Brief Report

PTPN22 R620W Functional Variant in Type 1 Diabetes and Autoimmunity Related Traits

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The *PTPN22* gene, encoding the lymphoid-specific protein tyrosine phosphatase, a negative regulator in the T-cell activation and development, has been associated with the susceptibility to several autoimmune diseases, including type 1 diabetes. Based on combined case-control and family-based association studies, we replicated the finding of an association of the *PTPN22* C1858T (R620W) functional variant with type 1 diabetes, which was independent from the susceptibility status at the insulin gene and at HLA-DR (DR3/4 compared with others). The risk contributed by the 1858T allele was increased in patients with a family history of other autoimmune diseases, further supporting a general role for this variant on autoimmunity. In addition, we found evidence for an association of 1858T allele with the presence of GAD autoantibodies (GADA), which was restricted to patients with long disease duration (>10 years, $P < 0.001$). This may help define a subgroup of patients with long-term persistence of GADA. The risk conferred by 1858T allele on GAD positivity was additive, and our meta-analysis also supported an additive rather than dominant effect of this variant on type 1 diabetes, similar to previous reports on rheumatoid arthritis and systemic lupus erythematosus. *Diabetes* 56:522–526, 2007

Type 1 diabetes is a multifactorial disease, resulting from autoimmune destruction of insulin-secreting pancreatic β-cells. In addition to the major histocompatibility complex, which is a major genetic risk factor, the contribution of two susceptibility genes has been replicated in multiple independent studies: the insulin gene (*INS*) and the cytotoxic T lymphocyte associated protein 4 (*CTLA4*) gene (1). The C1858T nonsynonymous variant (R620W) in the lymphoid protein tyrosine phosphate nonreceptor type 22 (*PTPN22*) gene, encoding the lymphoid-specific tyrosin phosphatase (LYP), has been shown to be associated with type 1 diabetes and several other autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, Graves' disease, Addison's disease, and myasthenia gravis, suggesting a general role of LYP in the autoimmune process (2–5). The murine homologue of LYP, Pep, acts as a negative regulator in T-cell activation and development (6), and mice knockout for this gene show enhanced expansion of effector/memory T-cell population and increased serum antibody level (7). In contrast, the PTPN22 620W disease-associated variant was validated as a gain-of-function variant, with increased catalytic activity compared with the nonassociated variant (8). These observations may suggest functional differences between the human and mouse homologues and stress the complexity of mechanisms by which LYP regulates the T-cell–mediated immunity (9).

The validation of original association reports requires replications in various study designs, especially in the absence of linkage to the corresponding locus, as is currently the case for *PTPN22* in type 1 diabetes (10). Here, we performed a combined case-control and family-based association replication study of the *PTPN22* C1858T variant with type 1 diabetes in French, U.S., and Danish populations. We also evaluated the interaction of the risk contributed by this variant with other type 1 diabetes susceptibility genes and its effects on autoimmunity markers.

RESEARCH DESIGN AND METHODS

We studied 528 multiplex families (145 French, 159 Danish, and 224 U.S.), 161 families with one affected parent and one affected child (102 Danish and 59 French), and 241 simplex families (Danish). Most of these families have been previously described (11,12). In the multiplex Danish families, the presence of anti-glutamic acid decarboxylase-65 (GAD) and protein tyrosine phosphatase (insuliminoma-associated protein 2 [IA2]) autoantibodies was determined at the time of sampling. The case-control cohort consisted of 892 French-Caucasian type 1 diabetic patients and 456 French control subjects (12). Additional information on the presence of autoantibodies specific to other organs (thyroperoxydase and antigastric parietal cell autoantibodies and antigliadin and antitransglutaminase IgA antibodies) and familial history of type 1 diabetes and other autoimmune diseases (rheumatoid arthritis, celiac disease, and autoimmune thyroid disease) was available in a subset of type 1 diabetic patients from the case-control population. All individuals taking part in this study gave informed consent for genetic studies.

