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Association of *IL-1RAcP* rs16865597 gene polymorphism with susceptibility to essential hypertension: a case-control study in the Chinese Han population

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Abstract

Background The IL-33/ST2 pathway plays a crucial role in the development of essential hypertension (EH). This study aimed to investigate the relationship between EH and genetic variations in this pathway in the Chinese Han population.

Methods A total of 1,151 EH patients and 1,135 healthy controls were included in the study. Sixteen single nucleotide polymorphisms (SNPs) in the interleukin-33 (*IL-33*) and interleukin-1receptor associated protein (*IL-1RAcP*) genes were genotyped using the Sequenom MassArray and TaqMan assays. Genotype and allele frequencies were compared between the EH patients and controls using logistic regression analysis.

Results The rs16865597 SNP in the *IL-1RAcP* gene was found to be associated with the risk of EH. Specifically, the presence of the *C* allele of rs16865597 was negatively correlated with EH susceptibility in both the additive model ($P=0.014$, OR = 0.75, 95% CI = 0.59–0.94) and the recessive model ($P=0.011$, OR = 0.72, 95% CI = 0.56–0.93). Additionally, rs16865597 was linked to a reduced risk of EH in specific subgroups, including males (OR add = 0.73, 95% CI = 0.56–0.94, $P=0.015$), nonsmokers (OR add = 0.72, 95% CI = 0.54–0.96, $P=0.023$), nondrinkers (OR add = 0.70, 95% CI = 0.53–0.93, $P=0.013$), and individuals with low BMI (OR add = 0.69, 95% CI = 0.51–0.92, $P=0.013$). Moreover, the *C* genotype of rs16865597 was strongly associated with higher interleukin-10 levels in vivo.

Conclusion The rs16865597 SNP is significantly associated with a reduced risk of EH in the Chinese Han population, potentially due to its role in immune regulation.

Keywords Essential hypertension, Interleukin-33, interleukin-1receptor associated protein, Genetic polymorphisms, rs16865597

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Introduction

Hypertension is a crucial risk factor for cardiovascular disease morbidity and mortality. In China, hypertension affects about 23.2% of the adult population, with more than 244.5 million people suffering from this disease [1]. Essential hypertension (EH) is defined as high blood pressure in which secondary causes such as renovascular disease, renal failure, pheochromocytoma, aldosteronism, or other causes of secondary hypertension or mendelian forms (monogenic) are not present. EH accounts for 95% of all cases of hypertension. The interactions between genetic and environmental factors contribute greatly to the pathophysiology of EH. Besides traditional risk factors including high-salt diet, smoking, drinking, obesity, and metal stresses, approximately 30–50% of the variation in EH is due to genetics [2]. Thus, the mining of susceptibility genes is an important tool for exploring the etiology of EH.

Increasing evidence has suggested the pathophysiological role of systemic and local inflammation in the development of EH, which might induce the change of cardiac function, vascular resistance, and renal damage [3, 4]. interleukin-33(IL-33) belongs to the IL-1 family, which drives T helper 2(Th2) responses in vivo. This cytokine interacts with its receptor interleukin 1 receptor-like 1(ST2), which consists of four isoforms (sST2, ST2L, ST2V, and ST2LV), to trigger the secretion of proinflammatory factors, such as leukotrienes, IL-6, and TNF-α. The binding affinity of IL-33 and ST2 is determined by the presence of interleukin-1receptor associated protein (IL-1RAcP) [5–7]. Many studies have reported the role of the IL-33/ST2 pathway in the pathologies of several cardiovascular diseases, including atherosclerosis, myocardial fibrosis, and EH [8–10]. In 2013, Ho and coworkers indicated that high sST2 concentrations were associated with incident hypertension and the plasma level of sST2 predicted changes in blood pressure physiology in a 3-year follow-up study [11]. Among Framingham Heart Study participants, elevated sST2 was associated with EH and diabetes mellitus (DM) [12]. Moreover, our previous study also suggested that the genetic variant rs3821204 in the *ST2* gene may influence the development of EH by controlling sST2 expression, and miR-202-3p was involved in the development of EH partially by suppressing sST2 expression in a feedback manner [13, 14]. Yin and coworkers detected an obvious elevation of sST2 protein levels in serum and peripheral blood mononuclear cells (PBMC) in EH patients, meanwhile the levels of IL-33 in serum and PBMCs and ST2L in PBMCs did not change [15]. Given the essential role of IL-33/ST2 pathway in EH development, we hypothesized that genetic variations within *IL-33* and *IL1RAcP* might also influence the susceptibility to EH.

