



# Association Between Interleukin-33 Polymorphism and Henoch-Schönlein Purpura in Chinese Children

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Received 2017 October 19; Revised 2017 December 10; Accepted 2018 January 01.

## Abstract

**Objectives:** Interleukin-33 (IL-33) was one of the members of IL-1 family, and it was reported that the single nucleotide polymorphisms (SNPs) in the *IL-33* gene was contribute to the susceptibility to immune related diseases, including rheumatoid arthritis, asthma, Behcet's disease, systemic lupus erythematosus and ankylosing spondylitis. However, the potential association between SNPs in *IL-33* gene and Henoch-Schönlein purpura (HSP) was not explored.

**Methods:** We designed a case-control study, a total of 181 HSP patients and 202 healthy pediatric controls were included, which aimed to study the relationship between the SNPs in the *IL-33* gene (rs1929992, rs7044343) and HSP with a Chinese pediatric cohort.

**Results:** There were no evidence for the association of rs1929992 and rs7044343 polymorphism in *IL-33* gene with pediatric HSP patients (C versus T,  $P = 0.622$ , OR = 0.931, 95% CI: 0.7 - 1.238; TT versus CC,  $P = 0.742$ , OR = 0.908, 95% CI: 0.513 - 1.609; CT versus CC,  $P = 0.158$ , OR = 0.714, 95% CI: 0.446 - 1.141 and C versus T,  $P = 0.920$ , OR = 0.986, 95% CI: 0.742 - 1.309; TT versus CC,  $P = 0.939$ , OR = 0.978, 95% CI: 0.549 - 1.741; CT versus CC,  $P = 0.416$ , OR = 0.817, 95% CI: 0.501 - 1.331, respectively). Moreover, association studies were performed on the correlation between *IL-33* gene polymorphisms and HSP nephritis patients as well as patients with gastrointestinal manifestation and joint involvement. However, there were no significant association regarding the distribution of allele and genotype frequencies between HSP patients with different system involvement and healthy controls either.

**Conclusions:** The present findings indicated that both of rs1929992 and rs7044343 in gene *IL-33* polymorphism were not related to the susceptibility to HSP and the different system involvement of HSP patients.

**Keywords:** Henoch-Schönlein Purpura, Cytokines, Interleukin-33, Single Nucleotide Polymorphisms

## 1. Background

Henoch-Schönlein purpura (HSP) was recognized as leukocytoclastic vasculitis which involving small vessels. HSP was also the most common vasculitis during childhood (1). It usually occurs in children between three and 15 years of age. The most common clinical presentations of HSP include cutaneous palpable purpura, arthritis or arthralgias, hematuria and/or proteinuria, bowel angina and gastrointestinal (GI) bleeding (2). However, the etiology of HSP is not fully understand. Genetic predisposition may contribute to this immune mediated inflammatory disease. It is demonstrated that multiple genes and their interactions with environmental factors were involved in the susceptibility to HSP (3). *MEFV* and human leukocyte antigen haplotypes also played a role in susceptibility to HSP (4, 5). Gene-gene interaction effects of *CCL2*, *VEGF* and *ACE* genes also reported to relate with HSP (6). Moreover,

multiple studies have showed the role of polymorphisms of a variety of genes was associated with the risk of HSP, HSP nephritis (HSPN) and HSP associated joint diseases (7-9).

Interleukin-33 (IL-33) was a proinflammatory cytokine which was belonged to the IL-1 cytokine family (10), and the intracellular signaling pathway of IL-33 was similar with IL-1 (11). IL-33 activated nuclear factor (NF)-kappa B and mitogen-activated protein kinases (MAPKs) via IL-1 receptor ST2 (11). Furthermore, IL-33 was expressed in various cells which were response to tissue damage, and acted as an early alertor of inflammation (12). The production of IL-33 was increased in inflamed tissues, which lead to the further amplification of inflammatory responses (13).

