ORIGINAL ARTICLE

Evidence for susceptibility determinant(s) to psoriasis vulgaris in or near *PTPN22* in German patients

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Introduction: Variant R620W of protein tyrosine phosphatase non-receptor type 22 (*PTPN22*) has consistently been reported as a susceptibility factor for several autoimmune diseases. We investigated its role in susceptibility to psoriasis, the relevance of possibly other disease-causing variants, and interdependency of the major risk factor for psoriasis at PSORS1.

Methods: R620W was tested in a case-control study initially with 375 German patients and then with an enlarged sample of an additional 418 patients. Analyses were extended to linkage disequilibrium (LD) based haplotypes. Potential interaction between risk haplotypes of *PTPN22* and the PSORS1 associated risk allele was tested by regression analysis. *PTPN22* coding sequence was determined in 20 patients carrying the risk haplotype. Association and regression analysis were also performed in the extended case-control study.

Results: R620W was not associated in either case-control study, while significant association (corrected for multiple testing) with one haplotype (C-4) of the LD block encompassing *PTPN22* as well with another haplotype (B-3) within an adjacent telomeric LD block was detected. No evidence for interaction between risk haplotype C-4 and the PSORS1 associated risk allele was found. Sequencing excluded other coding variants within *PTPN22* as a basis for association findings. Analysis of the extended study group confirmed association for haplotypes B-3 and C-4 and independence of risk haplotypes C-4 and PSORS1.

Discussion: We exclude a major role of *620W in German psoriasis patients but suggest that other susceptibility determinant(s) within non-coding regions of *PTPN22* or its proximity might exist acting independently of the major PSORS1 risk factor.

Psoriasis is a chronic inflammatory skin disease. It occurs worldwide, although the highest prevalence of 2–3% is found in central and northern Europe. The disease affects the skin with epidermal hyperproliferation, altered differentiation of keratinocytes, and lymphocytic infiltration. Considerable evidence implicates T cell-dependent immune responses in the pathogenesis of psoriasis vulgaris.[1] This evidence includes the presence of T cells at sites of inflammation, the beneficial effects of T cell-directed therapeutic strategies, and the association of disease susceptibility with certain *HLA-C* alleles.[1–6]

In an attempt to elucidate the contribution of non-HLA genes to susceptibility to psoriasis, we investigated two large samples of German patients with psoriasis vulgaris for association with a recently described variant (rs2476601; 1858C→T) in protein tyrosine phosphatase non-receptor type 22 (*PTPN22*) located on chromosome 1p13.2.[7 8] *PTPN22* encodes a key regulator of TCR signalling in memory/effector T lymphocytes.[9] Variant 1858C→T affects the proximal proline rich SH3-binding domain of PTPN22, resulting in a non-conservative substitution of arginine by tryptophane (R620W). This amino acid exchange weakens the binding of PTPN22 with C-terminal Src tyrosine kinase, an important suppressor in TCR signalling of the src family kinases Lck and Fyn.[7 8] Whereas the initial report of association of the missense mutation was with type 1 diabetes,[7] subsequent studies in rheumatoid arthritis,[8] systemic lupus erythematosus (an autoimmune disease with multi-organ involvement including the skin and the joints),[10] and Graves' disease,[11 12] suggest that the minor allele PTPN22*620W is a common genetic risk factor for organ specific as well as systemic autoimmune disorders. It is noteworthy that association with the four above mentioned diseases has been confirmed by several independent studies. The potential importance of the *PTPN22* variant as a predisposing factor for the dysregulation of lymphocytes in a variety of autoimmune disorders and the broad experimental evidence for a crucial role of adaptive immune responses in psoriasis vulgaris is the rationale for the present case-control studies. In addition, we wanted to investigate whether other disease causing variants within this gene exist. Therefore, in an exploratory case-control study of 375 patients, we extended the association analysis to linkage disequilibrium (LD) based haplotypes covering *PTPN22* and its flanking genomic region on chromosome 1p13.2. Since the *HLA-C* region (PSORS1) harbours the major risk factor for psoriasis, we also tested for its possible interactions with the haplotype encompassing *PTPN22*. Furthermore, to explore the role of possible other coding variants, all exons of *PTPN22* were sequenced in 20 psoriasis patients. Variants identified were tested in the case-control study. Finally, we extended the analyses at haplotype level for the two strongest associated haplotypes by including an independent case-control study of 418 patients and 561 controls. In the extended study the hypothesis of possible interaction with the PSORS1 risk allele was tested as well.

