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Research article

Associations of *MEFV* gene variants, IL-33, and sST2 with the risk of Henoch-Schönlein purpura in children

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ABSTRACT

Objective: Henoch-Schönlein purpura (HSP) is the most common systemic vasculitis in children. HSP is a multifactorial inflammatory disease, but its pathogenesis is still unclear. The pathogenicity of familial Mediterranean fever gene (*MEFV*) variants in HSP remains controversial. The objective of this study was to evaluate relationships between *MEFV* variants and susceptibility to HSP and their associations with clinical outcomes. We also investigated levels of IL-33 and soluble suppression of tumorigenicity 2 (sST2) in children with HSP and their clinical significance.

Methods: We selected 100 children with HSP as the case group. The control group consisted of 50 children who visited the hospital for physical health examinations. All subjects were screened for *MEFV* gene exon mutations, and levels of IL-33 and sST2 were measured.

Results: The frequency of *MEFV* variants was significantly greater in HSP patients than in healthy controls. The variant with the highest frequency was E148Q. The frequency of the C allele of the *MEFV* variant E148Q was 32 % in HSP patients and 18 % in controls (P-adjust = 0.04). Patients with the *MEFV* E148Q variant had more frequent joint involvement and recurrent purpura and higher levels of IL-33 and C-reactive protein (CRP). Levels of IL-33 and sST2 in children with HSP were significantly higher than those in the control group, and the sST2/IL-33 ratio in children with HSP was unbalanced (P-adjust <0.05). Logistic regression analysis revealed the presence of E148Q and an unbalanced sST2/IL-33 ratio to be independent risk factors for HSP.

Conclusion: The results of this study suggest that the *MEFV* variant E148Q is associated with HSP susceptibility in Chinese children and that carriers of the variant may have more severe clinical manifestations and greater inflammatory responses. E148Q and the sST2/IL-33 ratio may play important roles in the pathogenesis of HSP.

1. Introduction

Henoch-Schönlein purpura (HSP) is the most common systemic vasculitis in children and often involves the skin, gastrointestinal tract, joints, kidneys, and other organs. Some patients die of chronic renal failure due to a prolonged disease course [1]. The incidence of HSP has been increasing in recent years. However, the pathogenesis and etiology of HSP have not been fully elucidated. In addition to often affecting multiple systems and organs, HSP has complex and variable symptoms and recurs easily. HSP is associated with an

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obvious genetic predisposition [2]. Some studies have shown that the incidence of HSP varies among countries. Even under the same environmental conditions, only some of the manifestations of the disease occur in individuals of the same race, suggesting that genetic factors play a vital role in the pathogenesis of HSP [3]. The familial Mediterranean fever gene (*MEFV*) is the pathogenic gene of familial Mediterranean fever (FMF) [4]. *MEFV* encodes a protein called pyrin, which is an essential active component of the inflammasome [3]. The findings of some studies suggest that the *MEFV* gene variants may lead to decreased expression of the pyrin protein or abnormal protein function such that reactive cells continue to be active. Thus, the body's response to harmful stimuli increases, causing auto-inflammatory damage [5]. The *MEFV* gene plays a vital role in the pathogenesis of vascular diseases and HSP-related diseases [6].

