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Association between PTPN22/CTLA-4 Gene Polymorphism and Allergic Rhinitis with Asthma in Children

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ABSTRACT

Allergic rhinitis (AR) is an IgE-mediated upper airway disease, and its impact on asthma has been widely recognized. Protein tyrosine phosphatase non-receptor 22 (PTPN22) gene and the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) gene polymorphisms have been reported to be associated with several immune-related diseases. Here we investigated the reffect of these two genes' polymorphisms on the risk of AR and asthma in Chinese Han children.

A total of 106 AR patients, 112 AR with asthma patients, and 109 healthy children were enrolled in the study. The SNPs of PTPN22 (rs2488457, rs1310182, rs3789604) and CTLA-4 (rs3087243, rs11571302, rs11571315, rs231725, rs335219727, and rs4553808) were genotyped using a PCR-restriction fragment length polymorphism assay.

For PTPN22, an increased prevalence of the CC genotype and C allele in rs1310182 were identified in AR group. For CTLA-4, AA genotype and A allele in rs3087243 and rs231725 were increased in AR with asthma group while in AR group, AA genotype and A allele in rs231725 were obviously decreased.

This study reveals a significant association between SNPs in PTPN22, CTLA-4 gene and AR with asthma in Chinese Han children, which might be susceptibility factors for AR and asthma.

Keywords: Allergic rhinitis; Asthma; Pediatrics;Genetic polymorphism; Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4); Single nucleotide polymorphism (SNP); Protein tyrosine phosphatase non-receptor 22 (PTPN22)

INTRODUCTION

Allergic rhinitis (AR) is a chronic inflammatory disease induced by IgE-mediated inflammation and regulated by T cells. As another IgE-mediated inflammation of the upper airway, asthma is commonly associated with AR. For example, allergic rhinoconjunctivitis and asthma may occur simultaneously in children.[1] According to statistics, about 50% of 5-year-old children with asthma have coexisting rhinitis,[2] so AR is regarded as a risk factor for asthma;[3] however, in clinical work, there are still some children with allergic rhinitis who do not suffer from asthma, the reason of which remains unknown.

At present, the difference between AR children with asthma or without asthma is studied focusing on

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environmental and genetic factors.[4,5]

As an important element of genetics, single nucleotide polymorphism (SNP) has been targeted on many autoimmune diseases, and it includes coding sequences of genes, non-coding regions of genes, and intergenic regions between genes. With changing the expression of proteins, polymorphism could influence the development of diseases. The protein tyrosine phosphatase non-receptor 22 (PTPN22) gene is located at chromosome 1p13.2. The target protein of PTPN22 is well known as LYP which contains a non-catalytic C-terminus. LYP is composed of four proline-rich domains and a catalytic N-terminal domain and it can interact with C-terminal Src kinase (Csk), zeta-associated protein-70 (ZAP70) and Vav (a guanine-nucleotide exchange factor for the GTPases). In the T-cell receptor (TCR) signaling pathway, Lyp could influence the phosphorylation of T cell responses, which would influence the proliferation and differentiation of T cell.[6,7]

The cytotoxic T-lymphocyte–associated antigen (CTLA-4) gene encodes a glycoprotein receptor of the immunoglobulin (Ig) family expressed on the surface of activated T cells .It maps to chromosome 2q33 which contains a cluster of T-lymphocyte immune regulating genes: CD28, CTLA-4 and inducible co-stimulator(ICOS). CTLA-4 gene is recently considered a susceptible gene of autoimmune diseases because it acts as a negative regulator of T-cell activation by antigen-presenting cells (APC) and of subsequent cellular immunity.[8] CTLA-4 and CD28 act as members of the same pathway and the CTLA-4 molecule binds the same ligands as CD28 but with at least a 10-fold greater affinity.[9]

PTPN22 and CTLA-4 have been shown to be non-HLA susceptibility genes for various autoimmune diseases, such as rheumatoid arthritis (RA), type 1diabetes (T1D), systemic lupus erythematosus (SLE), and Graves' disease (GD).[10-13] Even so, there is no evidence about the relationship of these genes and AR in children with asthma or without asthma. In this study, we attempted to examine the genetic influences of PTPN22 and CTLA-4 on AR in children with asthma and without asthma by identifying nine possible variation sites.

