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Original Article

Frequencies of HLA-E*01:01/*01:03 Alleles in an Iranian Healthy Population and Its Comparison with Hyperglycemia Patients

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Background and Aims: The human leukocyte antigen-E (HLA-E) is a member of non-classical HLA class-I genes which is highly conserved through evolution. In general, so far 25 alleles of HLA-E have been described. However, the existence of only two allelic group; HLA-E*01:01 and HLA-E*01:03 have been demonstrated in all the populations. HLA-E*01:01 and HLA-E*01:03 differ only at codon 107 of exon 3. The aim of this study was to survey on the frequency of HLA-E alleles; HLA-E*01:01 and HLA-E*01:03 in healthy and high blood sugar subjects.

Materials and Methods: Genomic DNA was extracted from the whole blood of 137 randomly selected healthy individuals and 86 patients with high blood sugar by using salting-out method. HLA-E*01:01 and HLA-E*01:03 alleles were determined by polymerase chain reaction sequence-specific primers. To overcome the ambiguity of some results, polymerase chain reaction-restriction fragment length polymorphism method saw used. Finally, the nucleotide sequence of a limited number of polymerase chain reaction products was determined.

Results: In healthy subjects, the allelic frequency of HLA-E*01:01 and HLA-E*01:03 were 48.9% and 51.1%, respectively. In high blood sugar subjects, the allelic frequency of HLA-E*01:01 and HLA-E*01:03 were 50.6% and 49.4%, respectively. The dominant allele in the healthy subjects was HLA-E*01:03 and in high blood sugar group was HLA-E*01:01 without significant differences for HLA-E*01:01 and HLA-E*01:03 frequencies in high blood sugar group.

Conclusions: Our results about the frequencies of HLA-E*01:01 and HLA-E*01:03 alleles in Iranian population showed similarities with French and Korean populations.

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Introduction

The human leukocyte antigen-E (HLA-E) is a non-classical HLA class I gene [1], which has been located between HLA-A and HLA-C loci on chromosome 6 P21.3 [2, 3]. Like other HLA class Ib molecules (HLA-F, -G), HLA-E is distinguished from the classical Ia molecules (HLA-A, -B, -C) in terms of low genetic diversity, low cellular expression and limited tissue distribution [4, 5]. The force of natural selection that led to the low diversity of HLA-E in the process of evolution, is still unknown. Despite the wide transcription of HLA-E in all human tissues [6], the protein expression of this molecule is often limited to endothelial cells (from non-lymphoid organs), T lymphocytes, B lymphocytes, monocytes, macrophages and the trophoblastic tissues in relation to the maternal-fetal tolerance [7- 10]. HLA-E plays a role as a modulator of NK cell activity through interaction with CD94/ NKG2A receptors. On the other hand, this molecule acts as an antigen-presenting molecule and accelerate both innate and adaptive immunity [11, 12].

So far, 25 alleles of HLA-E have been described in the literature (IMGT/HLA Database) [13]. In general, three allelic groups of HLA-E have been defined as different populations, including HLA-E*01:01, E*01:03 and E*01:04 [14]. The differences of these alleles are only in one amino acid, which can influence on the tendency of HLA molecules for binding to peptides [15].The existence of HLA-E*01:04 has not been proven by recent studies [6, 14, 16]. In fact, only the existence of HLA-E*01:01 and HLA-E*01:03 alleles have been proven in all populations [17, 18]. The allele frequencies of HLA-E*01:01 and HLA-E*01:03 are dependent on the ethnicity and the geographical location of the populations [19]. HLA-E*01:01 and HLA-E*01:03 differ by amino acid substitution at codon number 107 in exon 3. The codon number 107 encodes arginine and glycine in HLA-E*0101 and in HLA-E*0103, respectively. These two alleles differ in the surface expression levels, the peptide binding affinity and the stability of the molecule in particular, their thermal stability [2, 20]. A number of studies have shown the relationship between HLA-E alleles and some diseases such as recurrent spontaneous abortion [1, 21], autoimmune diseases such as Behcet's disease [20, 22], Ankylosing spondylitis [23], autoimmune diabete [24], varients of cancer, including cancer of the nose and throat, lymphomas, melanomas, glioblastomas, colorectal and kidney cancer [6, 25, 26], transplantation [27] and type I diabetes [28-30]. Impaired humoral and cell-mediated immunity have been shown in diabetic and hyperglycemia subjects [29]. Also at diabetic patients, different pathways include triacylglyceride synthesis, proteasome degradation, statin pathway, fluoropyrimidine activity, pathogenic infection, adipogenesis and ampk signaling have been changed. Defects in these pathways are associated with some genes such as HLA-B, HLA-E, HLA-J [30]. Diabetes causes high blood sugar levels either due to a lack of