A significant factor in the pathogenesis of HSP is immune abnormalities due to abnormal expression of inflammation-associated cytokines [7]. Studies have shown that an imbalance in Th1/Th2 cell activation and excessive activation of Th2 cells lead to over-secretion of IL-4, IL-6 and other cytokines that play vital roles in the pathogenesis of HSP [8]. Indeed, it has been reported that inflammatory factors such as IL-6, TNF-α, IL-17A and IL-23 are associated with HSP onset and disease progression [9,10]. After activation of the inflammasomes, they depend on Caspase-1 to produce mature IL-1β, IL-18 and IL-33 [11]. Compared with those in the control group, serum levels of the inflammasome-dependent cytokine IL-1β are increased in HSP patients, which may be related to the occurrence and development of HSP [12,13]. A lack of significant difference in IL-18 level between HSP and healthy control groups ($P > 0.05$) has been reported [13], and the relationship between IL-33 and HSP remains unclear. Interleukin-33 (IL-33) is an inflammatory cytokine. IL-33 can activate mast cells, lymphocytes and eosinophils; induce production of Th2 chemokines and inflammatory cytokines; and promote inflammation [14]. Suppression of tumorigenicity 2 (ST2) is a receptor for IL-33 and is divided into soluble ST2 (sST2) and transmembrane suppression of tumorigenicity 2 (ST2L) [15]. IL-33 binds to the ST2 receptor through its cytokine domain to initiate the inflammatory response [16]. Soluble ST2 binds to IL-33, inhibiting IL-33/ST2L pathway signaling [17]. These findings suggest that sST2 may inhibit release of Th2-type chemokines and cytokines. Numerous studies have confirmed that IL-33 plays a vital role in autoimmune diseases such as rheumatoid arthritis, Sjogren syndrome, systemic lupus erythematosus, and systemic sclerosis [18–20]. However, studies on the role of IL-33 and sST2 in children with HSP are relatively rare. The authors of recent studies have speculated that HSP patients with *MEFV* variants exhibit a more severe clinical course and laboratory outcomes due to an excessive inflammatory response caused by defects associated with these variants [21,22]. Nevertheless, to our knowledge, only two previous population-based studies [23,24] have focused on the association between *MEFV* variants and HSP risk in Chinese populations. Moreveor, to date, there has been no study on the effects of the interaction of the *MEFV* variant, IL-33, and ST2 on the risk of HSP in the Chinese population. Therefore, the aim of this study was to investigate the relationship between *MEFV* gene polymorphisms and susceptibility to HSP in Chinese children and to evaluate the expression and clinical significance of IL-33 and sST2, which may play important roles in its pathogenesis, in children with HSP.

2. Materials and methods

2.1. Research subjects

A total of 100 children with HSP treated at Hunan Children's Hospital were selected as the case group. The control group included 50 children who visited the hospital for a physical health examination. The inclusion criterion for the case group was clinical diagnosis of HSP. The HSP cases all met the diagnostic criteria of the European League Against Rheumatism and the European Pediatric Rheumatology Society (EULAR/PReS) for HSP [25]. All the HSP patients were in the acute phase of the disease, and no immunosuppressive agents or adrenocortical hormones had been used in the past two weeks. The definition of 'renal damage' is hematuria or proteinuria >0.5 g/d [26]. This study was approved by the Ethics Committee of Hunan Children's Hospital (No. HCHLL-2020-21).

2.2. Research methods

2.2.1. Detection of MEFV gene variants

Venous whole-blood samples were collected using EDTA tubes. Plasma was separated by centrifugation (1000 rpm, 15 min) within 2 h after blood collection and stored at −70 °C until analysis. A DNA extraction kit (Tiangen Biotech Corp) was used to extract DNA from the whole-blood specimens. The exon coding sequence of the *MEFV* gene was determined according to the GENE database, primers were designed, and the extracted DNA was sequenced by Sanger sequencing. The primer sequences of *MEFV* are shown in Table S1. DNA analysis of the *MEFV* gene was performed for all 150 research subjects. The demographic, clinical, genetic and laboratory characteristics of the groups were compared.

2.2.2. Measurement of IL-33, sST2 and other clinical parameters

IL-33 and sST2 serum concentrations were measured using ELISA (Cusabio Elisa kit, catalog no: CSB-E13000h and catalog no: CSB-E13789h, respectively). The minimum detection limit was 15.6 pg/mL for IL-33 and 78.0 pg/mL for sST2. The kit instructions were strictly followed. Other clinical parameters, such as the white blood cell (WBC) count, platelet (PLT) count and C-reactive protein (CRP), immunoglobulin A (IgA) and E (IgE) and anti-streptolysin O (ASO) levels, were determined for each patient by means of laboratory tests.

2.3. Statistics

SPSS 20.0 software was used for statistical analysis of the data obtained. Continuous variables are expressed as the mean ±

standard deviation. A *t*-test was used for comparisons between groups. Enumeration data are expressed as rates and percentages. The chi-square test and Wilcoxon rank sum test were used to compare data between the groups. False discovery rate (FDR) correction was applied for multiple comparisons. Multiple related factors were analyzed using logistic regression. Differences for which the *P* value was <0.05 were considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics of HSP patients and controls

A total of 100 patients with HSP and 50 healthy children were included in this study. The basic information of the study participants is shown in Table 1. The mean age and sex distribution were not significantly different between the patients and controls. Patients with HSP presented with palpable purpura (100 %), arthritis (44 %), renal damage (22 %), and abdominal pain (16 %). Compared with those in the control group, the WBC count, PLT, CRP, IgA, IL-33, and sST2 levels, and sST2/IL-33 ratio were significantly greater in the HSP group ($P < 0.05$) (Fig. 1 A,B and C).