Abbreviations: htSNP, haplotype tag SNP; LD, linkage disequilibrium; SNP, single nucleotide polymorphism

METHODS

Probands

Our exploratory group of 375 single patients with psoriasis vulgaris was mainly recruited through dermatology clinics at two large psoriasis rehabilitation hospitals and has been described before.[13] Briefly, most of the patients had an early onset form ($\leqslant$40 years) of psoriasis vulgaris and no signs of joint involvement; 26.9% of patients had juvenile onset disease (younger than 16 years of age). The study, including recruitment of controls, was approved by the ethical committee of the University of Münster.

The replication cohort consisted of 418 cases exclusively with an early onset form of psoriasis vulgaris with 29.4% of patients with juvenile onset. The average age of onset (21.6 ± 9.8 years) and proportion of males (59%) were similar to those in the exploratory group. Correspondingly, patients with signs of joint involvement were excluded.

In the first set of 376 control probands, no psoriasis vulgaris was noted at the time of recruitment, when median age was 32 ± 10 years. The same was true for the second group of 561 control probands with a corresponding median age of 30 ± 9 years. In both samples 59% of probands were male. All were healthy blood donors and were recruited in northern Germany. All patients and controls were of German descent.

Informed written consent was obtained from each patient or control subject prior to enrolment into any of the study groups. The investigations were conducted according to the principles of the Declaration of Helsinki.

SNPs, LD structure, and haplotypes

We genotyped all single nucleotide polymorphisms (SNPs) with TaqMan assays on a 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA) resulting in a genotyping rate of $\geqslant$95%. TaqMan genotypes for all SNPs could be confirmed through direct sequencing in a set of 24 randomly chosen probands. Sequences of primers and probes or the respective assay information are listed in supplementary table 1 which is available at http://www.jmedgenet.com/supplemental.

For analysis of the LD structure of the region around *PTPN22*, we obtained genotype data from Caucasian trio samples from the HapMap Project (data extraction October 2004). We analysed data of SNPs with a minor allele frequency of more than 0.1 with Haploview software[14] and observed strong LD within a haplotype block of about 335 kb comprising *PTPN22* and several neighbouring genes: round spermatid basic protein 1 (*RSBN1*), putative homeodomain transription factor 1 (*PHTF1*), and the major part of membrane associated guanylate kinase-related 3 (*MAGI3*). To cover more genomic sequence at the centromeric end of *PTPN22*, we included a further small (13.7 kb) LD block containing the 5'UTR and first exon of gene *FLJ22588* (hypothetical protein LOC440603). Coverage of the haplotype diversity was calculated with an EM accelerated algorithm by Haploview and with the program SNPtagger.[15] It resulted in a set of 19 haplotype tag SNPs (htSNPs).[16]

No significant deviation from Hardy-Weinberg equilibrium was found for any of the SNPs either in the control group or in the patient sample. To determine significant differences in allele frequencies (in the case of R620W we used genotype frequencies) between groups of patients and controls, a χ^2 statistics for a 2×2 contingency table was used. When the number of expected observations was low, a Fisher's exact test was performed. Calculations of odds ratios for associated single SNPs and risk haplotypes were based on allele/haplotype frequencies. All haplotypes were constructed using the program PHASE (version 1.0).[17]

In order to reduce the risk of false positive association results, we corrected for multiple testing after Bonferroni; haplotypes of a frequency of more than 5% in the controls were considered, resulting in a correction for five tests in the case of haplotype blocks A and B and for four tests in the case of haplotype block C.

To estimate the influence of the PSORS1 risk allele, the risk haplotype HCR*WWCC within the coiled-coil alpha-helical rod protein 1 (*CCHCR1*) gene was determined through two previously described htSNP alleles at positions 325 and 2327.[18 19] SNPs were genotyped and haplotypes were calculated as previously described.[18]

Regression analysis

Logistic regression analysis was carried out with SAS (version 9.1) to analyse the role of HCR*WWCC and the *PTPN22* risk haplotype as potential predictors for psoriasis vulgaris. The two groups, patients with psoriasis vulgaris and controls, were treated as categorical variables, controls being the reference category for the outcome, whereas the *PTPN22* risk haplotype for psoriasis (C-4, C A G G, abbreviated rhPTPN22) and the HLA-Cw6 associated risk haplotype HCR*WWCC (abbreviated rhHCR) were treated as explanatory variables. We tested a reduced model with respect to both risk haplotypes including the independent variables rhHCR and rhPTPN22 and a saturated model including the additional interaction term, rhHCR*rhPTPN22.

