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Correlation between TGFβ1 Gene Polymorphism and Asthma in Baise, Guangxi Children

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Abstract

Objective: This research was to study the correlation between the rs1800469, rs1800470, rs2241712, rs224171 and rs4803455 of TGFβ1 gene and asthma in Baise, Guangxi children. This research also studied the relationship between serum concentration of TGFβ1 and childhood asthma. **Method:** From June 2022 to December 2023, 121 children had physical examination in affiliated Hospital of Youjiang Medical University for Nationalities were selected as control group and 118 children suffered from asthma in affiliated Hospital of Youjiang Medical University for Nationalities during the same period were selected as asthma group. **Result:** There was no correlation between rs1800469, rs1800470, rs2241712, rs2241715, rs4803455 and asthma in Baise, Guangxi children. Linkage disequilibrium analysis showed that there were strong linkage disequilibrium among rs1800469, rs1800470, rs2241712, rs2241715 and rs4803455. Their haplotypes had no significant correlation with childhood asthma. The serum concentration of TGFβ1 in asthma group was lower than that in control group ($p < 0.01$), which may be a risk factor for asthma. The serum concentration of TGFβ1 had no significant relationship with the genotypes of rs1800469, rs1800470, rs2241712, rs2241715 and rs4803455.

Keywords

TGFβ1, Chilhood Asthma, SNP

1. Introduction

Asthma is a chronic disease characterized by reversible airflow limitation, which is affected by environmental factors and genetic factors. The clinical manifesta-

tions are recurrent wheezing, shortness of breath, cough and other symptoms. The pathological characteristics include airway inflammation, airway hyperresponsiveness, airway remodeling, etc. A variety of inflammatory cells and cytokines are involved in asthma. Asthma attack can be induced by many reasons, such as inhalation allergens, cold air, respiratory tract infection, air pollution, food allergy, etc. At the second exposure to allergens, allergic reactions through IgE dependent pathways induce asthma. After the allergen enters the body, it stimulates helper T cell 2 (Th2) to secrete interleukin 5 (IL-5), IL-4 and IL-13 after antigen presentation. It also activates B cells to produce IgE and induces mast cells to release mediators, such as leukotriene, histamine and interleukin, which induces asthma attack [1]. The imbalance of Th2 and Th1 cells is related to the occurrence of asthma. The imbalance of regulatory T cells (Treg cells) and helper T cell 17 (Th17) is also related to the occurrence of asthma. Th17 can produce IL-17, IL-6, il-2l, IL-22 and other inflammatory factors.

Single nucleotide polymorphism (SNP) is a common genetic variation in humans. About 300 - 1000 bases will produce one SNP. The single nucleotide polymorphisms are relatively stable and will not change significantly after several generations. Transforming growth factor-β1 (TGFβ1) can regulate cell proliferation, differentiation and maturation, and also regulate the expression and activation of other cytokines. The TGFβ1 gene is located on chromosome 19 which consists of seven exons. Shah *et al.* found that when the rs1800469 allele was cytosine, it inhibited the recruitment of AP1 and the transcription of TGFβ1 gene [2]. The T allele of rs1800469 may reduce the risk of diisocyanate asthma [3]. Sharma *et al.* Found that the A allele of rs2241712 and the C allele of rs1800469 were associated with airway hyperresponsiveness. TT and CT genotypes of rs1800470 reduced the risk of asthma hospitalization [4]. A study on childhood asthma in China found that in severe asthma group, patients with rs2241715 allele A had better lung function than patients with genotype GG [5]. A study on children in Brazil found that the CC genotype of rs1800470 may be a protective factor for asthma [6]. A meta-analysis found that the T allele of rs1800469 was associated with an increased risk of asthma in children [7].

2. Methods

2.1. Sample Size Estimation

Set the confidence level to 0.95, the sensitivity to 0.8, and the specificity to 0.9. The sample size was calculated to be 62.

2.2. Subjects

Children who suffered from asthma in our hospital from June 2022 to December 2023 were selected as asthma group. Inclusion criteria: 1) The asthma diagnosis and the severity were according to the guidelines for the diagnosis and prevention of bronchial asthma in children (2016 Edition) [8]. 2) Exclude other diseases that can cause wheezing and cough. Exclusion criteria: 1) Wheezing or cough

caused by other diseases, such as bronchopulmonary dysplasia, bronchiolitis, bronchial stenosis or softening, airway foreign bodies, cardiogenic asthma and other diseases. 2) Children used immunosuppressants within 6 months. 3) Combined with other diseases, such as Thalassemia, epilepsy, primary immune function defects, genetic metabolic diseases, etc.