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insulin (type 1 diabetes) or lack of proper response to insulin. In prediabetes, it is usually due to the cells not responding correctly. In type 2 diabetes, it is usually a combination. Although limited studies have been conducted on the relationship between HLA alleles and type I diabetes [28, 30], but no studies have been done on type 2 diabetes.

The aim of this study was to investigate the frequencies of HLA-E*01:01 and HLA-E*01:03 in a healthy population and in high blood sugar subjects of Iran to survey the possible association between HLA-E alleles and hyperglycemia.

Materials and Methods

Preparation of the samples

Based on the approval of the Medical Ethics Committee of Tarbiat Modares University (reference number; 5192/52 on date 2014), whole blood were prepared from 137 randomly selected Iranian healthy individuals and 86 patients with high blood sugar (fasting blood sugar (FBS) mean= 182.48±47.9 mg/dl) referred to Iranian Blood Transfusion Organization (IBTO). The demographic data of the studied groups were presented in table 1 and diagram 1.

Table 1. Demographic characteristics

Variable		Healthy group (n=137)	High blood sugar group (n=86)
Age (yr)*		46.96±12.94	54.81±10.17
Sex	**Male, No. (%)**	58 (42.4%)	40 (46.5%)
	Female, No. (%)	79 (57.6%)	46 (53.5%)

*Data presented as Mean±SD

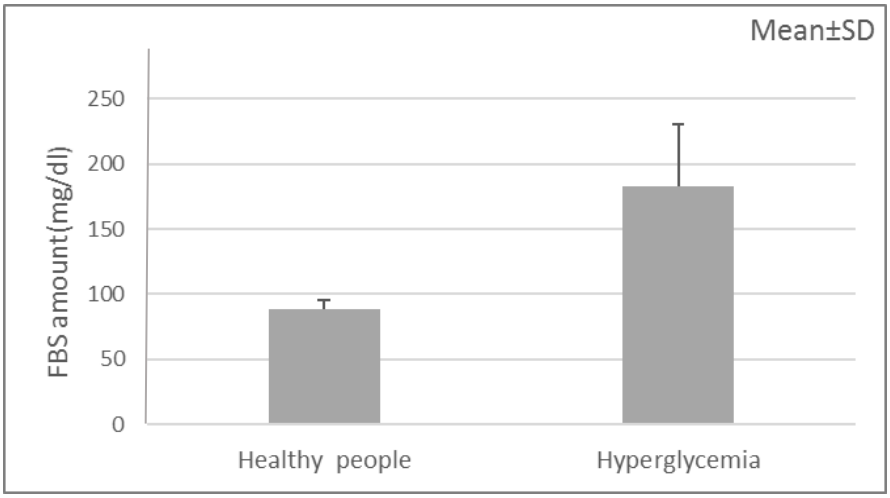

Diagram 1. Blood sugar distribution in two studied groups

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DNA extraction and the polymerase chain reaction-sequence specific primer (PCR- SSP)