Sequencing of *PTPN22*

The coding segments of *PTPN22* were covered in 24 amplicons; 20 of the patients were sequenced with intron based primers (primer sequences are available upon request). Patients were selected for risk haplotype C-4: 14 probands were homozygous and six heterozygous for this risk haplotype. After performing PCR reactions in an MJ Research thermocycler (Biozym, Hess, Oldendorf, Germany), the PCR products were purified on a robotic system (Tecan Miniprep 75-2 with vacuum station; Tecan, Crailsheim, Germany) with Millipore Montage PCR Cleanup Filter Plates (Millipore, Schwalbach, Germany). Sequencing reactions were performed using the BigDye Terminator Cycle Sequencing Kit Version 3.1 (Applied Biosystems) according to the manufacturer's instructions and were purified on the same robotic system with Millipore Montage SEQ Sequencing Reaction Cleanup Kit. They were analysed in an ABI Prism Model 3730 Sequencer (Applied Biosystems) while sequencing analysis was performed with the software SeqMan II (DNA-Star, Madison, WI).

Extension of the study

An analysis of the second study group of patients and controls was performed for the two *CCHCR1* SNPs as well as for the htSNPs covering the haplotype blocks B and C (fig 1). In the combined data set we determined the *CCHCR1* risk haplotype and tested for association with haplotypes within LD blocks B and C. In addition we tested the hypothesis of possible interaction between those two risk factors in this combined data set by regression analysis as in the exploratory study.

RESULTS

Lack of association with variant R620W

In the screening set no association with *PTPN22* 1858C→T was observed (table 1). We also stratified the patients for the following criteria: carrier/non-carrier of PSORS1 associated risk allele, sex, and manifestation of the disease before age 16 versus manifestation between 16 and 40 years of age. After stratification no evidence for association with any allele of R620W in any subgroup was noticed (data not shown). The

