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Association of toll-like receptor 10 polymorphisms with paediatric idiopathic uveitis in Han Chinese

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ABSTRACT

Aims We aimed to determine whether paediatric idiopathic uveitis (PIU) and juvenile idiopathic arthritis associated paediatric uveitis (JIA-PU) have an association with Toll-like receptor 10 (*TLR10*) gene polymorphisms in Han Chinese.

Methods Ten tag single nucleotide polymorphisms (SNPs) of *TLR10* were analysed in 992 PIU patients, 127 JIA-PU patients and 1600 controls using the Sequenom MassARRAY system and iPLEX Gold assay. Genotype and allele frequencies were analysed using the $\chi 2$ test. A stratified analysis was performed according to the clinical features of PIU.

Results Increased frequencies of the rs2101521 A allele, rs10004195 A allele, rs11725309 CC genotype and rs6841698 AA genotype were found in PIU patients compared with controls (corrected p values (Pc) $=1.81\times10^{-4}$, Pc= 1.12×10^{-2}, Pc=2.41×10^{-2} and Pc=3.29×10^{-3}, respectively). There was no association between these 10 tag SNPs and JIA-PU. In the stratified analysis, the frequency of the rs6841698 A allele was higher in PIU patients with cataract (Pc=1.45×10^{-6}). The frequencies of the rs2101521 A allele and rs6841698 AA genotype were increased in PIU patients with band keratopathy (BK) (Pc=2.32×10^{-2}, Pc=3.30×10^{-3}, respectively).

Conclusion *TLR10* gene polymorphisms (rs2101521, rs10004195, rs11725309 and rs6841698) confer susceptibility to PIU in Han Chinese. In a stratified analysis, rs2101521 and rs6841698 are associated with PIU with BK, and rs6841698 correlates with PIU with cataract.

INTRODUCTION

Uveitis is a common intraocular inflammatory disease and an important cause of visual impairment[1]. The pathogenesis of uveitis is multifactorial, which may be related to genetic predisposition, environmental triggers, immune system activation and infection[2]. Uveitis occurs more frequently in young and middle-aged adults than in children. Nonetheless, the morbidity of paediatric uveitis (PU) still comprises 5% to 10% of all patients with uveitis.[1 3–5] The PU spectrum includes almost all clinical entities occurring in adults, and is often associated with a high incidence of ocular complications and visual handicap.[3 4] Examples are specific entities such as juvenile idiopathic arthritis (JIA), Vogt-Koyanagi-Harada (VKH) disease, pars planitis, Behcet's disease (BD) and sarcoidosis.[6 7] Uveitis in children with an unclear aetiology or special aetiology is classified as paediatric idiopathic uveitis (PIU). Previous studies described PIU as the most predominant type, accounting for 57.8% to 74% of the PU population.[6–9]

Many immune and inflammatory pathways play a role in the pathogenesis of uveitis. Unravelling these pathways may lead to the development of novel treatments and one of the approaches to identify the mechanisms involved in uveitis includes the analysis of immunogenetic predisposition to this disease.[10 11] One of the candidate genes include the so called Toll-like receptors.[12]

Toll-like receptors (TLRs) belong to the pattern recognition receptors (PRRs) of the immune system. TLRs play an important role in the development of inflammatory and autoimmune diseases, including uveitis.[12 13] In the TLR family, Toll-like receptor 10 (*TLR10*) is the orphan receptor without a known specific ligand.[14 15] *TLR10* is mainly expressed in lymphoid tissues.[16] The expression of *TLR10* is predominantly observed in immune cells, such as B cells, dendritic cells (DCs), monocytes, neutrophils and eosinophils.[17 18] Blocking *TLR10* promotes the production of inflammatory factors[15] and *TLR10* variants have been reported to confer genetic susceptibility to various infectious diseases,[19–21] as well as to a number of autoimmune or autoinflammatory diseases, such as autoimmune thyroid disease (AITD), Crohn's disease (CD), rheumatoid arthritis (RA), sarcoidosis and vitiligo.[22–26] However, the relation between *TLR10* gene polymorphisms and susceptibility to PIU as well as JIA-associated paediatric uveitis (JIA-PU) has not yet been addressed and was therefore the subject of the study reported here.