DNA extraction was performed using salting out method and the concentration and purity of the extracted DNA were examined using a Nanodrop spectrophotometer (WPA, UK). Additionally, to ensure the integrity of the DNA molecules and the absence of smears, electrophoresis was carried out on a 1.5% agarose gel. In this study, PCR-SSP and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) were used to identify the alleles and resolve the ambiguities. PCR reactions were carried out by using 300-500 ng of genomic DNA in a total volume of 50 µl of the reaction mixture containing 0.4 µM of primers for HLA-E*01:01 (exon 3: forward: 5'-GCGAGCTGGG GCCCGTCA -3', reverse: 5'-CCGCCTCAG AGGCATCATTTG-3') and for HLA-E*01:03 primers (exon 3: forward: 5'-TGCGAGCTGGG GCCCGGCG-3', reverse: 5'-CCGCCTCAGA GGCATCATTTG-3'). It is of note that we used primers that have an extra mismatch at 3' terminal. This additional mismatch increases high powerfulness and specificity for intended HLA-E alleles amplification (primers adopted from Liu et al.) [3]. Other ingredients included 1x reaction buffer (Roche, Mannheim, Germany), 2.1 mM MgCL2, 200 µM dNTP and 2.5 U of Taq DNA polymerase (Genet Bio, Korea). The PCR-cycling conditions were as follows: initial denaturation at 98ºC for 5 min., followed by 34 cycles of 96ºC for 40 s, 60ºC for 25 s and 68ºC for 30 s and The program was followed by a final extension step at 72ºC for 5 min All PCR reactions were performed with a thermo cycler machine (Corbett-UK)).

Multiplex PCR-SSP

To ensure accuracy of the results, a multiplex PCR-SSP was used for all the PCR reactions in the presence of beta-actin gene as an internal control with the following primers: forward: 5'-TCAACCCTACAGTCACCCAT-3' and reverse: 5'-CTACAATTACGAACAGCATTGAG-3.' PCR reaction medium consisted of 0.4 µM HLA-E*01:01 or 0.4 µM HLA-E*01:03 primers accompanied with 0.2 µM of beta-actin primers, 1x reaction buffer (Roche, Mannheim, Germany), 2.1 mM MgCL2, 200 µM dNTP and 2.5 U of Taq DNA polymerase. According to the primers used in this study, PCR bands with the size of 500 bp, 159 bp and 160 bp were expected for β-actin (as internal control), HLA-E*01:01 and HLA-E*01:03, respectively. The annealing temperature was determined primarily due to the melting temperature of the primers and subsequently adjusted by the experiments. The PCR-cycling conditions were as follows: initial denaturation at 96ºC for 5 min., followed by 10 cycles of 94ºC for 15s, 62ºC for 30 s and 68ºC for 1 min and another 33 cycles of 94ºC for 30s, 60ºC for 25s and 68ºC for 30s. The program was followed by a final extension step at 72ºC for 6 min. Finally, the PCR products were visualized using electrophoresis on 1.5 % agarose gel included ethidium bromide as a fluorescent DNA intercalator. The sizes of the PCR products were determined using a 50 bp or 100 bp DNA ladder by electrophoresis.

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PCR-RFLP

In PCR-RFLP method, a restriction enzyme cuts the amplified DNA. The size of the generated fragments shows the kind of the allele. A fragment of exon 3 was amplified by using primers; forward 5'- GGCTGC GAG CTG GGG CCC GCC -3' [21] and reverse: 5'- CCGCCTCAGAGGCATCATTTG -3' [3]. PCR reactions were performed in a volume of 50 µl consisted of 0.2 µM HLA-E primers, 1x reaction buffer (Roche, Mannheim, Germany), 2.1 mM MgCL2, 200 µM dNTP and 2.5 U of Taq DNA polymerase. The PCR-cycling conditions were as follows: initial denaturation at 98ºC for 5 min., followed by 36 cycles of 94ºC for 45s, 61ºC for 45s and 72ºC for 45s. The program was followed by a final extension step at 72ºC for 6 min. The final product of PCR (163 bp) was exposed to MspI (HpaII) restriction enzyme (10U/µl; Thermo Scientific) to cleave DNA at specific sites of exon 3. For each reaction, 15 µl of the PCR product was mixed with 2 µl Tango Buffer, 1 µl enzyme, and 13 µl distilled water and incubated at 37°C for 16 hours. Subsequently, the DNA fragments were separated by gel electrophoresis. Unbroken template bands (163 bp) showed HLA-E*01:01 and the broken fragments (20 and 143 bp) of PCR products indicated the HLA-E*01:03 allele.