In the present study, we conducted a case-control study to investigate the associations of *IL-33* and *IL1RAcP* genetic variants and EH risk in the Chinese Han population. Furthermore, a correlation analysis was performed to determine the association between genetic polymorphisms and plasma levels of Th2 cytokines. The results might provide new insights into hypertension etiology.

Materials and methods

Study population

The sample population included 1151 EH patients and 1135 sex-matched controls. Patients were recruited from three hospitals (Union Hospital, Tongji Hospital, and Wugang Hospital) in Wuhan, China [16, 17]. Healthy Controls were from the same community as the patients. Hypertension was diagnosed as average systolic blood pressure(SBP)≥140 mmHg, and/or average diastolic pressure (DBP) ≥ 90 mmHg, and/or self-reported current treatment for hypertension with antihypertensive drugs. Control subjects were from the same community as the patients. Control subjects had SBP < 140 mmHg, DBP < 90 mmHg, and had never been treated for hypertension [18]. The 35 EH patients for IL-10 detection were consecutively recruited from the Second Affiliated Hospital of Nanchang University in China. All subjects completed an Inter-Heart questionnaire and were interviewed about their demographic data, medical history, history of disease, family history of cardiovascular disease, and lifestyle habits (including smoking and alcohol consumption) by trained interviewers.

Ethics statement

All participants signed the approved consent forms prior to the initiation of this study. This study was approved by the Ethics Committee of Tongji Medical College (project identification code: S073; 21 February, 2011) and the ethics committee of the Second Affiliated Hospital of Nanchang University (5 March, 2017).

Selection of SNPs

TagSNPs were selected based on the HapMap phase I & II database (available online:http://www.hapmap.org, accessed on 15 October 2012,CHB and JPT as the reference set). According to the criteria of $r^2 \geq 0.8$ and minor allele frequency (MAF) ≥ 0.05, we extended 2000 bp into the 5′ and 3′ ends of *IL-33* and *IL-1RAcP*. Eventually, 16 tagSNPs within *IL-33* and *IL-1RAcP* genes were selected (Table 1).

DNA extraction and genotyping

Genomic DNA was extracted from fasting venous blood with a Puregene kit (Gentra Systems Inc., Minneapolis, MN, USA). The genotype distributions of 15 SNPs were assayed with the Sequenom MassArray system

Table 1 SNP locations and allele frequencies

SNP	Gene	Location	Genotype	MAF*	HWE *P**
rs1929992	*IL33*	Intron	A/G	0.489	0.655
rs10975520	*IL33*	Intron	G/C	0.488	1
rs11792633	*IL33*	Intron	T/C	0.433	-
rs1157505	*IL33*	Intron	G/C	0.225	-
rs1624159	*IL33*	Between genes	A/G	0.06	0.02
rs1015704	*IL1RAcP*	intron	G/A	0.222	0.294
rs9817203	*IL1RAcP*	intron	T/C	0.395	0.439
rs1559018	*IL1RAcP*	intron	G/A	0.488	0.479
rs3773986	*IL1RAcP*	intron	T/C	0.067	1
rs6765375	*IL1RAcP*	intron	C/A	0.233	1
rs4624606	*IL1RAcP*	intron	A/T	0.213	0.294
rs16865597	*IL1RAcP*	intron	C/T	0.159	0.273
rs4687150	*IL1RAcP*	intron	T/C	0.341	0.403
rs3773958	*IL1RAcP*	intron	G/T	0.419	0.752
rs3773981	*IL1RAcP*	intron	C/A	0.182	0.584
rs6444435	*IL1RAcP*	intron	A/G	0.251	0.233

*: Data from the NCBI

-: Data were not found in http://www.ncbi.nlm.nih.gov/snp/,accessed*on 15 October 2012*

Abbreviations: SNP, single nucleotide polymorphisms; MAF, minor allele frequency; HWE, Hardy–Weinberg equilibrium

(Sequenom Inc., San Diego, CA, USA), the primers and probes used in this method are listed in S1 Table. The remaining SNP of rs1157505 and rs6444435were genotyped by TaqMan SNP allelic discrimination assay (Applied Biosystems, Foster City, CA, USA). The catalogue number used for genotyping rs1157505 was AHZAA5R and rs6444435 was C_2782293_10. PCR cycling conditions for the TaqMan assay included:95 °C for 10 min, followed by 45 cycles of 92 °C for 15 s and 60 °C for 1 min. TaqMan data collection and analysis were performed with SDS 2.2.1. Finally, 15 SNPs were successfully genotyped with a call rate above 95%, except for rs6444435, which had a call rate of 93.7%.

