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Original Article

Molecular Analysis of SLC22A4 Gene Polymorphisms (Rs3792876, Rs1050152) in Palindromic Rheumatism and Rheumatoid Arthritis

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Abstract

Introduction: Palindromic rheumatism (PR) is an inflammatory rheumatic disease distinguished by episodic, self-limiting flares of arthritis or periarthritis. It may progress over time to other rheumatic diseases, particularly rheumatoid arthritis (RA). SLC22A4, located on chromosome 5, encodes an organic cation transporter (OCTN1) that mediates the transport of small molecules across cell membranes. Immune cells express OCTN1, which regulates oxidative stress, cell survival, and inflammatory signaling by transporting specific small molecules. This study analyzes the SLC22A4 gene polymorphisms in PR and RA patients compared to healthy controls (HCs).

Methods: We included 27 PR patients; 40 RA patients and 40 HCs matched for age and gender. All participants were Azeri. The SLC22A4 (rs3792876 and rs1050152) polymorphisms were genotyped.

Results: No notable differences were detected between the PR and control groups in the distribution of rs3792876 genotypes (CC, CT) and alleles (C, T). In addition, we examined the frequencies of rs1050152 genotypes (CC, CT, TT) and alleles (C, T) between the studied groups. No significant differences were detected.

Conclusion: The similar distribution of genotypes and alleles across study groups indicates that these variants are unlikely to play a major role in susceptibility to PR or RA in the Azeri population. Future research should include larger sample sizes, additional candidate polymorphisms, and exploration of potential gene–gene and gene–environment interactions to more comprehensively define the genetic landscape underlying PR and RA.

Introduction

Palindromic rheumatism (PR) is a type of inflammatory rheumatic disease characterized by episodic, self-limiting attacks of arthritis or periarthritis. Although PR is relatively rare, with a prevalence of 7 to 21 out of every 100,000 individuals,[1] the condition may transition to other rheumatic diseases over time, especially rheumatoid arthritis (RA).[2] The pathology of PR is not well understood; however, it exhibits features that overlap with both autoimmune and autoinflammatory diseases [1], and genetic factors likely play a significant role in its development.[1] The upregulation of tumor necrosis factor (TNF)-α and interleukin (IL)-6, along with augmented levels of IL-17 and IL-23,[3,4] together with findings of mild neutrophil infiltration, synovial hyperplasia, and immune-complex deposition in synovial blood vessels,[5] all support the involvement of immune dysregulation in the pathogenesis of PR. The familial occurrence of PR,[6] its associations with HLA class I and II alleles,[7–10] its association with single-nucleotide polymorphisms (SNPs) in the TNF-α receptor 1 (TNFRSF1), IL-10, and interferon regulatory factor 4 (IRF4) genes,[11–12] as well as the higher frequency of Mediterranean Fever gene variants in autoantibody-negative PR patients [8], all support a significant role for genetic factors in the pathogenesis of PR.

SLC22A4, located on chromosome 5, encodes an organic cation transporter (OCTN1) that mediates the transport of small molecules across cell membranes.[13] OCTN1, transports small molecules, such as ergothioneine and other endogenous metabolites involved in cellular redox balance.[14] Immune cells, particularly neutrophils, macrophages, and T cells, express OCTN1, which regulates oxidative stress, cell survival, and inflammatory signaling by transporting specific small molecules.[14] SLC22A4 gene polymorphisms by disrupting this transport can lead to

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heightened inflammatory responses.[15,16] Polymorphisms in SLC22A4, especially rs3792876 and rs1050152, have shown a relationship with several autoimmune and inflammatory diseases, including RA and Crohn's disease.[15-17]

Considering the proposed autoimmune nature of PR and the progression of some PR patients to RA, this study analyzes the SLC22A4 gene polymorphisms rs3792876 and rs1050152 in PR and RA patients compared to healthy controls (HCs).

Materials and Methods

Patient Selection and Study Protocol

Data for this cross-sectional study were obtained from 27 patients diagnosed with PR, 40 patients with RA, and 40 HCs matched for age and gender. PR patients were diagnosed according to the criteria of Hannonen et al. [18], and RA patients according to the 2010 ACR/EULAR criteria. All participants were aged ≥ 18 years, Azeri, and free of other autoimmune or autoinflammatory diseases, whereas HCs had no history of autoimmune or autoinflammatory disorders.

Written informed consent forms were obtained from all participants prior to enrollment, and the study was conducted in accordance with ethical guidelines. We have obtained approval under the ethical code IR.TBZMED.REC.1401.457 from the Tabriz University of Medical Sciences, Tabriz, Iran.

