Association of interleukin-18 gene polymorphisms with Takayasu arteritis in a Chinese Han population

Dan Wen[1], Xian-Liang Zhou[2], Xin Du[1], Jian-Zeng Dong[1], Chang-Sheng Ma[1]

[1]Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University; National Clinical Research Center for Cardiovascular Diseases; Beijing Advanced Innovation Center for Big Data-Based Precision Medicine for Cardiovascular Diseases, Beijing 100029, China;
[2]Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing 100037, China.

Abstract

Background: Interleukin-18 (*IL18*) gene polymorphisms are related to many inflammatory and autoimmune diseases. However, a correlation analysis between *IL18* −607C/A and −137G/C gene polymorphisms and Takayasu arteritis (TA) is lacking.

Methods: This study enrolled 200 patients with TA as the case group and 334 region-, age-, and sex-matched healthy subjects as the control group. We genotyped alleles and genotypes at positions −607 and −137 of the *IL18* gene and analyzed the distribution frequencies. Mann-Whitney *U* test, *t* test, Chi-squared test and Hardy-Weinberg equilibrium were performed.

Results: After adjusting for risk factors, the adjusted odds ratios and 95% confidence intervals at position −607C/A were 0.533, 0.391 to 0.880 ($P = 0.010$); 0.266, 0.586 to 1.002 ($P = 0.051$); and 0.122, 0.552 to 1.420 ($P = 0.613$) under the dominant, additive, and recessive models, respectively. For the −137G/C polymorphism, the adjusted odds ratios and 95% confidence intervals were 1.571, 1.068 to 2.311 ($P = 0.022$); 1.467, 1.086 to 1.980 ($P = 0.012$); and 1.815, 0.901 to 3.656 ($P = 0.095$) under the dominant, additive, and recessive models, respectively. Moreover, regardless of the model used, we found no statistical difference in distribution frequency between the active and quiescent states of TA for the −607C/A ($P = 0.355$, 0.631, and 0.705, respectively) and −137G/C polymorphisms ($P = 0.205$, 0.385, and 0.208, respectively).

Conclusions: The *IL18* −607C/A gene polymorphism may decrease the risk of TA, and thus is a protective factor, whereas −137G/C may increase the risk of TA, and thus is a risk factor. However, neither polymorphism was related to activity (active *vs*. quiescent) of TA.

Keywords: Gene polymorphism; Interleukin-18; Takayasu arteritis

Introduction

Takayasu arteritis (TA) is a chronic, non-specific granulomatous vasculitis affecting the aorta and its main branches, the coronary and pulmonary arteries. TA is heterogeneous in terms of ethnic population, regional, age, and sex distribution. Multiple factors may be involved in the pathogenesis of TA, including autoimmunity, inflammation, genetic, and environmental factors. Several studies have shown that the human leukocyte antigen gene is closely related to the occurrence and development of TA.[1-5] These studies indicate the relevance of genetic abnormalities in TA pathogenesis, disease progression, response to treatment, and prognosis.

Interleukin-18 (*IL18*) is an important inflammatory cytokine with multiple biologic functions in regulating inflammatory and immune responses. *IL18* can induce monocytes, macrophages, and natural killer cells to produce interferon-γ, which enhances the activity of natural killer cells, results in immune disorders, and thus is involved in the pathogenesis of many diseases.[6-8] The human *IL18* gene is located on 11q22.2-22.3 and has six exons. Numerous studies have shown that *IL18* gene polymorphisms are related to many inflammatory and autoimmune diseases, such as chronic hepatitis B, asthma, coronary heart disease, rheumatoid arthritis, systemic lupus erythematosus, Crohn disease, multiple sclerosis, and graft-*vs*.-host disease.[9-17]

Studies have demonstrated that single-nucleotide polymorphisms (SNPs) −607C/A and −137G/C in the upstream promoter region of the *IL18* gene significantly affect