MATERIALS AND METHODS

Subjects

In our study, 106 children with AR alone (55 boys, 51 girls) and 112 children with both AR and asthma (69 boys, 43 girls) were recruited from May 2013 to May 2014,whose age were between 1 and 16 years. All patients were identified by and treated at the outpatient clinic of the Department of Otolaryngology Head and Neck Surgery at the Hospital of Chongqing Medical University, Chongqing, China. The patients were diagnosed based on medical history, symptoms, the presence of a positive skin prick test (SPT) (Allergopharma, Hamburg, Germany), and bronchial provocation test (BPT) which were defined in the ARIA 2008 guidelines.[14] According to the recommendations of the Subcommittee on Allergen Standardization and Skin Tests of the European Academy of Allergy and Clinical Immunology,[15] the SPT result was positive when there was at least 3 mm larger than the diameter of the negative control wheal. A total of 18 inhaled allergens were tested, including house dust, grass, tree, mold, food, and cat and dog dander. About BPT, a decrease of more than 20% in FEV1 is regarded as positive. Patients with a systemic disease were excluded from the study. 169 healthy subjects of the same ethnicity as the patients were regarded as the healthy control. The clinical characteristics of the AR, AR with asthma and control subjects were assessed at the time of diagnosis and are summarized in Table 1.

Ethics Statement

The Ethics Committee of the Chongqing Medical University had vetted the study protocol (No.2011-201123). Written informed consent was obtained from all parents, the next of kin, caretakers, or guardians on behalf of all minors participating in this study.

DNA Extraction

Genomic DNA was extracted by the Wizard Genomic DNA Purification Kit (Promega, Beijing, China) after peripheral blood leukocytes were anti coagulated with ethylene diamine tetraacetic acid (EDTA). Leucocytes were spun down and lysed with nuclei lysis solution (Promega, Beijing, China) after mixing 300μl of blood with cell lysis solution.

The protein was eliminated using precipitation solution and centrifugation.. DNA was recovered by precipitation with methyl alcohol and reconstituted in 100 μL DNA rehydration solution.

Determination of Genotype

The candidate sites rs2488457, rs1310182 and rs3789604 were selected for PTPN22 gene; meanwhile, we also chose six associated SNPs (rs3087243,

rs11571302, rs11571315, rs231725, rs335219727 and rs4553808) of CTLA-4 from certain immune-related diseases. These SNPs were genotyped using the polymerase chain reaction–restriction fragment length polymorphism method (PCR–RFLP). The primers were found by primer3 (http://frodo.wi.mit.edu/) and the enzymes were chosen on the NEB net (https://www.neb.com/). The primer sequences and enzymes used in this study are shown in Table 2. The PCR products were incubated with restriction enzymes for 1 or 16 hours. 4% agarose gel with Gold View (SBS Genentech, Beijing, China) was used to visualize the obtained digestion products. 20% of PCR-amplified DNA samples were examined by direct sequencing to confirm the genotyping results, which was 100% concordant.

Statistics Analysis

All statistical analyses were performed by SPSS version 19.0 software (SPSS Inc., Chicago, Illinois, USA). It was considered statistically significant when *p*- values were less than 0.05. A chi-square teat (χ^2 test) was used to evaluate the quality of the genotyping data by verifying the Hardy-Weinberg equilibrium (HWE) through the online software platform SHEsis (http://analysis2.bio-x.cn/myanalysis.php). Logistic regression analysis with OR was used to compare the association between different genotypes and different phenotypes, adjusting for the children's age and gender. The differences in prevalence of allergen sensitivity in every two groups were verified by the chi-square test. The association between genotypes/alleles and prevalence risk was estimated by calculating OR and 95% confidence intervals (CI).

RESULTS

Clinical Characteristics of the Study Participants

The demographics of the cases and controls enrolled in this study are shown in Table 1. There were no significant differences between the cases and controls in terms of the mean age and gender distribution. 109(50.3%), 45(20.8%) and 64(28.9%) of children in patient group group were sensitive to house dust mite, to tree pollen, and multiple allergens, respectively.

Table 1. Demographics of the study population in which association between PTPN22/ CTLA-4 gene polymorphism and allergic rhinitis with asthma was investigated.