Previous study showed IL-33/ST2 signal transduction pathway was associated with a brunch of autoimmune and allergic diseases, as well as a variety of renal diseases (14). The levels of serum IL-33 in rheumatoid arthritis (RA) patients were observed significantly higher than these in

healthy controls. And CC genotype of rs7044343 in the gene of *IL-33* was associated with RA patients and down regulated IL-33 expression in RA patients (15). IL-33 also played a crucial role in Th2-mediated airway diseases like asthma (16). However, the relationship between IL-33 and HSP was poorly understand. Chen et al. (17) showed the level of serum IL-33 were elevated in acute stage of HSP patients and they were related to the severity of the disease. These findings suggested that IL-33 might contribute to the pathogenesis of HSP. The polymorphism of SNPs (rs1929992 and rs7044343) in *IL-33* gene were the most commonly reported SNPs associated with immune related diseases.

## 2. Objectives

The purpose of this study was to explore the relationship of SNPs (rs1929992 and rs7044343) polymorphism in *IL-33* gene with HSP.

## 3. Methods

### 3.1. Patients and Methods

181 patients who diagnosed as HSP and 202 healthy pediatric controls between June 2011 and June 2013 in Children's hospital, Zhejiang University School of medical were included in this study. HSP patients were diagnosed according to the American College of Rheumatology criteria for the classification of HSP (18). All patients were diagnosed as HSP first time and followed up more than 6 months. Patients accompanied with other systemic vasculitis and other immune related diseases were excluded. A total of 202 healthy children without a history of HSP and immune related diseases were randomly chosen as control in the study. HSP patients were divided into three groups based on main clinical manifestations, patients with HSPN which was defined as the presence of proteinuria and/or hematuria, joint manifestations refer to arthralgia or peripheral arthritis, patients with GI involvement including bowel angina and gastrointestinal bleeding.

The general information and clinical features of HSP patients and controls were obtained from the medical recording system. Laboratory findings such as white blood count, serum levels of albumin, creatinine, and complement 3 (C3), immunoglobulin (Ig) A and urine protein of HSP patients during the acute stage were extracted. Glomerular filtration rate (GFR) was calculated by Schwartz formula.

The study was approved by the Ethics Committee of Children's Hospital, Zhejiang University School of Medicine, and written informed consent was obtained from all the parents of children.

### 3.2. Analysis of *IL-33* Gene Polymorphism

EDTA anti-coagulated peripheral venous blood was obtained from each HSP patient and control. DNA of the leukocytes was extracted with a DNA extraction kit (Tissue-bank Biotechnology Co, Ltd., Shanghai, China) following the instruction protocol. DNA samples were stored at -20°C for polymerase chain reaction analysis.

SNP genotyping was performed in a 384-well plate format on the Sequenom MassARRAY platform (Sequenom, San Diego, USA), as described previously (19). The primers for *IL-33* rs1929992 were 5'-ACGTTGGATGGGTCAATTAGTTGGTGAAA-3' (forward) and 5'-ACGTTGGATGTAGCTTTCTTTCATGG-3' (reverse). The primers for *IL-33* rs7044343 were 5'-ACGTTGGATGAAGAGGAATGAATATTGGG-3' (forward) and 5'-ACGTTGGATGTGTGACCCTAATGGTTA-3' (reverse). *IL-33* rs1929992 and rs7044343 were amplified with total volume 5  $\mu$ L in each tube. Each tube was consisted of 5 ng of DNA, 1  $\mu$ M forward and reverse primers, 0.5 mM dNTP, PCR buffer and 0.1  $\mu$ L HotStar Taq (Qiagen). The PCR thermal-cycling condition was as follow: 15 minutes at 94°C and 45 cycles of 20 seconds at 94°C, 30 seconds at 56°C and 1 minute at 72°C. After dNTPs were removed, Single base extension for SNP was performed in reaction buffer: 1 X iPLEX buffer, 0.2  $\mu$ L stop mixture, 0.041  $\mu$ L iPLEX enzyme (Sequenom, San Diego, USA), 0.804  $\mu$ L 10  $\mu$ M extension primer and H2O. The PCR thermal-cycling condition for extension was as follow: 30 seconds at 94°C and 40 cycles of 5 seconds at 94°C, 5 seconds at 52°C and 5 seconds at 80°C. Genotype calling was performed in real time with MassARRAY RT software (version 3.0.0.4) (Sequenom, San Diego, USA). SNP genotyping was performed via MassARRAY Typer software (version 3.4) (Sequenom, San Diego, USA).