3.2. Distribution of MEFV genotypes in HSP patients and controls

MEFV variant analysis revealed at least 8 variant types, including E148Q, D102D, G138G, P369S, R408Q, R501R, R202Q, and L110P. At least one *MEFV* variant or polymorphism was detected in 81 of 100 HSP patients (81 %). Twenty (20 %) patients were heterozygous with one variant, 34 (34 %) patients were heterozygous with two variants, and 24 (24 %) patients were heterozygous with three or more variants. The genotype with the highest *MEFV* variant rate was E148Q/N, followed by D102D/G138G and E148Q/L110P (Table 2). The genomic coordinates and rsIDs of the *MEFV* variants are shown in Table S2.

3.3. Genotypic and allelic frequencies of the four genetic variants

The distributions of the genotypic and allelic frequencies of E148Q, P369S, L110P, and R408Q are shown in Table 3. The frequency of the C allele of E148Q was greater in HSP patients than in controls. The prevalence of the E148Q C allele was 32 % in HSP patients and 18 % in controls (*P*-adjust = 0.04). No significant difference between the groups was observed with regard to P369S, L110P, and R408Q genotypic or allelic frequencies (Table 3).

3.4. Relationship between E148Q and the clinical and laboratory features of HSP patients

The clinical and laboratory features of HSP patients with and without the E148Q variant are shown in Table 4. The age and sex distributions of the patients in both groups were similar. The arthritis frequency, recurrent purpura frequency, and CRP and IL-33 levels were significantly higher in patients with the E148Q variant than in patients without the E148Q variant (Table 4, Fig. 1 D and E). Therefore, E148Q may affect the clinical presentation of HSP.

Table 1
Demographic and clinical characteristics of HSP patients and controls.

Clinical characteristics	n (%)		*P*	*P − adjust*
	HSP patients (n = 100)	Controls (n = 50)		
Sex				
Male	56 (56.0)	34 (68.0)		
Female	44 (44.0)	16 (32.0)	0.157	
Age	7.52 ± 2.92	6.73 ± 3.72	0.194	
Clinical findings				
Purpura	100 (100)	0 (0)	NA	
Abdominal pai	16 (16)	0 (0)	NA	
Renal damage	22 (22)	0 (0)	NA	
Arthritis	44 (44)	0 (0)	NA	
WBC count ($\times 10^9$/L)	11.82 ± 6.14	7.69 ± 2.29	<0.001	**0.001**
PLT count ($\times 10^9$/L)	345.53 ± 91.99	311.70 ± 70.37	0.014	**0.014**
CRP (mg/L)	13.82 ± 22.26	1.33 ± 0.94	<0.001	**0.001**
IgA (g/L)	2.23 ± 0.98	0.72 ± 0.21	<0.001	**0.001**
IgE (IU/mL)	143.77 ± 294.52		NA	
ASO (IU/mL)	131.17 ± 207.03		NA	
IL-33 (pg/mL)	299.31 ± 193.89	177.66 ± 92.35	<0.001	**0.001**
sST2 (pg/mL)	407.69 ± 1106.09	50.16 ± 145.39	0.002	**0.002**
sST2/IL-33 ratio	1.56 (0.04, 1.54)	0.26 (0, 0.12)	<0.001	**0.001**

NA not applicable. *P*-adjust *P* values adjusted by FDR correction. The ± ranges in demographic and clinical parameters represent are Mean ± Standard Deviation.

