REV BRAS REUMATOL. 2015;xxx(xx):xxx–xxx

REVISTA BRASILEIRA DE REUMATOLOGIA

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Original article

Association of *PDCD1* polymorphism to systemic lupus erythematosus and rheumatoid arthritis susceptibility

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ARTICLE INFO

Article history:
Received 4 July 2014
Accepted 6 May 2015
Available online xxx

Keywords:
Rheumatoid arthritis
Systemic lupus erythematosus
Autoimmunity
PDCD1 gene
PD1.3 polymorphism

ABSTRACT

Objective: This study aims to analyze the relationship of programmed cell death 1 (*PDCD1*) gene polymorphism (*PD1.3G/A* – rs11568821) with features of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) in a Southern Brazilian population.
Methods: Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was performed in 95 SLE and 87 RA patients and 128 control group individuals from Santa Catarina, Southern Brazil. The Hardy–Weinberg equilibrium (HWE) test, and odds ratio (OR) were analyzed, considering CI 95% and $p \leq 0.05$.
Results: The *PD1.3A* allele frequencies were 0.095 (SLE), 0.115 (RA) and 0.078 (controls). The genotypes of the control group were in HWE, while those of SLE and RA patients were not. However, we found no association between *PD1.3* polymorphism and the SLE or RA susceptibility, nor clinical or epidemiological data.
Conclusion: There was no significant association between *PD1.3* polymorphism and SLE or RA susceptibility in this Southern Brazilian population.

Associação do polimorfismo do gene *PDCD1* à susceptibilidade ao Lúpus Eritematoso Sistêmico e à Artrite Reumatoide

Palavras-chave:
Artrite reumatoide
Lúpus eritematoso sistêmico

RESUMO

Objetivo: Este estudo teve como objetivo analisar a relação entre o polimorfismo do gene *PDCD1* (Programmed cell death 1) (*PD1.3G/A* – rs11568821) com caraterísticas do lúpus eritematoso sistêmico (LES) e da artrite reumatoide (AR) em uma população do sul do Brasil.

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http://dx.doi.org/10.1016/j.rbre.2015.07.008
2255-5021/

Autoimunidade
Gene *PDCD1*
Polimorfismo *PD1.3*

Métodos: A técnica de PCR-RFLP (*Polymerase Chain Reaction-Restriction Fragment Lenght Polymorphism*) foi utilizada para analisar amostras de 95 pacientes com LES e 87 com AR e 128 indivíduos do grupo controle de Santa Catarina, sul do Brasil. Foi analisada a probabilidade de equilíbrio de Hardy–Weinberg (EHW) e o odds ratio (OR), considerando um IC 95% e $p \leq 0.05$.
Resultados: As frequências alélicas *PD1.3A* foram de 0,095 (LES), 0,115 (AR) e 0,078 (controles). Os genótipos do grupo controle estavam em EHW, enquanto aqueles dos pacientes com LES e AR não estavam. No entanto, não foi encontrada nenhuma associação entre o polimorfismo *PD1.3* e a susceptibilidade ao LES ou à AR, nem com dados clínicos ou epidemiológicos.
Conclusão: Não foi encontrada associação significativa entre o polimorfismo *PD1.3* e a susceptibilidade ao LES ou à AR nesta população do sul do Brasil.

Introduction

Autoimmune rheumatic diseases share clinical findings and are caused by multiple factors including a complex genetic basis coupled with non-genetic factors, which contribute in different degrees for each affected individual.[1] Genetic polymorphisms of the human genome have been investigated and new evidence of genetic contribution to rheumatic diseases has been discovered. Among autoimmune diseases, systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), have been the main targets of genetic variation studies, once they represent multisystem disorders with a wide spectrum of clinical manifestations.[1,2]