Additionally, several samples with heterozygous and homozygous alleles of HLA-E were randomly selected for sequence based typing by Bioneer-Korea. The sequences were analyzed by Blast tool and the softwares of Chromas and Codon code were used to verify the type of HLA-E allele.

Statistical analysis

The analysis was performed using SPSS 21 software. The statistical tests of χ^2 and frequencies were used to analyze the data.

Results

PCR and PCR-SSP results

Diagnosis of HLA-E alleles was done by PCR method using the specific primers of HLA-E*01:01 and HLA-E*01:03. Positive and negative results can be seen in fig. 1A. Because of the uncertainty of the negative results, a multiplex PCR-SSP method was used in the presence of beta-actin primers as an internal control. The results of PCR-SSP were shown for HLA-E*01:01 and HLA-E*01:03 alleles (Fig. 1B, Fig. 1C & Fig. 2).

The polymorphism of HLA-E genotype and allele frequencies

Gene and allele frequencies of HLA-E at both groups are presented in table 2. The relationship between two alleles of HLA-E gene was determined in healthy and high blood sugar subjects using SPSS and Chi-square test. The frequency of HLA-E*01:03 allele at healthy group was significantly higher (p=0.001, 95% CI= 1.212-1.523) than HLA-E*01:01 allele, but at high blood sugar group no significant differences were observed between two alles (p=0.115, 95% CI= 1.106-1.384).

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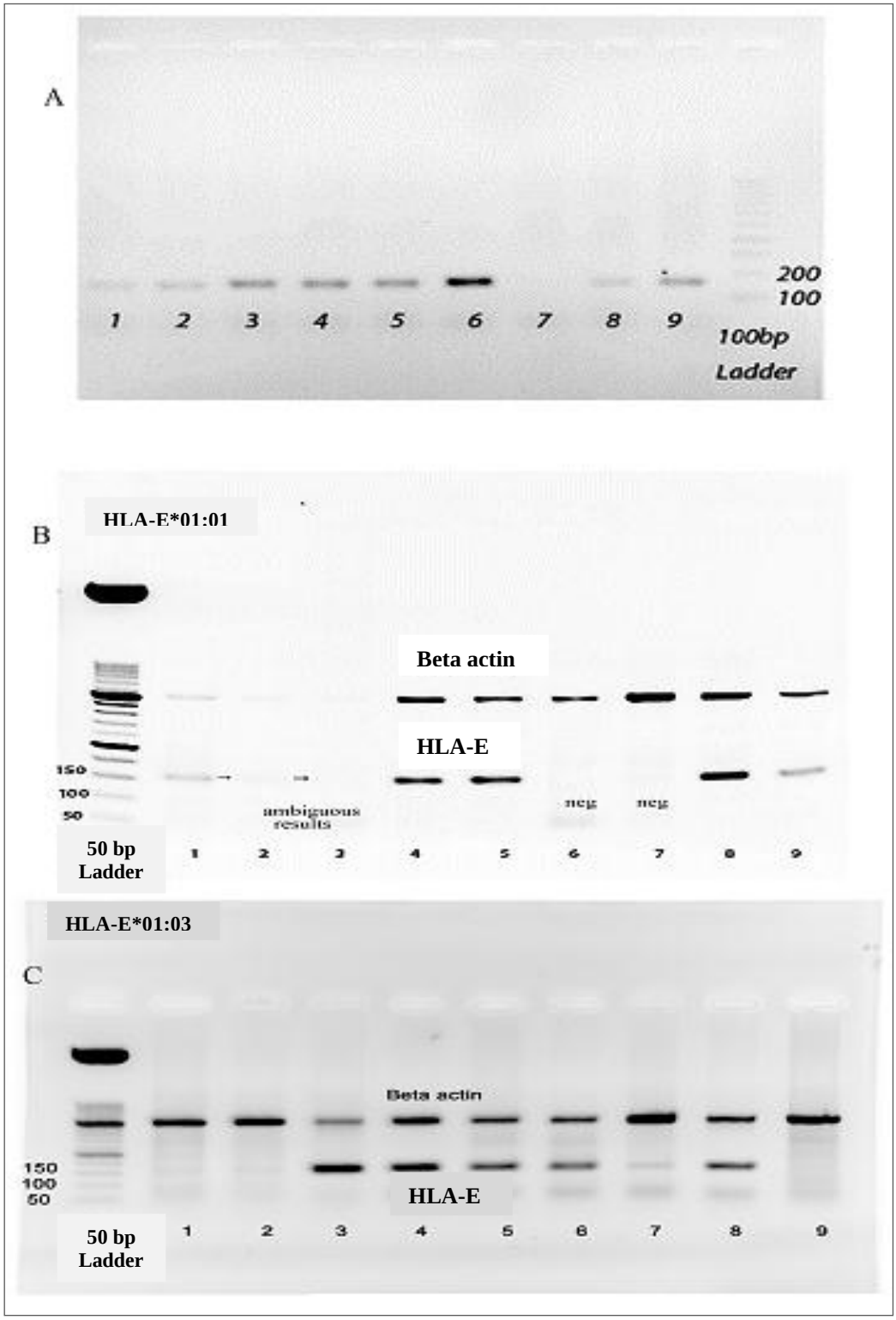

