study.

Characteristic	Patients *n* = 100	Control *n* =100	*P value*
	Age (years)		
Mean ±SD	49.31 ± 7.89	46.04 ± 13.77	0.277 † NS
≥ 45 *n* (%)	61 (61.00)	59 (59.00)	0.598 ¥ NS
< 45 *n* (%)	49 (49.00)	41 (41.00)	
	Gender		
Male, *n* (%)	58 (58.00)	56 (56.00)	0.299 ¥ NS
Female, *n* (%)	42 (42.00)	44 (44.00)	

n: number of cases; SD: standard deviation;+: independent samples t-test; : Chi-square test; NS: not significant at P>0.05; HS: highly significant at P ≤ 0.05.

Table 2. IL1B polymorphisms (rs2853550) A < G POLY genotype frequency in patients with rheumatoid arthritis and control group.

IL1B polymorphisms (rs2853550) A < G						
Genotype	**Patients** *n* **= 100**	**Control** *n* **=100**	***P*1**	***P*2**	**OR**	**95% CI**
GG	48	42		0.005 ¥ S	1.5038	0.7274-3.1086
AG	33	25	0.003 ¥ S	0.553 ¥ NS	1.7368	0.7873-3.8314
AA	19	33		Reference	Reference	Reference

*P*l: overall comparison; *P*2: Individual genotype comparison versus reference; n: number of cases; ¥: Chi-square test; OR: odds ratio; CI: confidence interval; NS: non-significant.

Table 3. IL1B polymorphisms (rs2853550) A < G POLY allele frequency in patients with rheumatoid arthritis and control group.

IL1B polymorphisms (rs2853550) A < G	**Patients** *n* **= 200**	**Control** *n* **= 200**	***P***	**OR**	**95%CI**
G	129	109	0.0021 ¥ HS	1.5169	1.0151-2.2667
A	71	91		0.6593	0.4412-0.9851

n: number of alleles; : Chi-square test; OR: odds ratio; CI: confidence interval; HS: highly significant at P<0.01.

intercellular communication. An inflammatory cascade is set off when IL-1β, a significant inducer of inflammatory immune responses, binds with the same receptors on cell surfaces [6]. Chronic inflammation mediated by IL-1β was discovered in inflammatory bone illnesses, including amyotrophic lateral sclerosis, multiple sclerosis, extremities chronic osteomyelitis, osteonecrosis of the femoral head, and ankylosing spondylitis. According to previous research, there is strong evidence linking IL1B SNPs to RA [13,14]. Three novel IL1B SNPs linked to RA risk in Chinese individuals were identified in our investigation. Research has demonstrated that having the AG genotype of rs2853550 raises the likelihood of developing steroid-induced osteonecrosis of the femoral head [10,11]. Research on ankylosing spondylitis has shown that the "A" allele of rs2853550 may reduce the likelihood of developing the condition. No research has shown that rs2853550 influences the risk of RA as far as we know. Our research only indicated that rs2853550 enhanced the risk of RA in people 54 and older. Numerous studies have examined the functional significance of IL-1B gene SNPs. More populations need to have their results repeated. Increased IL-1β expression was linked to IL1B-rs16944, and gene transcription and function alterations could be caused by its gene polymorphism [15]. However, further experimental verification is needed to determine the specific chemical mechanism. There are several caveats to remember despite this study finding three IL-1B SNPs (rs2853550) linked to RA susceptibility across models. First, we couldn't investigate the possible gene-environment interactions impacting RA risk since environmental exposure data wasn't obtained. Secondly, the significance of SNPs has yet to be well demonstrated by clarifying their function. Finally, we missed some information regarding other possible susceptibilities because we only chose a small number of SNPs from the IL-1B gene. Hence, additional experimental and clinical data are required to provide a more complete picture of the unique impacts of these SNPs.

5. Conclusion

The IL1B (rs2853550) polymorphism is linked to the risk of rheumatoid arthritis in the Iraqi population. The heterozygous AG genotype is more prevalent in RA patients, suggesting increased vulnerability. The G allele is more common, indicating its potential as a genetic risk factor. This study highlights the importance of genetic markers in RA treatment and disease prevention. Further research is needed to understand the molecular pathways influencing RA risk and its potential as a diagnostic or prognostic biomarker.