MATERIALS AND METHODS

Study population

A total of 992 PIU patients, 127 JIA-PU patients and 1600 controls were recruited for this study. All patients and controls were Han Chinese. PIU was defined as PU (age at onset <16 years old) with no specific clinical classification. Those children who were diagnosed with BD, VKH disease, underlying diseases or other defined uveitis types, such as toxoplasmosis, tuberculosis and masquerade syndrome, were excluded from this study. JIA was identified as arthritis with an unexplained cause in children under the age of 16 and the duration of arthritis should last for at least 6 weeks.[27] Sixteen hundred healthy individuals were selected as normal controls, and were matched with cases according to race and geography. Both the case and control cohorts were obtained from the First Affiliated Hospital of Chongqing Medical University between May 2009 and July 2017.

Ethical review

This study was approved by the First Affiliated Hospital of Chongqing Medical University Ethics Research Committee, and was conducted according to authorised guidelines. All the procedures were done in accordance with the Declaration of Helsinki. Prior to enrolment, all participants provided written informed consent. Permission and informed consent was obtained from patients' parents or their guardians when the patient was younger than 18 years old.

SNP selection

All the candidate single nucleotide polymorphisms (SNPs) were located within a gene fragment, 2000 base pairs upstream and downstream of the *TLR10* gene (according to the International HapMap Project for Han Chinese from Beijing; http://browser.1000genomes.org/, http://grch37.ensembl.org/index.html). We used Haploview V.4.2 software to capture candidate tag SNPs having a minor allele frequency ≥1%. To exclude linkage disequilibrium, an r^2 critical value of 0.8 was taken. Based on the above criteria, we finally included 10 tag SNPs (rs10004195, rs10024216, rs10776483, rs11466617, rs11466651, rs11725309, rs2101521, rs4129009, rs6841698 and rs7694115). The detailed information of the 10 *TLR10* variants is described in online supplementary table 1.

DNA extraction and genotyping

Peripheral whole venous blood samples obtained from cases and controls were collected into EDTA blood collection tubes and stored at −80°C. Genomic DNA was extracted with the QIAamp DNA Blood Mini Kit (Qiagen, Valencia, California, USA) and Auto-Pure32A Nucleic Acid Purification System (Allsheng, Hangzhou, China), and stored at −20°C until used. The Nanodrop 2000 (Thermo Fisher Scientific, Wilmington, Delaware, USA) was used to qualify and quantify isolated DNA samples. MassARRAY Assay Design software was used to design the primers of all examined SNPs. The primers were stored at −20°C after dilution with DNase-free. The genotypes of the 10 tag SNPs were analysed by MassARRAY platform (Sequenom, San Diego, California, USA) and iPLEX Gold Genotyping assay. We used TYPER software V.4.0 to analyse and evaluate the experimental data. PCR was performed on a GeneAmp PCR System 9700 instrument (ABI, Foster City, California, USA). All experimental steps were performed in strict accordance with manufacturer's instructions.

SNP association with clinical features

PIU patients were subdivided according to whether they had band keratopathy (BK) or cataract, and included 331 PIU patients with BK (BK +group) and 430 PIU patients with cataract (cataract +group) (table 1). A single patient could belong to more than one group. Each subgroup was compared with the healthy control group.

Statistical analysis

Hardy–Weinberg equilibrium (HWE) in controls was analysed by the χ2 test. None of the candidate SNPs deviated from HWE. We compared the allele and genotype frequencies using the χ2 test, followed by the calculation of the ORs and the 95% CIs. In the analysis of multiple comparisons, the Bonferroni correction method was applied to correct the p values. The corrected p values (Pc) less than 0.05 were defined as statistically significant. All the statistical analyses were performed using SPSS V.17.0 software (SPSS Inc, Chicago, Illinois, USA).