Fig. 1. PCR-SSP results for the alleles of HLA-E. (A) PCR-SSP implementation without usage of internal control. In this image, samples in lanes; 1, 3, 5 and 9 were positive for HLA-E*01:01 allele, sample numbers; 2, 4, 6 and 8 represented HLA-E*01:03 allele and sample number 7 was negative for HLA-E*01:01 allele. (B & C) represented the results of multiplex PCR-SSP for HLA-E alleles. β-actin gene was used as internal control. In this condition, because of the existence of the internal control (β-actin) bands, the results for each of the alleles can be evaluated more accurately.

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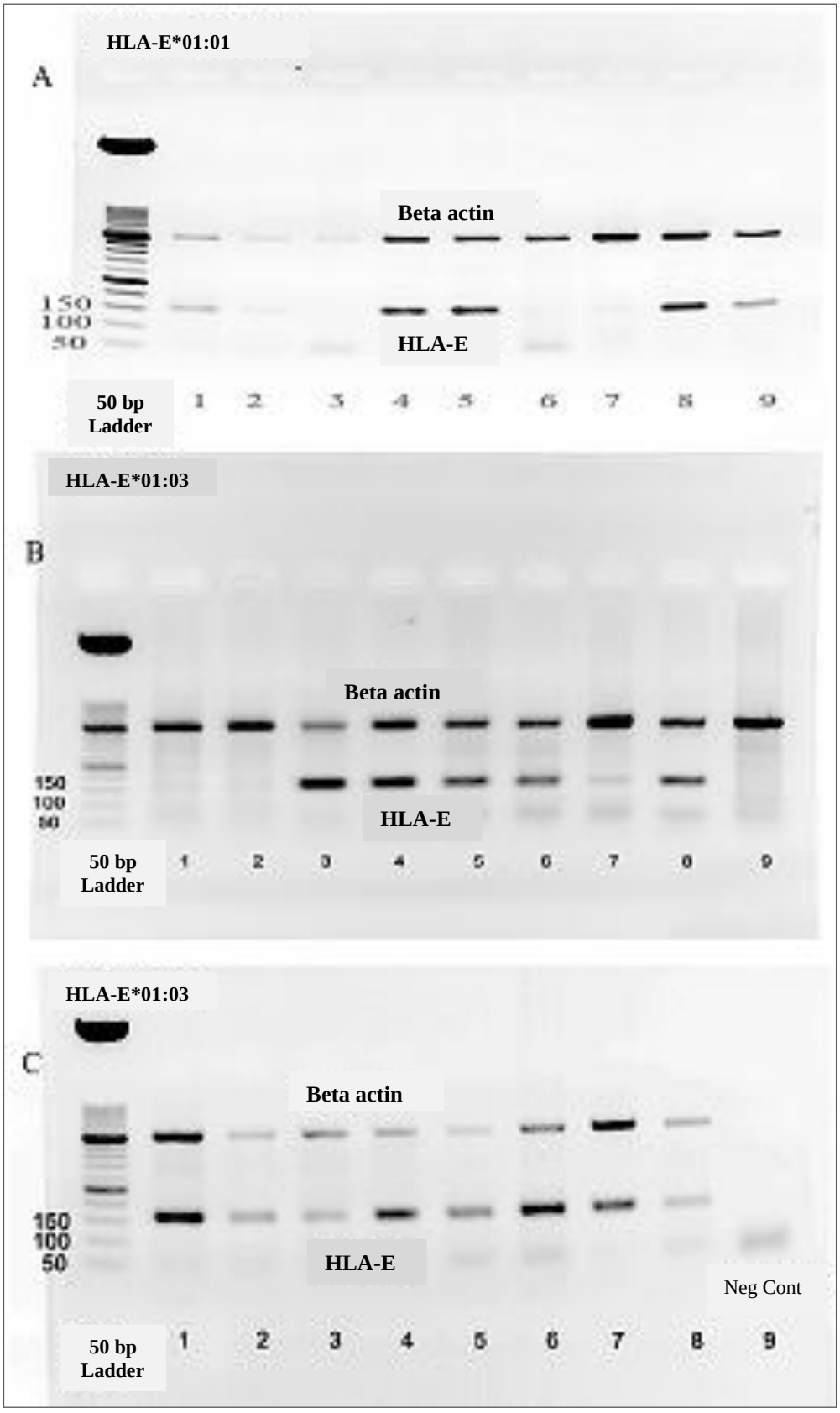

