Cardiology in the Young

cambridge.org/cty

Original Article

Cite this article: Si F, Wu Y, Wang X, Gao F, Yang D, Liu R, Yi Q. (2018). The relationship between *Interleukin-27* gene polymorphisms and Kawasaki disease in a population of Chinese children. *Cardiology in the Young* **28**: 1123–1128. doi: 10.1017/S1047951118000914

Received: 10 April 2018
Revised: 28 April 2018
Accepted: 4 May 2018

Key words:
Interleukin-27; Kawasaki disease; coronary arterial lesions; polymorphisms

Author for correspondence:
Q. Yi, Department of Cardiovascular Medicine, Children's Hospital of Chongqing Medical University, Chongqing 400014, People's Republic of China; Tel: +86 023 6362 4344; Fax: +86 023 6362 4344;
E-mail: qjyi2003@hotmail.com

CAMBRIDGE UNIVERSITY PRESS

The relationship between *Interleukin-27* gene polymorphisms and Kawasaki disease in a population of Chinese children

Feifei Si[1], Yao Wu[2], Xianmin Wang[1], Fang Gao[1], Dan Yang[3,4], Ruixi Liu[2] and Qijian Yi[2]

[1]Department of Padiatric Cardiology, Chengdu Women's and Children's Central Hospital, Chengdu, People's Republic of China, [2]Department of Cardiovascular Medicine, Children's Hospital of Chongqing Medical University, Chongqing, People's Republic of China, [3]Key Laboratory of Pediatrics in Chongqing, Chongqing, People's Republic of China and [4]Chongqing International Science and Technology Cooperation Center for Child Development and Disorders, Chongqing, People's Republic of China

Abstract

Background: Kawasaki disease is the leading cause of acquired heart disease in children from developed countries. The Interleukin-6/ Interleukin-12 cytokine family has many members, including the paradoxical anti- and pro-inflammatory Interleukin-27. Recent studies have demonstrated that Interleukin-27 plays a role in immune diseases. Given this, we sought to evaluate the association between *Interleukin-27* genetic polymorphisms and Kawasaki disease in Chinese children. *Methods and results:* Interleukin-27 was genotyped in 100 Kawasaki disease children and 98 healthy children (controls), resulting in the direct sequencing of eight Single-nucleotide Polymorphisms: rs17855750, rs40837, rs26528, rs428253, rs4740, rs4905, rs153109, and rs181206). There were no significant differences in Interleukin-27 genotypes between Kawasaki disease and control groups. Of the eight Single-nucleotide Polymorphisms, there was a significant increase in the risk of Kawasaki disease with coronary arterial lesions in children with the rs17855750 (T > G), rs40837 (A > G), rs4740 (G > A), rs4905 (A > G), rs153109 (T > C), and rs26528 (A > G) Single-nucleotide Polymorphisms. This was particularly true for rs17855750 (T > G), which had a greater frequency in Kawasaki disease children with coronary arterial aneurysm. *Conclusion:* These findings may be used as risk factors when assessing a child's likelihood of developing Kawasaki disease, as well as for the development of future therapeutic treatments for Kawasaki disease.

Kawasaki disease is a disorder of acute, systemic vasculitis that predominantly affects infants and young children. The most serious complication of Kawasaki disease is the occurrence of coronary artery lesions, which can include myocardial infarction, formation of coronary artery fistulae,[1] coronary artery dilatation, and/or coronary artery aneurysm.[2] Although the clinical picture is clear, the pathogenesis of Kawasaki disease remains unknown.

Interleukin-27 belongs to the Interleukin-6/ Interleukin-12 cytokine family and is a heterodimeric cytokine that is composed of the Epstein–Barr virus-induced gene 3 and Interleukin-*27p28*.[3] It is located on chromosome 16 (16p11).[4] Interleukin-27 has been previously and paradoxically reported to exert both anti- and pro-inflammatory effects, in addition to a role during the acute phase to infections.[5–7] To date, we have reported that the serum Interleukin-27 levels are increased in Kawasaki disease patients, suggesting that Interleukin-27 may be involved in Kawasaki disease.[8]

Single-nucleotide Polymorphisms have been proposed as next-generation biomarkers for use in the identification of gene loci associated with various disease and their complications. Recently, *Interleukin-27* polymorphisms have been associated with several types of diseases. For example, recent work has found an association between the Interleukin-*27p28* (−964 a/G) Single-nucleotide Polymorphisms rs153109 in a Korean population and susceptibility to both asthma and inflammatory bowel disease.[9] However, there have been no reports regarding the association between *Interleukin-27* Single-nucleotide Polymorphisms and Kawasaki disease. Given this, we sought to investigate the role of eight *Interleukin-27* Single-nucleotide Polymorphisms in a cohort of Chinese children with Kawasaki disease.

