J. Cell. Mol. Med. Vol 12, No 3, 2008 pp. 1061-1062

No evidence for association of *PTPN22* R620W functional variant C1858T with type 1 diabetes in Asian Indians

Dear Editor,

Type 1 diabetes (T1D) is a typical organ specific autoimmune disease with an annual incidence of 10.5/100,000 in Asian Indians [1]. It is characterized by T cell-mediated destruction of pancreatic beta cells influenced by multiple genetic factors, such as *HLA-II* locus on chromosome 6p21.3 [2], insulin gene on 11p15.5 [3] and the *CTLA4* locus on 2q33 [4], all of these are involved in T cell activation, immune homeostasis and development of T cell receptor (TCR)-repertoire. Recently, we have shown a significant association of *CTLA*4 - 318, 1661 and tumour necrosis factor *(TNF)*-α -308 promoter polymorphism with T1D in Asian Indians [5, 6]. Another important gene currently under intense investigation is *PTPN22* on chromosome 1p13.3–13.1, which encodes lymphoid-specific phosphatase (LYP), a protein of tyrosine phosphatase family. LYP is involved in the negative regulation of T cell signalling by interacting with C-terminal Src tyrosine kinases (Csk), Lck and Fyn [7]. A nonsynonymous single nuclestide polymorphism (SNP) at nucleotide 1858 in codon 620 of this gene results in amino acid substitution (Arg620Trp). It was hypothesized that 620Trp decreases the affinity of LYP to Csk. The C1858T SNP in the *PTPN22* gene was found to be associated with several autoimmune disorders, including T1D in Caucasians [8–10]. In a recent survey and meta-analysis of T allele and T/T genotype, it was suggested that the *PTPN22* C1858T SNP confers susceptibility to T1D and other subgroup of autoimmune diseases [11].

The *PTPN22* R620W disease-associated variant was validated as a gain-of-function variant, with increased catalytic activity compared with the non-associated variant [12], in different ethnic groups of T1D patients [9, 10, 12]. However, there are no reports on its association with T1D in Asian Indians. We performed PCR-RFLP analysis to genotype *PTPN22* R620W C1858T variant in 129 T1D patients and 109 age, sex and ethnicity matched normal individuals. The mean age at onset of the disease was 15.4±6.6 years, and sex (male: female) ratio was 78:51. The mean body mass index (BMI) of patients was 19.0±3.0 kg/m^2, and HbA1c at the time of study was 9.0±2.5. All patients required insulin for glycaemic control, and 58% of them had ketosis at presentation. The local institutional ethics committee approved the study protocol, and written informed consent was obtained from the study subjects. Statistical analysis (chi-square test) was performed using EPI INFO version 6.04d (CDC, Atlanta, GA, USA).

The frequency of wild type homozygous C/C genotype and C allele was higher (>95%), and the mutant C/T genotype and T allele was rare (<5%), but almost equally distributed in patients and in normal subjects. The mutant T/T genotype was very rare (0.8%) in patients, but absent in normal subjects (Table 1). With 2.75%

Table 1 Frequency of genotypes and alleles at 1858 site of PTPN 22 gene in type 1 diabetes patients and normal controls.

PTPN 22	Patients (%)	Controls (%)	*P*-value P_c	OR (95% CI)
1858 C/T				
CC	121 (93.8)	103 (94.5)	0.81 NS	1 (0.32–3.1)
CT	7 (5.4)	6 (5.5)		
TT	1 (0.8)	-		
Alleles				
C	249 (96.5)	212 (97.25)	0.64 NS	0.78(0.27–2.23)
T	9 (3.5)	6 (2.75)		1.27 (0.44–3.6)

The patients were diagnosed as per the criteria laid down by the American Diabetes Association Expert Committee (Expert committee on the diagnosis and classification of diabetes mellitus 2001), and controls included normal healthy individuals. Statistical analysis was performed by chi-square test test. Pc, corrected P-value; NS, not significant.

doi: 10.1111/j.1582-4934.2008.00222.x

prevalence of 1858T allele in Asian Indians, and with 129 patients and 109 controls, our study has 80% power at 95% confidence level. Thus, a larger cohort of 784 patients and 1270 controls would be required to detect the significant risk conferred by 1858T allele. However, C1858T SNP appears to be a rare variant, and seems to play no role in T1D susceptibility in Asian Indians. Similarly, C1858T SNP was not related to T1D susceptibility in other Asians such as Japanese and Koreans [13]. Moreover, −1123G>C SNP appeared to be more likely a causative variant in these populations but not in Caucasians [10]. Functionally, *PTPN22* is a compelling candidate gene for T1D, as protein tyrosine phosphatases play important roles in TCR signalling. Since the polymorphism in *PTPN22* gene maps to 293-kb linkage disequilibrium block [14], it seems reasonable to presume that some other potentially functional SNPs may be responsible for T1D susceptibility in Asian Indians.

