THE ROLE OF GENETIC FACTORS IN SPONDYLOARTHROPATIES

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ABSTRACT

The spondyloarthropaties (SpAs) are chronic inflammatory diseases that involve the sacroiliac joints, axial skeleton, and, to a lesser degree, peripheral joints and certain extra-articular organs, including the eyes, skin, and cardiovascular system. Current research has demonstrated that genetics play an integral role in the development of SpAs. Genome screens have identified regions that may contain susceptibility genes for SpAs. The spondyloarthropaties are associated strongly with HLA-B27, an HLA class-I gene. Several genotypic subtypes of HLA-B27 are associated with the SpAs, with HLA-B*2705 having the strongest association. HLA-B*2702, *2703, *2704, and *2707 are also associated with ankylosing spondylitis (AS). HLA-B27-restricted CD8+ (cytotoxic) T cells may play an important role in bacterial-related SpAs such as reactive arthritis. It has been shown that the presence of the genetic marker HLA-B27 increases the likelihood of developing AS. HLA-B27 testing is of limited value. It is important to note that being HLA-B27 positive does not mean that someone will get ankylosing spondylitis (AS) nor does the gene appear in all those who have AS. The pathogenesis of SpAs is linked to a genetic predisposition (essentially HLA-B27). This article reviews the literature concerning the genetics in the most common SpAs.

Keywords: genetic disorders, spondyloarthropathies

Spondyloarthropathies (SpAs) are prevalent and disabling diseases, presenting mainly with spondylitis, pauciarticular peripheral arthritis and enthesopathy. Ankylosing spondylitis (AS), which literally means "inflamed spine growing together" is the prototypical SpA. The SpAs, a group of diseases affecting the spine and other joints, occur in 0.2-1% of the population with a male:female ratio of 3:1. Diagnosis is based primarily on the history and physical examination. There are no specific diagnostic tests for SpAs. Supporting laboratory findings include absence of rheumatoid factor, elevation of the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level, and presence of anemia of chronic disease. The SpAs are associated with other kinds of chronic inflammation for example of the bowel, the genito-urinary tract, or the skin. The primary pathology of the SpAs is enthesitis with chronic inflammation, including $CD4^+$ and $CD8^+$ T lymphocytes and macrophages. Hereditary factors are noted and there is a possibility of different variants of these syndromes, occurring within families (1,2).

The disease prevalence also parallels the frequency of the HLA-B27 allele in different populations. HLA-B27 itself is a serologic specificity, which encompasses 25 different alleles that encode 23 different products (proteins): HLA-B*2701 to B*2723. These alleles may have envolved from the most widespread subtype. Substantial evidence strongly favors a direct role for HLA-B27 in genetic susceptibility to AS and related SpAs, although the underlying molecular basis has yet to be identified. HLA-B27 contributes only 16-50% of the total genetic risk for the disease, clearly indicating that other genes must be involved (3,4).

The SpAs constitute a group of inflammatory joint diseases linked by shared characteristics that include a strong common genetic background. Persons who carry HLA-B27 marker have a 20-fold

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higher risk of developing SpAs, such as AS and reactive arthritis, than those lacking the genetic marker. Otherwise, having HLA-B27 marker did not appear to significantly affect the clinical manifestations of AS. Persons who were HLA-B27 positive had an earlier onset age of AS than people who were HLA-B27 negative. AS develops in 2-6% of unrelated HLA-B27 positive individuals. The risk for the disease increases to 20% in cases of HLA-B27 positive relatives of a diseased person, whereas almost no risk exists for HLA-B27 negative relatives (5-7).

However, no other putative disease genes have yet been absolutely proven. Genetic factors include major histocompatibility complex (MHC) genes, among which HLA-B27 contributes 30% of the overall genetic susceptibility to SpAs, and non-MHC genes, none of which have been identified to date. Potential genes include MHC (HLA class II, low molecular weight proteasome (LMP) transporter associated with antigen processing (TAP), tumor necrosis factor (TNF)-alpha, and major histocompatibility complex class I chain-related gene A (MICA), as well as non-MHC genes (IL-1RA, IL-6, IL-10, and CYP2D6). Genome-wide screens have identified other chromosomal areas of interest: 1p, 2q, 6p, 9q, 10q, 18q, and 19q. Significant linkage to SpAs on 9q31-34 (8,9). 90-94 percent of people with AS have the HLA-B27 gene. 7-10 percent of the general population have the HLA-B27 gene (depending on the region). HLA-B60 and B61 are strongly associated with AS in HLA-B27 negative. Scientists are working to find the other genes involved in the SpAs (10,11).

The agreement in the scientific community is that these diseases are multifactorial, which means that they are the result of a combination of genetic predisposition and exposure to environmental factors (probably infections) that are still unknown. The polygenic nature of the disease needs further elucidation and study.

CONCLUSIONS

Spondyloarthropathies are a heterogeneous group of rheumatic disorders that commonly present with axial skeleton or sacroiliac joints involvement. Genetic factors play a part in the pathogenesis of SpAs. The spondyloarthropathies are linked by common genetics HLA class-I gene, HLA-B27. A strong genetic association with class I HLA-B27 gene (on chromosome 6) is described. Genetic factors, and in particular HLA-B27, refer to disease susceptibility. They are not sufficient for disease development. The associations with the HLA-B27 and diseases vary to a degree. Different studies have given conflicting results. The HLA-B27 is useful in orientating the diagnosis. It is not useful to test other siblings for the HLA-B27 if they do not have any symptoms that can be linked to a SpA. Therefore, it is not the presence of HLA-B27 by itself, but its association with the characteristic signs and symptoms of SpAs, which has relevance. In HLA-B27-negative AS patients, it was found that HLA-B60 occurred more frequently along with HLA-B61.

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