Table 1 Clinical characteristics, gender and age distribution of PIU patients, JIA-PU patients and controls

Clinical features	Total (n)	Percent (%)
PIU	992	
Mean age ±SD	9.7±4.1	
Male	506	51.0
Female	486	49.0
Cataract +	430	43.3
BK +	331	33.4
JIA-PU	127	
Mean age ±SD	9.7±8.2	
Male	46	36.2
Female	81	63.8
Cataract +	86	67.7
BK +	74	58.3
Controls	1600	
Mean age ±SD	39.5±10.6	
Male	803	50.2
Female	797	49.8

PIU, paediatric idiopathic uveitis; SD, standard deviation; BK, band keratopathy; JIA-PU, juvenile idiopathic arthritis associated paediatric uveitis; +, having this feature.

RESULTS

Clinical features and demographics of PIU, JIA-PU and controls

We enrolled 992 PIU patients, 127 JIA-PU patients and 1600 normal controls. The clinical features of the cases and controls are shown in table 1. The control population consisted of 1590 adults and 10 children. In the PIU patients, the average age of onset was 9.7±4.1 years. The male-to-female ratio was 1.0 and was similar in the control group. PIU patients had a high prevalence of cataract (43.3%) and BK (33.4%). In the JIA-PU patients, the average age of onset was 9.7±8.2 years. The male-to-female ratio was 0.6. JIA-PU patients also had a high prevalence of cataract (67.7%) and BK (58.3%).

TLR10 SNP associations in PIU and JIA-PU

Ten tag SNPs of the *TLR10* gene were successfully genotyped. In the PIU patients (n=992), significantly increased frequencies of the rs2101521 A allele ($Pc=1.81\times10^{-4}$, OR=1.30, 95% CI=1.16 to 1.47) and AA genotype ($Pc=1.05\times10^{-3}$, OR=1.43, 95% CI=1.21 to 1.70) were found in the PIU patients compared with healthy controls (table 2). For SNP rs10004195, the frequencies of the A allele ($Pc=1.12\times10^{-2}$, OR=1.22, 95% CI=1.09 to 1.37) and AA genotype ($Pc=4.44\times10^{-3}$, OR=1.42, 95% CI=1.18 to 1.70) were higher in PIU patients than in the healthy controls (table 2). The rs11725309 CC genotype frequency ($Pc=2.41\times10^{-2}$, OR=1.40, 95% CI=1.15 to 1.71) and rs6841698 AA genotype frequency ($Pc=3.29\times10^{-3}$, OR=1.47, 95% CI=1.21 to 1.78) were also found to be associated with PIU (table 2). There was no association between the other 6 tag SNPs and PIU (online supplementary table 2). No significant association of the 10 tag SNPs with JIA-PU was observed, when compared with controls (online supplementary table 5).

TLR10 SNP associations in PIU with cataract

In the PIU patients with cataract (n=430), a significant association of the AA genotype and A allele of rs6841698 ($Pc=9.48\times10^{-10}$, OR=2.23, 95% CI=1.76 o 2.84; $Pc=1.45\times10^{-6}$, OR=1.53, 95% CI=1.31 to 1.78; respectively)

Table 2 Genotype and allele frequencies of examined SNPs of *TLR10* in PIU patients, PIU subgroups and healthy controls

