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Polymorphism of the IL-10 gene in Azeri population of Iran

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Abstract

Background: Interleukin (IL)-10 is one of the key interleukins in the immune system. It plays an anti-inflammatory role in body by inhibition of the synthesis of pro-inflammatory cytokines and reducing the expression of major histocompatibility complex II molecules. The single-nucleotide polymorphism in the gene of this interleukin affects its expression level. Thus, this study was conducted to investigate the IL-10 gene polymorphism at position -1082A/G in Azeri population of Iran.

Methods: Blood samples were taken from 254 healthy and non-relevant Iranian Azeri individuals. After DNA extraction, the frequency of IL-10 genotypes and alleles at -1082A/G position was determined by allele specific-PCR method. Then, q-square test was used to compare allele frequencies and IL-10 genotypes with other populations, and p value of < 0.05 was considered significant.

Results: In Iranian Azeri population, the frequency percentage of AA, AG and GG genotypes in IL-10 gene at the -1082A/G location was 37.4, 43.3 and 19.3%, respectively. The frequency percentage of A and G alleles also were 59.1 and 40.9%, respectively. Based on statistical analysis, frequency of IL-10 genotypes in the current study was very similar to the population of Saudi Arabia, but it had a significant difference with East Asia and Ireland populations.

Conclusion: Results of the present study indicate similar polymorphism of IL-10 genotype with neighbor ethnicities in Middle East country. Based on patients backgrounds mentioned in their questioners, this polymorphism was associated with the susceptibility to asthma and Alzheimer in this population which are common in the region.

Keywords: IL-10, Genotype, Single-nucleotide polymorphisms, Iranian Azeri population

Background

Cytokines are hormone-like intercellular mediators that are produced during immunological responses. They regulate the immune system and modulate immune responses by regulating the growth, migration and differentiation of cells, especially leukocytes [1]. IL-10 is a class-II cytokine with the strongest anti-inflammatory activity, and it plays a central role in innate and adaptive immune system. IL-10 is mostly produced by T helper(Th)2 cells, but numerous other immune cells like regulatory T cells, Th1 cells, macrophages, natural killer cells(NK-cells), dendritic cells, mast cells, B cells, neutrophils and eosinophils also produce IL-10 [2, 3]. IL-10 influences a variety of cells and suppresses inflammatory responses through the blocking of pro-inflammatory cytokines production and reducing the expression of MHCII molecules. IL-10 also minimizes the host injury by acting on Th1 cells and macrophages and inhibits the secretion of pro-inflammatory cytokines including IFN-γ, IL-1 and IL-6 [4, 5]. The type and severity of stimulation, as well as the individual's genetic makeup, influence IL-10

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secretion. The human IL-10 gene is located on the long arm of chromosome and spans about 4.7 kb, with 5 exons and 4 introns. IL-10 gene encodes a homodimer polypeptide with 178 amino acids in each subunit [6]. SNPs are located in the IL-10 gene promoter region, and one of the most important of them is -1082A/G (rs1800896) [7]. IL-10 polymorphism at position -1082A/G affects gene expression level so that a higher incidence of the G allele is linked to higher IL-10 expression, and higher IL-10 level is linked to increased susceptibility to some diseases [8].

Azeri population is one of Iran's largest and most populous ethnic groups residing mostly in northwestern Iran. Like other Iranians, Azeri are Aryan and their language shifted to Turkish after Ilkhanate dynasty in northwestern Iran [9]. Due to the IL-10's role and characteristics in susceptibility to various diseases and pathological processes as well as variations in its production level based on genetic polymorphism, it is necessary to study it in different populations. Therefore, in this study IL-10 polymorphism at -1082A/G position in the Azeri population of northwestern Iran was investigated.

Methods

Blood samples were collected from 254 non-kin Azeri healthy individuals living in East Azerbaijan province in Iran. Enrolled individuals were not infected to human immunodeficiency virus (HIV), hepatitis B, hepatitis C as well as tuberculosis based on their recent laboratory results provided on the questioner. They also had no cancer, or autoimmune diseases. Consent was obtained from all participants, and this study was approved by the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1397.889). DNA extraction was performed through the described method by [10]. 150 µl TE buffer (10 M Tris–Cl, 1 mM EDTA, pH 8.0) was blended with 300 µl of buffy-coat through shaking. Then, 60 µl of 10% sodium dodecyl sulfate (SDS) and10 µl of 20 mg/ml of proteinase K (Cinnaclone, Iran) were blended with the solution and then incubated in 60 °C overnight. Later 100 µl of 5 M NaCl and 80 µl 10% cetyltrimethylammonium bromide (CTAB) + 0.7 M NaCl were added and vortexed, respectively. After 10 min of incubation at 65 °C, about 700 µl of chloroform/isoamyl (Merck, Germany) (24:1) was added and shaken for 20 s and then centrifuged for 8 min at 11,000 g. After centrifugation, the supernatant was transferred to a new microtube, and then, 2-propanol was added by the amount of 0.6 volume of solution and after mixing it was incubated at − 20 °C for 30 min. The suspension was then centrifuged for 15 min at 1200 g, and thereafter, 1 ml cold 70% ethanol was added to the solution for washing the DNA pellet. Finally, the DNA pellet was dissolved in 60 µl of distilled water and stockpiled at − 20 °C.

