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Association of interleukine-18 polymorphisms with susceptibility to prostate cancer in Iranian population

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Interleukin-18 (IL-18) is a multifunctional cytokine that augments interferon-γ production, promotion of the Th1 immune response and acts as an important immunomediator in the development of some cancers. The current study aimed to analyze the association of the five most common polymorphisms in the IL-18 gene with prostate cancer in the Iranian population. We examined a possible association of IL-18 –137G>C, –607C>A, –656G>T, +105A>C and +127C>T polymorphisms with prostate cancer occurrence by PCR-RFLP assay. Odds ratio (OR) and 95% confidence interval (CI) were used to assess the strength of the association between IL-18 polymorphisms and prostate cancer. Statistical analysis revealed that individuals carrying the mutant homozygote genotype of IL-18 –607C>A (OR=2.251, 95% CI=1.062–4.768, p=0.034) and –137G>C (OR=2.364, 95% CI=1.121–4.984, p=0.024) polymorphisms had an increased risk of prostate cancer. However, for IL-18 –656G>T, +105A>C and +127C>T polymorphisms, there were no differential distributions of their genotypes between patients with prostate cancer and healthy subjects. Our results indicated that the IL-18 –137G>C and –607C>A polymorphisms were significantly associated with an increased risk of prostate cancer in the Iranian population. Thus, these polymorphisms might be used as a molecular biomarker in the early diagnosis of prostate cancer.

Key words: prostate cancer, interleukin 18, association, polymorphism, genotype

Prostate cancer is the most common non-skin cancer and the second cause of death due to malignancy in men in developed countries [1]. Since prostate cancer is most common among older men and the population is aging, prostate cancer incidence is expected to increase over the coming years. Moreover, a family history of prostate cancer and ethnicity are the only established risk factors for the disease [2]. Prostate cancer is a clinically heterogeneous disease in which genetic variants may influence the clinical outcome [3]. According to the estimates, approximately 161,360 new cases and 26,730 deaths were reported in the United States in 2017 [4]. The incidence rate of prostate cancer is approximately 9.6 per 100,000 in Iran, which considerably lower than worldwide (32.8 per 100,000) [5]. Prostate cancer is suggested to arise from a combination of genetic, lifestyle and environmental factors [6]. The heritability of prostate cancer susceptibility was recently estimated to 58% in a Nordic twin study, indicating that there is a strong genetic component and familial aggregation in the development of prostate cancer [7]. Thus, given the high heritability of prostate cancer, several studies have been performed to identify the inherited genetic susceptibility loci for this disease. To date, several genome-wide association studies (GWAS) have identified more than 100 common SNPs such as CYP19A1, HSD3B1, HSD17B4, CYP17A1, SRD5A2, and interleukins that were associated with the susceptibility of prostate cancer [8, 9].

Interleukin-18 (IL-18), originally called interferon-(IFN-) γ-inducing factor, is a novel cytokine belonging to the IL-1 family and plays a strategic role in inflammation and immune reactions [10, 11]. IL-18 is produced by a wide range of immune cells, such as monocytes, Kupffer cells, dendritic cells and activated macrophages [12, 13]. Moreover, IL-18 belongs to proinflammatory cytokines, which, on the other hand, are capable of influencing the Th1/Th2 imbalance in Th2 direction in the suitable cytokine milieu [14]. It was recently established that IL-18 acts via a complex receptor,

which possesses a binding chain (IL-18Rα) and a signaling chain (IL-18Rβ) [15, 16].

Human IL-18 gene is located on chromosome 11q22.2-q22.3 and comprises six exons and five introns. To date, several different single nucleotide polymorphisms (SNPs) at IL-18 gene such as –656G>T, –607A>C, –137C>G, +113T>G and +127C>T have been identified, especially in the promoter region [17]. However, only –607C>A (rs1946518) and –137G>C (rs187238) polymorphisms were confirmed to affect gene expression. It is well established that the 137G>C polymorphism changes the H4TF-1 nuclear factor binding site, while the 607C>A polymorphism disrupts the bind of potential cAMP-responsive element binding protein [18]. IL-18 is also associated with tumorigenesis and has been reported to contribute to both anticancer and procancer processes [10]. Further, the polymorphisms in IL-18 have been found to be probably associated with the risk of prostate cancer. However, the results were inconsistent and controversial results. Thus, we have performed this study to evaluate the association of IL-18 –656G>T, –607C>A, –137G>C, +105A>C and +127C>T polymorphisms with susceptibility to prostate cancer in an Iranian population.

Patients and methods

Subjects. This study was approved by a local ethics committee and an informed consent was obtained from all participants included in this study. A total of 180 consecutive patients diagnosed with prostate cancer were included in this study between March 2015 and May 2018. In addition, 180 healthy matched (age and geographic origin) men with normal PSA levels (≤4.0 ng/ml), without a history of malignancy, and prostate complications from the general population (population based) were included.