Biological variable determination

Fasting blood glucose (FBG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TG) were assayed using standard laboratory procedures in the clinical laboratory at Union Hospital [19].

IL-10 levels detection

IL-10 concentrations were measured using sandwich enzyme-linked immune-sorbent assay (Shu zhou, JiangShu, China, 4 A Biotecn). Test procedures were performed according to the manufacturer's instructions.

Statistical analysis

Continuous data were compared by Student's t-test or Mann–Whitney rank-sum test. Chi-square test was used to compare categorical variables and the Hardy–Weinberg equilibrium (HWE). Unconditional logistic regression analysis was used to estimate the associations between SNPs and EH risk by odds ratios (ORs) and 95% confidence intervals (CIs). The interactions of covariates with SNP genotypes were tested using the Wald test in unconditional logistic regression models. The significance of multiplicative interactions between SNPs and covariates was determined by the likelihood ratio test using the logistic regression model. Mann–Whitney rank-sum tests was used to examine differences in IL-10 levels in patients with different rs16865597 genotypes. Power calculations were performed using the QUANTO software program (version 1.2.3) [20]. All analyses were performed with the SPSS 12.0 (SPSS Inc., Chicago, IL, USA). $P<0.05$ was considered significant.

Results

Characteristics of the study participants

Table 2 presents the characteristics of the 2,286 participants, including 1,151 EH patients and 1,135 controls. Both groups had a similar gender distribution, but EH patients were older and had higher body mass index (BMI), SBP, DBP, FBG, and TG levels compared to controls ($P<0.01$). In addition, EH patients were more likely to have a history of coronary heart disease (CHD) and DM, and a family history of EH ($P<0.01$). Interestingly, the healthy subjects showed higher levels of smoking and drinking than the EH patients ($P<0.01$ for smoking and $P=0.012$ for drinking), which may have been due to quitting smoking and alcohol abstinence after diagnosis. We also found that TC levels were significantly lower in EH patients than in controls (4.44 ± 1.04 mmol/L versus 4.59 ± 1.00mmol/L, $P<0.01$), which might be attributed to cholesterol-lowering therapies in the patients.

Associations between *IL-33* variants and EH risk

Most of the SNPs conformed to HWE ($p>0.05$), except for rs1157505 and rs1624159 within the *IL-33* gene, and rs1015704 and rs4687150 within the *IL-1RAcP* gene, which significantly deviated from HWE in both controls and cases ($p<0.05$). Thus, 12 SNPs were selected for further analysis (Table 3).

Then, we compared the allele and genotype frequencies of 12 SNPs between cases and controls. The association between these SNPs and the risk of EH was analyzed using additive/recessive models. Table 4 indicates that the genotype distribution of the three SNPs (rs1929992, rs10975520, and rs11792633) within the *IL-33* gene did not show significant differences between cases and controls. The *IL-33* SNPs rs1929992 (OR = 1.03, 95% CI = 0.90–1.19, $P=0.637$), rs10975520 (OR = 1.05, 95% CI = 0.92–1.21, $P=0.480$), and rs11792633 (OR = 1.03, 95% CI = 0.90–1.19, $P=0.637$) were not associated with the risk of EH in the additive model after adjustment

