

ARTICLE

The polymorphisms of protein-tyrosine phosphatase receptor-type delta gene and its association with pediatric asthma in the Taiwanese population

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We previously reported an association between genetic differences of pediatric asthma subtypes and a short tandem repeat (STR) marker, D9S286. It has been known that the protein-tyrosine phosphatase receptor-type delta (PTPRD) gene is located downstream of D9S286 and that the physical distance between them is about 0.25 Mb. We selected and conducted genotyping on 76 single-nucleotide polymorphisms (SNPs) that encircle the genomic region of PTPRD in Taiwanese children with or without asthma. A total of 996 subjects were divided into testing group (674 subjects) and validation group (322 subjects). The results were further validated with the third subject group (611 subjects) recruited from different geographical regions. After Bonferroni correction, 3 out of 80 SNPs were found to be strongly significant ($P < 0.05/76 = 0.000658$) in the allele frequency test. This association was confirmed by validation groups. The results indicate that polymorphisms of PTPRD are strongly associated with pediatric bronchial asthma in the Taiwanese population.

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Introduction

A whole-genome linkage disequilibrium mapping study for asthma was conducted on 190 allergic and nonallergic asthma children in Taiwan. The initial association study was conducted using a phenotypic definition of 'asthma' that meets the criteria of diagnosis of asthma by physicians and that is currently under treatment. Marker-to-marker synergistic analysis indicated that six STR loci may play

important roles in asthma. D9S286, one of the six STR loci, was located on chromosome 9p arm and its physical distance from p terminus is 8.04 Mb.¹ Protein-tyrosine phosphatase receptor-type delta (PTPRD) gene is the closest gene to the D9S286 locus with a physical distance of 8.3–8.72 Mb from chromosome 9p terminus (ref. NCBI map viewer, *Homo sapiens* Build 36).

Protein-tyrosine phosphatases (PTPases) play essential roles in the regulation of cell growth, proliferation, differentiation, metabolism, cell cycle, cell–cell communication, cell migration, gene transcription, ion channel activity, the immune response and survival.² Transmembrane-type PTPase is a major subfamily of PTPases that contains extracellular regions composed of immuno (Ig)-like and fibronectin type III (FN-III)-like domains. Human PTPRD is also known as human transmembrane PTPase

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delta (HPTP δ). The full length of PTPRD gene includes an extracellular region containing three Ig-like and eight FN-III-like domains connected by a transmembrane peptide to an intracellular region with two PTPase domains, whereas another splicing variant lacks four of the eight FN-III-like domains. It has also been reported that some splicing variants of PTPRD lack nine amino acids at the junction of the second and third Ig-like domains or nine amino acids within the fifth FN-III-like domain.³

The purpose of this study was to evaluate the significance of PTPRD as an allergy or asthma-susceptibility gene. In this study, about 1500 subjects, including southern (Tainan) and northern (Taipei) Taiwanese children, were recruited. The genotype of PTPRD polymorphisms was performed in the first-recruited subject group, and the alleles with significant association were validated in two independently ascertained subject groups. The results indicate that polymorphisms of PTPRD are strongly associated with pediatric bronchial asthma in the Taiwanese population.

Materials and methods

Sample composition and clinical evaluation

Our study population consists of asthmatic children of age ranging from 3 to 12 years. The study protocol was approved by the Ethical and Clinical Trial Committee of National Cheng-Kung University Hospital and Mackay Memorial Hospital. An informed consent form was given to all participants or their guardian after answering a modified British Medical Society respiratory questionnaire, which is exactly the same as that of the European Community Respiratory Health Survey (ERCHS). These surveys have similar validity as ISAAC pertinent to the diagnosis and assessment of asthma.^{4,5} Pulmonary function was tested using standard methods, including spirometry, before and after the administration of two puffs of inhaled salbutamol (200 μ g per puff). The definition of asthma must meet the following criteria: (1) a history of having wheezing and experiencing shortness of breath during or without concurrent respiratory infections, (2) chronic coughing for more than 1 month and being diagnosed by a physician for the presence of wheezing episode(s) and (3) positive bronchodilator test showing a 15% increase in FEV1. Nonasthma controls were defined as those without an asthma history as in criteria (1) or those who did not meet criteria (2). Other evaluations included skin prick tests for responsiveness to six common aeroallergens, a differential blood count (including total eosinophil count) and levels of total serum IgE, as well as IgE specific to house dust and mixed pollens, using the Unicap system (Pharmacia Diagnostic, Sweden). A positive skin test was defined as the presence of ≥ 1 reaction with a wheal diameter ≥ 5 mm. Total serum IgE was measured by solid-phase immunoassay (Pharmacia IgE EIA; Pharmacia

Diagnostics). Nonallergy group was defined as total serum IgE <200 and negative skin test. The subjects of group 1 (674 subjects) and group 2 (322 subjects) were recruited from National Cheng-Kung University Hospital during 2002–2003 and 2004, respectively. The third subject group (611 subjects) was recruited from MacKay Memorial Hospital and National Cheng-Kung University Hospital in 2006.