V. Baniasadi, S. N. Das *
Department of Biotechnology,
All India Institute of Medical Sciences,
Ansari Nagar, New Delhi, India.

References

1. **Kochupillai N.** Clinical endocrinology in India. *Curr Sci.* 2000; 79:1061–7.
2. **Cudworth AG, Woodrow JC.** Evidence for HLA linked genes in 'juvenile' diabetes mellitus. *Br Med J.* 1975; 3: 133-5.
3. **Bell GI, Horita S, Karam JH.** A polymorphic locus near the human insulin gene is associated with insulin – dependent diabetes mellitus. *Diabetes.* 1984; 33: 176–83.
4. **Ueda H, Howson JM, Esposito L, Heward J, Snook H, Chamberlain G, Rainbow DB, Hunter KM, Smith AN, Di Genova G, Herr MH, Dahlman I, Payne F, Smyth D, Lowe C, Twells RC, Howlett S, Healy B, Nutland S, Rance HE, Everett V, Smink LJ, Lam AC, Cordell HJ, Walker NM, Bordin C, Hulme J, Motzo C, Cucca F, Hess JF, Metzker ML, Rogers J, Gregory S, Allahabadia A, Nithiyananthan R, Tuomilehto-Wolf E, Tuomilehto J, Bingley P, Gillespie KM, Undlien DE, Rønningen KS, Guja C, Ionescu-Tîrgovişte C, Savage DA, Maxwell AP, Carson DJ, Patterson CC, Franklyn JA, Clayton DG, Peterson LB, Wicker LS, Todd JA, Gough SC.** Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. *Nature.* 2003; 423: 506–11.
5. **Baniasadi V, Narain N, Goswami R, Das SN.** Promoter region C/T and -1661 A/G CTLA-4 single nucleotide polymorphisms and type 1 diabetes in North Indians. *Tissue Antigens.* 2006; 67: 383–9.
6. **Das SN, Baniasadi V, Kapuria V.** Association of −308 TNF-α promoter polymorphism with type 1 diabetes in North Indians. *Int J Immunogenet.* 2006; 33: 411–6.
7. **Hill RJ, Zozulya S, Lu YL, Ward K, Gishizky M, Jallal B.** The lymphoid protein tyrosine phosphatase Lyp interacts with the adaptor molecule Grb2 and functions as a negative regulator of T-cell activation. *Exp Hematol.* 2002; 30: 237–44.
8. **Bottini N, Musumeci L, Alonso A, Rahmouni S, Nika K, Rostamkhani M, MacMurray J, Meloni GF, Lucarelli P, Pellecchia M, Eisenbarth GS, Comings D, Mustelin T.** A functional variant of lymphoid tyrosine phosphatase is associated with type 1 diabetes. *Nat Genet.* 2004; 36: 337–8.
9. **Zheng W, She JX.** Genetic association between a lymphoid tyrosine phosphatase (PTPN22) and type 1 diabetes. *Diabetes.* 2005; 54: 906–8.
10. **Chelala C, Duchatelet S, Joffret ML, Bergholdt R, Dubois-Laforgue D, Ghandil P, Pociot F, Caillat-Zucman S, Timsit J, Julier C.** PTPN22 R620W Functional variant in type 1 diabetes and autoimmunity related traits. *Diabetes.* 2007; 56: 522–6.
11. **Lee YH, Rho YH, Choi SJ, Ji JD, Song GG, Nath SK, Harley JB.** The PTPN22 C1858T functional polymorphism and autoimmune diseases-a-meta-analysis. *Rheumatology.* 2007; 46: 49–56.
12. **Vang T, Congia M, Macis MD, Musumeci L, Orrú V, Zavattari P, Nika K, Tautz L, Taskén K, Cucca F, Mustelin T, Bottini N.** Autoimmune-associated lymphoid tyrosine phosphatase is a gain-of-function variant. *Nat Genet.* 2005; 37: 1317–9.
13. **Kawasaki E, Awata T, Ikegami H, Kobayashi T, Maruyama T, Nakanishi K, Shimada A, Uga M, Kurihara S, Kawabata Y, Tanaka S, Kanazawa Y, Lee I, Eguchi K.** Systematic search for single nucleotide polymorphisms in a lymphoid tyrosine phosphatase gene (PTPN22): association between a promoter polymorphism and type 1 diabetes in Asian populations. *Am J Med Genet.* 2006; 140: 586–93.
14. **Kim MS, Polychronakos C.** Immunogenetics of Type 1 diabetes. *Horm Res.* 2005; 64: 180–6.

*Correspondence to: Prof. Satya N DAS,
Department of Biotechnology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi-110029, India.
E-mail: satyandas@gmail.com