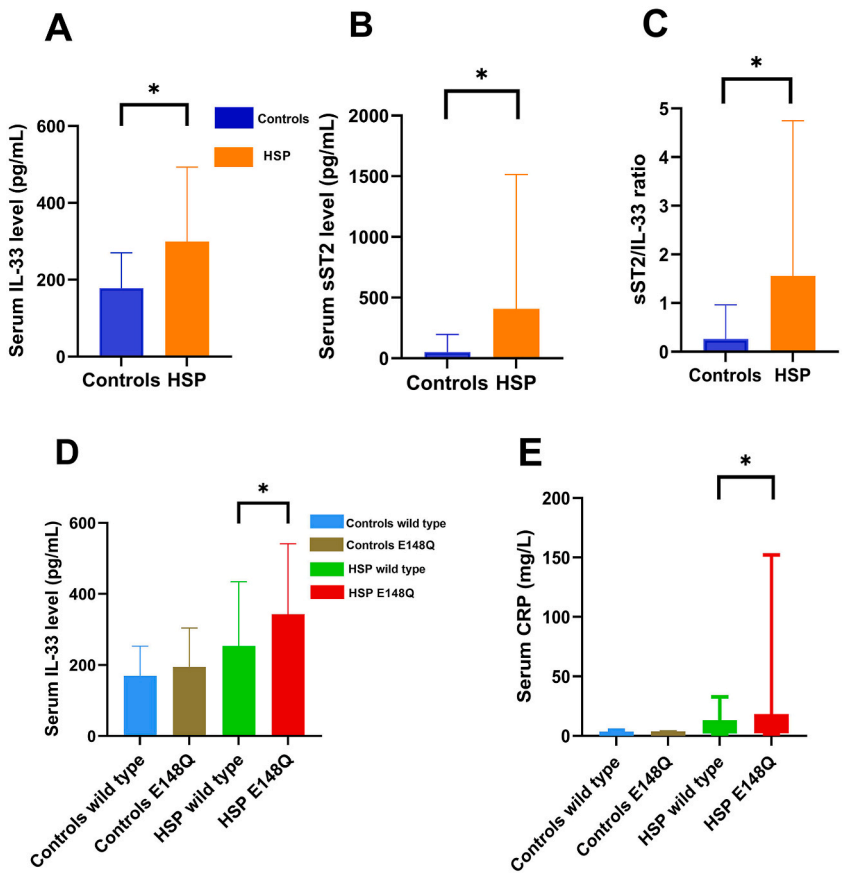

Fig. 1. Comparisons of serum IL-33, CRP and sST2 levels between patients with HSP and healthy controls. (A) Serum levels of IL-33 in patients with HSP and healthy controls. (B) Serum levels of sST2 in patients with HSP and healthy controls. (C) The sST2/IL-33 ratio in patients with HSP and healthy controls. (D) Serum levels of IL-33 in children with HSP and healthy controls with and without E148Q variant. (E) Serum CRP levels in children with HSP and healthy controls with and without E148Q variant. *$P < 0.05$. The error bars represent Mean with SD.

Table 2
MEFV gene variants in HSP patients and controls.

Genotype	HSP patients (n = 100)	Controls (n = 50)
Variant (−)	19 (19 %)	17 (34 %)
Heterozygous for one variant		
E148Q/N	18 (18 %)	6 (12 %)
R501 R/N	2 (2 %)	1 (2 %)
L110 P/N	0	3 (6 %)
Compound heterozygous for two variants		
E148Q/L110P	13 (13 %)	2 (4 %)
D102D/G138G	15 (15 %)	8 (16 %)
E148Q/R501R	6 (6 %)	2 (4 %)
Compound heterozygous for three variants		
E148Q/D102D/G138G	5 (5 %)	3 (6 %)
P369S/R408Q/R501R	5 (5 %)	2 (4 %)
D102D/G138G/R202Q	7 (7 %)	2 (4 %)
E148Q/L110P/R501R	1 (1 %)	0
Compound heterozygous for four variants		
E148Q/D102D/L110P/G138G	1 (1 %)	1 (2 %)
E148Q/P369S/R408Q/R501R	4 (4 %)	2 (4 %)
E148Q/D102D/G138G/R202Q	1 (1 %)	0

Table 3
Distributions of E148Q, P369S, L110P, and R408Q genotypic and allelic frequencies in HSP patients and controls.

Variants	Genotype/allele	HSP patients (n = 100)	Controls (n = 50)	*P*	*P* − *adjust*
E148Q	GG	49 (49 %)	34 (68 %)	**0.027**	0.243
	GC	38 (38 %)	14 (28 %)	0.225	0.675
	CC	13 (13 %)	2 (4 %)	0.083	0.374
	C allele	64 (32 %)	18 (18 %)	**0.010**	**0.040**
P369S	CC	88 (88 %)	45 (90 %)	0.716	0.806
	CT	10 (10 %)	5 (10 %)	1.000	1.000
	TT	2 (2 %)	0	0.314	0.707
	T allele	14 (7 %)	5 (5 %)	0.503	0.671
L110P	TT	85 (85 %)	44 (88 %)	0.618	0.795
	TC	14 (14 %)	5 (10 %)	0.487	0.795
	CC	1 (1 %)	1 (2 %)	0.615	0.795
	C allele	16 (8 %)	7 (7 %)	0.759	0.795
R408Q	GG	88 (88 %)	45 (90 %)	0.716	0.806
	GA	10 (10 %)	5 (10 %)	1.000	1.000
	AA	2 (2 %)	0	0.314	0.707
	A allele	14 (7 %)	5 (5 %)	0.503	0.671

P-adjust *P* values are adjusted by FDR correction.