DNA preparation

Genomic DNAs were extracted from blood samples of the study subjects using the QIAamp DNA Blood kit (QIAGEN), according to the manufacturer's instructions. The extracted genomic DNAs were analyzed by agarose gel electrophoresis, quantified by spectrophotometer and stored at -80°C until use.

SNP genotyping

The PTPRD gene has 35 exons spanning 416.68 kb. We selected 72 SNPs within and near PTPRD gene to examine the genotyping association results. All SNP genotypings were performed using the Taqman[®] SNP genotyping assays (ABI). The primers and probes of the PTPRD SNPs were from the ABI assay on demand (AOD) kit. The SNPs were selected by even distribution in the genomic region of the PTPRD gene and using the Taqman ABI AOD kit (Supplementary Table 1). Reactions were carried out according to the manufacturer's protocol. The probe fluorescence signal detection was performed using the ABI Prism 7900 Real-Time PCR System.

DNA fragments of the PTPRD gene containing well-known coding region SNP (NCBI, SNP database) in exon7, exon13, exon14, exon16, exon17 and exon18 were amplified on the ABI 9700 thermal cycler using two pairs of forward and reverse primers. The sequences and the related information of primers are listed in Supplementary Table 2. The fragments of PCR products were sequenced using the ABI 3700 automatic sequencer, according to the manufacturer's protocols. The sequence data were analyzed by PolyPhred software to identify the potential SNP candidates. The potential SNPs were manually checked to ensure the presence of true SNPs and only those that confirmed SNP data were subjected to subsequent statistical analysis.

Statistical analysis

For identifying the association between asthma and asthma-related phenotype and SNPs in PTPRD, an evaluation, including allele frequency and genotype frequency, was performed by χ^2 test. The haplotypes were constructed using HAP website information (<http://research.calit2.net/hap>), which was based on the assumption of imperfect phylogeny. According to the results of haplotype analysis, the tag SNPs in each haplotype were selected. The association analyses for haplotype were performed by

Monte Carlo simulation⁶ using the CLUMP program (<http://www.mds.qmw.ac.uk/statgen/dcurtis/software.html>) and the χ^2 -test.

Results

Characteristics of study subjects

A total of 674 DNA samples extracted from 251 nonasthma children and 423 asthmatic children were collected as group 1 and genotyping was performed on all selected SNPs. It was found that there was statistically significant difference in the distribution of characteristics of study subjects between asthma and nonasthma, as listed in Table 1. The 322 subjects (including 42 asthmatic children and 270 controls) in group 2 were recruited from the same hospital as those in group 1 at a different time. The characteristics with statistically significant difference between case and control of a total of 996 subjects are shown in Table 1. Group 3 subjects (including 414 asthmatic children and 197 controls) were recruited from two different hospitals, and only asthma status and total serum IgE were evaluated by fulfilling earlier-described criteria. The results showed that asthma subjects had a higher level of total serum IgE than did nonasthma subjects in all case-control comparisons (Table 1). According to allergy phenotype, 674 subjects in group 1 were further divided into four subgroups, 337 allergic asthma, 86 nonallergic asthma, 113 allergy subjects without asthma and 138 nonallergy and nonasthma subjects.

The SNPs of PTPRD gene associated with asthma

Seventy-six SNPs were identified in the study subjects. The locations of these SNPs are shown in Supplementary Table 1. Six coding regions or near the coding regions of SNPs

were not detected by direct sequencing (Supplementary Table 2), and two intron SNPs did not display polymorphism by Taqman genotyping (Supplementary Table 3) in our study population. After Bonferroni correction (P -value $< 0.05/76 = 0.000658$), three SNPs (rs2279776, rs767674 and rs2175595) with significantly different frequencies between asthma and nonasthma children in testing allele and/or genotype were observed (Table 2 and Supplementary Table 3). The power to detect significant association was calculated by power for association with errors (PAWE; <http://linkage.rockefeller.edu/pawe/>).^{7,8} For example, rs2279776, given 423 cases and 251 controls, adjusts P -value 0.0456 ($= 0.0006 \times 76$) and data without error, and the power for allelic and genotypic tests was 0.97 and 0.94, respectively.