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Correspondence to: Dr. Chang-Sheng Ma, Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, National Clinical Research Center for Cardiovascular Diseases, Beijing 100029, China
E-Mail: chshma@vip.sina.com
Dr. Xian-Liang Zhou, Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing 100037, China
E-Mail: zhouxianliang0326@hotmail.com

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transcription of *IL18*, and thus change its expression levels and plasma concentrations.[18,19] Significantly increased plasma *IL18* concentrations are observed in TA, especially in the active stage of the disease.[20]

However, to date, studies of the relationship between *IL18* and TA have only evaluated plasma levels. No studies have described correlations between −607C/A and −137G/C SNPs and TA. It is convenient to enroll patients with TA because of the relatively high incidence of TA in the Chinese Han population. We hypothesized that the −607C/A and −137G/C gene polymorphisms may be associated with TA, and describing these correlations may further provide genetic evidence for the pathogenesis of TA.

Methods

Ethical approval

Informed consent was signed by all the enrolled subjects before the study. The study protocol was approved by the local hospital ethical committee.

Study population

The study subjects were enrolled consecutively and comprised two groups: 200 patients with TA as case group and 334 region-, age-, and sex-matched healthy controls, which were admitted to Fuwai Hospital, between May 2006 and September 2011. All the subjects enrolled in this study had normal hepatic and renal function. Those subjects who had history of autoimmune, collagen, and cardiovascular disease, Marfan syndrome, diabetes mellitus, cancer, and had current inflammatory symptoms were excluded.

Diagnostic criteria for Takayasu arteritis

The commonly used diagnostic criteria of TA in adults, which was proposed by the American College of Rheumatology in 1990, were listed as follows: age of onset ≤40 years; limb claudication; decreased branchial artery pulse; the difference in bilateral limb systolic blood pressure >10 mmHg; subclavian or abdominal aortic murmur; abnormal arteriography indicating narrowing or occlusion of the entire aorta and its main branches.[21]

Criteria for Takayasu arteritis activity

The natural course of TA consists of active and quiescent phases. The criteria in evaluating disease activity are the National Institute Health (NIH) criteria including: (1) systemic features such as fever or musculoskeletal problems (no other cause identified); (2) elevated erythrocyte sedimentation rate; (3) features of vascular ischemia or inflammation, such as claudication, diminished or absent pulse, bruits, vascular pain (carotidynia), asymmetric blood pressure in either upper or lower limbs (or both); and (4) typical angiographic features. Patients who demonstrate new onset or worsening of at least two of the five features listed above are considered as active phase.[22,23]

Genotyping

DNA from patients and controls was obtained from peripheral blood using standard methods. For the determination of *IL18* alleles, Taqman probe produced by American ABI Company was performed. The Taqman probe sequences for –607C/A and –137G/C were 5′-ACGGATACCATCATTAGAATTTTAT[G/T]TAATAATTTTTACACTTTCTGCAAC and TGTAATATCACTATTTTCATGAAAT[C/G]TTTTCTTCCGTAAAAGTTGGGGCTC-3′, respectively. The probes were labeled with fluorescent dyes VIC and FAM. Polymerase chain reaction was performed in a total volume of 7.50 μL consisting of 3.75 μL 2 × Universal polymerase chain reaction Master Mix, 0.19 μL 20×Probe/Primer mix, 1 μL DNA, and 2.50 μL double distilled H_2O. The cycling parameters included denaturation at 95°C for 10 min, followed by 40 cycles of denaturation at 92°C for 15 s, and annealing and extension at 60°C for 1 min.

Statistical analysis

Data were presented as numbers, percentages, or mean ± standard deviation. Continuous variables were compared by means of *t* test and analysis of variance for normally distributed data, non-parametric Mann-Whitney *U* test for abnormally distributed data. Categorical variables were compared by Chi-squared test or Fisher exact test. Correlations were assessed using Spearman rank correlation.