Healthy children who had physical examination in our hospital from June 2022 to December 2023 were selected as control group. Exclusion criteria: 1) Children had wheezing during the period. 2) Children had a history of wheezing, eczema, allergic rhinitis, food allergies, drug allergies and other allergic diseases. 3) Three generations of immediate family members had a history of asthma and allergic diseases. 4) Children had other diseases, such as Thalassemia, epilepsy, congenital heart disease, primary immune deficiency, genetic metabolic diseases, etc.

2.3. Genotyping of Target SNP

Use the Sangon Biotech DNA Rapid Extraction Kit to extract DNA from blood samples. Primer sequence of target SNPs are shown in Table 1. After two round PCR and purification, sequencing was performed using the HiSeq XTen sequencer (Illumina, San Diego, CA).

Data QC and SNP calling: 1) Removing adaptor sequence if reads contains by cutadapt (v 1.2.1). 2) Removing low quality bases from reads 3' to 5' ($Q < 20$) by PRINSEQ-lite (v 0.20.3). And the remaining clean data were mapped to the reference genome by BWA (version 0.7.13-r1126) with default parameters. Samtools (Version: 0.1.18) was used to calculate each genotype of target site. Annovar (2018-04-16) was used to detect genetic variants.

2.4. Serum Concentration of TGFβ1

Use the human/mouse/rat TGFβ1 ELISA kit provided by Lianke biology to detect serum concentration of TGFβ1.

Table 1. Primer sequence of target SNP.

SNP	Primer sequence
rs1800469	forward: GCTCAGTAAAGGAGAGCAATTCTTA reverse: GTAGGAGAAGAGGGTCTGTCAACAT
rs1800470	forward: CCCTCCTACCTTTTGCCGGGAGACC reverse: CGCTTCACCAGCTCCATGTCGATAG
rs2241712	forward: AGCAGTCAAGCCCATGAACTACAAC reverse: GTCCAAAATAACCTTTTCGGGTTCA
rs2241715	forward: TGCCTCTTTCTTTTCGTCTCCGTTA reverse: GCCCTATTCTTGGCCCGGAGGTTAC
rs4803455	forward: GAGCCACCGTGCCCAGCCGGAATCA reverse: CACGCCTGTAGTCGCCACTATTTGG

2.5. Statistical Analysis

SPSS 26.0 was used for calculation. Mann Whitney U test was used to compare the TGFβ1 serum concentrations of the two groups. Mann Whitney U test was used to compare the ages of the two groups. The genotype and serum concentrations of TGFβ1 were compared by Kruskal Wallis test. Chi square test was used for gender comparison between the two groups. The genotype and allele frequencies of the two groups were compared by chi square test. Linkage disequilibrium and haplotype analysis were completed by the online tool of SHEsis [9] [10]. The test is bilateral and the $P < 0.05$ is considered to be statistically significant.

3. Result

3.1. Gender and Age of Research Objects

The age of asthma group between 0.7 - 12 years and the age of control group between 1 - 13 years. The age of asthma group and control group did not conform to the normal distribution, and Mann Whitney U test was used for comparison. Chi square test was used for gender comparison between the two groups. There was no significant difference in gender and age between the two groups ($P > 0.05$). The results are shown in Table 2.

3.2. Hardy Weinberg Equilibrium

The genotype frequency of rs1800469, rs1800470, rs2241712, rs2241715 and rs4803455 in both groups were consistent with Hardy Weinberg equilibrium ($P > 0.05$).

3.3. Relationship between Target SNP and Asthma

In the asthma group, there were 113 people with mild or moderate asthma and 5 people with severe asthma. Rs1800469, rs1800470, rs2241712, rs2241715 and rs4803455 were not significantly associated with childhood asthma. The results are shown in Table 3.

Table 2. Gender and age of research objects.

Group	*n*	Gender		Age (year)	IQR
		man	female		
asthma	118	84	34	4.32	4.03
control	121	73	48	4.00	4.00
χ^2		3.124			
Z				−0.358	
P		0.077		0.720	

Table 3. Comparison of genotypes and alleles between asthma group and control group.