Table 2 General characteristics of the study population

Variables	Cases($n=1151$)	Controls($n=1135$)	*P* value
Sex, m/f(%)	899/252(78.1/21.9)	888/247(78.2/21.8)	0.939[†]
Age, years	62.3 ± 9.5	58.2 ± 11.7	< 0.01[‡]
Blood pressure, mmHg			
Systolic	143.8 ± 24.2	125.5 ± 27.0	< 0.01 [‡]
Diastolic	86.3 ± 14.1	78.4 ± 11.3	< 0.01[‡]
Body mass index, kg/m2	24.7 ± 3.2	23.4 ± 3.2	< 0.01 [‡]
Fasting glucose, mmol/L	6.2 ± 3.0	5.6 ± 2.2	< 0.01 [‡]
Total cholesterol, mmol/L	4.44 ± 1.04	4.59 ± 1.00	< 0.01 [‡]
Triglyceride, mmol/L	1.72 ± 1.41	1.57 ± 1.26	< 0.01[‡]
Smoking, no/yes(%)	796/353(69.3/30.7)	660/475(58.1/41.9)	< 0.01[†]
Drinking, no/yes(%)	830/314(72.6/27.4)	766/365(67.7/32.3)	0.012 [†]
Past history			
CHD, no/yes	361/790(31.4/68.6)	784/351(69.1/30.9)	< 0.01[†]
Diabetics, no/yes	861/287(75.0/25.0)	1041/92(91.9/8.1)	< 0.01[†]
Family history of Hypertension, no/yes(%)	689/443(60.9/39.1)	862/266(76.4/23.6)	< 0.01 [†]

Variables are presented as mean ± SD or percentages. [†]*P*-values were calculated using chi-square tests. [‡]*P*-values were calculated using independent-samples *t*-tests

Abbreviations: coronary artery disease

Table 3 The frequencies of *IL33* and *IL1RAcP* SNPs in the population under observation

SNP	Location	Genotype	HWE *P*	MAF
rs1929992	Intron	A/G	0.302	0.433
rs10975520	Intron	G/C	0.416	0.459
rs11792633	Intron	T/C	0.385	0.435
rs1624159	Between genes	A/G	0.034	0.046
rs1157505	Intron	G/C	< 0.001	0.246
rs1015704	intron	G/A	0.003	0.204
rs9817203	intron	T/C	0.97	0.325
rs1559018	intron	G/A	0.958	0.493
rs3773986	intron	T/C	0.658	0.126
rs6765375	intron	C/A	0.294	0.197
rs4624606	intron	A/T	0.374	0.187
rs16865597	intron	C/T	0.637	0.111
rs4687150	intron	T/C	0.025	0.297
rs3773958	intron	G/T	0.661	0.424
rs3773981	intron	C/A	0.064	0.198
rs6444435	intron	A/G	0.07	0.218

Abbreviations: SNP, single nucleotide polymorphisms; MAF, minor allele frequency; HWE, Hardy–Weinberg equilibrium

for conventional EH risk factors, such as age, sex, smoking, drinking, BMI, TG, FBG, and a family history of EH. We did not find any significant association between the three SNPs—rs1929992 (OR = 1.08, 95% CI = 0.87–1.33, $P = 0.487$), rs10975520 (OR = 1.11, 95% CI = 0.90–1.38, $P = 0.324$), and rs11792633 (OR = 1.07, 95% CI = 0.87–1.32, $P = 0.526$)—and the risk of EH in the recessive model.

Associations between *IL-1RAcP* variants and EH risk

We also investigated differences in the genotype distribution of 9 polymorphisms (rs9817203, rs1559018, rs3773986, rs6765375, rs4624606, rs16865597, rs3773958, rs3773981, and rs6444435) between cases and controls and analyzed the genotypes using dominant/recessive models. Table 4 shows that among the 9 SNPs evaluated, only rs16865597 exhibited a statistically significant association with EH risk in both the additive model (OR = 0.75, 95% CI = 0.59–0.94, $P = 0.014$) and the recessive model (OR = 0.72, 95% CI = 0.56–0.93, $P = 0.011$). Table 5 further details the genotype and allele frequency distribution for rs16865597 between the case and control groups. *CT* genotype showed a significant association with reduced EH risk (OR = 0.72, 95% CI = 0.56–0.93, $P = 0.012$) after adjusting for age, sex, smoking, drinking, BMI, TG, FBG, and family history of EH. For the *C* allele, a significant inverse association with EH risk was observed in the univariate analysis (OR = 0.80, 95% CI: 0.66–0.97, $P = 0.024$). In summary, the presence of the *C* allele of rs16865597 was negatively correlated with EH susceptibility. However, *p*-values for rs16865597 failed to reach significance after Bonferroni correction. ($P < 0.05/9 = 0.0056$).