Hardy-Weinberg equilibrium (HWE) was performed to test whether the samples get genetic equilibrium. The frequencies of genotypes and alleles of *IL18* gene at positions of –607 and –137 were compared using Chi-squared test or Fisher exact test. Odds ratio (OR) and 95% confidence interval (CI) were calculated by logistic regression. A *P* value <0.05 was considered statistically significant. Data analysis was performed using a commercially available statistical software package (SPSS II for windows, version 18.0, Chicago, IL, USA).

Table 1: Clinical baseline data in patients with Takayasu arteritis and healthy controls.

Clinical variables	Case group (*n* = 200)	Controls (*n* = 334)	*P*
Age at diagnosis (years)	23.71 ± 6.52	22.76 ± 6.12	0.089
Females	176 (88.0)	299 (89.5)	0.588
Active phase	65 (32.5)	–	–
Smoking	4 (2.0)	5 (1.5)	0.686
Hypertension	49 (24.5)	6 (1.8)	<0.001
TC (mmol/L)	4.41 ± 1.00	4.48 ± 1.11	0.874
TG (mmol/L)	1.32 ± 0.53	1.33 ± 0.59	0.859
HDL-C (mmol/L)	1.06 ± 0.32	1.05 ± 0.33	0.678
LDL-C (mmol/L)	2.34 ± 0.85	2.42 ± 0.90	0.476

Data were presented by mean ± standard deviation or *n* (%). TC: Total cholesterol; TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; –: No data available.

Results

Clinical baseline data in patients with Takayasu arteritis and healthy controls

Other than history of hypertension, which was higher in the case group ($P < 0.001$), no other significant differences were found between the two groups [Table 1].

Allele and genotype frequencies in IL18 −607 C/A between cases and controls

The C and A alleles and the CC, CA, and AA genotypes at position −607 were identified in cases and controls [Table 2]. The genotype frequency conformed to HWE. Risk factors assessed in this study included age, sex, history of hypertension, smoking, total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. Before adjusting for risk factors, the crude ORs and 95% CIs at position −607C/A were 0.532, 0.406–0.851 ($P = 0.005$); 0.320, 0.568–0.928 ($P = 0.011$); and 0.294, 0.481–1.154 ($P = 0.188$) under the dominant, additive, and recessive models, respectively. After adjusting for risk factors, the adjusted ORs and 95% CIs at −607C/A were 0.533, 0.391–0.880 ($P = 0.010$); 0.266, 0.586–1.002 ($P = 0.051$); and 0.122, 0.552–1.420 ($P = 0.613$), under the dominant, additive, and recessive models, respectively [Table 3].

Allele and genotype frequencies in IL18 −137G/C between cases and controls

The alleles at *IL18* position −137 were G and C, and the genotypes were GG, GC, and CC [Table 2]. The genotype frequency conformed to HWE. Before adjusting for risk factors, the crude ORs and 95% CIs for SNP −137G/C were 1.658, 1.164–2.361 ($P = 0.005$); 1.554, 1.185–2.039 ($P = 0.001$); and 2.141, 1.150–3.986 ($P = 0.016$), under the dominant, additive, and recessive models, respectively. After adjusting for risk factors, the adjusted ORs and 95% CIs at −137G/C were 1.571, 1.068–2.311 ($P = 0.022$); 1.467, 1.086–1.980 ($P = 0.012$); and 1.815, 0.901–3.656 ($P = 0.095$), under the dominant, additive, and recessive models, respectively [Table 4].

Genotype frequency in IL18 −607C/A between active and quiescent stages

The genotype frequency in *IL18* −607C/A showed no significant difference between patients with active and quiescent stages of TA ($\chi^2 = 0.855$, $P = 0.652$) [Table 5]. Moreover, the differences were not statistically significant under the dominant ($\chi^2 = 0.855$, $P = 0.355$), additive ($\chi^2 = 0.920$, $P = 0.631$), or recessive models ($\chi^2 = 0.144$, $P = 0.705$) [Table 6].