SNP A/G IL-10 -1082 (rs1800896) in the promoter section was genotyped by using the allele-specific-PCR method described previously [11]. The sequences of the primers used for genotyping include: (common primer) 5′-CAG TGCCAACTGAGA ATT TGG-3′, (primer A) 5′-ACT ACTAAGGCTTCTTTGGGA ACA-3′, (primer G) 5′-CTA CTAAGG CTT CTTTGGGAG-3′.

PCR was carried out in a total volume of 20 µl with approximately 100 ng genomic DNA, 100 µM dNTP, 0.5 µM of each primer, 50 mM Kcl, 20 Mm Tris–Cl (pH = 8.4), 1.5 mM MgCl2 and 1.25 units of recombinant Taq DNA polymerase (Cinnaclone, Iran). Cycling was carried out in Mastercycler gradient (Eppendorf, Germany) with the thermal cycling protocol of 94 °C for 7 min as initial denaturation, 35 cycles of 94 °C for 45 s, 60 °C for 45 s, 72 °C for 50 s and 72 °C for 7 min as final extension. After electrophoresing PCR products on 1.5% agarose gel, they were stained with ethidium bromide and analyzed under ultraviolet (UV) light. PCR products were 258 base pairs (bp) in size as compared to 100 bp DNA ladder plus (Fermentas, Lithuania). The q-square test was used to compare differences in IL-10 genotype and allele frequencies among different populations, and P value of < 0.05 was considered as significant level [12].

Results

IL-10 genotype and allele frequencies in healthy Azeri population in northwestern Iran at position -1082 A/G are shown in Table 1. Frequency percentages of AA, AG and GG genotypes were 37.4, 47.3 and 19.3%, respectively. The frequencies of A and G alleles frequencies were 59.1 and 40.9%, respectively. The frequency of IL-10 genotypes and alleles at -1082 A/G position from current sample population and other populations is observed in Tables 2 and 3. As can be seen, the genotypic and allele

Table 1 Genotype and allele frequency of IL-10(-1082) in Azeri population (Northwest of Iran)

	Frequency (%)
Genotype	
AA	95(37.4%)
AG	110(43.3%)
GG	49(19.3%)
Total	254
Allele	
A	300(59.1%)
G	208(40.9%)
Total	508

Table 2 Frequency of IL-10 genotypes -1082 in healthy populations from various populations

Population	AA (%)	AG (%)	GG (%)	Number	*p*-value
Azeri, Iran (current study)	95(37.4%)	110(43.4%)	49(19.3%)	254	NA
Iranian [19]	69(35.8%)	101(52.3%)	23(11.9%)	193	0.06
Han Chinese [8]	326(93.1%)	23(6.6%)	1(0.3%)	350	0.000
Mexican [15]	169(50%)	139(41%)	32(9%)	340	0.000
Egyptian [23]	43(36.1%)	61(51.3%)	15(12.6%)	119	0.19
Saudi [20]	58(38.6%)	64(42.7%)	28(18.7%)	150	0.97
Omani [17]	35(43.7%)	34(42.5%)	11(13.8%)	80	0.43
Polish [16]	99(51%)	50(26%)	44(23%)	193	0.001
Bulgarian [18]	41(47.6%)	36(41.9%)	9(10.5%)	86	0.1
Finnish [42]	135(34%)	177(44%)	88(22%)	400	0.56
Northern Ireland [17]	20(20%)	46(46%)	34(34%)	100	0.001
Korean [14]	435(87.9%)	56(11.3%)	4(0.8%)	495	0.003
Greek [21]	44(44%)	42(42%)	14(14%)	100	0.38
Italian [22]	46(32.9%)	77(55%)	17(12.1%)	140	0.06

NA not applicable

Table 3 Frequency 0f IL-10 alleles -1082 in healthy populations from various populations