Table 4
Relationship between E148Q and the clinical characteristics of children with HSP.

Clinical characteristics	E148Q n (%)		*P*	*P*-adjust
	Variant	Wildtype		
Clinical findings				
Abdominal pain				
Yes	8 (15.69)	8 (16.33)		
No	43 (84.31)	41 (83.67)	0.930	0.935
Renal damage				
Yes	10 (19.61)	12 (24.49)		
No	41 (80.39)	37 (75.51)	0.556	0.935
Arthritis				
Yes	31 (60.78)	13 (26.53)		
No	20 (39.22)	36 (73.47)	0.001	**0.015**
Recurrent purpura				
Yes	17 (33.33)	5 (10.20)		
No	34 (66.67)	44 (89.80)	0.005	**0.038**
Sex				
Male	30 (58.8)	7 (43.8)		
Female	21 (41.2)	9 (56.2)	0.290	0.621
Age	7.45 ± 2.89	7.59 ± 2.97	0.805	0.935
WBC count ($\times 10^9$/L)	12.61 ± 7.57	10.99 ± 4.10	0.191	0.478
PLT count ($\times 10^9$/L)	346.45 ± 97.41	344.57 ± 86.98	0.919	0.935
CRP (mg/L)	18.99 ± 29.32	8.43 ± 8.27	**0.016**	0.079
IgA (g/L)	2.24 ± 0.83	2.22 ± 1.13	0.913	0.935
IgE (IU/mL)	146.13 ± 306.77	141.31 ± 284.36	0.935	0.935
ASO (IU/mL)	119.54 ± 197.58	143.27 ± 217.82	0.569	0.935
IL-33 (pg/mL)	342.87 ± 198.16	253.96 ± 180.32	**0.021**	0.079
sST2 (pg/mL)	567.48 ± 1500.36	241.38 ± 350.88	0.137	0.411
sST2/IL-33	1.85 (0.04, 2.25)	1.25 (0.05, 1.32)	0.63	0.935

The ± ranges in demographic and clinical parameters represent are Mean ± Standard Deviation. *P*-adjust *P* values are adjusted by FDR correction.

3.5. Logistic regression analysis

Logistic regression analysis showed that the presence of E148Q and the sST2/IL-33 ratio correlated significantly with an increased risk of HSP ($P < 0.05$). Children with the E148Q variant had a greater risk of HSP than did those with wildtype *MEFV* (OR 1.961, 95 % CI 1.072–3.585) (Table 5). The ROC curves showed that the E148Q and the sST2/IL-33 were predictive of HSP with AUC of 0.595 and

Table 5
Results of logistic regression analysis.

	β	SE	Wald	OR	95 % CI	*P*
E148Q	0.673	0.308	4.779	1.961	1.072–3.585	**0.029**
sST2/IL-33 ratio	1.513	0.449	11.355	4.539	1.883–10.942	**0.001**

0.783, respectively (95 % CI, 0.500–0.690 and 0.705–0.861). The Youden of the sST2/IL-33 was 0.52, with a sensitivity of 80 % and a specificity of 72 % (Table 6).

4. Discussion

HSP is a common systemic small vasculitis disease in children that often involves multiple systems and organs. At present, the molecular mechanism of HSP development is not fully understood. Studies have shown that the pathogenesis of HSP may be related to environmental and genetic factors as well as immune system abnormalities [27]. An association between *MEFV* variants and HSP susceptibility or outcome has been reported [28,29]. Bonyadi et al. [30] measured the variant rate of *MEFV* in 40 Turkish patients with HSP and reported that 7.5 % of the patients carried variants in two gene sites. This finding suggests that the incidence of HSP in Turkish individuals is closely related to *MEFV*. Salah et al. [31] suggested that *MEFV* may be associated with susceptibility to HSP in Egyptian children. However, the findings of other studies have suggested that there is no correlation between *MEFV* variants and HSP; therefore, the pathogenicity of *MEFV* variants remains controversial [29,31–33].