Genotype frequency in IL18 −137G/C between active and quiescent stages

The genotype frequency in *IL18* −137G/C showed no significant difference between patients with active and quiescent stages of TA ($\chi^2 = 1.907$, $P = 0.385$) [Table 5]. Moreover, the differences were not statistically significant under dominant ($\chi^2 = 1.604$, $P = 0.205$), additive ($\chi^2 = 1.907$, $P = 0.385$), or recessive models ($\chi^2 = 1.583$, $P = 0.208$) [Table 6].

Discussion

In this study, we found that SNPs in the upstream promoter region of the *IL18* gene, −607C/A and −137G/C, were associated with TA in a Chinese Han population.

Table 2: Distribution frequency of interleukin-18 –607C/A and –137G/C alleles and genotypes in 200 patients with Takayasu arteritis and 334 healthy controls, *n* (%).

SNP	Allele	Genotype	Case group ($n = 200$)	Controls ($n = 334$)
–607	C		243 (60.8)	350 (52.4)
		CC	80 (40.0)	94 (28.1)
		CA	83 (41.5)	162 (48.5)
	A		157 (39.2)	318 (47.6)
		AA	37 (18.5)	78 (23.4)
–137	G		272 (68.0)	516 (77.2)
		GG	96 (48.0)	202 (60.5)
		GC	80 (40.0)	112 (33.5)
	C		128 (32.0)	152 (22.8)
		CC	24 (12.0)	20 (6.0)

SNP: Single-nucleotide polymorphism.

Table 3: Relationships between *IL18* –607 C/A and Takayasu arteritis under different genetic models.

Genetic model	Crude OR (95% CI)	Crude *P*	Adjusted OR (95% CI)	Adjusted *P*
Dominant	0.532 (0.406–0.851)	0.005	0.533 (0.391–0.880)	0.010
Additive	0.320 (0.568–0.928)	0.011	0.266 (0.586–1.002)	0.051
Recessive	0.294 (0.481–1.154)	0.188	0.122 (0.552–1.420)	0.613

IL: Interleukin; OR: Odds ratio; CI: Confidential interval.

Table 4: Relationships between *IL18* –137G/C and Takayasu arteritis under different genetic models.

Genetic model	Crude OR (95% CI)	Crude *P*	Adjusted OR (95% CI)	Adjusted *P*
Dominant	1.658 (1.164–2.361)	0.005	1.571 (1.068–2.311)	0.022
Additive	1.554 (1.185–2.039)	0.001	1.467 (1.086–1.980)	0.012
Recessive	2.141 (1.150–3.986)	0.016	1.815 (0.901–3.656)	0.095

IL: Interleukin; OR: odds ratio; CI: Confidential interval.

Table 5: Comparison of *IL18* –607C/A and –137G/C genotype distribution frequency between active and quiescent phases in Takayasu arteritis.

SNP	Genotype	Active, *n* (%)	Quiescent, *n* (%)	χ^2	*P*
–607	CC	23 (35.4)	57 (42.2)	0.855	0.652
	CA	29 (44.6)	54 (40.0)		
	AA	13 (20.0)	24 (17.8)		
–137	GG	4 (6.1)	16 (11.9)	1.907	0.385
	GC	16 (24.7)	36 (26.6)		
	CC	45 (69.2)	83 (61.5)		

IL: Interleukin; SNP: Single-nucleotide polymorphism.

Table 6: Comparison of *IL18* –607C/A and –137G/C genotype distribution frequency between active and quiescent phases in TA under different genetic models.

SNP	Genetic model	χ^2	*P*
–607	Dominant	0.855	0.355
	Additive	0.920	0.631
	Recessive	0.144	0.705
–137	Dominant	1.604	0.205
	Additive	1.907	0.385
	Recessive	1.583	0.208

IL: Interleukin; TA: Takayasu arteritis; SNP: Single-nucleotide polymorphism.