SLE affects mainly women of reproductive age, and its major characteristic is the production of autoantibodies against nuclear antigens, as double stranded DNA (dsDNA), ribonucleoproteins (RNP) and Smith (Sm) antigen; as well as cytoplasmic, and cell-surface antigens.[3] These autoantibodies deposit on several organs causing inflammation and leading to symptoms that could range from subtle to life-threatening. Constitutional manifestations including fever, fatigue and weight loss may occur, as well as joint pain due to arthritis, malar and discoid rashes, photosensitivity, and involvement of the central and peripheral nervous system, kidneys, heart and lungs.[1] Progression of the disease is individual and heterogeneous, so different biomarkers have been sought in order to unveil disease susceptibility and development as well as to guide therapeutic decisions.[4,5]

RA pathogenesis is complex and results in chronic inflammation of joints and, in many patients, systemic complications, such as subcutaneous nodules, pulmonary involvement and early atherosclerosis, that may be challenging regarding treatment.[6] In order to come to better prognosis and outcomes in RA, the development of biomarkers that allow disease sub-categorization are needed.[7] So far, serologic factors such as rheumatoid factor (RF) and anti-citrullinated protein autoantibodies (ACPA); and the acute inflammation marker C-reactive protein (CRP), have helped classifying RA clinical phenotypes.[8–11] Rheumatoid factor is an autoantibody directed against the Fc portion of IgG, and correlates with the severity of the disease[12]; whereas the ACPA are directed against citrullinated proteins, and can also help to predict a more severe and erosive disease.[13]

Although the etiology of SLE and RA are not well established, it is hypothesized that deregulated lymphocyte activation play an important role in the breakdown of immune tolerance, leading to autoreactivity.[2,14] Involved in this processes, co-stimulatory molecules are critical for the balance between T cell activation and inhibition.[15] Among those, the programmed cell death 1 (PD-1) is shown to be an important molecule involved in profound loss of self-tolerance leading to rapid lethality associated with lymphocyte infiltration in many organs.[16] This protein is expressed on the surface of T, B and myeloid cells, and is a member of the CD28 family that belongs to the immunoglobulin superfamily and acts as an inhibitory molecule on T cells, after interacting with its ligands PDL-1 and PDL-2 (programmed cell death 1 ligand 1 and 2).[17] After initial activation of T cell interactions, PD-1-PD-L may limit autoreactive T cell proliferation and cytokine production, whereas stimulated by antigens the PD-1 dampens T cell receptor (TCR) signaling. The amount of expression of PD-1 and the degree of involvement between this protein and its ligands regulate the threshold of T cell activation and the amount of cytokines produced.[18,19] PD-1-deficient mice develop spontaneous autoimmune diseases, indicating an essential function of PD-1 in the mechanisms of tolerance.[20–23]

PD-1 is encoded by the *PDCD1* gene, located at 2q37.3 *locus*. Among the SNPs found within this region, the *PD1.3G/A* (rs11568821) potentially represents a functional polymorphism associated with the transcriptional regulation of PD-1.[24] The *PD1.3A* allele alters the binding site of RUNX1 (or AML1) transcription factor, located on the intron 4 enhancer region, which could lead to aberrant protein expression, suggesting a mechanism for the self-tolerance breakdown.[25,26] Association studies correlated the presence of the allele *PD1.3A* with SLE in Mexican and Scandinavian populations,[25] and with diabetes mellitus 1 and RA in Denmark and Sweden respectively.[26,27] However, some populations in Asia are non-polymorphic for this genomic region, presenting only the *PD1.3G* allele,[28–30] which emphasizes the diversity of allelic frequency among populations, and supports the necessity to study the association of this *PDCD1* polymorphism in other localities. In Brazil, three studies have evaluated the frequencies of *PD1.3* polymorphism. One in patients with pemphigus foliaceus (also an autoimmune disease),[31] in silica-exposed workers,[32] and in a cohort of patients with Chagas disease,[33] demonstrating the presence of both alleles in this population.

Please cite this article in press as: do Canto LM, et al. Association of *PDCD1* polymorphism to systemic lupus erythematosus and rheumatoid arthritis susceptibility. Rev Bras Reumatol. 2015. http://dx.doi.org/10.1016/j.rbre.2015.07.008