### 3.3. Statistical Analysis

The age of disease onset and laboratory results were described as mean  $\pm$  SD, the mean values compared between patients and controls used the unpaired student's *t* test. Hardy-Weinberg equilibrium (HWE) for each SNP in patients and controls were tested by chi-square goodness-of-fit test. The frequencies of gender, allele and genotype between the two groups were compared using chi-square ( $\chi^2$ ) test. The odds ratios (OR) and the significant of OR were calculated to evaluate the risk of developing HSP. *P* < 0.05 was considered statistically significant difference. All statistical analyses were conducted with SPSS 22.0 statistical software (SPSS Inc., IBM Corp. Armonk, NY, United States).

## 4. Results

### 4.1. The General Information, Clinical Features of HSP Patients

The general information and clinical features of the 181 HSP patients and 202 healthy controls were listed in Table

1. Mean age of disease onset was  $7.8 \pm 2.6$  years, mean age of healthy control was  $7.0 \pm 2.1$  years. There were no statistical differences between the HSP patients and controls regarding to age of disease onset and gender,  $P > 0.05$ .

#### 4.2. HWE and Statistical Power Examination

The P-value for HWE examination of the prevalence of genotypes regarding two SNPs in healthy controls and HSP group were both higher than 0.05, there were no statistically differences (Table 2).

#### 4.3. Association of IL-33 Gene Polymorphisms and Risk of HSP

There were no significant differences between HSP patients and healthy controls for the association of rs1929992 and rs7044343 polymorphism with risk of HSP. With respect to rs1929992, C versus T,  $P = 0.622$ , OR = 0.931, 95% CI: 0.700-1.238; TT versus CC,  $P = 0.742$ , OR = 0.908, 95% CI: 0.513-1.609; CT versus CC,  $P = 0.158$ , OR = 0.714, 95% CI: 0.446-1.141 (Table 3). With respect to rs7044343, C versus T,  $P = 0.920$ , OR = 0.986, 95% CI: 0.742-1.309; TT versus CC,  $P = 0.939$ , OR = 0.978, 95% CI: 0.549-1.741; CT versus CC,  $P = 0.416$ , OR = 0.817, 95% CI: 0.501-1.331 (Table 4).

**Table 1.** General Information and Clinical Features of HSP Patients and Controls<sup>a</sup>

Parameters	Patients	Controls
N	181	202
Age at disease onset	$7.8 \pm 2.6$	$7.0 \pm 2.1$
Gender		
Male	99	108
Female	82	94
Arthralgias and/or arthritis	103	-
Gastrointestinal involvement	108	-
Renal involvement	81	-
WBC ( $\times 10^9/L$ )	$10.08 \pm 4.46$	-
CRP	$7.97 \pm 13.94$	-
ESR	$16.66 \pm 16.51$	-
Serum creatinine, mg/dL	$0.51 \pm 1.87$	-
C3, g/L	$1.23 \pm 0.25$	-
IgA, g/L	$2.00 \pm 0.80$	-
ALB, g/L	$40.36 \pm 5.84$	-
GFR, mL/min/1.73 m <sup>2</sup>	$146.51 \pm 44.33$	-

Abbreviations: ALB, albumin; C3, complement 3; CRP, C-reactive protein; GFR, glomerular filtration rate; HSP, Henoch-Schönlein purpura; IgA, immunoglobulin A; SD, standard deviation; WBC, white blood count.

<sup>a</sup> Values are expressed as No. or mean  $\pm$  SD.

