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The balance of expression of *PTPN22* splice forms is significantly different in rheumatoid arthritis patients compared with controls

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Abstract

Background: The R620W variant in protein tyrosine phosphatase non-receptor 22 (PTPN22) is associated with rheumatoid arthritis (RA). The *PTPN22* gene has alternatively spliced transcripts and at least two of the splice forms have been confirmed to encode different PTPN22 (LYP) proteins, but detailed information regarding expression of these is lacking, especially with regard to autoimmune diseases.

Methods: We have investigated the mRNA expression of known *PTPN22* splice forms with TaqMan real-time PCR in relation to *ZNF592* as an endogenous reference in peripheral blood cells from three independent cohorts with RA patients (n = 139) and controls (n = 111) of Caucasian origin. Polymorphisms in the *PTPN22* locus (25 SNPs) and phenotypic data (gender, disease activity, ACPA and RF status) were used for analysis. Additionally, we addressed possible effects of methotrexate treatment on *PTPN22* expression.

Results: We found consistent differences in the expression of the *PTPN22* splice forms in unstimulated peripheral blood mononuclear cells between RA patients and normal controls. This difference was more pronounced when comparing the ratio of splice forms and was not affected by methotrexate treatment.

Conclusions: Our data show that RA patients and healthy controls have a shift in balance of expression of splice forms derived from the *PTPN22* gene. This balance seems not to be caused by treatment and may be of importance during immune response due to great structural differences in the encoded PTPN22 proteins.

Background

It is well established that rheumatoid arthritis (RA) is a heritable disease with a substantial genetic influence on the outcome. *PTPN22* is one of the few undisputed genetic risk factors for RA that has been replicated in many Caucasian populations, and evidence for its being a true susceptibility gene is strong [1,2]. Since the discovery of the importance of PTPN22 in the function of lymphocytes [3,4], and especially after its association with different autoimmune diseases [1], several attempts have been made to explain the biological mechanism of how *PTPN22* gene variants may influence protein activity and subsequent differences in cell function. The best-associated polymorphism, rs2476601, which affects amino acid 620, is an R to W missense polymorphism that may alter the function of the protein. Many studies have focused on this change of function and have indeed found evidence for immune regulatory effects, suggesting that cells with the disease-associated allele may have a gain of function for PTPN22 resulting in stronger negative regulation of T-cell activation [5] and B-cell activation [6]. There is, however, evidence for other common genetic variants in the locus that associate with disease independently of rs2476601 [7], although the independent effect has been questioned [8], and recently another missense variant at amino acid 263, rs33996649 (an R to Q polymorphism) has been associated with RA [9]. Also, a genetic interaction was previously described between

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