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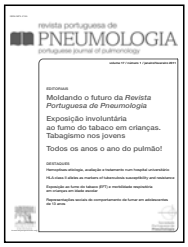

ARTIGO ORIGINAL

HLA class II alleles as markers of tuberculosis susceptibility and resistance

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KEYWORDS
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Abstract
Background: Not every individual exposed to *Mycobacterium tuberculosis* becomes infected. One host genetic factor, involved in modulating the immune response that has been studied in many ethnic groups is the association of human leukocyte antigens (HLA) with susceptibility to tuberculosis (TB).
Objective: To investigate the association between TB, HLA-DRB1 and HLA-DQB1 alleles in a Portuguese population.
Methods: HLA-DRB1 and HLA-DQB1 gene polymorphisms were analyzed by PCR-SSP in 92 TB patients, and 82 healthcare professionals without TB but exposed on a daily basis to infectious patients for more than two years (healthy exposed - HE). Tuberculin skin test reaction (TST), was positive in 69 individuals (all over 15 mm) in the HE group (HE+) and negative in thirteen (HE—).
Results: HLA-DRB1*14 frequency is higher in the TB patients group (7% vs. 0; $p = 0.038$) than in HE+.
Conclusions: No genetic marker clearly indicative of disease susceptibility or resistance was identified in this study. However, HLA-DRB1*14 was more frequent in TB patients suggesting that it may be involved in the evolution infection towards active TB in our population.

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PALAVRAS-CHAVE
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Tuberculose;
Susceptibilidade;
Resistência;
Profissionais de saúde

O papel do HLA classe II na susceptibilidade/resistência à tuberculose

Resumo
Introdução: Nem todos os indivíduos expostos ao *Mycobacterium tuberculosis* ficam infectados. Um dos factores genéticos envolvidos na modulação da resposta imune e estudado em muitos grupos étnicos é a associação entre moléculas HLA *(human leukocyte antigens)* e a susceptibilidade à tuberculose (TB).
Objectivo: Investigar a relação entre TB e os alelos HLA-DRB1, DQB1 numa população Portuguesa.
Métodos: Os polimorfismos dos genes HLA-DRB1 e HLA-DQB1 foram analisados por PCR-SSP em 92 doentes com TB e 82 profissionais de saúde saudáveis, expostos diariamente a doentes baciliferos por um período superior a 2 anos (expostos saudáveis: ES). Neste grupo de ES, o teste tuberculínico foi positivo (TST ≥ 10 mm) em 69 indivíduos (todos com valor superior a 15 mm) (ES+) e negativo (TST < 10 mm) em 13 (ES—). Resultados: A frequência do alelo HLA-DRB1*14 é superior no grupo de doentes com tuberculose em relação ao grupo de ES+ (7% vs. 0; p = 0,038).
Conclusões: Não foi identificado neste estudo, nenhum marcador genético de susceptibilidade/resistência à doença. No entanto, o alelo HLA-DRB1*14 foi mais frequente nos doentes com tuberculose, sugerindo que possa estar envolvido na evolução da infecção para tuberculose activa na nossa população.

Introduction

Infection with *Mycobacterium tuberculosis* (MT) results in a variety of conditions ranging from asymptomatic infection to active tuberculosis (TB) with pulmonary or extrapulmonary involvement. In extreme cases MT infection may be fatal. One third of the World's population is infected with MT;[1] however, only a minority ever develop clinical disease. In 90% of infected individuals, bacilli remain under control in a latent state[2] (latent TB infection).

The various clinical features of TB result from cell-cell interactions that are promoted by cytokines produced by immune cells in response to MT infection. Studies of the diverse consequences of infection in twins[3] and under similar exposure conditions in a familial context[4] suggest the importance of genetics in susceptibility and/or resistance to TB. Several case-control studies have identified associations between TB disease and gene polymorphisms. Among the candidate genes potentially involved in the immune response to TB are the murine natural resistance-associated macrophage protein 1 (NRAMP1) gene,[5] the vitamin D receptor (VDR) gene,[6-8] tumor necrosis factor alpha (TNFα,[9] IL-10,[10-12] and IL-1.[13]

HLA class II molecules are crucial in modulating the adaptative immune response, and their association with various diseases, including TB, has been described. However, results have been controversial concerning to TB,[14-20] with ethnic and/or geographic variations[21,22] apparently playing a major role in such discrepancies. The majority of published studies do not report MT exposure status in the control group and lack information about the role of HLA alleles and the outcome of TB infection.

In Portugal, the incidence of TB has been steadily decreasing since 1985, reaching a frequency of 25.3 per 100,000 individuals in 2008[23] still higher than in the rest of the European Union.[24]

Some hospitals were once TB sanatoriums, and for several years maintained an important tradition of inpatient TB treatment. Until recently, there were no special measures to prevent against nosocomial transmission, and well-equipped isolation rooms have only become available in the last decade. However, after having worked in an inpatient setting with high TB exposure and without special conditions during the sanatorium phase, most are disease-free and/or uninfected.

The aim of this study was to evaluate allelic associations with outcome of TB exposure, particularly in healthcare professionals heavily exposed to TB in the past, focusing on the importance of HLA-DRB1 and HLA-DQB1 alleles.

Methods

Subjects

All individuals were vaccinated with bacillus Calmette-Guerin (BCG) at birth, according to the national guidelines.

Patients

Ninety-two unrelated TB patients (33 women and 59 men) at the Pneumologic Diagnostic Center of Vila Nova de Gaia (CDP), Portugal, were studied. All had newly detected, active pulmonary TB diagnosed using standard clinical, radiographic and bacteriological criteria. The diagnosis of TB was confirmed in all patients by positive sputum culture of *M. tuberculosis* (Table 1).

Healthy exposed

Eighty-two healthcare workers without active TB disease who had been exposed on a daily basis (for more than 8 hours a day in a confined environment) to infectious patients (inpatient and outpatient settings without protective