REVISTA BRASILEIRA DE REUMATOLOGIA

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SOCIEDADE BRASILEIRA DE REUMATOLOGIA

Review article

Genetics of rheumatoid arthritis: a new boost is needed in Latin American populations

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ARTICLE INFO

Article history:
Received 27 January 2015
Accepted 30 August 2015
Available online 19 November 2015

Keywords:
Rheumatoid arthritis
HLA
Genome wide association studies
Genetic susceptibility
Single nucleotide polymorphism

ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune inflammatory rheumatic disease which affects several organs and tissue, predominantly the synovial joints. Like many other autoimmune diseases, RA is a complex disease, where genetic variants, environmental factors and random events interact to trigger pathological pathways. Genetic implication in RA is evident, and recent advances have expanded our knowledge about the genetic factors that contribute to RA. An exponential increment in the number of genes associated with the disease has been described, mainly through gene wide screen studies (GWAS) involving international consortia with large patient cohorts. However, there are a few studies on Latin American populations. This article describes what is known about the RA genetics, the future that is emerging, and how this will develop a more personalized approach for the treatment of the disease. Latin American RA patients cannot be excluded from this final aim, and a higher collaboration with the international consortia may be needed for a better knowledge of the genetic profile of patients from this origin.

Genética da artrite reumatoide: é necessário um novo impulso em populações latino-americanas

Palavras-chave:
Artrite reumatoide
HLA
Estudo de associação genômica ampla
Susceptibilidade genética
Polimorfismo de nucleotídeo único

RESUMO

A artrite reumatoide (AR) é uma doença reumática inflamatória autoimune que afeta vários órgãos e tecidos, predominantemente as articulações sinoviais. Como muitas outras doenças autoimunes, a AR é uma doença complexa, em que variantes genéticas, fatores ambientais e eventos aleatórios interagem e desencadeiam vias patológicas. A implicação genética na AR é evidente e avanços recentes têm expandido nosso conhecimento sobre os fatores genéticos que contribuem para a doença. Houve um incremento exponencial na quantidade de genes associados à doença descritos, principalmente por estudos de associação genômica ampla (GWAS) que envolveram consórcios internacionais com grandes

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http://dx.doi.org/10.1016/j.rbre.2015.10.004

grupos de pacientes. No entanto, há poucos estudos em populações latino-americanas. Este artigo descreve o que é conhecido sobre a genética na AR, o que vem a seguir e como isso vai desenvolver uma abordagem mais personalizada para o tratamento da doença. Os pacientes latino-americanos com AR não podem ser excluídos desse objetivo final e pode ser necessária uma maior colaboração com os consórcios internacionais para se obter um melhor conhecimento do perfil genético dos pacientes provenientes dessa região.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune inflammatory rheumatic disease that affects many tissues and organs, mainly synovial joints. This disease leads to progressive destruction of articular cartilage and ankylosis of the joints.[1] Subsequent, pannus formation may lead to destruction of underlying cartilage and bony erosions. RA diagnosis is based on clinical criteria and laboratory tests.[2] Anti-citrullinated protein autoantibodies (ACPA) show a high specificity for RA, even ACPA testing has become a substantial component of the current American College of Rheumatology (ACR)-European League Against Rheumatism (EULAR) classification criteria for RA.[3] Additionally, it has been described that ACPA may play a role in disease pathogenesis.[4]

RA affects approximately 1% of the population worldwide.[5] In the last years, several epidemiological studies of RA have been published, showing variations in the incidence and prevalence of RA across populations. Most of the studies have been developed in countries from the North Europe and North America, estimating prevalences of 0.5–1.1%.[5] Another studies made mainly in countries from South Europe reported a lower prevalence around 0.3–0.7%.[6–8] The lowest prevalence data have been reported in areas from Africa and Asia, and the highest in Native American populations.[5] In fact, the prevalence of RA is 10 times higher among Canadian or Native Americans than Europeans (3% and 0.3%, respectively).[9,10] Although the disease can develop at any age, RA affects females more frequently than males and it is diagnosed mainly in age 40–60 years, although the mechanism by which gender influences the susceptibility to RA remains unclear. Other characteristic of RA is heterogeneity: patients do not form a homogenous population and some clinical RA subgroups, such as ACPA seropositive versus seronegative, erosive versus non-erosive, progressive versus mild-course, have been identified.[11–13]

RA genetics and pathogenesis

Like many autoimmune diseases, the etiology of RA is multifactorial. Genetic susceptibility is evident in familial clustering and monozygotic twin studies, with a 50% of RA risk attributable to genetic factors, and heritability of RA has been estimated to be about 60%.[4] Moreover, disease progression, outcome and RA phenotype have been associated with genetic factors.[11,14,15] Thus, understanding the genetics basis of RA is required in order to develop a more personalized approach for the disease treatment. RA genetic risk factors can be classified into two groups: (1) major histocompatibility complex (MHC) genes and (2) non-MHC regions. Interestingly, HLA and some non-HLA genes have been linked to the development of antibodies against citrullinated proteins, differentiating between two entities with distinctive characteristics, ACPA seropositive and seronegative RA.[16] Interestingly, several genetic polymorphisms have been described associated to environmental factors in RA patients, primarily smoking.[17] Smoking and possibly other environmental factors may trigger ACPA production and the development of ACPA seropositive RA (Fig. 1).[11,16] Although the etiology of RA has not been elucidated yet, their symptoms develop gradually in different phases.[18] In this development of the disease has been described a “preclinical phase”, in which several immunological markers, as ACPA or rheumatoid factor (RF), become positive sometimes years before of the onset of clinical symptoms. To sum up, RA develops in genetically predisposed individuals subjected to an unclear set of life events, specially smoking (Fig. 1).

HLA region

The genomic map of the human MHC (HLA) spans about 7.6 Mb and contains approximately 421 gene loci on a contiguous region on chromosome 6.[19] The classical HLA loci, which play a central role in the immune system, are called -A, -B, and -C (class I) and -DRB1, -DQB1, and -DPB1 (class II). Particularly, the HLA class I and class II genes encode for proteins that bind to small antigen peptides and carry them into the cell surface thus presenting them to the immune system. Therefore, this genomic region is crucial for the organism resistance and susceptibility to pathogenic factors.

It has been 35 years since it was published that the HLA region contributes to RA susceptibility, specifically HLA-DR4 allele,[20] but the exact mechanism that determines the predisposition is unknown. Among the HLA genes, the HLA-DRB1 shared epitope (SE) alleles that encode for a common amino acid sequence, is the most important risk factor described for RA susceptibility and progression.[21] The presence of SE suggest that the HLA alleles containing it bind the same antigen, postulating the presentation of arthritogenic self-peptides or molecular mimicry with foreign antigens,[22,23] and/or shaping the T-cell-antigen repertoire.[24] HLA-DRB1 SE alleles are strongly associated with ACPA-positive RA. Indeed, HLA-DRB1 SE alleles contribute in 18% to the heritability of ACPA-positive RA, whereas they only contribute in 2.4% to the heritability of ACPA-negative RA.[25] The relationship between HLA-DRB1 SE