Study groups	Number （boy/girl）	Age[mean (min, max)]years
Group1(AR*)	106(55/51)	5.83(1-16)
Group2(AR*+asthma)	112(69/43)	3.72(1-16)
control	169(85/84)	5.14(2-15)

*AR: allergic rhinitis

Table 2. The primer sequences and restriction enzyme used in the PCR reaction to investigate association between PTPN22/ CTLA-4 gene polymorphism and allergic rhinitis with asthma in children

SNPs number	Primers	Restriction enzyme
rs2488457	F:5'-CCATTGAGAGGTTATGCGAGCT-3'	SacI
	R: 5'-CGCCACCTTGCTGACAACAT-3'	
rs1310182	F: 5'-AAACCCAATGACCAATGACA-3'	Hsp92II
	R: 5'-AAGCATTTAATTATATGGTGCTGAG-3'	
rs3789604	F: 5'-GCGAGAGGGGGCTCCTGGCTCGGCCGC-3'	PauI
	R: 5'- CGGCGGGGGCGCGGCGGAACTACAGC-3'	
rs3087243	F: 5'-GGACAAATAATGCTTCATGAGTCAGC-3'	TaiI
	R: 5'-GTTGCCATGACAACTGTAATGCCT-3'	
rs11571302	F: 5'-CTTCCAGAGGACTTAGGAGAAGCATCTC-3'	MspI
	R: 5'- TTCTTACAATTCCTCTCAGAGGAAGCTG-3'	
rs11571315	F: 5'- TTAAAAAGTGAAAAACAAATGTTCCTG-3'	TasI
	R: 5'-AACTTTAGCCCATGTTATTCTTCTTGT-3'	
rs231725	F: 5'- CGTCAGATTTGCTGACACTTTAAG-3'	BssSI
	R: 5'-GATCAAATGGGAAAGAGATTAAGCT-3'	
rs35219727	F: 5'- GGGCTATAATCACTGCTCACAGGA-3'	ForkI
	R: 5'-CAGAAGAGAAAACAGTTTGGCAGC-3'	
rs4553808	F: 5'-CTTCAATTCCAGCATTGATCTCACTCT-3'	DraI
	R: 5'-TATACATGTGCCATGTTGGTGTGATG-3'	

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Genotype and Allele Frequencies of PTPN22 Polymorphisms

Three SNPs of PTPN22 (rs2488457, rs1310182 and rs3789604) were genotyped in 112 AR with asthma patients, 106 AR patients and 109 healthy controls. Our results showed that they were in Hardy–Weinberg equilibrium and the call rate for the examined three SNPs was 100%.

An increased frequency of the CC genotype and C allele of rs1310182 (p=0.001, OR=4.667, 95%CI [1.882-11.574]; p=0.3×10^{-5}.OR= 2.419, 95% CI 1.669-3.505, respectively) (Table 3) were identified when comparing AR group with control, which were not found in the AR with asthma group and control.

No significant association was found for the rs2488457 and rs3789604 SNP in the three groups (Table 3).

Genotype and Allele Frequencies of CTLA-4 Polymorphisms

Six SNPs of CTLA-4 (rs3087243, rs11571302, rs11571315, rs231725, rs35219727, rs4553808) were genotyped in the same patients and controls.

The results showed a significantly higher prevalence of AA genotype and A allele of rs3087243 in the AR with asthma group compared to control group (p=0.1×10^{-4}. OR=0.233, 95%CI [0.121-0.450]; p=0.1×10^{-5}. OR=0.417, 95%CI [0.295-0.591], respectively).

Table 3. Frequencies of alleles and genotypes of PTPN22/CTLA-4 polymorphisms in patients with allergic rhinitis and asthma, and control subjects.