References

1. Song S, Wang Y, Fang Y, Teng F, Yue T, Chen L, Wan X, Hong R, Xue M (2024) Glucocorticoids promote joint microenvironment alteration of GABBR1 expression associated with mitigating rheumatoid arthritis: GABBR1 promotes RA by glucocorticoids. Cell Mol Biol (Noisy-le-grand). 70(6):73-77. doi: 10.14715/cmb/2024.70.6.12
2. Hwang IR, Kodama T, Kikuchi S, Sakai K, Peterson LE, Graham DY, Yamaoka Y (2002) Effect of interleukin 1 polymorphisms on gastric mucosal interleukin 1β production in Helicobacter pylori infection. Gastroenterol 123(6): 1793-1803. doi: 10.1053/gast.2002.37043
3. Jahid M, Chawla D, Avasthi R, Ahmed RS (2018) Association of polymorphic variants in IL1B gene with secretion of IL-1β protein and inflammatory markers in north Indian rheumatoid arthritis patients. Gene 641: 63-67. doi: 10.1016/j.gene.2017.10.042
4. Kim EY, Moudgil K. D (2017) Immunomodulation of autoimmune arthritis by pro-inflammatory cytokines. Cytokine 98: 87-96. doi: 10.1016/j.cyto.2017.04.012
5. Kondo N, Kuroda T, Kobayashi D (2021) Cytokine networks in the pathogenesis of rheumatoid arthritis. International J Mol Sci 22(20): 10922. doi: 10.3390/ijms222010922
6. Li L, Shi B, Zheng W, Xing W, Zhao Y, Li F, Xin D, Jin T, Zhu Y, Yang X (2017). Association of IL-1A and IL-1B polymorphisms with ankylosing spondylitis among the Chinese Han population: a case-control study. Oncotarget 8(17): 28278. doi: 10.18632/onco-

target.15771
7. Lukens JR, Gross JM, Calabrese C, Iwakura Y, Lamkanfi M, Vogel P, Kanneganti TD (2014) Critical role for inflammasome-independent IL-1β production in osteomyelitis. Proc Natl Acad Sci 111(3): 1066-1071. doi: 10.1073/pnas.1318688111
8. McInnes, I. B, Schett, G. (2011). The pathogenesis of rheumatoid arthritis. N Engl J Med 365(23): 2205-2219. doi: 10.1056/NEJMra1004965
9. Petrackova A, Horak P, Radvansky M, Fillerova R, Smotkova Kraiczova V, Kudelka M, Mrazek F, Skacelova M, Smrzova A, Kriegova E (2020) Revealed heterogeneity in rheumatoid arthritis based on multivariate innate signature analysis. Clin Exp Rheumatol 38(2):289-298. doi: 10.55563/clinexprheumatol/qb2ha3.
10. Saberi D, Ott B, Dahlke C, Matschke V, Schmitt-John T, Theiss C (2016) The Spatiotemporal Pattern of Degeneration in the Cerebellum of the Wobbler Mouse. J Neuropathol Exp Neurol 75(4):347-57. doi: 10.1093/jnen/nlw005.
11. Witkin SS, Gerber S, Ledger WJ (2002) Influence of interleukin-1 receptor antagonist gene polymorphism on disease. Clin Infect Dis 34(2)204-9. doi: 10.1086/338261. Epub 2001 Dec 7. PMID: 11740709.
12. Yao ZL, Lin QR, Hu YJ, Hou YL, Ma YF, Yu B, Jiang N (2019) Interleukin-1 Beta Gene Polymorphism rs16944 May Associate with Increased Susceptibility to Extremity Chronic Osteomyelitis in Chinese Han Population. Biomed Res Int 7483537. doi: 10.1155/2019/7483537.
13. Yu Y, Zhang Y, Wu J, Sun Y, Xiong Z, Niu F, Lei L, Du S, Chen P, Yang Z (2019) Genetic polymorphisms in IL1B predict susceptibility to steroid-induced osteonecrosis of the femoral head in Chinese Han population. Osteoporos Int 30(4):871-877. doi: 10.1007/s00198-019-04835-9.
14. Jurisic V (2020) Multiomic analysis of cytokines in immuno-oncology. Expert Rev Proteomics 17(9): 663-674. doi: 10.1080/14789450.2020.1845654
15. Koudriavtseva T, Mainero C (2016) Neuroinflammation, neurodegeneration and regeneration in multiple sclerosis: intercorrelated manifestations of the immune response. Neural Regen Res 11(11): 1727. doi: 10.4103/1673-5374.197125