Group	*n*	Genotypes (%)			χ^2	*P*	Alleles (%)		χ^2	*P*
rs1800469		AA	AG	GG			A	G		
asthma	118	52 (44.1)	54 (45.8)	12 (10,2)			158 (66.9)	78 (33.1)		
control	121	52 (43.0)	55 (45.5)	14 (11.6)	0.125	0.939	159 (65.7)	83 (34.3)	0.083	0.773
rs1800470		AA	AG	GG			A	G		
asthma	118	12 (10.2)	54 (45.8)	52 (44.1)			78 (33.1)	158 (66.9)		
control	121	13 (10.7)	55 (45.5)	53 (43.8)	0.021	0.989	81 (33.5)	161 (66.5)	0.009	0.922
rs2241712		CC	CT	TT			C	T		
asthma	118	55 (46.6)	51 (43.2)	12 (10.2)			161 (68.2)	75 (31.8)		
control	121	52 (43.0)	55 (45.5)	14 (11.6)	0.351	0.839	159 (65.7)	83 (34.3)	0.342	0.558
rs2241715		AA	AC	CC			A	C		
asthma	118	51 (43.2)	55 (46.6)	12 (10,2)			157 (66.5)	79 (33.5)		
control	121	52 (43.0)	55 (45.5)	14 (11.6)	0.126	0.939	159 (65.7)	83 (34.3)	0.036	0.849
rs4803455		AA	AC	CC			A	C		
asthma	118	10 (8.5)	45 (38.1)	63 (53.4)			65 (27.5)	171 (72.5)		
control	121	8 (6.6)	49 (40.5)	64 (52.9)	0.362	0.834	65 (26.9)	177 (73.1)	0.028	0.866

3.4. Linkage Disequilibrium Analysis

SHEs is online tool was used for Linkage disequilibrium analysis. There is a strong linkage disequilibrium between these 5 SNPs (rs1800469, rs1800470, rs2241712, rs2241715, rs4803455). The results are shown in Figure 1.

3.5. Haplotype Analysis

SHEs is online tool is used for haplotype analysis. There are no significant differences in the frequency of haplotypes between the asthma group and the control group. The results are shown in Table 4.

3.6. The Relationship between Serum Concentration of TGFβ1 and Asthma

The TGFβ1 serum concentration of the two groups did not conform to the normal distribution. Mann Whitney U test was used to compare the TGFβ1 serum concentration of the two groups ($P < 0.001$). The median of TGFβ1 serum concentration in asthma group is 361.42 pg/ml and the median of TGFβ1 serum concentration in control group is 788.96 pg/ml. The results were shown in Table 5.

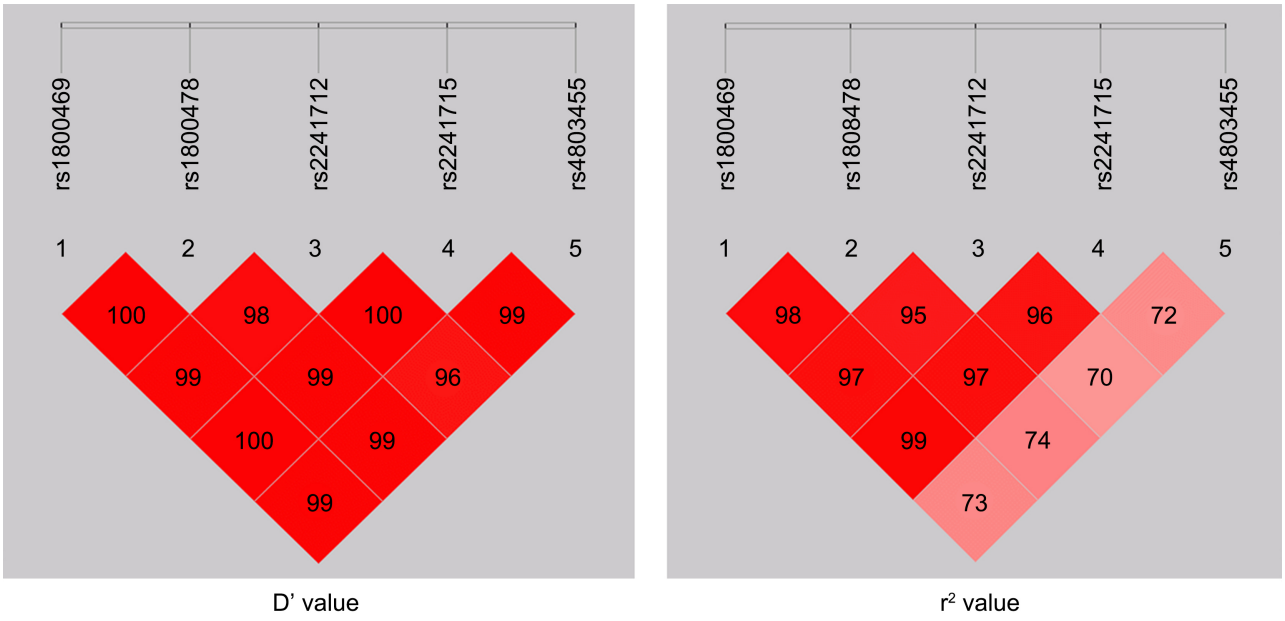

Figure 1. Linkage disequilibrium analysis of rs1800469, rs1800470, rs2241712, rs2241715, rs4803455.