Molecular analysis. Peripheral blood samples (5 ml per participant) were collected into a standard tube and stored at –80 °C. Then genomic DNA was extracted from peripheral blood samples by a commercial QIAamp DNA Mini kit (Qiagen Co Ltd, Tehran, Iran), and stored at –20 °C before use. The quantity and quality of extracted DNA were estimated by a Nanodrop. In this study, the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay was used to genotype the IL-18 –656G>T, –607C>A, –137G>C, +105A>C and +127C>T polymorphisms. The used primers characteristics, fragments sizes, restriction enzymes and annealing temperature for each polymorphism are summarized in Table 1. The PCR reaction was carried out in a total volume of 25 μl containing 50 ng of template DNA, 1 X of DNA polymerase Taq buffer, 2.5 mM of $MgCl_2$, 0.5 μl of dNTP, 0.5 pmol/μl of each primer and 1 U of Taq DNA polymerase. The PCR reaction conditions were as follows: initial denaturation for 5 min at 95 °C, then 40 cycles of 30 sec at 95 °C, annealing for 45 sec, extension for 60 sec at 72 °C, followed by 6 min at 72 °C. Then, PCR products were digested by a restriction enzyme (Table 1) digestion at 37 °C overnight. The PCR product was resolved by 3.0% agarose gel electrophoresis gel at 100 V for 30 min and visualized by UV radiation after EtBr staining.

Statistical analysis. All analysis was performed by Microsoft Excel and SPSS software (version 21.0; SPSS Inc, Chicago, Illinois). IL-18 polymorphisms allele and genotype frequencies were calculated by counting. We used the χ^2 test to evaluate the significant departure from the Hardy-Weinberg equilibrium in the control group by the software package Arlequin (version 3.01). Moreover, minor allele frequencies (MAFs) in healthy subjects were estimated by a Microsoft Excel based test (Court lab). Odds ratio (OR) and 95% confidence interval (CI) were used to examine the association of IL-18 polymorphisms with prostate cancer. All tests were 2 tailed; a p-value of <0.05 was considered statistically significant.

Results

The clinical characteristics of the patients with prostate cancer and the cancer-free controls are shown in Table 2. There were no significant differences for the distributions of age, residence, family history of prostate cancer, and smoking statue between cases with prostate cancer and healthy subjects *(*p>0.05).

Table 1. Genotyping features and oligonucleotide sequences of PCR amplification primers for genotyping the IL-18 polymorphisms.

SNP-ID	Polymorphism	Residue	Sequence Name	RE	AT(° C)	Fragments
rs187238	–137G>C	NR	F: 5'-TTGTAACATTGTAGGAATTACC-3' R: 5'-ATGTAATATCACTATTTTATGAGA-3'	EcoRI	60	G: 107, 24 C: 131
rs1946518	–607C>A	NR	F: 5'- CCCTCTCCCCAAGCTTACTT-3' R: 5'-TTCAGTGGAACAGGAGTCCA-3'	MseI	54	C: 171 A: 101, 70
rs549908	+105A>C	Ser>Ser	F: 5'-TGTTTATTGTAGAAAACCTGG AATT-3' R: 5'-CCTCTACAGTCAGAATCAGT-3'	Taq I	62	A: 148 C: 123, 25
rs1946519	–656G>T	NR	F: 5'-AGGTCAGTCTTTGCTATCATTCCAGG-3' R: 5'-CTGCAACAGAAAGTAAGCTTGCGGAGAGG-3'	Mwo I	60	G: 96, 24 T: 120
rs360717	+127C>T	NR	F: 5'-CCAGCTTGCTGAGCCCTTTGCTCC-3' R: 5'-CTGTGTAGACTGCAGCAGGTGGCGGCC-3'	Eag I	63	C: 113, 21 T: 134

NR: Not Reported; RE: Restriction Enzyme; AT: Annealing Temperature.

Distributions of IL-18 −656G>T, −607C>A, −137G>C, +105A>C and +127C>T polymorphisms in control group were found to be in Hardy Weinberg equilibrium (p=0.762, 0.205, 0.124, 0.436, and 0.119, respectively). Moreover, the minor allele frequencies (MAFs) of IL-18 −656G>T, −607C>A, −137G>C, +105A>C and +127C>T polymorphisms in the control group were 0.447, 0.283, 0.311, 0.344 and 0.422, respectively.

