

Protein Tyrosine Phosphatase Gene PTPN22 Polymorphism in Psoriasis: Lack of Evidence for Association

To the Editor:

LYP, the protein product of the protein tyrosine phosphatase gene PTPN22 located on human chromosome 1p13.2, is involved in downregulation of T cell signaling through its interaction with C-terminal Src tyrosine kinase (Csk) (Cloutier and Veillette, 1996), by phosphorylation of regulatory tyrosines on the Src family kinase Lck (Cloutier and Veillette, 1999). A missense mutation of this gene (C1858T, R620W), found in 15%–17% of the Caucasian population, has been associated with autoimmune pathology in type I diabetes (T1D) (Bottini *et al*, 2004; Onengut-Gumuscu *et al*, 2004; Smyth *et al*, 2004; Ladner *et al*, 2005), rheumatoid arthritis (RA) (Begovich *et al*, 2004), systemic lupus erythematosus (SLE) (Kyogoku *et al*, 2004), and Graves disease (GD) (Smyth *et al*, 2004; Velaga *et al*, 2004) but not in multiple sclerosis (Begovich *et al*, 2005). It has also been shown to be functionally relevant in terms of binding to Csk (Bottini *et al*, 2004) and inhibition of signalling via the T cell antigen receptor (Begovich *et al*, 2004).

Although no genome-wide search has identified human chromosome 1p13.2 as a psoriasis susceptibility locus, the widely accepted concept that psoriasis is mediated at least in part by activated T cells (Lew *et al*, 2004; Sugiyama *et al*, 2005) suggests PTPN22 as a prime target for candidate gene testing in psoriasis. In this study, we investigated association of the PTPN22 C1858T polymorphism in our collection of 517 families containing 1,146 affected individuals. This study was carried out in accordance with the Principles of Helsinki and was approved by the ethical boards of the University of Michigan, the University of Kiel, and the Henry Ford Health System. Written informed consent was obtained from all subjects. Genomic DNA was amplified using primers flanking the C1858T variation and the polymorphisms were scored using the SnapShot SNP assay reagents and GeneMapper software (Applied Biosystems, Foster City, California). Three different statistical tests were applied to the data: the transmission/disequilibrium test (TDT) (Spielman *et al*, 1993), the pedigree disequilibrium test (PDT) (Martin *et al*, 2000, 2001), and the family-based association test (FBAT) (Rabinowitz and Laird, 2000; Horvath *et al*, 2001, 2004). All three methods were implemented as biallelic two-sided tests of the null hypothesis of no asso-

ciation in the presence of linkage. For the TDT, a single trio was randomly extracted from each pedigree, as recommended by Spielman and Ewens (1996). Since results vary depending upon the particular random selection, the analysis was repeated 999 times with different random number seeds, and the median result was reported. In the FBAT, we used with the empirical variance and an offset of 0 (i.e., unaffecteds do not contribute to the test statistic but do aid inference of parental genotypes).

As shown in Table I, none of these three methods yielded significant evidence for association. This outcome appeared to be because of a lack of association, rather than a lack of statistical power. As shown in Table I, measures of LD show only a weak negative association of the minor (T) allele with psoriasis (47.3% transmission, $\bar{D} = -0.072$) that differ little from the expected values of 50% transmission and $\bar{D} = 0$ under the null hypothesis of no association. Power calculations, performed by the first approximation method of Knapp (1999) (Table II), revealed excellent power of the TDT to detect association under all models except recessive, a model that is not supported for PTPN22 in T1D (Smyth *et al*, 2004), RA (Begovich *et al*, 2004), SLE (Kyogoku *et al*, 2004), or GD (Velaga *et al*, 2004). Our sample, however, would probably not detect an association with psoriasis if PTPN22 does indeed act in a recessive fashion as a psoriasis locus or if the genetic effect of PTPN22 under other models is weak (GRR1 < 1.56 for a dominant model, GRR1 < 1.50 for an additive model, and GRR1 < 1.47 for a multiplicative model).

It seems unlikely that our negative results are due to genetic heterogeneity, as the frequency of the T allele among our founder chromosomes was similar to Caucasian control populations in previous studies (0.1087 for 2669 founder chromosomes in this study, as compared with 0.0864 for 3922 pooled control chromosomes in SLE (Kyogoku *et al*, 2004) and 0.104 for 3,436 control chromosomes in T1D (Smyth *et al*, 2004).