PTPRD polymorphism and asthma phenotype

For evaluating the association between asthma phenotypes and PTPRD polymorphisms, genotype frequencies of SNPs were compared between (1) allergic asthma and allergy without asthma, (2) asthma without allergy subjects and healthy control subjects and (3) asthma and nonasthma subjects. The statistically significant or marginal significant SNPs are listed in Table 2. The distribution patterns of significant SNPs were not sporadic in each comparison. Three SNPs showed statistical significance in all three comparisons (rs2279776, rs767674 and rs2175595) after Bonferroni correction in some comparisons.

PTPRD polymorphism and allergy phenotype

For evaluating the association between allergy phenotypes and PTPRD polymorphisms, the genotype frequencies of SNPs were compared between (1) allergic asthma and asthma without allergy subjects, (2) allergy without asthma

Table 1 Demographic information of the study subjects

	674 subjects (996 subjects ^a)		611 subjects	
	Asthma	Non-asthma	Asthma	Non-asthma
<i>Mast</i>			—	—
Positive	339 (379)	113 (239)		
Negative	84 (96)	138 (282)		
<i>Der p</i>			—	—
Positive	343 (380)	104 (220)		
Negative	80 (95)	147 (301)		
<i>Der f</i>			—	—
Positive	322 (358)	69 (184)		
Negative	101 (117)	182 (337)		
ln(IgE)	Mean \pm Std		Mean \pm Std	
	6.0669 \pm 1.4602 (6.0277 \pm 1.4530)	4.5668 \pm 1.7499 (4.3697 \pm 1.7231)	5.8062 \pm 1.4364	4.3243 \pm 1.7579
	<i>t</i> -test $P < 0.0001$	$(P < 0.0001)$	<i>t</i> -test $P < 0.0001$	

^a996 (674+322) subjects represented total group1 and group2 subjects, all subjects recruited from National Cheng-Kung University hospital during 2002–2004; —: no evaluation for this character.

Table 2 Significant ($P < / \sim 0.05$) results in SNPs genotype/allele by subgroups of asthma phenotype

SNP ID	AA vs NA		AN vs NN		Asthma vs Non-asthma	
	Genotype P-value	Allele P-value	Genotype P-value	Allele P-value	Genotype P-value	Allele P-value
rs966924	0.0146	0.0165	—	—	—	—
rs3780336	0.0340	0.0141	—	—	—	—
rs1039336	0.0275	0.0081	0.0127	0.1685	—	—
rs2279776	0.0009	0.0004	0.0674	0.0283	0.0006	0.0001
rs3803826	—	—	0.0974	0.0290	—	—
rs4742500	—	—	0.0262	0.0611	0.0123	0.0627
rs2281747	—	—	—	—	0.0457	0.0170
rs767674	0.0008	0.0001	0.0288	0.0066	0.0016	0.0002
rs13294631	0.0268	0.0098	—	—	—	—
rs11788439	—	—	0.0182	0.0095	—	—
rs12685150	—	—	0.0011	0.0011	—	—
rs2175595	0.0002	0.0001	0.0300	0.0065	<0.0001	<0.0001
rs1415723	—	—	0.0382	0.0060	—	—
rs10815923	—	—	0.0388	0.0153	—	—
rs1368982	—	—	0.1283	0.0344	—	—
rs1434249	—	—	0.0023	0.0276	0.0190	0.2225
rs6477331	—	—	0.0045	0.0228	—	—
rs2033555	—	—	—	—	0.1526	0.0485
rs723145	0.0654	0.0184	—	—	0.0754	0.0215

AA: asthma with allergy; AN: asthma without allergy; NA: nonasthma with allergy; NN: nonasthma without allergy. The genotypic test results of asthma vs nonasthma were selected from Supplement Table 3.

and healthy control subjects and (3) allergy and nonallergy subjects. The statistically significant or marginally significant SNPs are listed in Table 3. Although there is not a single SNP displaying statistically significant difference in all three comparisons after Bonferroni correction, nevertheless, the distribution patterns of significant SNPs were not sporadic in each comparison.