Fig. 2. Multiplex PCR-SSP results for HLA-E and β-actin genes. The heterozygosity for HLA-E alleles was demonstrated for the JEG-3 cell line (lane 6 in B&C) as a control. Lane 9 in (C) shows a negative control (the reaction without DNA).

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PCR-RFLP and sequence based typing results

The presence of HpaII restriction site was identified on an amplified fragment of exon 3 of HLA-E gene. This enzyme cuts the HLA-E*0103 allele into two fragments, 143 and 20 bp fragments. The JEG-3 cell line was used as a control. Then, the results were interpreted and evaluated on gel electrophoresis images. The presence of both cut and uncut fragments indicated the presence of both HLA-E*01:01 and HLA-E*01:03 alleles in the sample whereas uncut single bond and cut single bound showed HLA-E*01:01 and HLA-E*01:03 alleles, respectively (Fig. 3).

Additionally, the genotype study related to the nucleotide number 382 of exon 3 revealed that, at the healthy group the most frequent genotype was AG (56.93%) and GG (22.63%) and AA (20.44%) followed it, whereas in the higher blood sugar group, the frequent genotype was AG (68.6%) and AA (16.3%) and GG (15.1%) followed it.

Sequence alignment with HLA-E gene was shown by the Basic Local Alignment Search Tool. Furthermore, sequencing-based typing results of HLA-E were analyzed in heterozygous and homozygous samples by Chromas and Codon code softwares. Aligned DNA sequence chromatogram images are shown in fig. 4. The results of a sequence based typing confirmed the results of multiplex PCR-SSP method.

Table 2. The allelic and genotype frequencies of HLA-E in a population of Iran. The most frequent allele and genotype are shown

Allele	Healthy group (n=137)	High blood sugar group (n=86)
	No. (%)	No. (%)
HLA-E*01:01 (nucleotide number 382 in exon 3: A)	134 (48.9%)	87 (50.6)
HLA-E*01:03 (nucleotide number 382 in exon 3: G)	140 (51.1)	85 (49.4)
Genotype		
AA	28 (20.44)	14 (16.3)
AG	78 (56.93)	59 (68.6)
GG	31 (22.63)	13 (15.1)