Genotype and allele distributions of IL-18 −656G>T, −607C>A, −137G>C, +105A>C and +127C>T polymorphisms are shown in Table 3. For IL-18 −656G>T polymorphism, the TT, TG, and GG genotypes in cases with prostate cancer were 30.6%, 52.2% and 17.2%, while in controls were 30.0%, 50.6% and 19.4%, respectively. For IL-18 +105A>C polymorphism, the CC, CA, and AA genotypes patients with prostate cancer were 40.0%, 51.7% and 8.3%, while in controls were 41.7%, 47.8% and 10.5%, respectively. For IL-18 +127C>T polymorphism, the TT, TC, and CC genotypes in prostate cancer patients were 27.2%, 55.6% and 17.2%, while in controls were 30.6%, 54.4% and 15.0%, respectively. Genotype and allele distribution of the IL-18 −656G>T, +105A>C and +127C>T polymorphisms in prostate cancer patients and control groups were not statistically significant in comparison between patient and control group (p>0.05, Table 3).

Table 2. Clinicopathological characteristics of patients with prostate cancer with and controls.

Variables	Cases (n=180)	Controls (n=180)	p-value
Age (year)			
Range	44–77	42–75	
Mean ± SD	65.47±7.64	63.24±8.35	0.196
Residence			
Urban	148 (82.2)	150 (83.3)	0.265
Rural	32 (17.8)	30 (16.7)	
Family history of prostate cancer			
Yes	4 (2.2)	1 (0.6)	0.129
No	176 (97.8)	179 (99.4)	
Clinical stage			
Localized	64 (35.6)		
Advanced	116 (64.4)		
PSA at diagnosis (ng/ml)			
<4	8 (4.4)	156 (86.7)	
4–10	19 (10.6)	21 (11.7)	
>10	153 (85.0)	3 (1.6)	
Mean ± SD	81.63±31.26	5.18±2.52	
Smoking status			
Nonsmokers	98 (54.4)	111 (61.7)	0.075
Smokers	82 (45.6)	69 (38.3)	

SD, Standard Deviation

Table 3. Analysis of IL-18 SNPs genotypes and alleles in prostate cancer and controls.

SNPs	Genotype/Allele	Cases (n=180)	Controls (n=180)	Odds Ratio		
				OR	90% CI	p-value
−656G>T	GG	55 (30.6)	54 (30.0)	Ref.		
	GT	94 (52.2)	91 (50.6)	1.069	0.707–1.616	0.752
	TT	31 (17.2)	35 (19.4)	0.862	0.505–1.471	0.589
	G	204 (56.7)	199 (55.3)	Ref.		
	T	156 (43.3)	161 (44.7)	0.945	0.704–1.269	0.707
−607C>A	CC	74 (42.8)	89 (49.5)	Ref.		
	CA	83 (46.1)	80 (44.4)	1.070	0.706–1.620	0.751
	AA	23 (11.1)	11 (6.1)	2.251	1.062–4.768	0.034
	C	231 (64.2)	258 (71.7)	Ref.		
	A	129 (35.8)	102 (28.3)	1.143	1.031–1.935	0.031
−137G>C	GG	84 (46.7)	81 (45.0)	Ref.		
	GC	72 (40.0)	84 (47.8)	0.729	0.480–1.106	0.137
	CC	24 (13.3)	13 (7.2)	2.364	1.121–4.984	0.024
	G	240 (66.7)	246 (68.3)	Ref.		
	C	120 (33.3)	114 (31.7)	1.079	0.790–1.474	0.633
+105A>C	AA	72 (40.0)	75 (41.7)	Ref.		
	AC	93 (51.7)	86 (47.8)	1.168	0.773–1.767	0.461
	CC	15 (8.3)	19 (10.5)	0.770	0.378–1.568	0.472
	A	237 (65.8)	236 (65.5)	Ref.		
	C	123 (34.2)	124 (34.4)	0.988	0.726–1.344	0.937
+127C>T	CC	49 (27.2)	55 (30.6)	Ref.		
	CT	100 (55.6)	98 (54.4)	1.046	0.690–1.584	0.832
	TT	31 (17.2)	27 (15.0)	1.179	0.671–2.070	0.567
	C	198 (55.0)	208 (57.8)	Ref.		
	T	162 (45.0)	152 (42.2)	1.120	0.834–1.503	0.452

OR: Odds Ratio; CI: Confidence Interval.

Frequency of homozygote mutant genotype for IL-18 –607C>A and –137G>C polymorphisms between prostate cancer cases and controls were significantly different (p<0.05). Analysis showed that individuals carrying the AA genotype of IL-18 –607C>A (OR=2.251, 95% CI=1.062–4.768, p=0.034) and CC genotype of –137G>C (OR=2.364, 95% CI=1.121–4.984, p=0.024) polymorphisms had an increased risk of prostate cancer. Moreover, the occurrence of prostate cancer was increased by A allele of –607C>A polymorphism (OR=1.143, 95% CI=1.031–1.935, p=0.031), but not with C allele of –137G>C polymorphism (OR=1.079, 95% CI=0.790–1.474, p=0.633, Table 3).