Materials and methods

Patient recruitment

We enrolled 100 patients with Kawasaki disease from the Children's Hospital of Chongqing Medicine University in Chongqing, China. All enrolled patients met the criteria proposed by the Japanese Kawasaki Disease Research Committee.[10]

Echocardiography was obtained either within 2 weeks of the onset of the study or immediately before intravenous immunoglobulin administration. Coronary arterial lesions were defined by an internal arterial diameter >3.0 mm (<5 years) or >4.0 mm (≥5 years), or if the internal diameter of a segment was at least 1.5 times that of an adjacent coronary artery. An arterial diameter ≥4 mm is defined as an aneurysm.[11] Patients with Kawasaki disease were divided into two groups according to the presence (45 patients) or absence (55 patients) of coronary arterial lesions. Patients with coronary arterial lesions were then subdivided into two groups depending on the extent of coronary arterial lesions. Coronary arterial lesion severity assessment was visualised using echocardiography or coronary artery angiography along with dilatation and/or evidence of ectasia and aneurysms.

All blood samples were drawn before intravenous Immunogloblin therapy in the Kawasaki disease group. The majority of blood samples were collected in the 1st week of illness. Serum was harvested from all samples and then frozen at −80°C until later assessment.

Sample collection and processing

Venous blood samples were obtained from both patients and healthy patients. For biochemical analyses, blood samples were allowed to clot at room temperature, and then immediately centrifuged to separate the serum. Serum was then kept at −80°C until later assessment. For molecular studies, blood samples were collected in ethylene diamine tetra acetic acid tubes to prevent the coagulation of blood samples.

DNA extraction and genotyping

Genomic DNA was extracted from patients' whole blood samples using a Qiagen DNA Extraction kit (Qiagen, Duesseldorf, Germany) according to the manufacturer's instructions. The extracted DNA was subsequently sent to the Huada Gene Research Institute (Wuhan, China) for direct DNA sequencing. A MassARRAY system (Sequenom) was used to select eight *Interleukin-27* Single-nucleotide Polymorphisms: rs17855750, rs40837, rs26528, rs428253, rs4740, rs4905, rs153109, and rs181206. DNAstar software (DNASTAR Corp., Madison, Wisconsin, United States of America) was used to compare the resulting DNA sequencing diagrams and find related polymorphism sites.

Statistical analyses

Clinical phenotypes, including white blood cell counts, platelet counts, red blood cell counts, haemoglobin levels, platelet count, C-reactive protein, and erythrocyte sedimentation rate, were each analysed as a quantitative trait. We presented the data as mean ± standard deviation for the general values. Statistical significance of the differences between the continuous variables was evaluated by Student's t-test or the Mann–Whitney test. All eight Single-nucleotide Polymorphisms were assessed for Hardy–Weinberg equilibrium using χ^2 statistics. Comparisons between genotype and allelic frequencies were also evaluated using χ^2 statistics. The association between *Interleukin-27* gene polymorphisms and Kawasaki disease risk was estimated by computing odds ratios and 95% confidence intervals from a multivariate logistic regression analysis. All statistical analyses were performed using SPSS 17.0 software (SPSS Inc., Chicago, Illinois, United States of America). In addition, haplotype constructions and Mendelian linkage disequilibria were analysed using both the online computer platform SHEsis and Haploview software (http://analysis.bio-x.cn/myAnalysis.php).[12] Haplotypes with frequencies >3% in both the combined cases and controls were examined. A value of $p < 0.05$ was regarded as statistically significant.

Results

As shown in Table 1, platelet count, white blood cell counts, C-reactive protein, and erythrocyte sedimentation rate were higher in Kawasaki disease patients compared with controls ($p < 0.001$), whereas red blood cell counts and haemoglobin levels were significantly lower in Kawasaki disease patients compared with controls ($p < 0.05$).