Genotyping. Genotyping of *PTPN22* C1858T (R620W, rs2476601) was performed using a TaqMan assay (Applied Biosystems), or a PCR–restriction fragment–length polymorphism assay, with identical results obtained on duplicate genotyping in a subset of 190 DNA samples. Genotyping of *PTPN22* rs3789604 ([single nucleotide polymorphism] SNP37 [13]) and rs2488457 (SNP −1,123 [14]) were performed using TaqMan assays. All primer sequences are available on request. Genotyping of *HLA-DRB1* alleles (DR3 and DR4) and

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GADA, GAD autoantibodies; IA2, insuliminoma-associated protein 2; LYP, lymphoid-specific phosphate; SNP, single nucleotide polymorphism; TDT, transmission disequilibrium test.

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TABLE 1
TDT of *PTPN22* C1858T in type 1 diabetic families

All type 1 diabetic patients	Allele transmitted		Transmission of 1858T allele (%)	*P* value (TDT)*	*P* value (heterogeneity) test†
	1858C	1858T			
	249	339	57.7	0.0002	
Population origin					
French	46	51	52.6	0.61	
U.S.	89	127	58.8	0.01	
Danish	114	161	58.5	0.005	0.54
Parental origin					
Father	112	156	58.2	0.007	
Mother	99	145	59.4	0.003	0.78
Sex of patient					
Male	130	183	58.5	0.003	
Female	119	156	56.7	0.03	0.67
Parental affection status					
Affected	41	48	53.9	0.46	
Unaffected	206	288	58.3	0.0002	0.44
HLA risk status					
DR34+	97	128	56.9	0.05	
DR34−	151	208	57.9	0.003	0.80
INS risk status					
INS+	184	265	59.0	0.0002	
INS−	63	72	53.3	0.43	0.24
Unaffected siblings	157	165	51.2	0.66	

Data are *n*. *Two-sided χ^2 test. In TDT analyses of multiplex families, all the affected siblings were studied (test of linkage and association). †Heterogeneity tests within subgroups.

INS-23/HphI was performed as described (11). In addition, full *HLA-DQB1* genotyping was performed in the Danish families, as previously described (15). All genotypes were found to be in Hardy-Weinberg equilibrium.

Statistical analyses. Transmission disequilibrium test (TDT) analyses were done using ANALYZE (16). Data were stratified based on *HLA-DRB1* risk: patients heterozygous *DR3/DR4* (DR34+), and all others (DR34−), and *INS* risk: patients homozygous for *INS-23/HphI* allele A (susceptible, or INS+), and all others (nonsusceptible, or INS−). In the case-control population, four additional stratifications were performed: presence of type 1 diabetes cases in first- or second-degree relatives of the proband (FT1D+) or not (FT1D−); presence (AAB+) or absence (AAB−) of autoantibodies specific to other organs; presence of additional autoimmune diseases (AID+) or absence (AID−); and familial history of other autoimmune diseases in first- and second-degree relatives as positive (FAID+) or negative (FAID−). Association tests and heterogeneity tests were performed using two-sided χ^2 tests. We used the haplo.stats package for haplotype estimation and association studies (17). ANOVA and logistic regression analyses were performed using STATVIEW and were restricted to the Danish multiplex families, where relevant data were available; in these analyses we used a more detailed HLA-DR genotype, consisting of the six genotypes determined by the three alleles DR3, DR4, and DRX (non-DR3 and -R4), based on HLA-DR3, DR4, and full *HLA-DQB1* genotypes.

RESULTS

We first performed TDT analysis of the C1858T SNP in a total of 930 multiplex and simplex families from France, Denmark, and the U.S. (Table 1). We confirmed overtransmission of the T allele to type 1 diabetic patients (339 vs. 249, 57.7% transmission of allele T, $P = 0.0002$), with no evidence of heterogeneity according to family origin, while there was no transmission distortion of this allele to unaffected siblings. Since there was no difference in C1858T allele frequencies in family founders between the three population groups, and no heterogeneity in TDT results between these groups, subsequent analyses were performed in all families combined. There was no heterogeneity in the overtransmission of the T allele to affected children depending on the sex of patients, the paternal or maternal origin, and the affection status of the parents; however, in the latter case, the number of affected parents was relatively small (89 heterozygous affected parents), and the test did not reach significance. Similarly, the stratification based on the risk status at HLA-DR and INS did not show any evidence of heterogeneity between subgroups.