After adjusting for risk factors (including age, sex, history of hypertension, smoking, total cholesterol, triglyceride, high-density lipoprotein cholesterol , and low-density lipoprotein cholesterol), we demonstrated that, under the dominant and additive models, the −607C/A polymorphism may decrease the risk of TA, and thus is a protective factor. In contrast, the −137G/C polymorphism may increase the risk of TA, and thus is a risk factor. At the −607 position, the risk of occurrence of TA was decreased by about 47% in individuals carrying the A allele compared with carriers of the C allele. At the −137 position, the risk of occurrence of TA was increased by about 57% in individuals carrying the C allele compared with carriers of the G allele. However, the −607C/A and −137G/C SNPs in *IL18* were not associated with activity of TA (active or quiescent stage).

IL18 is mainly generated by monocyte-macrophage cells and can induce proliferation of T helper 1 cells. It not only stimulates production of interferon-γ, but also induces tumor necrosis factor-α and IL-2 synthesis, which may enhance Fas and its ligand-mediated cytotoxicity effect. Therefore, *IL18* is an important pro-inflammatory cytokine with multiple biologic functions involved in antitumor, anti-inflammatory, and autoimmune mechanisms.[6-8]

The *IL18* −607C/A and −137G/C polymorphisms significantly affect expression levels and plasma concentrations of *IL18*.[18,19] Patients with the active state of TA show increased levels of *IL18* compared with patients with the quiescent state.[20] However, on the genetic level, our data did not indicate show correlations of *IL18* −607C/A and −137G/C polymorphisms and activity of TA under the dominant, additive, or recessive models.

Recent studies have demonstrated that SNPs in the *IL18* gene promoter region at positions −607 and −137 are involved in many inflammatory and autoimmune diseases.[9-17] Carriers of the A allele at position −607 have a 28% increased risk of chronic hepatitis B. Moreover, the risk of chronic hepatitis B is increased about 53% in individuals with the AA genotype at position −607.[9] Ma *et al*[24] reported that presence of the AC or CC genotype at position −607C/A could increase the risk of asthma by 28%. In addition, the −607C/A and −137G/C SNPs are associated with susceptibility to ulcerative colitis.[25]

Furthermore, the −607C/A and −137G/C SNPs in the *IL18* gene promoter region are associated with a protective effect in many diseases. Presence of the C allele at the −137 locus significantly reduced the risk of insulin resistance in Chinese patients with polycystic ovary syndrome[26]; and presence of the G allele may significantly increase the risk of insulin resistance in patients with acquired human immunodeficiency syndrome.[27] In the kidney transplant allograft rejection process, the C allele at the −137 locus has a protective effect and might reduce the occurrence of rejection.[28] However, some reports have shown no association between *IL18* −607C/A and −137G/C SNPs and inflammatory or autoimmune diseases. The −607C/A SNP has no relationship with tuberculosis, type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus, Crohn disease, ulcerative colitis, or asthma.[29-31] Moreover, −607C/A and −137G/C SNPs are not related to gout in the male Chinese Han population.[32]

Regarding the association between −607C/A and −137G/C SNPs and non-specific vasculitis, Palomino-Morales *et al*[33] reported that the −137G/C SNP was not associated with the incidence of giant cell arteritis, whereas the A allele at the −607C/A locus significantly increased the risk of giant cell arteritis (OR, 1.32; 95% CI, 1.04–1.69; $P = 0.02$), and thus was a susceptibility gene. Lee *et al*[34] found that *IL18* −607C/A and −137G/C SNPs were susceptibility genes for Behcet disease in a Korean population. However, Jang *et al*[35] reported no such correlation in a Korean population.