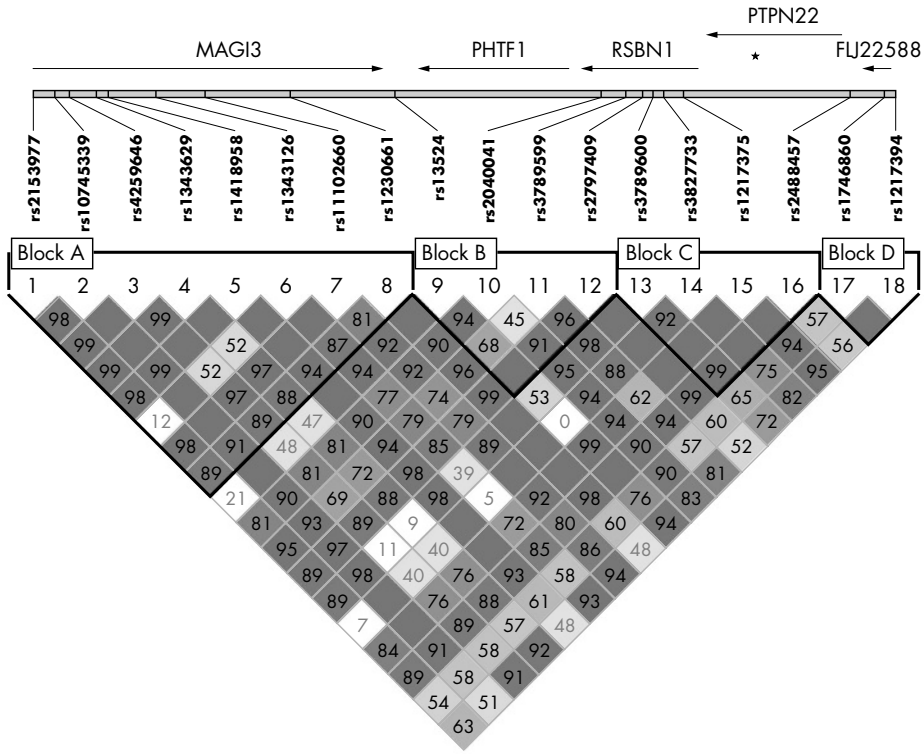

Figure 1 LD structure of *PTPN22* genomic region. Haploview plot showing pairwise LD (D′ values) for 18 SNPs with minor allele frequency >0.1 based on genotypes of 751 individuals of the exploratory case-control study. Each square plots the level of LD between a pair of SNPs; comparisons between neighboring SNPs lie along the first line under the names of the SNPs. Dark grey coloring indicates strong LD, medium grey indicates less strong LD, light grey indicates intermediate LD, and white indicates weak LD. LD blocks are framed in black and were classified according to the ''solid spine'' option. The arrows indicate the position and orientation of Refseq genes; the asterisk corresponds to variant R620W.

allele and genotype frequencies of R620W were similar in the second case-control study. We observed no evidence for association after combining both data sets either before or after stratification for the above mentioned criteria.

LD structure

Genotypes of the 19 htSNPs in the exploratory case-control study composed of 375 psoriasis patients and 376 control subjects were used for LD analysis. We omitted SNP rs6679677 due to its minor allele frequency of 0.1. Considering the data of the 751 individuals, we were able to confirm the LD structure based on HapMap data. The 335 kb large LD block comprising *PTPN22* was subdivided into three sub-blocks A, B, and C according to the ''solid spine'' option as implemented in Haploview[14] (fig 1). The corresponding haplotypes in the three sub-blocks A–C and the small LD block D were composed of two to eight single htSNPs (fig 1).

Associations at haplotype level

Within the four LD blocks we observed five common haplotypes in block A (frequency of ⩾5% in controls), six in block B, five in block C, and three in block D. These common haplotypes accounted for the majority of haplotypes (total coverage of 95.3–99.2%). Significant association with one haplotype in blocks A, B, and C (A-3, B-3, and C-4) was discovered while no association was observed with any haplotype in block D (table 2). After Bonferroni correction for multiple testing, association findings for B-3 and C-4 remained significant. Corresponding odds ratios and their confidence intervals (ORs (95% CI)) for the three haplotypes were in the range of 1.35 (1.07 to 1.74) to 1.42 (1.12 to 1.81).

Interaction with PSORS1 associated risk haplotype

In the exploratory study the regression analysis resulted in significant Wald χ^2 values for both main effects. As expected, in terms of p values the effect of rhHCR ($p<1.50\times10^{-14}$) was more than ten magnitudes stronger than the effect of rhPTPN22 ($p<0.0046$) (table 3). Since these tests were done on the same sample, p values could be taken as a proxy for effect size, however in a non-linear way. We also observed a combined effect of the variables as both risk haplotypes act in the same direction (estimates of –0.60 for rhHCR and –0.22 for rhPTPN22). Regarding the interaction effect

Table 1 Genotype frequencies of R620W (rs2476601) and results of χ^2 statistics

		No. of genotypes (%)		Statistical parameters	
		C/T+T/T	C/C	χ^2 (df = 1)	p value
A	375 psoriasis vulgaris patients	78+3 (21.8)	289 (78.2)	1.53	0.22
	376 controls	65+2 (18.3)	299 (81.7)		
B	793 psoriasis vulgaris patients	158+11 (21.5)	611 (78.5)	1.69	0.19
	937 controls	164+9 (18.9)	741 (81.1)		

A: exploratory case-control study; B: combined case-control studies.

Table 2 Frequencies of associated haplotypes within defined LD blocks and statistical parameters

	Block-haplotype	Allele combination	Frequency		Statistical parameters			
			Controls	Psoriasis vulgaris patients	χ^2 (df = 1)	p value	p_c value	OR (95% CI)
A	A-3	A G G C A A A A	0.183	0.232	5.362	0.021	NS	1.35 (1.05 to 1.74)
	B-3	A C A G	0.203	0.265	8.216	0.004	0.02	1.42 (1.12 to 1.81)
	B-4	A C A A	0.137	0.095	6.657	0.010	NS	
	C-3	C G G C	0.209	0.169	NS	NS	–	
	C-4	C A G G	0.189	0.243	6.433	0.011	0.044	1.38 (1.07 to 1.76)
B	B-3	A C A G	0.222	0.264	8.495	0.004	0.02	1.26 (1.08 to 1.47)
	B-4	A C A A	0.137	0.100	11.435	0.00072	0.0036	
	C-3	C G G C	0.206	0.162	10.505	0.001	0.004	
	C-4	C A G G	0.199	0.239	7.733	0.005	0.02	1.26 (1.07 to 1.48)

A: exploratory case-control study (375 cases and 376 controls); B: combined study cohorts (793 cases and 937 controls). CI, confidence interval; NS, not significant; OR, odds ratio; P_c, corrected p value.