We performed a case-control association study of *PTPN22* C1858T with type 1 diabetes in an independent French case-control population (Table 2). We confirmed association of the T allele with type 1 diabetes, with a frequency of carriers of this allele of 29.6% in patients, compared with 17.9% in control subjects ($P = 4 \times 10^{-6}$). Again, there was no heterogeneity in association between patients stratified by sex, HLA-DR, and INS risk subgroups, and there was no heterogeneity depending on the family history of type 1 diabetes (FT1D+ vs. FT1D−).

Recent studies have explored the genetic variability of *PTPN22* in rheumatoid arthritis and in type 1 diabetes and suggested that additional variants, in addition to C1858T variant, may contribute to disease susceptibility (13,14). Hence, we tested two additional SNPs in *PTPN22*, rs3789604, located 3′ of *PTPN22*, which marks a haplotype associated to rheumatoid arthritis independently of C1858T (13), and rs2488547, located in the *PTPN22* promoter region, which was found to be associated to type 1 diabetes in a Japanese population (14). Using haplotype association analysis in our case-control population, we found no evidence of association for these two SNPs, independently of C1858T (Table 3).

To gain some insight into the genetic model underlying the susceptibility to type 1 diabetes contributed by the T allele, we explored the genotype distribution in the case and control subjects from the French population and in the case subjects from the families. The odds ratio (OR) estimates for the C/T and T/T genotypes (compared with C/C) were not significantly different in our data, both in the family cases (C/T, 1.43 [95% CI 1.16–1.76]; T/T, 1.92

TABLE 2
Association of *PTPN22* C1858T in the French type 1 diabetic case-control population

Group	Individuals	Genotypes C/C	C/T	T/T	Frequency of T carrier (%)	OR for T carrier (95% CI)	*P* value (association)*†	*P* value (heterogeneity)*‡
Control subjects	442	363	73	6	17.9			
Cases								
All	885	623	243	19	29.6	1.93 (1.46–2.56)	4×10^{-6}	
DR34−	577	399	163	15	30.8	2.05 (1.52–2.77)	2×10^{-6}	
DR34+	306	222	80	4	27.4	1.74 (1.23–2.47)	0.002	NS
INS−	228	155	69	4	32.0	2.16 (1.49–3.13)	3×10^{-5}	
INS+	642	455	173	14	29.1	1.89 (1.40–2.54)	2×10^{-5}	NS
FT1D−	401	279	113	9	30.4	2.01 (1.45–2.78)	2×10^{-5}	
FT1D+	129	87	39	3	32.6	2.22 (1.43–3.45)	0.0003	NS
AAB−	200	138	59	3	31.0	2.06 (1.40–3.04)	0.0002	
AAB+	155	101	48	6	34.8	2.46 (1.63–3.70)	1×10^{-5}	NS
AID−	249	170	74	5	31.7	2.13 (1.49–3.06)	3×10^{-5}	
AID+	98	63	31	4	35.7	2.55 (1.58–4.12)	9×10^{-5}	NS
FAID−	334	233	94	7	30.2	1.99 (1.42–2.79)	5×10^{-5}	
FAID+	50	28	21	1	44.0	3.61 (1.96–6.64)	1×10^{-5}	0.05

Data are *n*. All *P* values were based on two-sided χ^2 tests. Contrasted risk subgroups, DR34+/DR34− (HLA-DR3/DR4 risk); INS+/INS− (INS risk); FT1D+/FT1D− (familial history of type 1 diabetes); AAB+/AAB− (presence of other autoantibodies); AID+/AID− (presence of other autoimmune diseases); and FAID+/FAID− (familial history of autoimmune diseases), are described in RESEARCH DESIGN AND METHODS. *Test of T carriers versus noncarriers. †Test of association compared with control subjects. ‡Test of heterogeneity between contrasted subgroups. NS, nonsignificant ($P > 0.05$).

[1.23–3.01]) and in the population cases (C/T, 1.94 [1.45–2.60]; T/T, 1.85 [0.75–4.53]). We combined our data with previously published independent association data with similar frequencies of the 1858T allele in a meta-analysis (online appendix available at http://dx.doi.org/10.2337/db06-0942). Overall, the risk conferred by the T/T genotype was greater than the risk conferred by the C/T genotype (OR compared with C/C genotype: 3.22 vs. 1.94, respectively), resulting in an OR for the T/T compared with the C/T genotype of 1.72 (95% CI 1.20–2.48, $P = 0.003$), showing that the T allele has a dose-dependent effect on the risk of type 1 diabetes, as suggested in a previous meta-analysis (4).

