

Ability of the PTPN22 1858C/T SNP to Predict RA Development

Summarized by Jon Giles, M.D.

A single nucleotide polymorphism (SNP) in the PTPN22 gene has recently been shown to associate with rheumatoid arthritis (RA) with a strength of association second only to that of the HLA region encoding the MHC class II “shared epitope” (SE). To date, the mechanism by which the altered PTPN22 gene contributes to the pathogenesis of RA has largely been unstudied. Here, Johansson et al (*Arthritis Res Ther* 2005;(8); R19) examine the prognostic ability of the PTPN22 1858C/T SNP, alone and in combination with other RA-associated biomarkers, to predict the development of RA.

Methods Samples were derived from an established population-based blood sample repository, the Medical Biobank of Northern Sweden. Early RA patients diagnosed at the University Hospital, Umea, Sweden who had donated to the Biobank before the onset of RA symptoms were identified. For each RA case, 4 controls matched for gender, age at sampling, and rural or urban residence were randomly selected. Samples were assayed for SE genes (DRB1*0404 and *0401 only), IgM, IgG, and IgA rheumatoid factor (RF) isotypes, anti-CCP antibodies, and the 1858C/T SNP of the PTPN22 gene.

Results 92 RA patients (69 women, 23 men) who had donated to the Biobank prior to the development of RA (pre-RA patients) were compared to 368 matched controls. The mean age of all subjects was 54 years. Among the RA patients, samples were banked a median of 2.4 years prior to the onset of RA symptoms.

The prevalence of the PTPN22 variant of interest (the 1858T variant) was significantly greater in RA pre-patients compared to controls (39.3% vs. 19.7%, respectively; $p < 0.001$). Thus, the diagnostic ability of the PTPN22 T variant to identify a pre-RA patient (sensitivity) was 39.3%, which was *more sensitive* than IgG RF (16.9%) or IgM RF (22%), of *comparable sensitivity* to anti-CCP antibodies (37.1%), and *less sensitive* than either of the two SE genes evaluated (55.6%). Combinations of the PTPN22 T variant with SE genes or anti-CCP antibodies were less sensitive than the PTPN22 T variant alone.

The diagnostic ability to exclude pre-RA by not detecting the PTPN22 T variant (specificity) was 80.3%, which was *more specific* than not detecting either SE genes (61.8%), but *less specific* than not detecting any of the RF isotypes (94.1 – 95.8%) or anti-CCP antibodies (98.6%). Since none of the controls demonstrated both the PTPN22 T variant and anti-CCP antibodies, the specificity of the combination was 100%.

In conditional logistic regression analysis, the odds of being a pre-RA patient if both the PTPN22 T variant and anti-CCP antibodies were present was 132 times greater than if the PTPN22 T variant and anti-CCP antibodies were both negative (95% CI 17.8 – 2720.9).

Both present vs. both absent	Odds Ratio for being a pre-RA patient	95% Confidence Interval
PTPN22 T variant and anti-CCP antibodies	132.03	17.84 – 2720.9
PTPN22 T variant and IgG RF	1.50	0.15 – 14.84
PTPN22 T variant and IgA RF	21.42	4.45 – 103.16
PTPN22 T variant and IgM RF	10.70	1.78 – 64.23

PTPN22 T variant and SE	7.85	3.03 – 20.30
-------------------------	------	--------------

Conclusions The PTPN22 T variant is associated with RA. The risk of developing RA is significantly associated with PTPN22 T variant carriage, particularly when in combination with anti-CCP antibodies.

Editorial Comment This is an interesting study that helps to identify the dynamics of a biomarker that may have some diagnostic capability in RA. In addition, the high specificity of the combination of PTPN22 polymorphisms with anti-CCP antibodies would suggest a possible interaction. The function of the protein encoded by the altered PTPN22 gene, lymphoid protein tyrosine phosphatase (Lyp), in the pathogenesis of RA has not been elucidated, although it also appears to be involved in other rheumatic and non-rheumatic auto-immune disorders.

The value of this study design is the ability to identify the potential interaction of altered PTPN22 gene expression and RA-associated factors as present *before* clinical disease has developed, implying that these processes may be active in the initiation steps of RA. Thus, better understanding of the initiation steps of RA coupled with early and reliable identification of pre-RA patients may eventually lead to preventive therapeutic interventions even before symptoms have developed.