Haplotypes constructed by tag-SNPs of PTPRD gene region associated with asthma

Seventy-six SNP loci were selected in constructing haplotypes using the method of imperfect phylogeny. The haplotypes of 18 haploblocks were presented by tag-SNP (tSNP) and are shown in Supplementary Table 4. The tSNPs were general HAP (website mentioned) as described in the Materials and methods section shown in Supplementary Table 3. Blocks 4, 11, 15 and 17 were each presented by only one SNP. To evaluate haploblock associated with the difference between case and control, the haplotype frequencies between the two groups were tested by χ^2 -test and the very rare haplotypes were not included in the statistical test. Blocks 4, 5, 7, 12 and 17 showed statistical significance and the P -values were 7.8×10^{-5} , 0.0294, 2.2×10^{-6} , 4.0×10^{-8} and 0.0403, respectively. Common haplotypes (frequency >1%) of all the haploblocks were subjected to 2×2 χ^2 -test (compared to sum of other haplotypes) and the results are listed in Supplementary Table 4. The haplotype(s) of haploblocks 4, 5, 6, 7, 12, 13 and 17 showed significantly ($P < 0.05$) different frequencies between asthma and nonasthma groups.

Validation of the strongest association for asthma phenotype

The SNPs rs2279776 (in exon27), rs767674 (in intron 20) and rs2175595 (in intron 4) showed significantly different allele and genotype frequencies after Bonferroni correction between asthma and nonasthma subjects. For validating the results described above, genotyping of the three strongly associated SNPs for group 2 and group 3 subjects was performed. It showed that SNP rs2279776 displayed statistical significance or marginal significance in both groups. Validation also showed that all three SNPs have statistical significance in the comparison of total subjects (Table 4). The odds ratio analysis showed that the risk genotypes of rs2279776, rs767674 and 2175595 were CC + GG, GG + AG and TT, respectively (Table 5). Some conflict results, such as rs2279776 in 311 subjects, may be due to the small sample size or sampling bias. The genotype frequencies of rs767674 in individual patient groups differ from each other, but the frequencies of GG + AG genotype of case are higher than those of control in every study group (Table 5).

Discussion

In the current study, we investigated asthma and allergy phenotypes. After analysis and Bonferroni correction, it revealed that the testing polymorphism of PTPRD is associated with asthma but not with allergy phenotype. We found that the association between allergy phenotype and PTPRD polymorphism was significant before Bonferroni correction. It is not clear if PTPRD polymorphism is really associated with the general allergic state. The

Table 3 Significant ($P < / \sim 0.05$) results in SNPs genotype/allele by subgroups of allergy phenotype

SNP ID	AA vs AN		NA vs NN		Allergy vs Non-allergy	
	Genotype P-value	Allele P-value	Genotype P-value	Allele P-value	Genotype P-value	Allele P-value
rs996924	—	—	0.0351	0.0390	—	—
rs3780336	—	—	0.0626	0.0267	—	—
rs1039336	0.0296	0.2466	0.0185	0.0082	—	—
rs1359119	—	—	0.0333	0.0585	0.0396	0.0251
rs2296100	—	—	0.0434	0.0933	0.0802	0.0563
rs767674	—	—	—	—	0.0033	0.0010
rs6477311	—	—	0.0054	0.0053	0.0548	0.0481
rs3763653	—	—	—	—	0.0424	0.0251
rs13293506	—	—	0.0580	0.0215	—	—
rs12685150	0.0113	0.0029	—	—	—	—
rs1415723	0.0837	0.0261	—	—	—	—
rs7041298	—	—	0.0119	0.0923	—	—
rs10815923	0.0518	0.0137	—	—	—	—
rs1434249	0.0611	0.0300	—	—	—	—
rs6477331	0.0409	0.0337	—	—	—	—
rs3887368	—	—	0.0005	0.0607	0.0165	0.1130

AA: asthma with allergy; AN; asthma without allergy; NA: nonasthma with allergy; NN: nonasthma without allergy.