Because of the reported association of the 1858T allele to several autoimmune diseases, we tested the association of this allele in subgroups of patients stratified according to several criteria of autoimmunity (Table 2). There was no heterogeneity in association between subgroups of patients with or without autoantibodies specific to other organs (AAB+ vs. AAB−) or affected or not by other autoimmune diseases (AID+ *vs.* AID−). Interestingly, the frequency of the 1858T carrier genotype was increased in patients with familial history of other autoimmune diseases (FAID+, 44.0%, OR = 3.61) compared with patients without (FAID−, 30.2%, OR = 1.99), with heterogeneity between these two subgroups ($P = 0.05$). However, these results remain preliminary, due to the small number of individuals tested.

The presence of GAD and IA2 autoantibodies (positivity) was determined at the time of sampling in members of the Danish multiplex families. We tested the association between C1858T and GAD and IA2 positivity in type 1 diabetic patients, taking into account covariates that may affect these traits. For GAD positivity, significant covariates were disease duration at the time of sampling ($P = 2 \times 10^{-8}$), age at onset of diabetes ($P = 0.0001$), and HLA genotype ($P = 0.002$); and for IA2 positivity: disease duration at the time of sampling ($P = 7 \times 10^{-8}$), HLA genotype ($P = 7 \times 10^{-8}$), and age at onset ($P = 0.02$); there was no effect of sex and INS risk. To evaluate the residual effect of *PTPN22* genotype on GAD and IA2 positivity, we performed a logistic regression analysis, taking into account these covariates (Table 4). Overall, the C1858T genotype was significantly associated with GAD positivity ($P = 0.008$). The risk of GAD positivity showed an increasing gradient from C/C, C/T, to T/T, and the test of dominance (dominant vs. additive model) was significant ($P = 0.01$), suggesting that the T allele has an additive effect on GAD positivity. In contrast, the effect of C1858T genotype on IA2 positivity was marginal ($P = 0.02$), and the test of dominance was not significant. Since GAD positivity is strongly affected by disease duration, we then subdivided

TABLE 3
Haplotype association analysis of three selected *PTPN22* SNPs

Haplotype	SNP rs3789604 (SNP37)*	rs2476601 (C1858T)	rs2488457 (−1123)†	Haplotype frequency Control subjects	Case subjects	*P* value
1	A	C	C	0.614	0.570	0.025
2	C	C	C	0.170	0.173	0.885
3	A	T	G	0.093	0.156	$<10^{-6}$
4	A	C	G	0.119	0.094	0.044

Other rare haplotypes had an overall frequency <0.01 and are not shown in this table. *Carlton et al. (12). †Kawasaki et al. (13).

TABLE 4
Logistic regression analysis of *PTPN22* C1858T on the positivity for GAD and IA2 autoantibodies in type 1 diabetic patients

Model tested	χ^2	Degrees of freedom	*P* value
GAD positivity (n = 491)			
Disease duration at sampling	28.742	1	8×10^{-8}
Age at onset	16.196	1	6×10^{-5}
HLA-DR genotype	20.537	5	0.001
PTPN22 genotypes (C/C, C/T, T/T)	9.694	2	0.008
Submodel: dominant vs. additive models			
PTPN22 T carrier/noncarrier vs. *PTPN22* genotypes	6.668	1	0.01
GAD+ (disease duration ≥10 years, n = 338)			
Disease duration at sampling	5.660	1	0.02
Age at onset	12.380	1	0.0004
HLA-DR genotype	11.603	5	0.041
PTPN22 genotypes (C/C, C/T, T/T)	13.950	2	0.0009
Submodel: dominant vs. additive models			
PTPN22 T carrier/noncarrier vs. *PTPN22* genotypes	6.402	1	0.01
GAD positivity (disease duration <10 years, n = 153)			
Disease duration at sampling	3.542	1	0.06
Age at onset	3.953	1	0.5
HLA-DR genotype	9.266	5	0.1
PTPN22 genotypes (C/C, C/T, T/T)	0.796	2	0.67
IA2+ (n = 492)			
Disease duration at sampling	35.846	1	2×10^{-9}
Age at onset	12.085	1	0.0005
HLA-DR genotype	55.481	5	1×10^{-10}
PTPN22 genotypes (C/C, C/T, T/T)	7.877	2	0.02
Submodel: dominant vs. additive models			
PTPN22 T carrier/noncarrier vs. *PTPN22* genotypes	2.992	1	0.08