SNP	Genotype	Group 1**	Group 2**	Control	Group 1 VS. Control		Group 2 VS. Control	
					OR95%CI*	*p* value	OR95%CI*	*p* value
Rs2488457	GG	18	18	32	-	-	-	-
	CG	56	63	86	1.158(0.539-2.259)	0.768	1.302(0.671-2.526)	0.435
	CC	32	31	51	1.115(0.539-2.308)	0.668	1.081(0.521-2.242)	0.835
	G	92	99	150	-	-	-	-
	C	120	125	188	1.041(0.736-1.471)	0.821	1.007(0.717-1.415)	0.966
Rs1310182	TT	30	62	100	-	-	-	-
	CT	62	47	59	3.503(2.038-6.022)	0.6×10^{-5}	1.285(0.781-2.112)	0.323
	CC	14	3	10	4.667(1.882-11.574)	0.001	0.484(0.128-1.827)	0.284
	T	122	171	259	-	-	-	-
	C	90	53	79	2.419(1.669-3.505)	0.3×10^{-5}	1.016(0.683-1.513)	0.937
RS3789604	TT	75	84	113	-	-	-	-
	GT	28	24	48	0.879(0.507-1.523)	0.645	0.673(0.382-1.184)	0.169
	GG	3	4	8	0.565(0.145-2.198)	0.410	0.673(0.196-2.308)	0.528
	T	178	192	274	-	-	-	-
	G	34	32	64	0.818(0.518-1.291)	0.388	0.714(0.449-1.133)	0.153
Rs3087243	GG	41	20	61	-	-	-	-
	AG	44	40	71	1.092(0.568-2.101)	0.792	0.401(0.226-0.711)	0.002
	AA	21	52	37	1.184(0.608-2.305)	0.619	0.233(0.121-0.450)	0.1×10^{-4}
	G	126	80	193	-	-	-	-
	A	86	144	145	1.101(0.777-1.560)	0.590	0.417(0.295-0.591)	0.1×10^{-5}
Rs11571302	CC	33	41	55				
	AC	50	62	88	0.947(0.544-1.648)	0.847	0.945(0.563-1.588)	0.831
	AA	23	9	26	1.474(0.726-2.992)	0.282	0.464(0.197-1.096)	0.080
	C	116	144	198				
	A	96	80	140	1.170(0.828-1.655)	0.373	0.786(0.554-1.113)	0.175
Rs11571315	GG	16	24	48				
	AG	59	45	72	2.458(1.268-4.767)	0.008	1.250(0.675-2.313)	0.477
	AA	31	43	49	1.898(0.921-3.910)	0.082	1.775(0.927-3.324)	0.084
	G	91	93	168				
	A	121	131	170	1.134(0.930-1.856)	0.121	1.392(0.990-1.957)	0.057

Table continue

Rs231725	GG	22	2	19				
	AG	50	16	77	0.561(0.276-1.140)	0.561	1.974(0.418-9.332)	0.391
	AA	34	94	73	0.402(0.193-0.840)	0.015	12.233(2.760-54.211)	0.001
	G	94	20	115				
	A	118	204	223	0.647(0.455-0.921)	0.016	5.260(3.154-8.772)	0.2×10^{-9}
Rs35219727	GG	102	106	163	-		-	-
	AG	4	6	6	1.065(0.294-3.867)	0.923	1.538(0.483-4.894)	0.466
	G	208	218	332	-	-	-	-
	A	4	3	6	1.064(0.297-3.816)	0.924	0.761(0.188-3.077)	0.702
Rs4553808	GG	4	2	5				
	AG	44	31	53	1.038(0.263-4.101)	0.958	1.462(0.267-7.994)	0.661
	AA	58	79	111	0.653(0.169-2.526)	0.537	1.779(0.337-9.405)	0.498
	G	52	35	63				
	A	160	189	275	0.705(0.465-1.068)	0.099	1.237(0.787-1.946)	0.357

*AR:allergic rhinitis; OR: odds ratio; CI: confidence interval

*Group1 is the children with AR; group2 is the children with AR and asthma

There were obvious differences in the AR with asthma group and control concerning the frequencies of rs231725, which also existed between the AR group and control. A significantly decreased prevalence of AA genotype and A allele had been found in the AR group compared to control (p=0.015. OR=0.402, 95%CI 0.193-0.840; p=0.016. OR=0.647, 95% CI [0.455-0.921], respectively). But the frequencies of the AA genotype and the A allele were significantly increased in the AR with asthma group in comparison with control group (p=0.001. OR=12.233, 95%CI [2.760-54.211]; $p = 0.2\times10^{-9}$. OR=5.260, 95%CI [3.154-8.772]) (Table 3).