We first investigated genetic associations between the eight selected *Interleukin-27* Single-nucleotide Polymorphisms and susceptibility to Kawasaki disease. The genotype frequencies for these eight Single-nucleotide Polymorphisms in the Kawasaki disease control groups are listed in Table 2. There were no significant differences between children with Kawasaki disease and control patients. In the Kawasaki disease patient group, the genotype frequencies of Single-nucleotide Polymorphisms were compared between those with normal coronary arteries and those with coronary arterial lesions (Table 3). Results indicated significantly increased frequencies for the following polymorphisms when comparing Kawasaki disease patients with coronary arterial lesions with those Kawasaki disease patients without coronary arterial lesions: rs17855750 (T > G) (OR = 4.929, 95% CI = 1.311–18.522, p = 0.013), rs40837(A > G) (OR = 8.485, 95% CI = 1.822–39.512, p = 0.002), rs4740 (G > A) (GG to GA + AA: OR = 6.667, 95% CI = 1.806–24.607, p = 0.002; G to A: OR = 2.238, 95% CI = 1.243–4.030, p = 0.007), rs4905 (A > G) (AA to AG + GG: OR = 6.465, 95% CI = 1.749–23.894, p = 0.002; A to G: OR = 2.089, 95% CI = 1.161–3.759, p = 0.013), rs153109 (T > C) (TT to TC + CC: OR = 8.182, 95% CI = 1.754–38.163, p = 0.003), and rs26528 (A > G) (AA to AG + GG : OR = 8.182, 95% CI = 1.754–38.163, p = 0.003). In addition, and as shown in Table 4, there were significantly decreased frequencies for the polymorphism rs17855750 (T > G) (TT to GT + GG: OR = 0.059, 95% CI = 0.006–0.584, p = 0.003) in Kawasaki disease patients with coronary arterial lesions when compared with Kawasaki disease patients with coronary arterial aneurysm.

Table 1. Comparison of the general characteristics of Kawasaki disease (KD) patients and control patients.

	KD (n = 100)	Controls (n = 98)	p
Age (years)	2.57 ± 1.76	3.08 ± 2.02	0.064
Sex (male/female)	59/41	60/38	0.751
Haemoglobin (g/L)	105.23 ± 14.25	127.37 ± 11.45	**<0.001**
Platelet (10^9/L)	433.27 ± 216.60	294.64 ± 82.31	**<0.001**
WBC (10^9/L)	15.13 ± 6.53	7.64 ± 1.85	**<0.001**
RBC (10^{12}/L)	4.08 ± 0.57	4.81 ± 0.41	**<0.001**
CRP (mg/L)	44.93 ± 36.16	3.44 ± 2.02	**<0.001**
ESR	82.11 ± 33.29	6.12 ± 3.22	**<0.001**

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RBC = red blood cell counts; WBC = white blood cell counts
p Value is for comparison between patients and controls. The bold value is: P < 0.001

https://doi.org/10.1017/S1047951118000914 Published online by Cambridge University Press

Table 2. Genotype frequencies of polymorphisms of the interleukin-27 gene in Kawasaki disease (KD) patients and control patients.

Genotypes		KD (n = 100)	C (n = 98)	OR (95%)	p
rs17855750(T > G)	TT	86	75	0.814 (0.369, 1.796)	0.61
	GT + GG	14	15		
	T	186	162	0.677 (0.327, 1.405)	0.293
	G	14	18		
rs40837(A > G)	AA	37	41	1.369 (0.768, 2.439)	0.286
	AG + GG	63	51		
	A	123	119	1.146 (0.757, 1.736)	0.52
	G	77	65		
rs428253(G > C)	GG	3	4	1.490 (0.324, 6.850)	0.606
	GC + CC	95	85		
	G	37	43	1.369 (0.843, 2.247)	0.214
	C	159	135		
rs4740(G > A)	GG	30	25	0.845 (0.452, 1.581)	0.599
	GA + AA	70	69		
	G	105	94	0.905 (0.607, 1.348)	0.622
	A	95	94		
rs4905(A > G)	AA	31	25	0.806 (0.432, 1.505)	0.499
	AG + GG	69	69		
	A	111	94	0.802 (0.538, 1.195)	0.278
	G	89	94		
rs153109(T > C)	TT	38	40	1.165 (0.657, 2.066)	0.6
	TC + CC	62	56		
	T	124	121	1.045 (0.694, 1.573)	0.835
	C	76	71		
rs26528(A > G)	AA	38	40	1.165 (0.657, 2.066)	0.6
	AG + GG	62	56		
	A	127	121	0.980 (0.650, 1.477)	0.922
	G	73	71		
rs181206(T > C)	TT	86	80	0.814 (0.373, 1.774)	0.604
	TC + CC	14	16		
	T	184	175	0.895 (0.439, 1.827)	0.761
	C	16	17		