Population	*A* (%)	*G* (%)	Number	*p*-value
Azeri, Iran (current study)	300(59.1%)	208(40.9%)	508	NA
Iranian [19]	239(61.9%)	147(38.1%)	386	0.39
Han Chinese [8]	675(94.4%)	25(3.6%)	700	0.000
Mexican [15]	477(70%)	203(30%)	680	0.000
Egyptian [23]	147(61.8%)	91(38.2%)	238	0.48
Saudi [20]	180(60%)	120(40%)	300	0.79
Omani [17]	104(65.2%)	56(34.8%)	160	0.18
Polish [16]	199(52%)	187(48%)	386	0.02
Bulgarian [18]	118(68.6%)	54(31.4%)	172	0.03
Finnish [42]	447(55.9%)	353(44.1%)	800	0.26
Northern Ireland [17]	86(43%)	114(57%)	200	0.000
Korean [14]	926(93.5%)	64(6.5%)	990	0.000
Greek [21]	130(65%)	70(35%)	200	0.15
Italian [22]	169(60.4%)	111(39.6%)	280	0.72

NA not applicable

frequencies in this sample population are very similar to the genotypic frequency in Saudi Arabia ($P \geq 0.05$), but it is significantly different from the genotypic frequency in East Asia and Ireland ($P < 0.05$).

Discussion

Interleukins mediate intercellular contact in the immune system and are involved in inflammatory, tissue repair and host defense processes. Immunogenic loci influence susceptibility to a variety of diseases, especially inflammatory, neurological, infectious diseases and cancer, so that SNPs present in the promoter region of the IL-10 gene can affect expression, structure, quantity, function of IL-10 [13] and cause an imbalance between pro-inflammatory and anti-inflammatory interleukins. Distribution of alleles and SNP genotypes of IL-10 gene at -1082 position between healthy Azeri population and other healthy Asian populations as well as other European, African and American nations is compared in Tables 2 and 3. A significant difference in allelic and genotype distribution between healthy Azeri people and healthy Chinese population [8], Korean [14], Mexican [15], Polish [16], Northern Ireland [17] has been observed; however, there is only a significant difference in the distribution of alleles with healthy Bulgarian population, and no significant difference in genotypic distribution has been observed with Bulgarian population [18]. But there is a similarity with healthy people from Fars population of Iran [19], Saudi [20], Omani [17], Greek [21], Italian [22] and Egyptian [23]. In present study, AG genotype was the most abundant genotype which is greatly different with 6.6% frequency of AG genotype of Han population from China [8]. In terms of evolutionary trees, people of Azerbaijan are diverge from East Asian population and the genetic distance is at least 20,000 years [24]. According to the results of a study performed on Saudi Arabians, the prevalence of AA, AG and GG genotypes was 38.6, 42.7 and 18.7%, respectively, and is so similar to current study's results [20]. It seems that due to the special interest of the Iranian people, especially Azeris in Prophet Mohammad (PBUH) and his descendants, a widespread migration of Prophet Mohammad's descendants from Saudi Arabia and Iraq to Iran plateau, particularly northwestern Iran during Umayyad and Bani Abbas dynasties, had been occurred [25]. As a result of Sadat's marriage to

Azeris also, there has been a great genetic mixing which can be one of the reasons of the excessive similarity of IL-10 genotypes at position 1082A/G in Azeri and Saudi populations. Study of interleukins' gene polymorphism along with mtDNA haplogroups can be a tool to study genetic evolutionary and correlations between populations to identify ethnic similarities and differences. The prevalence of AG genotype in the Azeri community was the highest, similar to that of North Africans, and this may be due to a genetic link between Azeri population of Iran and African people, which is consistent with African migration to other continents through the Iran plateau [26]. IL-10 is an interleukin that eliminates macrophages activation which makes it impossible to eradicate *Mycobacterium tuberculosis* within macrophages. While IFN-γ is effective against *M. tuberculosis* by stimulating macrophages [27], IL-10 renders the person more susceptible to tuberculosis. Eradicating tuberculosis in Iran, especially in northwestern region of Iran, is noteworthy because tuberculosis is an infectious disease that has caused problems with the development of its resistant type to drugs. G Allele, which is associated with high expression of IL-10, inhibits the immune system and predisposes people to tuberculosis, as Asgharzadeh et al. [11] discovered a substantial association between the incidence of tuberculosis and G allele at -1082 position. It appears that the GG genotype of the IL-10 gene at position -1082 plays a role in decreasing resistance to *M. tuberculosis* through increasing IL-10 expression and disrupting Th1/Th2 balance [28]. Since immune system defects predispose people to infectious diseases, the G allele at position 1082 of the IL-10 gene predisposes people to sepsis. Sepsis is a life-threatening condition caused by the immune system's overreaction to microbial infections. To control the infection, body releases a huge amount of chemicals, which causes severe inflammation which ultimately spreads across the body, causing organ damage and even death in some cases [29]. As a result, identifying patients who are at a higher risk of developing sepsis may be preventative and life-saving.