DNA Extraction and Genotyping

For both the patient and control groups, 5 mL of peripheral blood was collected into sterile EDTA tubes. Genomic DNA was extracted immediately from whole blood samples using a commercial DNA extraction kit (GeneALL, Seoul, South Korea), according to the manufacturer's instructions. Total RNA was extracted from the collected blood samples using the appropriate RNA extraction kit, following the manufacturer's protocol. The quality and quantity of the extracted RNA were assessed using a NanoDrop spectrophotometer, ensuring that the RNA integrity was suitable for cDNA synthesis. The quality of the extracted DNA was verified by measuring the DNA concentration using a NanoDrop spectrophotometer (NanoDrop One/Onec, Thermo Scientific, USA). Primers used in the Tetra-ARMs PCR for the evaluation of SLC22A4 gene SNPs were designed based on the NCBI database and purchased from SinaClonBioScience, as shown in Table 1. The Tetra-ARMs PCR technique was employed for the detection of SNPs in the genomic DNA, by specific primers for mutant and wild-type alleles using a commercial master mix (Cat. No: 5200350-0050, Lot. No: 13C18, Amplicon, Denmark) in a Step OnePlus™ Real-Time PCR system (Applied Biosystems, California, USA). The PCR reaction was set up in a 10-µl final volume, which comprised 1 µl (25 ng) of genomic DNA, 5 µl of Real-time PCR master mix, 0.2 µl (0.2 µM) of each primer, and 3.6 µl of DNase-free water. Duplicate assessments were performed for all genes. Additionally, a no-template control (NTC) was added for each gene to ensure that any detected signal was not due to DNA contamination.

Statistical Analysis

Statistical analyses were performed using SPSS software (version 16; IBM SPSS Inc., Chicago, IL, USA). SNPs were tested for compliance with the Hardy–Weinberg equilibrium using a chi-square test. Genotype frequencies among the PR, RA, and HC groups were compared using chi-square analysis. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were subsequently calculated.

Results

Two SLC22A4 SNPs—rs3792876 and rs1050152— were genotyped in a total of 27 subjects with PR, 40 with RA, and 40 healthy controls (HCs). Table 2 provides an overview of the participants' demographic and clinical profiles. No meaningful differences in age or sex distribution were detected among the study groups. The genotype and allele frequencies of the SNPs in the HC population were consistent with Hardy-Weinberg equilibrium.

We compared the frequencies of rs3792876 genotypes (CC, CT) and alleles (C, T) between the PR and control groups (Table 3, Figure 1). The CC genotype and the C allele were the most prevalent in all groups. No significant differences were observed in the distribution of either genotypes or alleles between the groups. In addition, we examined the frequencies of rs1050152 genotypes (CC, CT, TT) and alleles (C, T) between the PR and control

Table 1. Primer sequences and characteristics for TETRA-ARMS PCR assays

GENE	Primer Type	Sequence 5'----------> 3'	TM	GC%	Mer
SLC22A (rs1050152)	Forward- Outer	5′-TCAAGAGTGCCCAGAGAGTCCT	62.5	54.55	22
SLC22A (rs1050152)	Forward- Inner	GGTAGTCTGACTGTCCTGATTAGAATCC	65.12	46.43	28
SLC22A (rS1050152)	Reverse- Inner	AACTTGCAGGGAAAAAAAGGGTGAA	59.7	40	25
SLC22A (rs1050152)	Reverse- Outer	TGTGCCCAGCCAACAATATGCT	60.25	50	22
SLC22A (rs3792876)	Forward- Outer	CGACTGGTAGTGGAGTTGATGGAG	64.43	54.17	24
SLC22A (rs3792876)	Forward- Inner	AGGCGAGACAGGTTATGTGGC	61.78	57.14	21
SLC22A (rs3792876)	Reverse- Inner	CAGGGGAAGAGGCATTATCCTTCA	62.72	50	24
SLC22A (rs3792876)	Reverse- Outer	ACCCGTGAGCAATGTCCCAG	61.40	60	20

Tetra-ARMs, Tetra-Amplification Refractory Mutation System; PCR, polymerase chain reaction.

groups (Table 3, Figure 2). Similarly, the CC genotype and the C allele were the most common across all groups, and no significant differences were detected in genotype or allele distributions.