			Case		Control					95% CIs	
SNPs	Group	Genotype	Frequencies	n(%)	Frequencies	n(%)	P value	Pc value	OR	Lower limit	Upper limit
rs2101521	PIU (n=992)	GG	128	13.4	272	18.1	2.19×10^{-03}	NS	0.70	0.56	0.88
		GA	456	47.7	770	51.1	NS	NS	0.87	0.74	1.03
		AA	372	38.9	464	30.8	3.51×10^{-05}	1.05×10^{-03}	1.43	1.21	1.70
		G	712	37.2	1314	43.6	9.05×10^{-06}	1.81×10^{-04}	0.77	0.68	0.86
		A	1200	62.8	1698	56.4	9.05×10^{-06}	1.81×10^{-04}	1.30	1.16	1.47
	Cataract +group (n=430)	GG	54	13.2	272	18.1	2.14×10^{-02}	NS	0.69	0.51	0.95
		GA	206	50.5	770	51.1	NS	NS	0.97	0.78	1.21
		AA	148	36.3	464	30.8	3.58×10^{-02}	NS	1.28	1.02	1.61
		G	314	38.5	1314	43.6	8.36×10^{-03}	NS	0.81	0.69	0.95
		A	502	61.5	1698	56.4	8.36×10^{-03}	NS	1.24	1.06	1.45
	BK +group (n=331)	GG	39	12.7	272	18.1	2.20×10^{-02}	NS	0.66	0.46	0.94
		GA	147	47.7	770	51.1	NS	NS	0.87	0.68	1.12
		AA	122	39.6	464	30.8	2.62×10^{-03}	NS	1.47	1.14	1.90
		G	225	36.5	1314	43.6	1.16×10^{-03}	2.32×10^{-02}	0.74	0.62	0.89
		A	391	63.5	1698	56.4	1.16×10^{-03}	2.32×10^{-02}	1.34	1.12	1.61
rs10004195	PIU (n=992)	AA	296	31.2	370	24.3	1.48×10^{-04}	4.44×10^{-03}	1.42	1.18	1.70
		AT	459	48.4	797	52.3	NS	NS	0.86	0.73	1.01
		TT	193	20.4	358	23.5	NS	NS	0.83	0.68	1.02
		A	1051	55.4	1537	50.4	5.61×10^{-04}	1.12×10^{-02}	1.22	1.09	1.37
		T	845	44.6	1513	49.6	5.61×10^{-04}	1.12×10^{-02}	0.82	0.73	0.92
	Cataract +group (n=430)	AA	109	26.8	370	24.3	NS	NS	1.15	0.89	1.47
		AT	210	51.7	797	52.3	NS	NS	0.98	0.79	1.22
		TT	87	21.4	358	23.5	NS	NS	0.89	0.68	1.16
		A	428	52.7	1537	50.4	NS	NS	1.10	0.94	1.28
		T	384	47.3	1513	49.6	NS	NS	0.91	0.78	1.06
	BK +group (n=331)	AA	94	30.7	370	24.3	1.78×10^{-02}	NS	1.38	1.06	1.81
		AT	152	49.7	797	52.3	NS	NS	0.90	0.71	1.15
		TT	60	19.6	358	23.5	NS	NS	0.80	0.59	1.08
		A	340	55.6	1537	50.4	1.97×10^{-02}	NS	1.23	1.03	1.47
		T	272	44.4	1513	49.6	1.97×10^{-02}	NS	0.81	0.68	0.97
rs11725309	PIU (n=992)	TT	271	28.0	467	30.4	NS	NS	0.89	0.75	1.06
		TC	469	48.5	792	51.6	NS	NS	0.88	0.75	1.04
		CC	228	23.6	277	18.0	8.02×10^{-04}	2.41×10^{-02}	1.40	1.15	1.71
		T	1011	52.2	1726	56.2	6.07×10^{-03}	NS	0.85	0.76	0.96
		C	925	47.8	1346	43.8	6.07×10^{-03}	NS	1.17	1.05	1.32
	Cataract +group (n=430)	TT	127	30.5	467	30.4	NS	NS	1.00	0.79	1.27
		TC	200	48.0	792	51.6	NS	NS	0.87	0.70	1.08
		CC	90	21.6	277	18.0	NS	NS	1.25	0.96	1.63
		T	454	54.4	1726	56.2	NS	NS	0.93	0.80	1.09
		C	380	45.6	1346	43.8	NS	NS	1.07	0.92	1.25
	BK +group (n=331)	TT	90	28.5	467	30.4	NS	NS	0.91	0.70	1.19
		TC	147	46.5	792	51.6	NS	NS	0.82	0.64	1.04
		CC	79	25.0	277	18.0	4.21×10^{-03}	NS	1.52	1.14	2.02
		T	327	51.7	1726	56.2	4.06×10^{-02}	NS	0.84	0.70	0.99
		C	305	48.3	1346	43.8	4.06×10^{-02}	NS	1.20	1.01	1.42
rs6841698	PIU (n=992)	AA	241	25.1	283	18.6	1.10×10^{-04}	3.29×10^{-03}	1.47	1.21	1.78
		AG	431	44.8	778	51.0	2.53×10^{-03}	NS	0.78	0.66	0.92
		GG	290	30.1	464	30.4	NS	NS	0.99	0.83	1.18
		A	913	47.5	1344	44.1	1.94×10^{-02}	NS	1.15	1.02	1.29
		G	1011	52.5	1706	55.9	1.94×10^{-02}	NS	0.87	0.78	0.98
	Cataract +group (n=430)	AA	140	33.7	283	18.6	3.16×10^{-11}	9.48×10^{-10}	2.23	1.76	2.84
		AG	173	41.7	778	51.0	7.49×10^{-04}	2.25×10^{-02}	0.69	0.55	0.85
		GG	102	24.6	464	30.4	2.01×10^{-02}	NS	0.75	0.58	0.96
		A	453	54.6	1344	44.1	7.24×10^{-08}	1.45×10^{-06}	1.53	1.31	1.78
		G	377	45.4	1706	55.9	7.24×10^{-08}	1.45×10^{-06}	0.66	0.56	0.76
	BK +group (n=331)	AA	88	28.2	283	18.6	1.10×10^{-04}	3.30×10^{-03}	1.72	1.31	2.28
		AG	133	42.6	778	51.0	6.93×10^{-03}	NS	0.71	0.56	0.91
		GG	91	29.2	464	30.4	NS	NS	0.94	0.72	1.23
		A	309	49.5	1344	44.1	1.26×10^{-02}	NS	1.25	1.05	1.48
		G	315	50.5	1706	55.9	1.26×10^{-02}	NS	0.80	0.68	0.95