Table 4. Comparison of rs1800469 rs1800470, rs2241712, rs2241715, rs4803455 haplotype frequencies between asthma group and healthy group [n(%)].

Haplotype	Asthma 2n (%)	Control 2n (%)	χ^2	*OR*	95%*CI*	*P*
A G C A C	157.00 (0.665)	159.00 (0.657)	0.108	1.066	0.727~1.565	0.742
G A T C A	62.00 (0.263)	65.00 (0.269)	0.008	0.982	0.654~1.475	0.930
G A T C C	13.00 (0.055)	16.00 (0.066)	0.231	0.831	0.391~1.768	0.630
G G T C C	0.00 (0.000)	2.00 (0.008)				
A G C C C	1.00 (0.004)	0.00 (0.000)				
G A C C A	3.00 (0.013)	0.00 (0.000)				

Frequency < 0.03 will be ignored in analysis. The composition of haplotypes is in the following order rs1800469, rs1800470, rs2241712, rs2241715, rs4803455.

Table 5. Comparison of TGFβ1 concentration in serum between asthma group and control group.

Group	*n*	TGFβ1 concentration (pg/ml)	*IQR*	*Z*	*P*
asthma	118	361.42	627.15	−4.457	0.001
control	121	788.96	1019.71		

3.7. The Relationship between TGFβ1 Serum Concentration and Genotypes

The TGFβ1 serum concentrations were grouped according to the genotypes of rs1800469, rs1800470, rs2241712, rs2241715 and rs4803455, which did not con-

form to the normal distribution. Kruskal Wallis test was used for comparison. There were no significant differences between genotype of rs1800469, rs1800470, rs2241712, rs2241715, rs4803455 and TGFβ1 serum concentration. The results are shown in Table 6 and Table 7.

3.8. The Frequencies of Genotypes and Alleles in Different Populations

The frequencies of genotypes and alleles in different populations in the 1000 Genomes Project database were compared with the control group. They were compared by chi square test. The results are shown in Table 8.

Table 6. TGFβ1 serum concentration were compared with genotypes of control group.

Control	Genotypes TGFβ1 serum concentration (pg/ml, *IQR*)			*H*	*P*
rs1800469	AA	AG	GG		
	723.95 (971.06)	880.45 (995.41)	909.87 (1028.79)	1.002	0.605
rs1800470	AA	AG	GG		
	924.91 (851.90)	876.27 (1016.12)	723.95 (971.06)	1.164	0.559
rs2241712	CC	CT	TT		
	723.94 (971.06)	880.44 (995.41)	909.87 (1028.79)	1.002	0.606
rs2241715	AA	AC	CC		
	723.94 (971.06)	880.44 (995.41)	909.87(1028.79)	1.002	0.606
rs4803455	AA	CA	CC		
	816.98 (845.58)	894.83 (981.01)	722.18 (1043.78)	1.443	0.486

Table 7. TGFβ1 serum concentration were compared with genotypes of asthma group.

Asthma	Genotypes TGFβ1 serum concentration (pg/ml, *IQR*)			*H*	*P*
rs1800469	AA	AG	GG		
	416.14 (710.93)	353.37 (611.19)	167.43(616.88)	1.327	0.515
rs1800470	AA	AG	GG		
	179.56 (641.45)	335.56(620.41)	435.87(684.67)	1.396	0.497
rs2241712	CC	CT	TT		
	400.82 (686.19)	337.06 (611.81)	167.43 (616.88)	1.205	0.547
rs2241715	AA	AC	CC		
	400.82 (697.36)	369.69 (611.81)	167.43 (616.87)	1.212	0.545
rs4803455	AA	CA	CC		
	167.43 (470.95)	374.21 (606.71)	373.46 (669.21)	0.935	0.627

Table 8. Comparison of genotypes and alleles between control group and other populations.