While this article was under review, a report appeared finding no association of the PTPN22 R620W polymorphism with psoriasis in a study of families with multiple autoimmune diseases (Criswell *et al*, 2005). This study had very little power to detect association of the PTPN22 R620W polymorphism with psoriasis as its sample of 265 multiple autoimmune disease families contained only 63 psoriatics.

Based on these results, we conclude that C1858T polymorphism of PTPN22 is unlikely to be associated in psoriasis. Similar negative results have recently been reported for multiple sclerosis (Begovich *et al*, 2005), indicating that the PTPN22 R620W variation is unlikely to be universally associated with autoimmune disease. Additional family-based and case-control association studies in psoriasis and other immunologically mediated disorders will clarify

Abbreviations: FBAT, family-based association test; GD, Graves disease; GRR, genotype relative risk; GRR1, genotype relative risk for carriers of one copy of the test allele; GRR2, genotype relative risk for carriers of two copies of the test allele; PDT, pedigree disequilibrium test; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphism; T1D, type 1 diabetes; TDT, transmission/disequilibrium test

Table I. Results of family-based tests of the association of psoriasis with the T allele of the C1858T (R620W) polymorphism of the PTPN22 gene

TDT				PDT				FBAT			
# fam ^a	# inf fam ^b	T:NT ^c	p-value ^d	# fam ^a	# inf fam ^b	\bar{D} ^e	p-value ^d	# fam ^a	# inf fam ^b	Z ^f	p-value ^d
469	182	88:98	0.51	505	194	-0.072	0.51	517	176	-1.66	0.097

^aThe number of families shown for each association test counts only those families with at least one typed and phenotypically informative unit. For the TDT, this unit is a trio (an affected child and both parents), for the PDT, it is a trio or a discordant sibpair (an affected and unaffected sib), and for the FBAT, with the settings used it is a trio, discordant sibpair, or a sibship with three or more affected sibs.

^bThe number of informative families is the subset of the typed and phenotypically informative families that are genotypically informative for the allele being tested.

^cT:NT is the ratio of transmissions to non-transmissions of the test allele from heterozygous parents to affected children in the TDT.

^dAll p-values are uncorrected for multiple testing.

^e \bar{D} is a standardized measure of marker-trait disequilibrium for the PDT which has been described by us previously (Collaboration, 2005).

^fLarge sample test statistic for association, distributed as a standard normal.

TDT, transmission/disequilibrium test; PDT, pedigree disequilibrium test; FBAT, family-based association test.

Table II. Genotype relative risks for putative disease allele heterozygotes (GRR1) and homozygotes (GRR2) needed to achieve power of 0.80 and 0.95 when using the TDT (and a type I error rate of 0.05) to test for association of psoriasis and the T allele of the C1858T (R620W) polymorphism of the PTPN22 gene

Model of inheritance	GRR2/GRR1 for 80% power	GRR2/GRR1 for 95% power
Dominant	1.56/1.56	1.75/1.75
Additive	1.99/1.50	2.34/1.67
Multiplicative	2.17/1.47	2.65/1.63
Recessive	5.44/—	7.02/—

TDT, transmission/disequilibrium test.

the spectrum of disorders associated with this functional polymorphism, which may ultimately serve as an important molecular classifier of autoimmune disease.

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References

Begovich AB, Caillier SJ, Alexander HC, Penko JM, Hauser SL, Barcellos LF, Oksenberg JR: The R620W polymorphism of the protein tyrosine phosphatase PTPN22 is not associated with multiple sclerosis. *Am J Hum Genet* 76:184–187, 2005

Begovich AB, Carlton VE, Honigberg LA, Schrodi SJ, Chokkalingam AP, Alexander HC, Ardlie KG, *et al*: A missense single-nucleotide polymorphism in a gene encoding a protein tyrosine phosphatase (PTPN22) is associated with rheumatoid arthritis. *Am J Hum Genet* 75:330–337, 2004