Association analyses for stratified traditional risk factors

Stratification analyses were utilized to clarify the interactions between traditional risk factors (sex, smoking, drinking, BMI) and genetic polymorphism rs16865597 for EH risk. As shown in Table 6, rs16865597 was associated with decreased risk in males (OR_{add} = 0.73, 95% CI = 0.56–0.94, $P = 0.015$), nonsmokers (OR_{add} = 0.72, 95% CI = 0.54–0.96, $P = 0.023$), nondrinkers (OR_{add} = 0.70, 95% CI = 0.53–0.93, $P = 0.013$), and low-BMI subjects (OR_{add} = 0.69, 95% CI = 0.51–0.92, $P = 0.013$). We did not detect any interactions between rs16865597 and sex, smoking, drinking, and BMI (all $p > 0.05$).

Table 4 Genotype frequencies of 12 SNPs and their association with EH risk in the Chinese population

SNPs	Case[†]	Control[†]	Additive Model[‡]		Recessive model[§]	
			OR (95% CI) [¶]	*P*[¶]	OR (95% CI) [¶]	*P*[¶]
rs1929992	360/539/216	362/523/211	1.03(0.90–1.19)	0.637	1.08(0.87–1.33)	0.487
rs10975520	327/555/244	335/534/236	1.05(0.92–1.21)	0.480	1.11(0.90–1.38)	0.324
rs11792633	362/545/221	361/533/212	1.03(0.90–1.19)	0.637	1.07(0.87–1.32)	0.526
rs9817203	525/487/113	493/493/122	0.93(0.80–1.08)	0.327	0.90(0.74–1.09)	0.277
rs1559018	293/565/268	281/552/273	0.94(0.82–1.08)	0.410	0.95(0.76–1.18)	0.635
rs3773986	868/238/18	833/257/15	1.00(0.81–1.24)	0.972	0.97(0.77–1.22)	0.784
rs6765375	737/346/43	695/377/36	0.92(0.77–1.09)	0.326	0.88(0.72–1.09)	0.242
rs4624606	743/338/38	720/349/33	0.97(0.81–1.16)	0.748	0.97(0.79–1.19)	0.761
rs16865597	**890/196/12**	**838/230/17**	**0.75(0.59–0.94)**	**0.014**	**0.72(0.56–0.93)**	**0.011**
rs3773958	379/546/201	367/534/205	0.98(0.85–1.12)	0.744	0.95(0.77–1.16)	0.597
rs3773981	703/328/64	716/337/35	1.15(0.97–1.37)	0.114	1.08(0.88–1.33)	0.477
rs6444435	655/361/59	671/341/57	1.11(0.94–1.31)	0.277	1.16(0.94–1.43)	0.158

[†]Wild-type homozygote/heterozygote/variant homozygote

[‡]Additive model (wild-type homozygote vs. heterozygote vs. variant homozygote)

[§]Recessive model (wild-type homozygote vs. heterozygote + variant homozygote)

[¶]*P*-values were calculated by unconditional logistic regression, after adjusting for age, sex, smoking, drinking, BMI, TG, FBG, and family history of EH

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; TG, triglycerides; FBG, fasting blood glucose; EH, essential hypertension

Table 5 Genotype and allele frequency distribution for rs16865597 between the case and control groups

SNP	Case, *n*(%)	Control, *n*(%)	Crude OR (95% CI)	Crude *P*	Adjusted OR[*] (95% CI)	Adjusted *P*[*]
rs16865597						
Genotype						
T	838(77.2)	890(81.1)	1.00		1.00	
CT	230(21.2)	196(17.9)	**0.80(0.65–0.99)**	**0.042**	**0.72(0.56–0.93)**	**0.012**
C	17(1.6)	12(1.1)	0.66(0.32–1.40)	0.282	0.77(0.28–2.11)	0.607
Allele						
T	1906(87.8)	1976(90.0)	1.00			
C	264(12.2)	220(10.0)	**0.80(0.66–0.97)**	**0.024**	-	-

[*]Adjusted for age, sex, smoking, drinking, BMI, TG, FBG, and family history of EH

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; TG, triglycerides; FBG, fasting blood glucose; EH, essential hypertension

Table 6 Stratification analysis for the association between rs16865597 and the risk of EH