Our results showed that under the dominant model, the risk of TA was decreased by about 47% in individuals carrying the A allele at the −607C/A SNP ($P = 0.005$). After adjusting for risk factors, the risk of TA was decreased by about 47% ($P = 0.010$). Under the additive model, the risk of TA decreased by about 68% in carriers of the A allele ($P = 0.011$). After adjusting for risk factors, the risk of TA decreased by about 73% ($P = 0.051$).

For the −137G/C SNP, under the dominant model, the risk of TA was increased by about 66% in individuals carrying the C allele ($P = 0.005$). After adjusting for risk factors, the risk of TA was increased by about 57% ($P = 0.022$). Under the additive model, the risk of TA increased by about 55% in carriers of the C allele ($P = 0.001$). After adjusting for risk factors, the risk of TA increased by about 47% ($P = 0.012$). These findings confirmed that *IL18* −607C/A may decrease the risk of TA, and thus is a protective factor, whereas the −137G/C SNP may increase the risk of TA, and thus is a risk factor.

Although we confirmed the importance of the *IL18* −607C/A and −137G/C SNPs in TA, there are some limitations to this study, as follows. First, the correlations might be caused by synergistic interactions with other SNPs in the same gene or in other candidate genes. Moreover, the study subjects may not fully represent the Chinese Han population, and population stratification can cause false-positive results. These results need to be verified in other countries and populations, with a larger sample size and additional prospective cohort studies. Finally, the potential functional mechanism of the *IL18* gene needs to be further elucidated.

The *IL18* −607C/A gene polymorphism may decrease the risk of TA, and thus is a protective factor, whereas −137G/C may increase the risk of TA, and thus is a risk factor. However, neither polymorphism was related to activity (active *vs*. quiescent) of TA.

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Conflicts of interest

None.