+, having this feature; BK, band keratopathy; 95% CIs, 95% confidence intervals; HWE, Hardy–Weinberg equilibrium; NS, not significant; OR, odds ratio; PIU, paediatric idiopathic uveitis; SNPs, single nucleotide polymorphisms; TLR10, Toll-like receptors 10; Pc value, Bonferroni corrected p value.

was found in cases, whereas the AG genotype ($Pc=2.25\times10^{-2}$, OR=0.69, 95% CI=0.55 to 0.85) and G allele ($Pc=1.45\times10^{-6}$, OR=0.66, 95% CI=0.56 to 0.76) of rs6841698 were much lower in PIU patients with cataract compared with healthy controls (table 2). The other 9 tag SNPs showed no significant association (online supplementary table 3).

TLR10 SNP associations in PIU with BK

In the PIU patients with BK (n=331), the data showed an increased frequency of the rs2101521 A allele ($Pc=2.32\times10^{-2}$, OR=1.34, 95% CI=1.12 o 1.61) while a decreased frequency of the G allele ($Pc=2.32\times10^{-2}$, OR=0.74, 95% CI=0.62 to 0.89) was observed in PIU patients with BK compared with healthy controls (table 2). Moreover, the frequency of the rs6841698 AA genotype ($Pc=3.30\times10^{-3}$, OR=1.72, 95% CI=1.31 to 2.28) was markedly increased in PIU patients with BK (table 2). No significant associations of the other 8 tag SNPs with PIU with BK were observed (online supplementary table 4).

DISCUSSION

In this study, we detected a significant association of 4 tag SNPs of *TLR10* (rs2101521, rs10004195, rs11725309 and rs6841698) with PIU in Han Chinese. A stratified analysis showed a significant correlation of rs6841698 in PIU complicated with cataract. Two SNPs (rs2101521, rs6841698) were associated with PIU complicated with BK. Ten tag SNPs of *TLR10* were not correlated with JIA-PU compared with controls. It is not clear why some of the tag SNPs show an association with these subgroups of PIU and whether these subgroups might represent a separate as yet not identified clinical uveitis entity. The higher prevalence of cataract and BK in JIA-PU patients than PIU patients may be due to the fact that the uveitis in these children is more difficult to control and the persistence of the intraocular inflammation.