(rhHCR*rhPTPN22), which is mathematically defined as the coefficient of exposure products in the model, results showed no evidence for interdependence such as synergy (a total effect greater than the sum of the separate effects), super-additivity, antagonism, or competitive action ($p<0.58$).

Sequencing of *PTPN22* in psoriasis patients

By sequencing *PTPN22* exons we were able to identify two coding variants: an amino acid change R263Q in one patient heterozygous for the risk haplotype C-4 and a synonymous change in position L247 in another patient homozygous for C-4. Testing of these two polymorphisms in the exploratory case-control study revealed very low minor allele frequencies for R263Q in patients (0.019) and controls (0.017), while the minor allele of L247L was only identified in one of the patients sequenced, but not in any other psoriasis patient or control. Fisher's exact test indicated no significant difference between cases and controls. Therefore, these polymorphisms do not explain the association findings at haplotype level.

Extension of study samples

We selected haplotype blocks B and C for extension of the study due to their association findings in the exploratory case-control study and their proximity to *PTPN22*. The range of statistical parameters indicating association with haplotypes B-3 and C-4 was similar to that in the exploratory case-control study (table 2).

Recalculation of the regression analysis for the combined data set confirmed the results of the exploratory study, while the effects were stronger for both main effects (table 3): we observed significant Wald χ^2 values for both main effects, again as expected with the effect of rhHCR ($p<6.55\times10^{-35}$) much stronger than that of rhPTPN22 ($p<0.0014$). Both effects also acted in the same direction (estimates of –0.66 for rhHCR and –0.17 for rhPTPN22). Again, there was no evidence for an interaction effect.

DISCUSSION

To investigate whether the previously described variant R620W within gene *PTPN22*[7 8] might also be a relevant susceptibility factor for a further T cell mediated disease, we tested this hypothesis for population based samples of controls and patients with psoriasis vulgaris. The variant was not found to be associated with psoriasis. This is in concordance with earlier data: Criswell *et al*[12] reported no evidence for association with R620W with this phenotype in 51 affected individuals of families with multiple autoimmune diseases, while Nistor *et al*[20] came to the same conclusion after investigating their large cohort of 517 psoriasis families. Another small study of 279 single patients with psoriasis described similar findings.[21] In a group of 375 patients with psoriatic arthritis, we observed association with PTPN22*620W after stratification for sex with a higher ratio of male patients in the carriers than in the non-carriers of the risk allele.[22] Also Orozco *et al*[23] showed a similar trend in a group of rheumatoid arthritis patients after stratification for sex and extra-articular manifestation. Thus, we were interested whether sex or different ages of onset (manifestation in childhood/early adolescence versus onset between 16 and 40 years of age) might influence association with PTPN22*620W. Due to lack of association within subgroups and similar results in the extended case-control study, we assume that this polymorphism does not contribute to susceptibility to psoriasis.

Table 3 Results of regression analysis shown separately for the exploratory case-control study and the combined data set

Sample	Model	Parameter	Estimate	Standard error	Wald χ^2 (df = 1)	p value
Exploratory case control study	Reduced model	Intercept	0.06	0.08	0.50	0.48
		rhHCR	−0.60	0.08	60.69	6.70×10^{-15}
		rhPTPN22	−0.22	0.08	8.02	0.0046
	Saturated model	Intercept	0.06	0.08	0.53	0.4660
		rhHCR	−0.61	0.08	59.10	1.50×10^{-14}
		rhPTPN22	−0.22	0.08	8.05	0.0046
		rhHCR*rhPTPN22	0.04	0.08	0.31	0.58
Combined case control studies	Reduced model	Intercept	−0.17	0.05	9.48	0.0021
		rhHCR	−0.66	0.05	157.93	3.21×10^{-36}
		rhPTPN22	−0.17	0.05	10.3511	0.0013
	Saturated model	Intercept	−0.16	0.05	9.37	0.0022
		rhHCR	−0.66	0.05	151.93	6.55×10^{-35}
		rhPTPN22	−0.17	0.05	10.21	0.0014
		rhHCR*rhPTPN22	0.02	0.05	0.12	0.73

Statistical parameters are presented for a reduced and a saturated model in both studies.