References

1. Kitamura H, Kobayashi Y, Kimura A, Numano F. Association of clinical manifestations with HLA-B alleles in Takayasu arteritis. Int J Cardiol 1998;66:S121–S126. doi: 10.1016/s0167-5273(98)00159-4.
2. Soto ME, Vargas-Alarcón G, Cicero-Sabido R, Ramírez E, Alvarez-León E, Reyes PA. Comparison distribution of HLA-B alleles in Mexican patients with Takayasu arteritis and tuberculosis. Hum Immunol 2007;68:449–453. doi: 10.1016/j.humimm.2007.01.004.
3. Khraishi MM, Gladman DD, Dagenais P, Fam AG, Keystone EC. HLA antigens in North American patients with Takayasu arteritis. Arthritis Rheum 1992;35:573–575. doi: 10.1002/art.1780350514.
4. Numano F, Ohta N, Sasazuki T. HLA and clinical manifestations in Takayasu disease. Jpn Circ J 1982;46:184–189. doi: 10.1253/jcj.46.184.
5. Kasuya K, Hashimoto Y, Numano F. Left ventricular dysfunction and HLA Bw52 antigen in Takayasu arteritis. Heart Vessels Suppl 1992;7:116–119. doi: 10.1007/BF01744556.
6. Niu XL, Huang Y, Gao YL, Sun YZ, Han Y, Chen HD, Gao XH, Qi RQ. Interleukin-18 exacerbates skin inflammation and affects microabscesses and scale formation in a mouse model of imiquimod-induced psoriasis. Chin Med J 2019;132:690–698. doi: 10.1097/CM9.0000000000000140.
7. Abbate A, Toldo S, Marchetti C, Kron J, Van Tassell BW, Dinarello CA. Interleukin-1 and the inflammasome as therapeutic targets in cardiovascular disease. Circ Res 2020;126:1260–1280. doi: 10.1161/CIRCRESAHA.120.315937.
8. Xiao H, Li H, Wang JJ, Zhang JS, Shen J, An XB, *et al*. *IL18* cleavage triggers cardiac inflammation and fibrosis upon (-adrenergic insult. Eur Heart J 2018;39:60–69. doi: 10.1093/eurheartj/ehx261.
9. Li N, Gao YF, Zhang TC, Chen P, Li X, Su F. Relationship between interleukin 18 polymorphisms and susceptibility to chronic hepatitis B virus infection. World J Hepatol 2012;4:105–109. doi: 10.4254/wjh.v4.i3.105.
10. Thompson SR, Humphries SE. Interleukin-18 genetics and inflammatory disease susceptibility. Genes Immun 2007;8:91–99. doi: 10.1038/sj.gene.6364366.
11. Higa S, Hirano T, Mayumi M, Hiraoka M, Ohshima Y, Nambu M, *et al*. Association between interleukin-18 gene polymorphism 105A/C and asthma. Clin Exp Allergy 2003;33:1097–1102. doi: 10.1046/j.1365-2222.
12. Heinzmann A, Gerhold K, Ganter K, Kurz T, Schuchmann L, Keitzer R, *et al*. Association study of polymorphisms within interleukin-18 in juvenile idiopathic arthritis and bronchial asthma. Allergy 2004;59:845–849. doi: 10.1111/j.1398-9995.
13. Tiret L, Godefroy T, Lubos E, Nicaud V, Tregouet DA, Barbaux S, *et al*. Genetic analysis of the interleukin-18 system highlights the role of the interleukin-18 gene in cardiovascular disease. Circulation 2005;112:643–650. doi: 10.1161/CIRCULATIONAHA.
14. Xu Q, Tin SK, Sivalingam SP, Thumboo J, Koh DR, Fong KY. Interleukin-18 promoter gene polymorphisms in Chinese patients with systemic lupus erythematosus: association with CC genotype at position -607. Ann Acad Med Singapore 2007;36:91–95. doi: 10.1097/00000441-200702000-00014.
15. Pawlik A, Kurzawski M, Drozdzik M, Dziedziejko V, Safranow K, Herczynska M. Interleukin-18 gene (IL18) promoter polymorphisms in patients with rheumatoid arthritis. Scand J Rheumatol 2009;38:159–165. doi: 10.1080/03009740802600748.
16. Tamura K, Fukuda Y, Sashio H, Takeda N, Bamba H, Kosaka T, *et al*. IL18 polymorphism is associated with an increased risk of Crohn's disease. J Gastroenterol 2002;37:S111–S116. doi: 10.1007/BF03326428.
17. Cardoso SM, DeFor TE, Tilley LA, Bidwell JL, Weisdorf DJ, MacMillan ML. Patient interleukin-18 GCG haplotype associates with improved survival and decreased transplant-related mortality after unrelated-donor bone marrow transplantation. Br J Haematol 2004;126:704–710. doi: 10.1111/j.1365-2141.2004.05128.x.
18. Giedraitis V, He B, Huang WX, Hillert J. Cloning and mutation analysis of the human *IL18* promoter: a possible role of polymorphisms in expression regulation. J Neuroimmunol 2001;112:146–152. doi: 10.1016/s0165-5728(00)00407-0.
19. Arimitsu J, Hirano T, Higa S, Kawai M, Naka T, Ogata A, *et al*. *IL18* gene polymorphisms affect *IL18* production capability by monocytes. Biochem Biophys Res Commun 2006;342:1413–1416. doi: 10.1016/j.bbrc.2006.02.096.
20. Sarkar PG, Gupta MD, Girish MP, Bansal A, Kohli S, Saijpaul R, *et al*. Tumor necrosis factor-alpha -308G/A gene polymorphism and