#### 4.4. Correlation Between IL-33 Gene Polymorphisms and Risk of HSPN, GI Involvement and Joint Involvement

In this study, 81 HSP patients (40.3%) accompanied with HSPN, 108 patients (53.7%) had GI manifestations, including abdominal pain and GI bleeding, and 103 patients (51.24%) had arthralgias. We also compared the allele and genotype frequencies of HSP patients with HSPN, accompanied GI manifestations and joint involvement with healthy controls, respectively. Results showed that there was no significant difference with allele and genotype frequencies for the two SNPs (rs1929992, rs7044343) in IL-33 gene between HSP patients with different manifestations and healthy controls (Table 3).

## 5. Discussion

HSP was known as an immune mediated vasculitis that might be associated with predisposition and infection of some pathogens. It most commonly happened in autumn or winter preceding upper respiratory tract infections with multiple pathogens, such as *Streptococcus* strains, parainfluenza virus and parvovirus B19 (20, 21). However, the pathophysiology of HSP was not completely understood so far. The deposition of immune complexes containing IgA1 in the vascular played a vital role in the pathogenic of disease (22). The disorder of immune reaction might result in inflammation and vasculitis without a granulomatous reaction (23). Many antibodies, cytokines, chemokines, receptors, and transmembrane proteins have been supposed to involved in the development of the disease (6). Several cytokines, such as tumor necrosis factor alpha (TNF-alpha), IL-6, IL-8 and IL-17 were also related to the risk and development of HSP (24).

IL-33 had been found to participate in asthma, inflammation, and variety of immune disorders (25). IL-33 induced pro-inflammatory effects via activates T helper type 2 (Th2) cells and mast cells, additionally, it also played a role depending on Th1/Th17 immune response (11, 26). IL-33 was considered as an 'endogenous danger signal' for its alerting effect in the immune system when tissue was damaged and infected, and it could lead to the initiation of a healing of damage further (27).

The variety of SNPs in IL-33 were studied in many immune related diseases and revealed that some allele genes and genotype of IL-33 gene were associated with risk to immune related diseases. GWAS studies revealed that rs1342326 (28), rs3939286 (29), and rs2381416 (30) SNPs in IL-33 gene were related to the risk of asthma (19). The CC genotype of rs7044343 in IL-33 was associated with susceptibility to RA, while, no association was detected between rs10975514 polymorphism and RA susceptibility (15). Another study showed that SNPs rs1891385, rs2210463,

**Table 2.** HWE and Statistical Power Examination of the Prevalence of Genotypes

SNP	$\chi^2$		P	
	Control		HSP Group	
	Control	HSP Group	Control	HSP Group
rs1929992	0.82	1.14	0.36	0.29
rs7044343	1.27	0.05	0.26	0.83

Abbreviation: SNP, single nucleotide polymorphism.

**Table 3.** IL-33 Gene Polymorphism with Different Manifestations and Healthy Controls

SNPs	HSPN (n = 81)	P Value	OR (95% CI)	GI (n = 108)	P Value	OR (95% CI)	Joint (n = 103)	P Value	OR (95% CI)
<b>rs1929992</b>									
<b>Allele</b>									
C	82	0.575	Reference	123	0.312	Reference	110	0.870	Reference
T	80		1.11 (0.771 - 1.598)	91		0.842 (0.603 - 1.175)	94		0.972 (0.694 - 1.362)
<b>Genotype</b>									
CC	24		Reference	35		Reference	33		Reference
CT	34	0.285	0.715 (0.386 - 1.324)	53	0.327	0.764 (0.446 - 1.309)	44	0.163	0.673 (0.385 - 1.175)
TT	23	0.515	1.262 (0.626 - 2.545)	19	0.34	0.715 (0.358 - 1.426)	25	0.995	0.998 (0.516 - 1.929)
<b>rs7044343</b>									
<b>Allele</b>									
C	77	0.490	Reference	112	0.706	Reference	101	0.774	Reference
T	85		1.137 (0.790 - 1.638)	102		0.938 (0.673 - 1.307)	103		1.051 (0.750 - 1.471)
<b>Genotype</b>									
CC	20		Reference	27		Reference	27		Reference
CT	37	0.531	0.815 (0.429 - 1.547)	58	0.848	0.946 (0.535 - 1.671)	47	0.370	0.767 (0.428 - 1.373)
TT	24	0.501	1.200 (0.623 - 2.628)	22	0.692	0.869 (0.434 - 1.741)	28	0.767	1.106 (0.568 - 2.155)