Table 4 Statistical analyses of three independent subject groups for SNPs rs2279776, rs767674 and rs2175595

SNP ID	Genotype	674 subjects		322 subjects		611 subjects		Total	
		Case	Control	Case	Control	Case	Control	Case	Control
rs2279776	CC	97	31	3	22	31	20	131	73
	CG	199	116	19	137	200	73	417	326
	GG	126	102	30	111	183	104	339	317
		$\chi^2 = 14.8081$	$P = 0.0006$	$\chi^2 = 4.8708$	$P = 0.0875$	$\chi^2 = 7.0149$	$P = 0.0300$	$\chi^2 = 10.2486$	$P = 0.0060$
rs767674	AA	88	77	20	112	151	76	259	265
	AG	188	116	23	119	195	85	406	320
	GG	143	57	9	39	68	36	220	132
		$\chi^2 = 12.8969$	$P = 0.0016$	$\chi^2 = 0.3370$	$P = 0.8449$	$\chi^2 = 0.8828$	$P = 0.6431$	$\chi^2 = 14.8008$	$P = 0.0006$
rs2175595	AA	5	12	1	0	2	0	8	12
	AT	74	74	5	47	63	21	142	142
	TT	340	161	46	223	349	176	735	560
		$\chi^2 = 27.2923$	$P < 0.0001$	$\chi^2 = 7.0114$	$P = 0.0300$	$\chi^2 = 3.3631$	$P = 0.1861$	$\chi^2 = 6.2329$	$P = 0.0443$

Table 5 Odds ratio analyses of three independent subject groups for SNPs rs2279776, rs767674 and rs2175595

SNP ID	Genotype	674 subjects		322 subjects		611 subjects		Total	
		Case	Control	Case	Control	Case	Control	Case	Control
rs2279776	CC+CG	296	147	22	159	231	93	548	399
	GG (ref.)	126	102	30	111	183	104	339	317
	OR(95% CI)	1.67 (1.20, 2.32)		0.51 (0.28, 0.93)		1.42 (1.00, 1.98)		1.28 (1.05, 1.57)	
	P-value	0.0021		0.0273		0.0468		0.0142	
rs767674	GG+AG	331	173	32	158	263	121	626	452
	AA (ref.)	88	77	20	112	151	76	259	263
	OR(95% CI)	1.67 (1.17, 2.39)		1.13 (0.62, 2.09)		1.09 (0.77, 1.55)		1.42 (1.15, 1.75)	
	P-value	0.0045		0.6851		0.6147		0.0011	
rs2175595	TT	340	161	46	223	349	176	735	560
	AA+AT (ref.)	79	86	6	47	65	21	150	154
	OR(95% CI)	2.30 (1.61, 3.29)		1.62 (0.65, 2.09)		0.64 (0.38, 1.08)		1.35 (1.05, 1.73)	
	P-value	<0.0001		0.2960		0.0940		0.0193	

Case: asthma subjects; Control: nonasthma subjects; OR: odds ratio; CI: confidence interval; ref.: reference genotype(s).

association between asthma phenotype and PTPRD polymorphisms was further analyzed and validated by the haplotype approach. The results of this study indicated a

strong possibility that the polymorphisms of the PTPRD gene may confer risk for pediatric asthma in the Taiwanese population. Because the results of validation showed only

weak association, further replication phases should be necessary.

Mouse PTPRD (also known as MPTP-delta) is expressed in the specialized regions of the brain and in the B-cell lineage.⁹ PTPRD is involved in the regulation of synaptic plasticity or in the processes regulating learning and memory in the mouse model.¹⁰ Furthermore, the results from the mouse study demonstrated that PTPRS (also known as RPTP-sigma) and PTPRD complement each other functionally during mammalian development. It also revealed that PTPRS and PTPRD played an essential role in appropriating motor neuron axon targeting during mammalian axonogenesis.¹¹

In human disease study, PTPRD has been reported as a tumor suppressor gene. As previously reported, PTPRD is potentially involved in carcinogenesis of lung cancer,^{12–14} cutaneous squamous carcinomas,¹⁵ hepatomas,¹⁶ melanomas¹⁷ and neuroblastomas.¹⁸ Though some receptor-like PTPs, such as CD45, RPTP- ϵ and CD148, play an important role in lymphocyte activation,¹⁹ PTPRD does not demonstrate potential function to immune response as yet.

The SNP rs2279776 (C4396G) is located in exon 27 of the PTPRD gene and is a silent polymorphism. The synonymous SNP is translated to the 1418th amino acid in the first tyrosine phosphatases domain of the PTPRD protein. Codon usage for the synonymous SNP rs2279776, with GGC changed to GGG (both encode glycine), changes from 34% (frequency per thousand: 22.3) to 25% (frequency per thousand: 16.4; codon usage database: <http://www.kazusa.or.jp/codon/>). A recent report of the Multi-drug Resistance 1 (MDR1) gene indicated that silent polymorphism can change the substrate specificity.²⁰ The SNP rs2279776 in the PTPRD gene may have a similar function as MDR1 gene's silent polymorphism, but it needs to be further elucidated.

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