Discussion

Genetic factors are of great importance in the pathogenesis of RA, with heritability estimates ranging from 50% to 60%.[19] Evidence from twin and familial studies further supports this genetic contribution: concordance rates of approximately 12–15% in monozygotic twins and around 5% in dizygotic twins indicate that while genetics is influential, it is not solely responsible for disease development.[19,20] Given that 20–70% of PR cases progress to RA and considering the substantial clinical and immunological overlap between these conditions—including the presence of RA-specific autoantibodies in most PR patients, the high prevalence of hand joint involvement, and the association of both conditions with shared epitope (HLA-DRB1) alleles—many researchers have proposed that PR represents an early or variant form of RA.[7,21-24]

Despite the strong genetic basis of RA, however, genetic association studies often yield inconsistent results across different ethnic populations.[20] Several susceptibility genes that are well established in European and East Asian cohorts—such as PTPN22, PADI4, STAT4, IRAK1, and TRAF1/C5—have not shown significant associations with RA in Iranian studies.[20] These discrepancies underscore the importance of population diversity in genetic research and illustrate how ethnic background may influence both the detection and magnitude of genetic effects.

In this context, we investigated two polymorphisms within SLC22A4 (rs3792876 and rs1050152), a gene implicated in immune regulation and previously associated with autoimmune diseases in the Azeri population of Iran. Despite their biological relevance, our study found no notable differences in the genotype

Table 2. Demographic and clinical characteristics of participants

Variables	PR group (n = 27)	RA group (n = 40)	HC group (n = 40)
Age (years), mean ± SD	48.4 ± 13.1	50.1 ± 12.8	52.9 ± 13.6
Female (%)	16 (59.3)	26 (65)	26 (65)
Disease duration (months), median (IQR)	51 (20.5, 96)	56 (27,134)	-
Involved Joints			
PIP (%)	16 (59.3)	34 (85.0)	-
MCP (%)	17 (63.0)	25 (62.5)	-
Wrist (%)	16 (59.3)	32 (80.0)	-
Elbow (%)	8 (29.6)	9 (22.5)	-
Knee (%)	17 (63.0)	17 (42.5)	-
Shoulder (%)	15 (55.6)	7 (17.5)	-
Ankle (%)	9 (33.3)	8 (20.0)	-
MTP (%)	7 (25.9)	3 (7.5)	-
Periarticular (%)	15 (55.6)	0	-
Autoantibodies			
RF (%)	16 (59.3)	24 (60.0)	-
ACPA (%)	17 (63.0)	35 (87.5)	-

PR: palindromic rheumatism; RA, rheumatoid arthritis; HC, healthy control; SD, standard deviation; IQR, interquartile range; PIP, proximal interphalangeal; MCP, metacarpophalangeal; MTP, metatarsophalangeal; RF, rheumatoid factor; ACPA, anti-citrullinated C peptide.

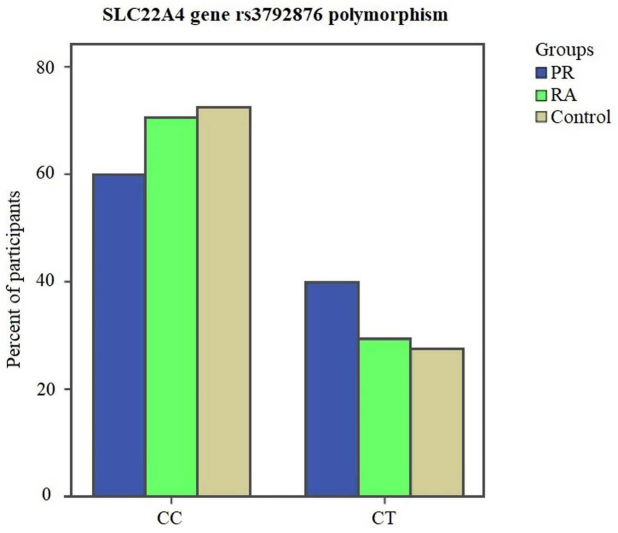

Figure 1. Frequency of rs3792876 genotypes in the studied groups. PR, palindromic rheumatism; RA, rheumatoid arthritis

Table 3. Genotype of SLC22A4 SNPs in the studied groups

Polymorphisms		PR group N (%)	RA group N (%)	OR (95%CI)	*P*-value	HC group N (%)	OR (95%CI)	*P*-value
rs3792876								
Genotype	CC	16 (59.3)	28 (70.0)	Reference		29 (72.5)	Reference	
	CT	11 (40.7)	12 (30.0)	1.60 (0.58-4.46)	0.436	11 (27.5)	1.81 (0.64-5.10)	0.297
Allele	T	11 (20.4)	12 (15.0)	Reference		11 (13.8)	Reference	
	C	43 (79.6)	68 (85.0)	0.69 (0.27-1.73)	0.284	69 (86.2)	0.64 (0.25-1.63)	0.241
rs1050152								
Genotype	CC	13 (48.1)	24 (60.0)	Reference		26 (65.0)	Reference	
	CT	12 (44.4)	13 (32.5)	1.70 (0.62-4.68)	0.308	12 (30.0)	2.1 (0.71-5.66)	0.189
	TT	2 (7.4)	3 (7.5)	1.23 (0.18-8.13)	0.876	2 (5.0)	2.0 (0.25-15.89)	0.506
Allele	T	16 (29.6)	19 (23.7)	Reference		16 (20.0)	Reference	
	C	38 (70.4)	61 (76.3)	0.74 (0.34–1.61)	0.45	64 (80.0)	0.59 (0.27–1.32)	0.200

PR, palindromic rheumatism; RA, rheumatoid arthritis; HC, healthy control; OR, odds ratio; CI, confidence interval.