C = control group; CAA = coronary artery aneurysm; CALs = coronary artery lesions; OR = odds ratio
p Value is for comparison between patients with KD and control patients

Discussion

To our knowledge, this is the first study to examine the association between *Interleukin-27* polymorphisms and the risk of Kawasaki disease. To this end, we investigated the association between *Interleukin-27* gene polymorphisms and the development of coronary arterial lesions in a group of Kawasaki disease patients. In our study population, we found no significant differences in *Interleukin-27* gene polymorphisms between Kawasaki disease and control patients. However, our analysis identified a statistically significant association between *Interleukin-27* polymorphisms rs17855750, rs40837, rs26528, rs4740, rs4905, and rs153109 and an increased risk of coronary arterial lesions in Kawasaki disease children. Interestingly, we found that the *Interleukin-27* polymorphism rs17855750 might also be associated with an increased risk of coronary arterial aneurysm in children with Kawasaki disease. Collectively, our data are the first to suggest that *Interleukin-27* polymorphisms may have an important role in the progression of coronary arterial lesions and coronary arterial aneurysm in children with Kawasaki disease.

Interleukin-27 is a heterodimeric cytokine composed of two domains: one encoded by the *EBI3* gene and the other encoded by the *Interleukin-27p28* gene. The rs17855750, rs181206, rs40837, and rs26528 polymorphisms are located in the promoter region of *Interleukin-2 p28*, whereas the rs428253, rs4740, and rs4905 polymorphisms are located in the promoter region of *Interleukin-27 EBI3*. The EBI3 subunit was first identified in 1996 from a subtractive hybridisation screen of genes expressed in Epstein–Barr virus-transformed B-cell lines.[13] A computational approach was then used to identify novel α-helical cytokines of the *Interleukin*-6 family, leading to the recognition of the *Interleukin*-27p28 subunit as the partner for EBI3.[14] Past work has investigated relationships between *Interleukin-27* polymorphisms and other diseases, finding no associations between such polymorphisms and immune thrombocytopaenia, oesophageal cancer, or type 1 diabetes.[15–17] In our results, allelic and genotypic frequencies in *Interleukin-27* variants did not differ between patients and controls. Although this work showed that *Interleukin-27* polymorphisms did not differ between Kawasaki disease patients and health controls, previous work from our lab has suggested that Interleukin-27 serum levels are elevated in Kawasaki disease patients when compared with healthy controls.[8] When taken together, these combined results suggest that *Interleukin-27* serum levels may not be directly associated with *Interleukin-27* polymorphisms.

We found decreased frequency of the rs17855750 TT/ GT + GG genotype in Kawasaki disease patients without coronary arterial lesions when compared with Kawasaki disease patients with coronary arterial lesions. In addition, the rs17855750 TT/ GT + GG genotype and T/G allele were observed in Kawasaki disease patients with coronary arterial aneurysm, but not in Kawasaki disease patients with coronary arterial lesions. This suggests that *Interleukin-27* rs17855750 may play a role in Kawasaki disease patients in the risk of developing coronary arterial aneurysm. To this end, recent studies have reported that rs153109 contributes to an increased risk of cancer – e.g. bladder cancer.[18] Given this, our findings indicate that it might also be a risk factor in other diseases.

In this study, Interleukin-27 rs428253 (G > C) and rs181206 (T > C) were not significantly different across groups, suggesting that rs428253 (G > C) and rs181206 (T > C) may not have an important role in the development of Kawasaki disease.

The potential effect of different *Interleukin-27* polymorphisms in inflammatory, allergic, and neoplastic conditions is possibly explained by the environment-dependent dual anti- and pro-inflammatory effects that Interleukin-27 can exert.

https://doi.org/10.1017/S1047951118000914 Published online by Cambridge University Press

Table 3. Genotype frequencies of polymorphisms of the interleukin-27 gene in the groups with coronary artery lesions (CALs) and without CALs.