Bottini N, Musumeci L, Alonso A, *et al*: A functional variant of lymphoid tyrosine phosphatase is associated with type 1 diabetes. *Nat Genet* 36:337–338, 2004

Cloutier JF, Veillette A: Association of inhibitory tyrosine protein kinase p50csk with protein tyrosine phosphatase PEP in T cells and other hemopoietic cells. *EMBO J* 15:4909–4918, 1996

Cloutier JF, Veillette A: Cooperative inhibition of T-cell antigen receptor signaling by a complex between a kinase and a phosphatase. *J Exp Med* 189:111–121, 1999

Collaboration: Fine mapping of the psoriasis susceptibility gene PSORS1: A re-assessment of risk associated with a putative risk haplotype lacking HLA-Cw6. *J Invest Dermatol*, 2005, in press

Criswell LA, Pfeiffer KA, Lum RF, *et al*: Analysis of families in the Multiple Autoimmune Disease Genetics Consortium (MADGC) collection: The PTPN22 620W allele associates with multiple autoimmune phenotypes. *Am J Hum Genet* 76:561–571, 2005

Horvath S, Xu X, Laird NM: The family based association test method: Strategies for studying general genotype–phenotype associations. *Eur J Hum Genet* 9:301–306, 2001

Horvath S, Xu X, Lake SL, Silverman EK, Weiss ST, Laird NM: Family-based tests for associating haplotypes with general phenotype data: Application to asthma genetics. *Genet Epidemiol* 26:61–69, 2004

Knapp M: A note on power approximations for the transmission/disequilibrium test. *Am J Hum Genet* 64:1177–1185, 1999

Kyogoku C, Langefeld CD, Ortman WA, *et al*: Genetic association of the R620W polymorphism of protein tyrosine phosphatase PTPN22 with human SLE. *Am J Hum Genet* 75:504–507, 2004

Ladner MB, Bottini N, Valdes AM, Noble JA: Association of the single nucleotide polymorphism C1858T of the PTPN22 gene with type 1 diabetes. *Hum Immunol* 66:60–64, 2005

Lew W, Bowcock AM, Krueger JG: Psoriasis vulgaris: Cutaneous lymphoid tissue supports T-cell activation and “Type 1” inflammatory gene expression. *Trends Immunol* 25:295–305, 2004

Martin ER, Bass MP, Kaplan NL: Correcting for a potential bias in the pedigree disequilibrium test. *Am J Hum Genet* 68:1065–1067, 2001

Martin ER, Monks SA, Warren LL, Kaplan NL: A test for linkage and association in general pedigrees: The pedigree disequilibrium test. *Am J Hum Genet* 67:146–154, 2000

Onengut-Gumusc S, Ewens KG, Spielman RS, Concannon P: A functional polymorphism (1858C/T) in the PTPN22 gene is linked and associated with type 1 diabetes in multiplex families. *Genes Immun* 5:678–680, 2004

Rabinowitz D, Laird N: A unified approach to adjusting association tests for population admixture with arbitrary pedigree structure and arbitrary missing marker information. *Hum Heredity* 50:211–223, 2000

Smyth D, Cooper JD, Collins JE, *et al*: Replication of an association between the lymphoid tyrosine phosphatase locus (LYP/PTPN22) with type 1 diabetes, and evidence for its role as a general autoimmunity locus. *Diabetes* 53:3020–3023, 2004

Spielman RS, Ewens WJ: The TDT and other family-based tests for linkage disequilibrium and association. *Am J Hum Genet* 59:983–989, 1996

Spielman RS, McGinnis RE, Ewens WJ: Transmission test for linkage disequilibrium: The insulin gene region and insulin-dependent diabetes mellitus (IDDM). *Am J Hum Genet* 52:506–516, 1993

Sugiyama H, Gyulai R, Toichi E, *et al*: Dysfunctional blood and target tissue CD4 + CD25 high regulatory T cells in psoriasis: Mechanism underlying unrestrained pathogenic effector T cell proliferation. *J Immunol* 174:164–173, 2005

Velaga MR, Wilson V, Jennings CE, *et al*: The codon 620 tryptophan allele of the lymphoid tyrosine phosphatase (LYP) gene is a major determinant of Graves’ disease. *J Clin Endocrinol Metab* 89:5862–5865, 2004