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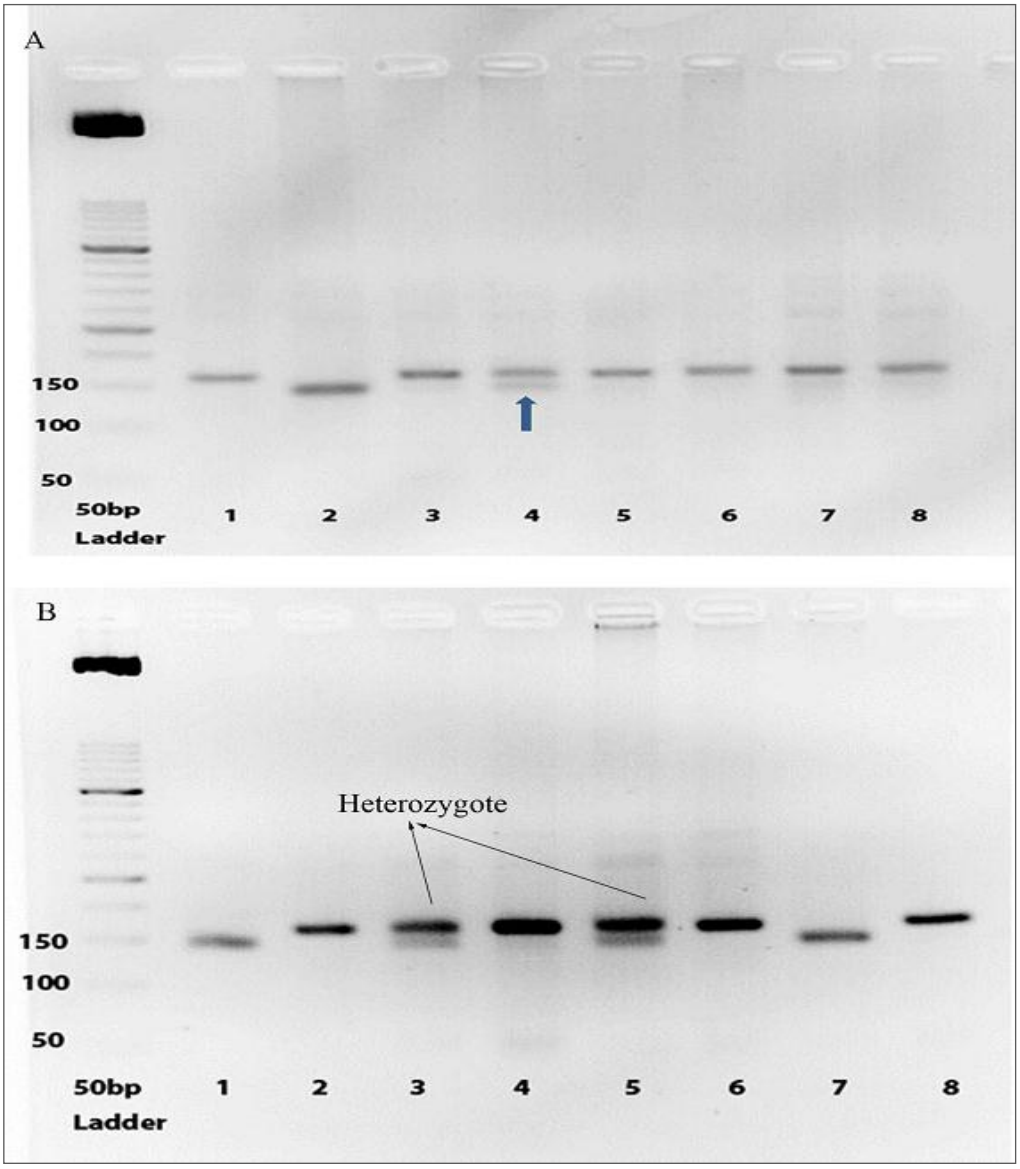

Fig. 3. PCR-RFLP results for HLA-E alleles. The existence of HpaII restriction site on the PCR product comprising the third exon of HLA-E gene was evaluated. Each sample had a different pattern of bands. lane 2 in (A) and lanes; 1,7 in (B) indicated the completely cut PCR products and showed the presence of HLA-E*01:03 allele in the samples. Lane 4 in (A) and lanes; 3,5 in (B) indicated both uncut and cut strands so showed the presence of both alleles of HLA-E*01:01 and HLA-E*01:03. The uncut single band in (A); lanes; 1,3 and 5-8 and (B); lanes; 2,6 and 8 indicated the presence of only HLA-E*01:01 allele in these samples.