Genotypes		KD with CALs (n = 45)	KD without CALs (n = 55)	OR (95%)	p
rs17855750(T > G)	TT	8	46	4.929 (1.311, 18.522)	0.013
	GT + GG	6	7		
	T	76	99	1.117 (0.360, 3.459)	0.848
	G	6	7		
rs40837(A > G)	AA	2	20	8.485 (1.822, 39.512)	0.002
	AG + GG	28	33		
	A	47	67	1.279 (0.710, 2.306)	0.412
	G	35	39		
rs428253(G > C)	GG	1	2	1.633 (0.143, 18.666)	0.691
	GC + CC	40	49		
	G	15	20	1.089 (0.518, 2.291)	0.821
	C	67	82		
rs4740(G > A)	GG	3	20	6.667 (1.806, 24.607)	0.002
	GA + AA	33	33		
	G	34	65	2.238 (1.243, 4.030)	0.007
	A	48	41		
rs4905(A > G)	AA	3	20	6.465 (1.749, 23.894)	0.002
	AG + GG	32	33		
	A	37	67	2.089 (1.161, 3.759)	0.013
	G	45	39		
rs153109(T > C)	TT	2	20	8.182 (1.754, 38.163)	0.003
	TC + CC	27	33		
	T	48	67	1.217 (0.674, 2.197)	0.515
	C	34	39		
rs26528(A > G)	AA	2	20	8.182 (1.754, 38.163)	0.003
	AG + GG	27	33		
	A	49	68	1.205 (0.666, 2.182)	0.538
	G	33	38		
rs181206(T > C)	TT	10	45	2.813 (0.758, 10.431)	0.113
	TC + CC	5	8		
	T	77	96	0.623 (0.204, 1.900)	0.402
	C	5	10		

C = control group; CAA = coronary artery aneurysm; KD = Kawasaki disease; OR = odds ratio
p Value is for comparison between patients with KD with CALs and without CALs

To date, we have reported an association between serum Interleukin-27 levels and Kawasaki disease. Although there was no association between Interleukin-*27* gene polymorphisms and Kawasaki disease, serum *Interleukin*-27 levels have been shown to be increased in Kawasaki disease patients when compared with controls.

One major limitation of this study was its relatively small sample size. Future analysis of a larger Kawasaki disease patient group is needed to verify the results presented here.

In conclusion, we found that the Interleukin-*27* Single-nucleotide Polymorphisms rs17855750 (T > G), rs40837 (A > G), rs4740 (G > A), rs4905 (A > G), rs153109 (T > C), and rs26528 (A > G)

https://doi.org/10.1017/S1047951118000914 Published online by Cambridge University Press

Table 4. Genotype frequencies of polymorphisms of the interleukin-27 gene in the groups with coronary artery lesions (CALs) and CAA.

Genotypes		KD with CALs (n = 32)	KD with CAA (n = 13)	OR (95%)	p
rs17855750(T > G)	TT	27	8	0.059 (0.006, 0.584)	0.003
	GT + GG	1	5		
	T	55	21	0.076 (0.008, 0.693)	0.005
	G	1	5		
rs40837(A > G)	AA	11	2	0.281 (0.052, 1.518)	0.126
	AG + GG	17	11		
	A	35	12	0.514 (0.201, 1.319)	0.164
	G	21	14		
rs428253(G > C)	GG	0	1	1.083 (0.926, 1.267)	0.137
	GC + CC	28	12		
	G	9	6	1.567 (0.492, 4.987)	0.445
	C	47	20		
rs4740(G > A)	GG	5	3	1.380 (0.275, 6.921)	0.695
	GA + AA	23	10		
	G	23	11	1.052 (0.410, 2.701)	0.916
	A	33	15		
rs4905(A > G)	AA	6	3	1.100 (0.228, 5.312)	0.906
	AG + GG	22	10		
	A	25	12	1.063 (0.418, 2.704)	0.898
	G	31	14		
rs153109(T > C)	TT	12	2	0.242 (0.045, 1.304)	0.084
	TC + CC	16	11		
	T	36	12	0.476 (0.185, 1.225)	0.121
	C	20	14		
rs26528(A > G)	AA	12	2	0.242 (0.045, 1.304)	0.084
	AG + GG	16	11		
	A	37	12	0.440 (0.170, 1.137)	0.087
	G	19	14		
rs181206(T > C)	TT	26	10	0.256 (0.037, 1.770)	0.147
	TC + CC	2	3		
	T	54	23	0.284 (0.044, 1.814)	0.161
	C	2	3		

C = control group; CAA = coronary artery aneurysm; KD = Kawasaki disease; OR = odds ratio
p Value is for comparison between patients with KD with CALs and with CAA

were associated with susceptibility to coronary arterial lesions and coronary arterial aneurysm in children with Kawasaki disease. In particular, rs17855750 (T > G) may be associated with the development of coronary arterial aneurysm in Kawasaki disease patients. After verification by larger-scale studies, some of the selected *Interleukin-27* Single-nucleotide Polymorphisms identified here may be candidates for future therapeutic approaches.