The allelic frequency of the E148Q variant is approximately 23.7 % in the healthy Japanese population [34], and it is approximately 11 % among Turks [35]. According to the findings of this study, the frequency of E148Q in the Chinese population is 18 %. This finding indicates heterogeneity in baseline allelic frequencies among individuals of different nationalities. Therefore, the association between E148Q and HSP may be race specific. In this study, 81 % of HSP patients had at least one *MEFV* variant, with 61 % complex heterozygosity. There were 8 types of *MEFV* variants, with the most common being E148Q (51 %), followed by L110P (15 %), P369S (12 %), and R408Q (12 %). The C allelic frequency of E148Q in HSP patients (32 %) was significantly greater than that in children in the control group (18 %) (P-adjust = 0.04). E148Q was the most common variant we detected, which was consistent with a study in Turkey [32]. However, the most common variant in another Turkish study [22] and in a study of Iranian HSP patients [36] was M694V. An Egyptian study found that V726A was the most common variant (22 %) [31]. Our findings are consistent with those of He et al. [23] in China and Gershoni et al. [37] in Israel, with E148Q being the most common variant in patients with HSP. Our results showed that no HSP patients harbored M694V or V726A variants. These findings suggest that the frequencies of the M694V, V726A, and E148Q variants differ among HSP patients of different races and genetic backgrounds. Altug U et al. [38] suggested that *MEFV* variants, especially E148Q and M694V, might be related to HSP and affect its clinical presentation (gastrointestinal reactions and edema). He et al. [23] reported that the E148Q polymorphism may be related to the incidence of HSP in Chinese children, which is similar to the reported findings in Japan, which is also an Asian population [39]. Therefore, E148Q may be not only a genetic marker but also an essential susceptibility factor for development of HSP.

In addition, our results showed that the WBC count and PLT, CRP, IgA, IL-33, and sST2 levels were significantly higher in HSP patients than in controls. The frequency of arthritis, frequency of recurrent purpura, and CRP and IL-33 levels in HSP patients with the E148Q variant were significantly greater than those in patients with wildtype *MEFV*. These results suggest that carriers of the E148Q variant may exhibit greater inflammatory responses and more severe clinical symptoms than noncarriers.

The *MEFV* gene encodes pyrin, which plays a crucial role in the inflammatory pathway of the innate immune system by reducing inflammation [40]. However, studies have shown that *MEFV* variants can lead to functional abnormalities in pyrin, resulting in increased inflammation, making *MEFV* variant carriers prone toward a proinflammatory state [21]. Development of severe vasculitis is particularly enhanced in the presence of *MEFV* variants [41]. E148Q is in exon 2 of the *MEFV* gene, the functionality of which is required to determine the cytoplasmic and nuclear localization of pyrin protein in cells [38]. Pyrin-activated inflammasome processes may be a susceptibility factor for chronic inflammatory diseases and vasculitis, including HSP [42]. NLRP3-dependent IL-33 expression is increased after inflammasome activation [43,44]. Therefore, we speculate that E148Q may lead to abnormal function of the pyrin protein and thus increase IL-33. It has been shown that serum IL-33 levels correlate with high-sensitivity CRP levels and disease activity [45]. Therefore, this correlation may explain why levels of IL-33 and CRP are greater in HSP patients with the E148Q variant than in patients with wildtype *MEFV*.

IL-33 belongs to the IL-1 cytokine family, the members of which regulate the innate and adaptive immune systems and promote inflammatory responses [15,46]. By activating local immune cells, IL-33 acts as a warning for the presence of injury-induced stress, pathogens, or cell death [47,48]. High expression of IL-33 is usually associated with the activity and severity of diseases such as asthma, atopic allergy, and cancer [49,50]. One study showed that the serum IL-33 concentration was significantly higher in adult HSP patients than in controls and that the IL-33 concentration correlated with the severity of HSP [51]. The level of IL-33 in children with HSP is significantly greater than that in healthy children, and the IL-33 expression level is related to the diagnosis and prognosis of HSP, suggesting that IL-33 is involved in the pathogenesis and immune mechanism of the disease [7]. This suggestion is basically consistent with the results of this study. IL-33 decreases expression of cadherin between vascular endothelial cells, thereby increasing the permeability of vascular endothelial cells [52]. This decreased permeability may be one of the causes of vascular endothelial damage in HSP. Vascular endothelial cell inflammation and injury may be important mechanisms of HSP pathogenesis [27]. Overall, these direct effects of IL-33 on endothelial cells may be related to the pathogenesis of HSP [51].