Discussion

Prostate cancer is one of the major threats to men's health worldwide. Studies showed that the IL-18 can suppress antitumor immunity in a PD-1-dependent manner, PD-1 is a co-inhibitory receptor and one of the major checkpoints [19]. Thus, the polymorphisms at the IL-18 gene might be associated with the susceptibility to prostate cancer. In the current study we have evaluated the association of IL-18 –656G>T, –607C>A, –137G>C, +105A>C and +127C>T polymorphisms with susceptibility to prostate cancer in the Iranian population.

To the best knowledge, this is the first study to evaluate the association of IL-18 –656G>T, –607C>A, –137G>C, +105A>C and +127C>T polymorphisms with the risk of prostate cancer in Iranian population. This is also the first study to investigate the association of IL-18 –656G>T and +127C>T polymorphisms with risk of prostate cancer worldwide. Our results showed that the mutant homozygote genotypes of –607C>A and –137G>C polymorphisms at the promoter region of IL-18 gene were significantly associated with an increased risk of prostate cancer in our population. To elaborate more specifically, carriers of A allele and AA genotype of IL-18 –607C>A polymorphism, and carriers of CC genotype of –137G>C polymorphism were significantly associated with an increased risk in prostate cancer. However, our results failed to show that the IL-18 –656G>T, +105A>C and +127C>T polymorphisms were significantly associated with the risk of prostate cancer in Iranian population.

To date, a few studies have been evaluated the role of the IL-18 polymorphisms in the development of prostate cancer in Indian, Chinese and Slovak populations [20–24]. In 2007, Liu et al. for the first time evaluated the association of IL-18 –137G>C and –607C>A polymorphisms with risk of prostate cancer in 265 cases and 280 controls in a Chinese population [23]. Their results showed that the IL-18 –137G>C polymorphism was significantly associated with an increased risk of prostate cancer in the population. In 2013, Liu et al. in a study of 375 cases with prostate cancer and 400 age-matched healthy controls examined the association of –137G>C and –607C>A polymorphisms at IL-18 gene with prostate cancer in Han Chinese [24]. Inconsistent with the previous study in the Chinese population, their results showed that none of these polymorphisms were significantly associated with an increased risk of prostate cancer. However, their results showed that individuals with wild homozygote genotype (GG) of the –137G>C polymorphism had a 2.165-times higher risk of prostate cancer progression than individuals with heterozygote genotype (GC) (95% CI 1.270–3.687). Dwivedi et al. have evaluated the relationship of IL-18 (–607C>A, and –137G>T) and IL-10 (–819C>T and –592C>A) polymorphisms with the risk of prostate cancer in an Indian population. Moreover, they have evaluated the circulating levels of IL-18 and IL-10 in the patients. Their results failed to show a significant association between –819C>T and –592C>A polymorphisms at IL-10 and an increased risk of prostate cancer. However, they have found that the IL-18 –607C>A, and –137G>T polymorphisms were significantly associated with an increased risk of prostate cancer. Moreover, their results indicated that polymorphisms at promoters region of IL-18 and IL-10 genes might influence the circulating levels of these interleukins [21]. In another study, Dwivedi et al. revealed that the promoter region polymorphisms of the IL-18 gene with various modes of tobacco exposure might affect not only the susceptibility of prostate cancer risk but also the severity of this disease [22]. A recently published study by Jurecekova et al. showed that the IL-18 –607C>A polymorphism might contribute to the development of prostate cancer in a Slovak population [20]. Their study also revealed that the IL-18 –607C>A polymorphism was associated with the development of higher-grade carcinomas, indicating that the polymorphism may influence the prognosis and aggressiveness of prostate cancer. In 2019, Yuanyuan et al. in a meta-analysis of nine case-control studies with 1,613 prostate cancer cases and 1,630 controls found that IL-18 –607C<A polymorphism could decrease the risk of prostate cancer risk in the Asians, but increase the risk in the Caucasians [25]. Therefore, based on the previous studies and our results, the genotype of the IL-18 –607C>A and –137G>C polymorphisms could be the determinant of susceptibility to prostate cancer.

In summary, our results suggest that the IL-18 –137G>C and –607C>A polymorphisms play an important role in the development of prostate cancer in the Iranian population. Thus, these polymorphisms might be used as a molecular biomarker in the early diagnosis of prostate cancer. However, there was no significant association between IL-18 –656G>T, +105A>C and +127C>T polymorphisms and an increased risk of prostate cancer in our population. Future studies with larger sample sizes and with well-matched controls are required to assess the effect of gene-gene and gene-environment and also the same gene polymorphisms interactions, as well as more types of interleukins, should be conducted in the future.

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