novel biomarker profiles in patients with Takayasu arteritis. Indian Heart J 2018;70:S167–S172. doi: 10.1016/j.ihj.2018.09.004.
21. Arend WP, Michel BA, Bloch DA, Hunder GG, Calabrese LH, Edworthy SM, *et al*. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum 1990;33:1129–1134. doi: 10.1002/art.1780330811.
22. Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, Rottem M, *et al*. Takayasu arteritis. Ann Intern Med 1994;120:919–929. doi: 10.7326/0003-4819-120-11-199406010-00004.
23. Noris M, Daina E, Gamba S, Bonazzola S, Remuzzi G. Interleukin-6 and RANTES in Takayasu arteritis: a guide for therapeutic decisions? Circulation 1999;100:55–60. doi: 10.1161/01.cir.100.1.55.
24. Ma Y, Zhang B, Tang RK, Liu Y, Peng GG. Interleukin-18 promoter polymorphism and asthma risk: a meta-analysis. Mol Biol Rep 2012;39:1371–1376. doi: 10.1007/s11033-011-0871-6.
25. Ben Aleya W, Sfar I, Habibi I, Mouelhi L, Aouadi H, Makhlouf M, *et al*. Interleukin-18 gene polymorphisms in Tunisian patients with inflammatory bowel disease. Digestion 2011;83:269–274. doi: 10.1159/000319755.
26. Yang Y, Qiao J, Li MZ. Association of polymorphisms of interleukin-18 gene promoter region with polycystic ovary syndrome in Chinese population. Reprod Biol Endocrinol 2010;8:125. doi: 10.1186/1477-7827-8-125.
27. Sobti RC, Sharma VL, Abitew AM, Berhane N, Mahdi SA, Askari M, *et al*. The -137G/C polymorphism of interleukin 18 promoter and risk of HIV-1 infection and its progression to AIDS. Acta Virol 2011;55:353–356. doi: 10.4149/av_2011_04_353.
28. Mittal RD, Srivastava P, Singh V, Jaiswal P, Kapoor R. Association of common variants of vascular endothelial growth factor and interleukin-18 genes with allograft survival in renal transplant recipients of North India. DNA Cell Biol 2011;30:309–315. doi: 10.1089/dna.
29. Pawlik A, Kurzawski M, Czerny B, Gawronska-Szklarz B, Drozdzik M, Herczynska M. Interleukin-18 promoter polymorphism in patients with rheumatoid arthritis. Tissue Antigens 2006;67:415–418. doi: 10.1111/j.1399-0039.
30. Taheri M, Hashemi-Shahri SM, Hamzehnejadi M, Naderi M, Moazeni-Roodi A, Bahari G, *et al*. Lack of association between interleukin-18-607 C/A gene polymorphism and pulmonary tuberculosis in Zahedan, Southeast Iran. Prague Med Rep 2012;113:16–22. doi: 10.14712/23362936.2015.33.
31. Pan HF, Leng RX, Ye DQ. Lack of association of interleukin-18 gene promoter -607 A/C polymorphism with susceptibility to autoimmune diseases: a meta-analysis. Lupus 2011;20:945–951. doi: 10.1177/0961203311400114.
32. Li C, Yuan Y, Wang X, Han L, Chu N, Wang H, *et al*. Lack of association of -607 C/A and -137 G/C polymorphisms in interleukin 18 gene with susceptibility to gout disease in Chinese Han male population. Rheumatol Int 2012;32:1805–1807. doi: 10.1007/s00296-011-1936-5.
33. Palomino-Morales RJ, Vazquez-Rodriguez TR, Torres O, Morado IC, Castañeda S, Miranda-Filloy JA, *et al*. Association between *IL18* gene polymorphisms and biopsy-proven giant cell arteritis. Arthritis Res Ther 2010;12:R51. doi: 10.1186/ar2962.
34. Lee YJ, Kang SW, Park JJ, Bae YD, Lee EY, Lee EB, *et al*. Interleukin-18 promoter polymorphisms in patients with Behçet's disease. Hum Immunol 2006;67:812–818. doi: 10.1016/j.humimm.
35. Jang WC, Park SB, Nam YH, Lee SS, Kim JW, Chang IS, *et al*. Interleukin-18 gene polymorphisms in Korean patients with Behçet's disease. Clin Exp Rheumatol 2005;23:S59–S63. doi: 10.1007/s00296-008-0664-y.

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