Populations	*n*	Genotypes (%)			χ^2	*P*	Alleles (%)		χ^2	*P*
rs1800469		AA	AG	GG			A	G		
control	121	52 (43.0)	55 (45.5)	14 (11.6)	-	-	159 (65.7)	83 (34.3)	-	-
CDX	93	32 (34.4)	51 (54.8)	10 (10.8)	1.949	0.377	115 (61.8)	71 (38.2)	0.685	0.408
CHB	103	24 (23.3)	50 (48.5)	29 (28.2)	14.433	0.001	98 (47.6)	108 (52.4)	14.954	0.001
AFR	661	39 (5.9)	210 (31.8)	412 (61.2)	174.838	0.001	288 (21.8)	1034 (78.2)	193.283	0.001
AMR	347	74 (21.3)	173 (49.9)	100 (28.8)	26.932	0.001	321 (46.3)	373 (53.7)	27.166	0.001
EUR	503	53 (10.5)	208 (41.4)	242 (48.1)	93.128	0.001	314 (31.2)	692 (68.8)	98.592	0.001
rs1800470		AA	AG	GG			A	G		
control	121	13 (10.7)	55 (45.5)	53 (43.8)	-	-	81 (33.5)	161 (66.5)	-	-
CDX	93	9 (9.7)	51 (54.8)	33 (35.5)	1.898	0.387	69 (37.1)	117 (62.9)	0.607	0.436
CHB	103	29 (28.2)	49 (47.6)	25 (24.3)	15.144	0.001	107 (51.9)	99 (48.1)	15.588	0.001
AFR	661	229 (34.6)	317 (48)	115 (17.4)	52.204	0.001	775 (58.6)	547 (41.4)	52.231	0.001
AMR	347	81 (23.3)	181 (52.2)	85 (24.5)	19.231	0.001	343 (49.4)	351 (50.6)	18.427	0.001
EUR	503	199 (39.6)	224 (44.5)	80 (15.9)	59.475	0.001	622 (61.8)	384 (38.2)	63.771	0.001
rs2241712		CC	CT	TT			C	T		
control	121	52 (43.0)	55 (45.6)	14 (11.6)	-	-	159 (65.7)	83 (34.3)	-	-
CDX	93	33 (35.5)	51 (54.8)	9 (9.7)	1.853	0.396	117 (62.9)	69 (37.1)	0.359	0.548
CHB	103	25 (24.3)	49 (47.6)	29 (28.2)	13.688	0.001	99 (48.1)	107 (51.9)	14.183	0.001
AFR	661	17 (2.6)	150 (22.7)	494 (74.7)	272.252	0.001	184 (13.9)	1138 (86.1)	320.381	0.001
AMR	347	71 (20.5)	174 (50.1)	102 (29.4)	29.206	0.001	316 (45.5)	378 (54.5)	29.204	0.001
EUR	503	58 (11.5)	211 (41.9)	234 (46.5)	84.967	0.001	327 (32.5)	679 (67.5)	90.416	0.001
rs2241715		AA	AC	CC			A	C		
control	121	52 (43.0)	55 (45.5)	14 (11.6)	-	-	159 (65.7)	83 (34.3)	-	-
CDX	93	32 (34.4)	51 (54.8)	10 (10.8)	1.949	0.377	115 (61.8)	71 (38.2)	0.685	0.407
CHB	103	25 (24.3)	48 (46.6)	30 (29.1)	14.408	0.001	98 (47.6)	108 (52.4)	14.954	0.001
AFR	661	49 (7.4)	252 (38.1)	360 (54.5)	140.892	0.001	350 (26.5)	972 (73.5)	143.381	0.001
AMR	347	77 (22.2)	173 (49.9)	97 (28.0)	24.571	0.001	327 (47.1)	367 (52.9)	24.825	0.001
EUR	503	56 (11.1)	204 (40.6)	243 (48.3)	89.669	0.001	316 (31.4)	690 (68.6)	97.300	0.001

Continued

rs4803455		AA	AC	CC			A	C		
control	121	8 (6.6)	49 (40.5)	64 (52.9)	-	-	65 (26.9)	177 (73.1)	-	-
CDX	93	8 (8.6)	44 (47.3)	41 (44.1)	1.672	0.433	60 (32.3)	126 (67.7)	1.482	0.223
CHB	103	20 (19.4)	54 (52.4)	29 (28.2)	17.222	0.001	94 (45.6)	112 (54.4)	17.126	0.001
AFR	661	239 (36.2)	312 (47.2)	110 (16.6)	89.669	0.001	790 (59.8)	532 (40.2)	89.335	0.001
AMR	347	44 (12.7)	177 (51.0)	126 (36.3)	11.102	0.004	265 (38.2)	429 (61.8)	10.081	0.001
EUR	503	134 (26.6)	234 (46.5)	135 (26.8)	38.735	0.001	502 (49.9)	504 (50.1)	41.773	0.001

CDX: Chinese Dai in Xishuangbanna, China; CHB: Han Chinese in Bejing, China; AFR: African; AMR: American; EUR: Europe.