No significant association was found for the other four CTLA-4 SNPs in two case groups compared with healthy control (Table 3).

DISCUSSION

In this study, we investigated the PTPN22 and CTLA-4 gene polymorphisms in children who have AR with asthma and who have AR alone. We demonstrated that SNPs rs1310182 of PTPN22 gene and rs3087243, rs231725 of CTLA-4 gene are associated with AR and asthma in Chinese Han children population. For PTPN22, the CC genotype and the C allele of rs1310182 could increase the risk of childhood AR. The AA genotype and the A allele at rs3087243 of CTLA-4 gene showed significant associations with asthma in children with AR. At the same time, we found that the AA genotype and the A allele at rs231725 were positively correlated in both childhood AR and asthma, and it may be a potential protective factor for AR but a risk factor for AR with asthma in children. To the best of our knowledge, this is the first time to consider the correlation of SNPs at rs1310182, rs3087243, rs231725 in Chinese Han children with AR and asthma.

AR, as the result of a deregulation of the immune system, is a common inflammatory disorder of the upper airway. It is influenced by a complex interplay between multiple genetic and environmental factors.[16] AR and asthma are not any more regarded as separate entities. The current theory regarding these two as acontinuum of inflammation involving a single common pathway, can better describe a large proportion of phenomenon,[17] which we entitle as “one airway, one disease”.[1] To date, there are a lot of data which point toward a systemic link between the upper and lower airways.[18] There are some polymorphisms which are the same when comparing the SNPs in AR and asthma. It has been reported that there may be an association between SNPs of ADAM33 and persistent AR.[19] Also, the genetic variants in ADAM33 has been shown to have an association with childhood asthma.[20] However, in this study we have not noted any similarity of genotype and allele trend in our positive locus.

These data demonstrated an association of SNPs rs1310182 in the PTPN22 gene with AR prevalence in children, which suggest that the genetic background of childhood AR may be similar to T1D.[21] However, this polymorphism could not decipher the prevalence of AR with asthma in children. Similarly a study implemented by Edyta et al. showed no association between

polymorphism and susceptibility to allergic asthma.[22] For the CTLA-4, the polymorphism of rs231725 appeared in AR children, while the polymorphism of rs3087243 and rs231725 existed in AR with asthma children. Also, the alleles of the three SNPs were the same as Sjogren's syndrome and T1D.[23,24] But there is no evidence to prove the association between other sites of SNPs and AR with asthma. Although there are some similar immunoreaction mechanisms in AR and asthma, there still exist many differences in polymorphism of these diseases. Andiappan et al. showed that the functional variants of 17q12-21 for high IgE levels are associated with allergic asthma but not allergic rhinitis.[25] It may suggest the existence of a gene-related differentiation in these two diseases.

Comparing with the data from our previous study on AR in adults, this study showed that a considerable different. SNPs rs2488457 in the PTPN22 gene could not be found in children, which was also confirmed in previous studies on Vogt-Koyanagi-Harada syndrome (VKH).[26]The polymorphsim of rs11571302 did not exist in AR children group. As for ADAM33 gene, there are difference between adult and children.[20,27] These results might suggest the discrepancy of SNPs in different ages, which may be due to environment factors and evolvement of the disease.

The polymorphisms of PTPN22 gene and CTLA-4 gene may contribute to the risk of AR and asthma in children, but the underlying mechanism is not clearly understood. According to the studies on these two genes using gene knocking- out technology, it could be suggested that PTPN22 and CTLA-4 SNPs might change the expression of TCR and CD4+CD28+ Treg cells by regulating and controlling related mRNA.[7,28] The polymorphisms may transform the expression of the proteins such as TCR and CTLA-4 to promote the antigen presenting, by which the allergic reaction could be activated.

To increase the credibility of the results, we took measures to avoid the influence of confounding factors. Participants were chosen using strict guidelines and genotyping results were confirmed by direct sequencing. There were some limitations to our study such as, environmental factors, which need to be further deliberated. Also more investigations into the function of PTPN22 and CTLA-4 and its influence on the protein levels should be performed.

In conclusion, this study has identified an association between PTPN22/CTLA-4, and AR with asthma or without asthma in children, suggesting the possible implications of these genes for the susceptibility to AR and asthma.

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