Variables	Cases[†]	Controls[†]	OR_{add} (95%CI) [‡]	P_{add} [‡]	$P_{interaction}$ [‡]
Sex					0.666
Male	695/158/9	654/185/12	0.73(0.56–0.94)	**0.015**	
Female	195/38/3	184/45/5	0.85(0.50–1.44)	0.537	
Somking					0.631
Yes	274/64/2	360/92/7	0.81(0.55–1.20)	0.294	
No	614/132/10	478/138/10	0.72(0.54–0.96)	**0.023**	
Drinking					0.381
Yes	245/58/4	278/67/6	0.86(0.57–1.29)	0.467	
No	639/137/8	556/163/11	0.70(0.53–0.93)	**0.013**	
BMI, kg/m^2					0.588
<25	465/107/6	534/152/13	0.69(0.51–0.92)	**0.013**	
≥25	391/75/5	236/61/1	0.79(0.54–1.15)	0.216	

[†]Wild-type homozygote/heterozygote/variant homozygote

[‡]*P*-values were calculated by unconditional logistic regression, after adjusting for age, sex, smoking, drinking, BMI, TG, FBG, and family history of EH

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; TG, triglycerides; FBG, fasting blood glucose; EH, essential hypertension

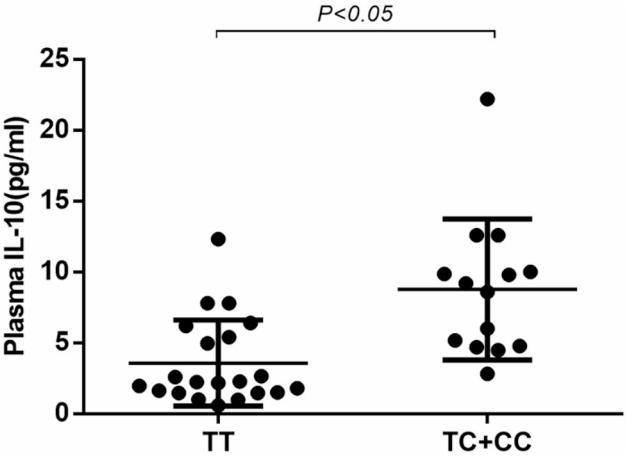

Fig. 1 Correlation of plasma interleukin-10 levels and the *IL-1RAcP* SNP rs16865597. PBMCs were isolated from 35 essential hypertension subjects, and the genotype was determined by TaqMan assay. The plasma levels of IL-10 in 35 EH patients were determined by an enzyme linked immunosorbent assay. The figure showed the distribution of IL-10 plasma levels clustered according to different genotypes. IL-10 plasma levels elevated significantly in subjects carrying *CC* alleles ($n=1$) + *TC* alleles ($n=13$) compared with *TT* alleles($n=21$), as analyzed by the Mann-Whitney rank-sum test

In vivo effect of the *IL-1RAcP* polymorphism rs16865597 on plasma IL-10 levels

To verify that the genetic polymorphisms in IL-33 pathways affect disease occurrence by modulating the function of this pathway, we examined the correlation between the genotype of rs16865597 and IL-10 plasma levels. ELISA was conducted to detect the plasma levels of IL-10 in 35 patients (median [25–75th percentile], 4.78 ng/ml [1.96–8.60 ng/ml]), while the genotype of rs16865597 was determined by a Taqman genotyping assay. We observed that plasma IL-10 concentrations were significantly lower in patients with $TC+CC$ genotypes compared to those with TT genotypes ($P<0.05$) (Fig. 1). These results suggest that rs16865597 $C>T$ is associated with increased plasma IL-10 levels in vivo.

Discussion

This study enrolled 1,151 patients and 1,135 healthy controls to examine the role of *IL-33* and *IL-1RAcP* genetic polymorphisms in the development of EH. The results suggest that individuals carrying the C allele of the rs16865597 polymorphism in the *IL-1RAcP* gene may have a reduced risk of developing EH. This association remained significant in both additive and recessive models after adjusting for age, sex, smoking, alcohol consumption, BMI, TG, FBG, and family history of EH. Furthermore, we observed that elevated IL-10 levels were correlated with the C genotype of rs16865597 in vivo.

IL-33 is a recently identified member of the interleukin-1 (IL-1) family, known to bind with ST2L and IL-1RAcP, initiating a Th2 immune response. Previous research, such as Ma and colleagues' work, suggested that IL-33 plays a role in hypertension treatment [21]. Atles and colleagues also found that IL-33 levels in patients with primary hypertension were significantly lower compared to a control group [22]. These findings suggest the IL-33–ST2 signaling pathway may play a role in EH pathogenesis. To investigate further, we analyzed the association between *IL-33* polymorphisms and EH. However, our study did not find a significant association between *IL-33* SNPs (rs1929992, rs10975520, rs11792633) and EH risk in either additive or recessive models. Additionally, no significant interactions were observed between these SNPs and traditional EH risk factors. These findings align with Yin's study, which found no significant differences in IL-33 levels between hypertensive patients and controls [15].