4. Discussion

In this research, it was found that the genotypes and alleles of rs1800469, rs1800470, rs2241712, rs2241715, and rs4803455 were not significantly associated with asthma. This is different from some previous studies. The frequencies of genotypes and alleles in different populations in the 1000 Genomes Project database were compared with the control group. It was found that the frequencies of genotypes and alleles in control group were similar to Chinese Dai in Xishuangbanna. It is different from Han Chinese in Bejing, the European populations, the American populations and the African populations. Gene polymorphisms may vary in different populations.

TGFβ1 has both protective and pathogenic effects in asthma. TGFβ1 has anti-inflammatory effect. Overexpression of Smad7 blocked TGFβ1/Smad signaling pathway in mature T cells which enhanced airway inflammation and airway hyperresponsiveness in allergic asthma [11]. TGFβ1 can maintain the anti-inflammatory effect of Treg cells by promoting the expression of forkhead box protein P3 (Foxp3) [12]. IL-10 and TGFβ1 significantly reduced the cytokine secretion of type II innate lymphocytes (ILC2). The use of IL-10 and TGFβ1 neutralizing antibody eliminated the inhibitory effect of iTreg cells on the secretion of IL5 and IL13 by ILC2 [13]. Treg cells need to receive TGFβ1 signals to control Th17 cells. The ability of TGFβ1 knockout Treg cells to inhibit the production of interleukin-17 was reduced [14]. TGFβ1 can promote the repair of airway epithelial cells after injury. The airway epithelial cells of asthmatic children and healthy children were collected. The use of siRNA to knockdown TGFβ1 expression slowed down the repair of airway epithelial cells after injury in these two groups [15].

In clinical research, Xu *et al.* found that the low level of TGFβ1 in peripheral blood is related to severe asthma [16]. Another study found that the number of CD4+CD25+Foxp3+Treg cells and the concentrations of IL-10 and TGFβ1 in hormone resistant asthma patients were lower than those in hormone sensitive patients. This suggests that the low concentration of TGFβ1 may be related to

the poor effect of hormone therapy in patients with asthma [17].

TGFβ1 can also aggravate asthma. TGFβ1 can promote the combination of Smad2 and IL-6 promoter which increased the production of IL-6 by human bronchial epithelial cells [18]. TGFβ1 promotes the expression of IL17. After the treatment with TGFβ1 antibody, the level of IL17 in the body decreased [19]. TGFβ1 promotes the phosphorylation of MLC20 and induces airway smooth muscle contraction by activating Rho and RhoA. TGFβ1 can aggravate airway hyperresponsiveness by reducing the intracellular cAMP level and reducing the response of human airway smooth muscle cells to isoproterenol [20]. Activation of TGFβ1/Smad3 pathway induces airway fibrosis in asthma [21]. Human bronchial epithelial cells stimulated by TGFβ1 produce fibronectin, which is deposited in Extracellular matrix (ECM) [22]. TGFβ1 induces the transformation of fibroblasts into myofibroblasts through p38 MAPK pathway [23]. TGFβ1 can promote airway remodeling through a variety of ways.

This research found that rs1800469, rs1800470, rs2241712, rs2241715 and rs4803455 in TGFβ1 gene may not be associated with the incidence rate of asthma in Baise, Guangxi children. The decrease in TGFβ1 serum concentration may be related to asthma in Baise, Guangxi children. Low TGFβ1 serum concentration may be a risk factor for asthma. The serum concentration of TGFβ1 had no significant relationship with the genotypes of rs1800469, rs1800470, rs2241712, rs2241715 and rs4803455.

In this research, the number of samples needs to be increased. This research focuses on the relationship between TGFβ1 gene polymorphism and the incidence of asthma, and the relationship with the severity of asthma, airway remodeling, drug sensitivity and airway hyperresponsiveness also needs more research.

Ethical Disclosures

This study was approved by the medical ethics committee of our hospital. The children and their legal guardians were informed and agreed to voluntarily participate in this study. They signed informed consent.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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