Cancer is a disorder that is linked to an individual's genetic polymorphism, and the prevalence of cancer is greater in people who do not have a good immune system. The immune system scans the body for cancer cells and kills them on a regular basis through cytotoxic T lymphocytes that sense cancer cell antigens with MHCI molecules. GG genotype and G allele raise IL-10 production and make people with this genotype more cancer-prone, so that the GG genotype in versus with AA genotype is a risk factor for gastric [30] and breast cancers [31]. It seems that IL-10 polymorphism can play a role in people's susceptibility to various cancers, severity, clinical course and outcome of the disease.

The balance between pro-inflammatory and anti-inflammatory interleukins is essential for a proper immune response, and any dysregulation in this region can be associated with pathological conditions like autoimmune diseases. Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder in which patient's platelets are attacked by antibodies. The etiology of ITP is unclear, but it has been linked to both environmental and genetic factors, as AA genotype in -1082 IL-10 location predisposes individuals to ITP ($p < 0.0013$) [32], whereas other important autoimmune disorders, such as multiple sclerosis [16, 18] and rheumatoid arthritis (RA) [33], have no substantial association with IL-10 genotypes at location 1082. According to studies, people with the AA genotype and the A allele have a higher susceptibility to juvenile idiopathic arthritis (JIA) [34], asthma [35], ischemic stroke [36] and Alzheimer [37] than people with the GG genotype. Conversely, in comparison with the AA and AG genotypes, the GG genotype of the IL-10 -1082 predisposes individuals to hepatitis B virus (HBV), hepatitis C virus (HCV) [38], acute pancreatitis [13] and type 2 diabetes [39]. In contrast in a study, type 2 diabetes was more common in people with homozygous AA and GG genotypes and the AG genotype was more prevalent in controls. This can imply that high or low IL-10 is not beneficial to individuals, and balanced production is good for people [40]. Different results in various populations can be due to specific genetic variations, distant promoter elements, linkage disequilibrium with other loci and the presence of functional variants close to discussed polymorphism. Therefore, further studies should be performed on other IL-10 gene polymorphisms as well as gene polymorphisms in other interleukins in populations; also, their association with disease susceptibility should be investigated. As IL-10 inhibits IL-12 production and Th1 differentiation and prevents the recognition of viral infected and cancer cells through downregulating MHCI expression on cancer cells and antigen-presenting cells, it can be a target for cancer immunotherapy [41]. As a result, the use of an anti-IL-10 antibody may be useful for the treatment of viral infections and cancers with elevated IL-10 basic levels. Based on the above, it can be concluded that identifying interleukin genotypes in patients can be used to classify diseases and determine the optimal dose of drugs to cure diseases and minimize their side effects.

Conclusion

Polymorphism in IL-10 gene in the -1082 A/G affects its expression that the GG genotype is associated with high levels of IL-10 production. In the current study, AA and AG genotypes were more frequent than GG genotype. Low levels of IL-10 can be associated with

susceptibility to some diseases. Results of the present study indicate similar polymorphism of IL-10 genotype with neighbor ethnicities in Middle East country. Based on patients backgrounds mentioned in their questioners, this polymorphism was associated with the susceptibility to asthma and Alzheimer in this population which are common in the region.

Abbreviations

HBV: Hepatitis B virus; HCV: Hepatitis C virus; IL: Interleukin; ITP: Idiopathic thrombocytopenic purpura; JIA: Juvenile idiopathic arthritis; MHC II: Major histocompatibility complex II; NK-cells: Natural killer cells; RA: Rheumatoid arthritis; SNP: Single-nucleotide polymorphism; Th: T helper.

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Author contributions

MA contributed to study design, sample collection, molecular analysis, data analysis, manuscript preparation and final proof. ZT was involved in sample collection, molecular analysis and final proof. VA contributed to sample collection and final proof. BM was involved in study design, data analysis and final proof. JR contributed to study design, manuscript preparation and final proof. BM was involved in sample collection, manuscript preparation and final proof. MP contributed to molecular analysis and final proof. AV was involved in sample collection, data analysis and final proof. ASV contributed to molecular analysis, manuscript preparation and final proof. ST was involved in study design, data analysis and final proof. HSK contributed to study design, molecular analysis, data analysis, manuscript preparation and final proof. All authors read and approved the final manuscript.

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Availability of data and materials

The data supporting this research project are available at corresponding author upon request.

Declarations

Ethics approval and consent to participate

This study was approved by local ethic committee with reference number 61930. 1398.12.11. All process was done according to Helsinki declaration. All consent forms are available, and study data were collected as blind forms with no identity from patients.

Consent for publication

All required consent for publications is collected before submission of the manuscript.

Competing interests

The authors declare that they have no competing interests.

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