To further explore our hypothesis that a *PTPN22* variant other than R620W might be relevant in the pathogenesis of psoriasis, we extended the analyses to haplotypes based on LD patterns, that is, haplotype blocks. When we used HapMap genotyping data from SNPs with minor allele frequencies of more than 0.15 around *PTPN22*, we detected a clear pattern of high LD in the proximity of this gene. Using 18 SNPs we were able to construct robust haplotypes extending over a genomic region of about 335 kb and covering *PTPN22* and some neighbouring genes. Surprisingly, association with one haplotype each within two of the three sub-blocks of the large LD block was detected in the exploratory case-control study, suggesting this genomic region on 1p13.2 has a role in the pathogenesis of psoriasis. This was confirmed in the regression analysis where we could show that the *PTPN22* haplotype C-4 confers risk of psoriasis. Although association for one further haplotype (A-3) of the third sub-block within the large LD block was weaker (not significant after Bonferroni correction), this sub-block can not be excluded as a region containing potential susceptibility factor(s) due to its high LD with haplotype blocks B and C.

Even though we were not able to confine the association findings to *PTPN22* itself, we considered it the most suitable candidate gene for psoriasis. Therefore, we checked this gene for other coding variants in a subset of psoriasis patients carrying the *PTPN22* risk haplotype C-4. We identified two very rare coding polymorphisms that could not explain the association found.

The HLA region on the short arm of chromosome 6 has long been known as the major psoriasis susceptibility factor (PSORS1) and the results of numerous genetic studies indicate that the HLA-Cw6 allele or a variant in strong disequilibrium with HLA-Cw6 represents the major risk factor especially for early onset psoriasis. There has been much controversy on the precise nature of the factor at PSORS1 that would influence immunological functions and predispose to psoriasis. The region exhibits an extraordinary high degree of LD, which has hampered the identification of this factor until today. We used the haplotype HCR*WWCC, which is in strong LD with the PSORS1 risk allele[18 19] but known to be only a rough estimate of this risk factor, to analyse possible interactions between the risk haplotype at *PTPN22* and PSORS1. We observed negative estimates for both risk haplotypes even though no evidence for interaction between them was observed. These results do not exclude effects of those two risk factors within the same pathway while a direct interaction between *HLA-C* risk allele and the genetic factor within *PTPN22* or its proximity can be ruled out. Regression analysis also revealed that the contribution of the genetic factor(s) within *PTPN22* or its genomic region play(s) a minor role as compared to the risk haplotype of the *CCHCR1* gene. This is not unexpected and in concordance with studies of psoriasis susceptibility regions other than PSORS1 that confer only a comparably modest susceptibility.

In the extended case-control study we could confirm association findings for the two haplotypes B-3 and C-4, although we did not observe a real strengthening of the results compared to the exploratory study. But when comparing the regression analyses in the exploratory case-control study and the combined data set, the results indicated a slightly stronger effect of the *PTPN22* risk haplotype in the larger study. The resulting odd ratios for the risk haplotypes in *PTPN22*'s genomic region are in the range that has been detected at other psoriasis loci and for susceptibility factors identified in other complex disorders like Crohn's disease. Therefore, these results underline the potential existence of a genetic susceptibility factor for psoriasis vulgaris within this genomic region. Due to the relatively small effect of this potential variant our results will need to be independently confirmed, and a very large group of patients will be required. If relevance of this genetic factor is confirmed, it will be interesting to determine if a non-coding variant within *PTPN22* is causal, since sequencing of our patients makes a further coding variant unlikely, or if a variant in another gene in LD constitutes the risk factor.

In summary, we exclude the possibility that R620W or another variant within the coding regions of *PTPN22* plays a role in susceptibility to psoriasis vulgaris in the German patients investigated but suggest that other variant(s) within *PTPN22* gene or in linkage disequilibrium with it are contributory susceptibility determinant(s) for psoriasis vulgaris in patients of German origin.

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