It has been reported that genetic variants are associated with childhood uveitis. Most genetic studies in PU focused on non-Hispanic White children with JIA and have found associations with gene polymorphisms of the *HLA* genes (*HLA-DR1*, *HLA-DRw5*, *HLA-DR5*, *HLA-DRB1*11*, *HLA-DRB1*13* and *HLA-B27* gene).[28–34] A recent study in children found an association between a *NOD2/CARD15* common variant *P268S/SNP5* and autoimmune chronic uveitis.[35] Further genetic studies in children with uveitis are scarce. Only two genetic studies on PU were reported in Han Chinese, and showed that variants of *miR-146a, Ets-1* and *TRAF5* conferred genetic predisposition to PU.[36 37]

To the best of our knowledge, this study is the first to investigate the association between genetic variants of *TLR10* and PIU in Han Chinese. Our study is in agreement with several other studies mentioned below, showing an association of *TLR10* polymorphisms with various autoimmune or autoinflammatory diseases (online supplementary table 6). *TLR10* rs2101521 (A allele) was for instance shown to be associated with allergy.[38] For SNP rs2101521, our study showed the same allele (A allele) to be associated with PIU. The G allele and AA genotype of rs2101521 were also found be associated with PIU in our study. Other studies showed that rs10004195 conferred susceptibility to childhood AITD and childhood IgA nephropathy (IgAN).[22 39] For SNP rs10004195, the T allele and AA genotype were both associated with PIU and childhood ATID, whereas our data also showed that the A allele was related to PIU. Childhood IgAN and PIU had the same susceptible genotype (AA genotype), while the TA genotype and a dominant model (AA/TA vs TT) were associated with childhood IgAN. *TLR10* rs11725309 (dominant model,CC/TC vs TT) was found to be associated with organic dust-mediated cytokine response,[40], while the CC genotype was related to PIU in our study. Other studies showed that rs6841698 (G allele) contributed to susceptibility to CD.[26] However, our study showed that the rs6841698 AA genotype was associated with PIU. Some allele/genotype associations are different with our study, which may be due to various factors including specific disease mechanisms, ethnical or geographical factors.

Activation of TLRs by recognising pathogen-associated molecular patterns to defend against the invasion of microbial pathogens, can trigger inflammatory cascades, activate innate immune responses and initiate antigen-specific adaptive immunity.[12 13] As a member of the TLR family, *TLR10* is a negative regulator, playing a suppressive role in MyD88- and TRIF-inducing IFN-β-mediated signalling pathways upstream of NFκB and MAPK activation.[41] *TLR10*, similar to *TLR1* and *TLR6*, is able to form a heterodimer with *TLR2*. *TLR10* acts as an inhibitory receptor when forming heterodimers with *TLR2*. Blocking *TLR10* promotes the production of proinflammatory cytokines, specifically after exposure to *TLR2* ligands.[17 41 42] Other studies suggest that *TLR10* is an unusual PRR that primarily inhibits *TLR2*-driven immune responses.[15 43 44] Additionally, *TLR10* affects DC-mediated adaptive immune responses by suppressing the activation and differentiation of monocytes through the MAPK and Akt signalling pathways.[45] These biological mechanisms may possibly be involved in the pathogenesis of PIU, although further evidence is definitely needed to prove this statement. Whether the gene variants of *TLR10* described above, also display an altered biological function in PIU is not known and also deserves further study.

It is worth mentioning some limitations of our study. This study only included Han Chinese and should be repeated in other ethnic populations. Our sample size of PU patients with JIA is relatively small and it is thus possible that we may have missed weak associations. Additionally, we realise that our PIU patient group probably represents various different clinical entities, which may weaken the statistical power to detect certain genetic associations. Careful analysis of the clinical features and regular follow-up of patients with a certain genotype profile may lead to the identification of new childhood uveitis subtypes. Another limitation is the fact that the possible biological function of the TLR10 SNPs described in our study is not yet known and deserves further investigation.

CONCLUSIONS

Taken together, our study shows that four loci of *TLR10* (rs2101521, rs10004195, rs11725309 and rs6841698) confer genetic susceptibility to PIU in Han Chinese. A stratified analysis according to the clinical features, suggests that two loci (rs2101521, rs6841698) are implicated in the development of PIU with BK, whereas rs6841698 confers susceptibility to PIU with cataract.

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Contributors ML and HT conceptualised and designed the study, coordinated and supervised data collection, drafted the initial manuscript and reviewed and revised the manuscript. PY and LD conceptualised and designed the study, and critically reviewed the manuscript for important intellectual content. GS, QW and KA critically reviewed the manuscript for important intellectual content and revised the manuscript. JD, ZyZ, XT and QC collected samples, collected data and carried out the initial analyses. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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