Acknowledgements. The authors thank Zhiming Li for his guidance in the statistical analyses.

https://doi.org/10.1017/S1047951118000914 Published online by Cambridge University Press

Financial Support. This study was funded by National Natural Science Foundation of China under grant no. 81270412 and National Natural Science Foundation of China under grant no. 81500273.

Conflicts of Interest. All authors declare that they have no financial or non-financial conflict of interest.

Ethical Standards. All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children: clinical observations of 50 cases. Jpn J Allerg 1967; 16: 178–222.
2. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Pediatrics 2004; 114: 1708–1733.
3. Boulay JL, O'Shea JJ, Paul WE. Molecular phylogeny within type I cytokines and their cognate receptors. Immunity 2003; 19: 159–163.
4. Pflanz S. IL-27, a heterodimeric cytokine composed of EBI3 and p28 protein, induces proliferation of naive CD4 + T cells. Immunity 2002; 16: 779–790.
5. Ihle JN. The Stat family in cytokine signaling. Curr Opin Cell Biol 2001; 13: 211–217.
6. Takeda A. Cutting edge: role of IL-27/WSX-1 signaling for induction of T-bet through activation of STAT1 during initial Th1 commitment. J Immunol 2003; 170: 4886–4890.
7. Sonobe Y. Production of IL-27 and other IL-12 family cytokines by microglia and their subpopulations. Brain Res 2005; 1040: 202–207.
8. Si F, Wu Y, Gao F, Feng S, Liu R, Yi Q. Relationship between IL-27 and coronary arterial lesions in children with Kawasaki disease. Clin Exp Med 2017; 17: 451–457.
9. Li CS. Interleukin-27 polymorphisms are associated with inflammatory bowel diseases in a Korean population. J Gastroenterol Hepatol 2009; 24: 1692–1696.
10. Research Committee on Kawasaki Disease. Report of Subcommittee on Standardization of Diagnostic Criteria and Reporting of Coronary Artery Lesions in Kawasaki Disease. Ministry of Health and Welfare, Tokyo, 1984.
11. Nakano H, Ueda K, Saito A, Nojima K. Repeated quantitative angiograms in coronary arterial aneurysm in Kawasaki disease. Am J Cardiol 1985; 56: 846–851.
12. Shi YY, He L. SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. Cell Res 2005; 15: 97–98.
13. Devergne O, Hummel M, Koeppen H, et al. A novel interleukin-12 p40-related protein induced by latent Epstein-Barr virus infection in B lymphocytes. J Virol 1996; 70: 1143–1153.
14. Pflanz S, Timans JC, Cheung J, et al. IL-27, a heterodimeric cytokine composed of EBI3 and p28 protein, induces proliferation of naive CD4(+) T cells. Immunity 2002; 16: 779–790.
15. Zhao H, Zhang Y, Xue F, Xu J, Fang Z. Interleukin-27 rs153109 polymorphism and the risk for immune thrombocytopenia. Autoimmunity 2013; 46: 509–512.
16. Tao YP, Wang WL, Li SY, et al. Associations between polymorphisms in IL-12A, IL-12B, IL-12Rbeta1, IL-27 gene and serum levels of IL-12p40, IL-27p28 with esophageal cancer. J Cancer Res Clin Oncol 2012; 138: 1891–1900.
17. Santos AS, Melo ME, Crisostomo LG, Fukui RT, Matioli SR, Silva ME. Lack of association between IL27 gene variants and type 1 diabetes susceptibility. Cytokine 2013; 61: 349–352.
18. Zhou B, Zhang P, Tang T, et al. Polymorphisms and plasma levels of *IL-27*: impact on genetic susceptibility and clinical outcome of bladder cancer. BMC Cancer 2015; 15: 433.

https://doi.org/10.1017/S1047951118000914 Published online by Cambridge University Press