The full model takes into account the duration of disease, age at onset, *HLA-DR* genotypes (six genotypes with three alleles, DR3, DR4, and non-DR3 non-DR4), and *PTPN22* genotype.

the samples in two subgroups, arbitrarily defined as disease duration <10 and ≥10 years. Interestingly, the C1858T genotype showed a strong effect on GAD positivity in the group with long disease duration (P = 0.0009), with heterogeneity between the two subgroups (P = 0.0008); in this group, GAD positivity was associated with C/T and T/T genotypes (C/T: OR = 1.73, P = 0.02; and T/T: OR = 8.00, P = 0.00005, compared with C/C).

DISCUSSION

Our study provides another replication of the association of *PTPN22* 1858T allele with type 1 diabetes, based on family and case-control association analyses, further confirming the initial report and subsequent replication studies (2,18). We found no evidence of genetic interaction of PTPN22 risk with HLA-DR3/DR4 and INS risks, as reported in other studies (19,20). Our haplotype study did not find evidence for the role or additional SNPs that may have an independent contribution in rheumatoid arthritis (13) or in Japanese type 1 diabetic patients (14) and supports that C1858T is the major risk determinant at PTPN22 for type 1 diabetes, consistent with recent studies (21,22).

Our finding of an increased association of 1858T allele in type 1 diabetic patients who have a family history of other autoimmune diseases supports the concept that this allele confers a general susceptibility to some autoimmune diseases, which are known to occur with increased frequency in type 1 diabetic patients, such as rheumatoid arthritis and autoimmune thyroid disease. In an independent study of families selected for segregating with at least two autoimmune diseases, the 1858T allele was found to be associated with type 1 diabetes, rheumatoid arthritis, SLE, and Hashimoto thyroiditis but not with multiple sclerosis (3).

In our study, the prevalence of GADA was correlated with the number of 1858T alleles in an additive way, and the meta-analysis showed an additive effect of this variant on type 1 diabetes. Similar findings have been reported previously to extend to several autoimmune diseases (4,5) and on the appearance of insulin autoantibodies (IAA) in individuals positive for islet cell autoantibodies (ICA+) (23) and the risk of RF-positive rheumatoid arthritis (24). These observations support that the 1858T allele has a dose-dependant effect on the risk of several autoimmune diseases, including type 1 diabetes, consistent with the hypothesis that the underlying mechanisms may depend on a specific threshold (5).

In type 1 diabetes, the presence of diabetes-related autoantibodies at the onset of disease is a critical parameter to define autoimmune diabetes. Here, we showed strong evidence for an association of *PTPN22* 1858T allele with the presence of GADA in type 1 diabetic patients, which was restricted in our analysis to patients tested after 10 years of disease duration. Hence, *PTPN22* C1858T variant may help define a subgroup of type 1 diabetes with long-term persistence of GADA. Recently, Hermann et al. (23) showed evidence that the *PTPN22* C1858T variant regulates type 1 diabetes–specific autoimmunity and strongly affects the progression from preclinical to clinical diabetes in ICA+ individuals. Studies will be required to further explore the underlying mechanisms by which

PTPN22 regulates the acquisition and persistence of type 1 diabetes–specific autoantibodies.

Based on their detailed study of autoantibodies in type 1 diabetic patients and their families, in association with HLA susceptibility, Knip et al. (25) proposed that the presence of GADA may be a marker of general autoimmunity. Our results would support this hypothesis. Additional prospective and cross-sectional studies are needed to explore further the role of *PTPN22* variants in the onset of disease, as well as on the prevalence and maintenance of autoantibodies in type 1 diabetes and other autoimmune diseases.

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