The *IL-1RAcP* gene, located on chromosome 3q28, encodes a co-receptor for IL-33. The soluble form of IL-1RAcP interacts with the sST2–IL-33 complex to inhibit IL-33 signaling [23]. Previous studies have shown that IL-1RAcP plays a crucial role in cardiovascular diseases, such as myocardial infarction and EH [24, 25]. For instance, Nikpay and colleagues found that the *IL-1RAcP* polymorphism rs4687150 was associated with increased risk of EH [25]. In our study, we conducted a large case–control analysis and found that rs16865597 was associated with a decreased risk of EH. This inverse association was particularly strong among males, nonsmokers, nondrinkers, and individuals with a low BMI. Additionally, individuals with the *C* genotype of rs16865597 exhibited significantly higher levels of IL-10, an important anti-inflammatory cytokine secreted primarily by Th2-type helper T cells [26, 27]. IL-10 plays a key role in modulating the immune system by promoting the production of Th2 cytokines, which counterbalance the pro-inflammatory effects of Th1 cytokines. This shift towards an anti-inflammatory state helps to reduce the risk of hypertension. As such, the *C* genotype of rs16865597 may lower the risk of EH by enhancing the production of Th2 cytokines and maintaining immune system balance.

This study has several strengths. First, it involved a large sample size and employed a case–control design to explore the relationship between *IL-33* and *IL-1RAcP* gene variants and the risk of EH. This approach contributes to understanding the role of the IL-33/ST2 pathway in EH development. Second, to our knowledge, this is the first study to report an association between the *IL-1RAcP* rs16865597 polymorphism and EH.

However, the study also has limitations. One potential concern is selection bias, which may have impacted the results. Additionally, while the sample population was not perfectly matched, we accounted for this by using unconditional logistic regression analysis, adjusting for factors such as age, sex, smoking, alcohol consumption,

BMI, TG, FBG, and family history of EH. Lastly, all participants were of Han Chinese ethnicity, so further research is needed to determine whether these genetic associations are consistent across other ethnic groups.

Conclusions

In summary, this study provides preliminary evidence that the *IL-1RAcP* rs16865597 polymorphism may play a role in reducing the risk of EH. The underlying mechanisms could involve immune modulation and cytokine regulation. However, further investigation is needed to elucidate the biological pathways and confirm these findings in other populations.

Abbreviations

BMI	Body mass index
CI	Confidence interval
EH	Essential hypertension
FBG	Fast blood glucose
MAF	Minor allele frequency
SNP	Single nucleotide polymorphism
OR	Odds ratio
TG	Triglyceride

Supplementary Information

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Supplementary Material 1

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Author contributions

Designing the experiments, Fangqin Wu and LuLi; methodology, Fangqin Wu; software, Xinlei Yang; formal analysis, Dongchen Liu; data curation, Suli Huang; writing—original draft preparation, Fangqin Wu and LuLi; writing—review and editing, Xin Xia, Dr. Xinghua Jiang. All authors agreed both to be personally accountable for the author's contributions and ensure related to accuracy of this work. All authors have read and agreed to the published version of the manuscript.

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Data availability

The datasets generated and/or analyzed during the current study are available in the OMIX, China National Center for Bioinformation / Beijing Institute of Genomics, Chinese Academy of Sciences repository, (https://ngdc.cncb.ac.cn/omix: Accession No. OMIX009243). They are also available from the corresponding author upon reasonable request.

Declarations

Human ethics and consent to participate

The study was approved by the Ethics Committee of Tongji Medical College (project identification code: S073; 21 February, 2011) and the ethics committee of the Second Affiliated Hospital of Nanchang University (5 March, 2017). All participants provided written informed consent. All procedures performed in this study involving human participants were in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All methods involved in this study were carried out in accordance with relevant guidelines and regulations. All participants provided their written informed consent in this study. Written informed consent was obtained for the publication of any original images or data included in this article.

Consent for publication

Not applicable.

Clinical trial number

Not applicable.

Competing interests

The authors declare no competing interests.

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