The IL-33 signaling pathway induces expression of lineage-specific transcription factors such as T-bet, GATA-3, and FOXP3, thereby promoting ST2 expression [53]. ST2 is a key amplifying factor of IL-33-mediated allergic inflammation and is expressed on basophil granulocytes, mast cells and their progenitor cells. ST2 activation leads to secretion of a variety of inflammatory cytokines [54]. Activation of the IL-33/ST2 signaling pathway can promote production of IL-4, IL-5, IL-13 and chemokines by basophils [55], and IL-33-induced eosinophilia plays an important role in airway or cutaneous allergic diseases [56]. Indeed, the IL-33-ST2-ILC2 (type 2 innate lymphocyte) axis is one of the central pathways involved in the pathogenesis of allergic inflammation [57]. Previous studies have shown that the IL-33/ST2 axis plays a crucial role in a variety of allergic and autoimmune diseases, such as asthma, rheumatoid

Table 6
ROC curve analysis for predicting HSP.

Parameter	AUC	Sensitivity (%)	Specificity (%)	95 % CI	Youden	*P*
E148Q	0.595	51.0 %	68.0 %	0.500–0.690	0.19	0.058
sST2/IL-33	0.783	80.0 %	72.0 %	0.705–0.861	0.52	**<0.001**

arthritis, inflammatory bowel disease, and atopic dermatitis [58–62]. The IL-33/ST2 axis plays a major adverse role in the occurrence and progression of autoimmune diseases, and IL-33/ST2 levels correlate with disease severity and treatment response [63].

In this study, IL-33 and ST2 were significantly increased in children with HSP, and the ratio of sST2/IL-33 was unbalanced in these children compared with the controls. In addition, logistic regression analysis revealed that an unbalanced sST2/IL-33 ratio and the presence of E148Q were independent risk factors for HSP, which further suggests that these factors may be closely related to the occurrence and development of HSP. Therefore, IL-33 and sST2 may play vital roles in immune disorders and development of HSP. The possible mechanism underlying these effects is that IL-33 binds to its receptor ST2 and helper proteins to transmit activation signals, activates the NF-kB and MAPK pathways, and thus induces release of Th2 cytokines and chemokines [51], leading to the occurrence of HSP.

In summary, the results of this study suggest that the MEFV variant E148Q is more frequent in Chinese children with HSP than in the general population. Compared with noncarriers, E148Q carriers showed greater inflammatory responses and more severe clinical manifestations. The serum levels of IL-33 and sST2 in children with HSP were significantly increased, and their sST2/IL-33 ratios were unbalanced. The area under the ROC curve was 0.783, with a sensitivity of 80 % and a specificity of 72 %. The sST2/IL-33 ratio may be a useful indicator for predicting HSP patients. An imbalance in the sST2/IL-33 ratio and the E148Q variant may be associated with the disease activity of HSP. Therefore, we speculate that the MEFV variant E148Q might lead to increased expression of IL-33 through pyrin dysfunction, thus inducing release of Th2 cytokines and chemokines and ultimately leading to the occurrence of HSP. E148Q and the sST2/IL-33 ratio may play vital roles in the pathogenesis of HSP. These findings provide new ideas and targets for treatment of HSP. Some limitations existed in our study. We measured serum levels of IL-33 and sST2 using ELISA. This detection method may lead to the low sensitivity of these two parameters, and some low-value specimens may become undetectable. Our study lacks a meta-analysis on the same variants from the same population due to the small sample size of reported relevant literature and studies. In addition, the relationship between MEFV variants except E148Q and IL-33/sST2 in HSP needs to be further investigated by expanding the sample size.

Compliance with ethical standards

This study was reviewed and approved by the Ethics Committee of the Hunan Children's Hospital, with the approval number HCHLL-2020-21. All legal guardians provided informed consent to participate in the study.

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Data availability statement

Data availability in https://data.mendeley.com/v1/datasets/publish-confirmation/8r2khtr44m/1.

CRediT authorship contribution statement

Yang Ruan: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Longlong Xie:** Writing – review & editing, Project administration, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e29469.

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