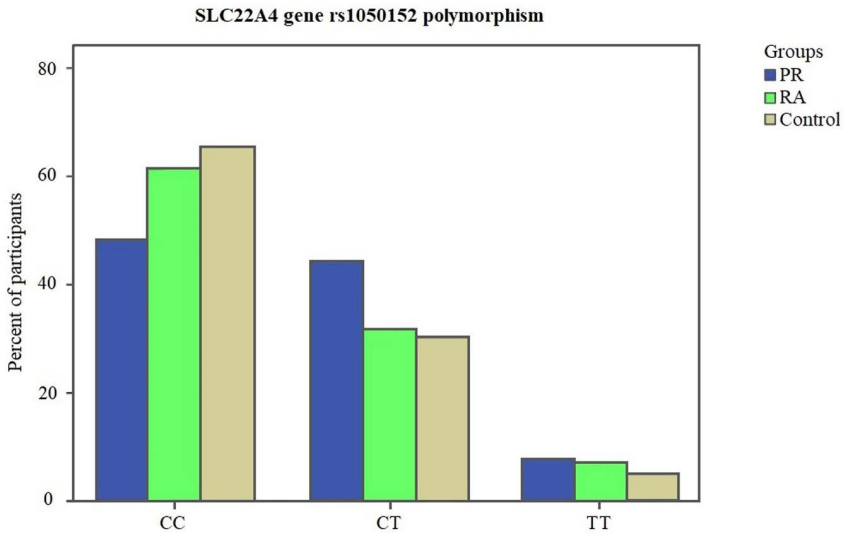

Figure 2. Frequency of rs1050152 genotypes in genotypes in the studied groups. PR, palindromic rheumatism; RA, rheumatoid arthritis

or allele distributions of these SNPs among PR patients, RA patients, and healthy controls. These findings align with prior Iranian studies reporting no association between SLC22A4 variants and RA. Furthermore, studies from Canada, Spain, and Japan have similarly failed to identify significant associations between these SLC22A4 polymorphisms and RA.[25–28] Collectively, these negative findings suggest that the contribution of SLC22A4 to RA susceptibility may be modest, population-specific, or influenced by gene–environment or gene–gene interactions that vary across ethnic groups.

Based on our current knowledge, this represents the first study to examine SLC22A4 genetic variation in PR and RA in an Iranian cohort. Nonetheless, our study has an important limitation: the comparatively small number of subjects. Because of the small sample size in each group, we were unable to adjust for possible confounders such as age, sex, disease duration, and autoantibody status in a multivariable framework. The limited number of subjects reduced the statistical power of adjusted models and may have contributed to the absence of significant associations. It is therefore possible that the lack of association may reflect limited statistical power in addition to potential ethnic differences. Larger, well-powered, multi-center studies will be necessary to more accurately assess the role of SLC22A4 polymorphisms in PR and RA susceptibility in Iran and to clarify whether these SNPs exert subtle or indirect effects that were not detectable in our sample.

Conclusion

In summary, the analysis of SLC22A4 polymorphisms rs3792876 and rs1050152 revealed no significant associations with RA or palindromic rheumatism compared with healthy controls. The similar distribution of genotypes and alleles across study groups indicates that these variants are probably not a significant factor in the risk of developing PR or RA among Iranians. These findings contribute to the broader understanding of genetic determinants of rheumatic diseases and reinforce the hypothesis that the genetic architecture of RA is complex and population-specific. Future research should include larger sample sizes, additional candidate polymorphisms, and exploration of potential gene–gene and gene–environment interactions to more comprehensively define the genetic landscape underlying PR and RA.

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Competing Interests
No potential conflict of interest was reported by the authors.

Consent for Publication
The patients provided written consent for the publication of their clinical information.

Data Availability Statement
The corresponding author will provide the data that support the findings of this study upon request.

Ethical Approval
The Institutional Review Board and Research Ethics Committees of Tabriz University of Medical Sciences in Tabriz, Iran (IR.TBZMED.REC.1401.457) approved the present study. Approval of the study protocol was also granted by the research ethics committees. Written informed consent was obtained from all participants in accordance with the relevant guidelines and regulations.

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