rs10118795, rs1929992, rs10975519, and rs1048274 in the *IL-33* gene were associated to the development of ankylosing spondylitis (AS) in a Chinese Han population (31). The rs7044343 and rs11792633 polymorphism of *IL-33* gene decreased risk of Behcet's disease (BD), which means it acted a protective role during the pathogenesis of BD (32). Xu et al. (33) found that there was significantly lower expression of allele G for rs1929992 in systemic lupus erythematosus (SLE) patients than that in controls, and genotype GG was associated to the susceptibility to SLE when compared with the AA. Meanwhile there is no evidence for the association of rs7044343 polymorphism in *IL-33* gene with SLE.

In this study, we investigated the correlation between the SNPs of *IL-33* gene polymorphism (rs1929992, rs7044343) and HSP in a Chinese Han pediatric cohort that consisted of 181 HSP patients and 202 healthy controls. We showed that there was no strong evidence for the association of *IL-33* gene (rs1929992, rs7044343) polymorphism with the risk of HSP. Furthermore, association studies performed on the relationship with these two polymorphisms

between healthy controls and HSP patients with different system involved (HSPN, joint involvement and GI involvement) showed no significant association as well. Although HSP was reported related to the immune disorder disease. Moreover, serum IL-33 level and SNPs in *IL-33* gene were related to the risk of disease, severity of autoimmune diseases and renal injury. Nevertheless, we didn't observe any relationship between *IL-33* gene polymorphism (rs1929992, rs7044343) and HSP in our study. It remained further investigation with larger population and different ethnicity.

In conclusion, to our knowledge, this was the first study to discuss the association between *IL-33* gene polymorphisms and the risk of HSP. The present research suggested that the *IL-33* gene (rs1929992 and rs7044343) were not related to HSP susceptibility in Chinese pediatric population.

**Table 4.** IL-33 Gene Polymorphism in HSP and Healthy Controls

SNPs	Controls (n = 202)		HSP (n = 181)		P Value		OR (95% CI)	
	rs1929992	rs7044343	rs1929992	rs7044343	rs1929992	rs7044343	rs1929992	rs7044343
<b>Allele</b>								
C	215 (53.22%)	205 (50.74%)	198 (55.00%)	185 (51.10%)	0.622	0.920	Reference	Reference
T	189 (46.78%)	199 (49.26%)	162 (45.00%)	177 (48.90%)			0.931 (0.700 - 1.238)	0.986 (0.742 - 1.309)
<b>Genotype</b>								
CC	54	48	58	48			Reference	Reference
CT	107	109	82	89	0.158	0.416	0.714 (0.446 - 1.141)	0.817 (0.501 - 1.331)
TT	41	45	40	44	0.742	0.939	0.908 (0.513 - 1.609)	0.978 (0.549 - 1.741)
<b>Dominant</b>								
CC	54	48	58	48	0.239	0.534	Reference	Reference
CT + TT	148	154	122	133			0.767 (0.494 - 1.193)	0.864 (0.544 - 1.371)
<b>Recessive</b>								
CC + CT	161	157	140	137	0.646	0.638	Reference	Reference
TT	41	45	40	44			1.122 (0.687 - 1.833)	1.121 (0.697 - 1.801)

## Footnotes

**Conflict of Interests:** The authors declare no conflicts of interests.

**Ethical Considerations:** The study was approved by the Ethics Committee of Children's Hospital, Zhejiang University School of Medicine, and written informed consent was obtained from all the parents of children.

**Funding/Support:** There is no financial support.

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