Discussion

The HLA-E gene is important in the modulation of the immune system. The association of the polymorphism of HLA-E alleles and some diseases has been identified [22]. In this study, the polymorphism of the common alleles of HLA-E (HLA-E*01:01 and HLA-E*01:03) were studied in the healthy population and high blood sugar subjects of Iran.

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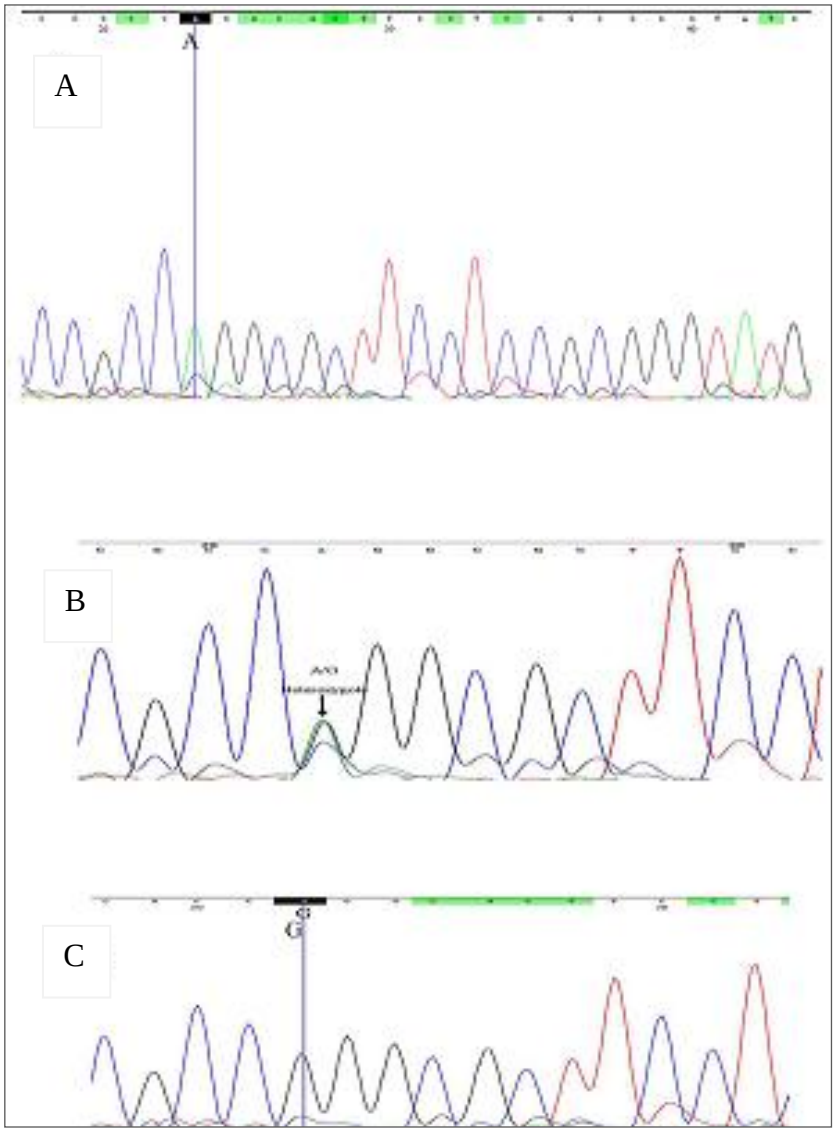

Fig.4. Sequencing chromatogram for a fragment of exon 3 of HLA-E gene. The chromatogram was converted into the DNA sequence using Chromas software. Hemozygocity (A, C) and heterozygocity (B) in the neucleotide position 382 was shown. The results of nucleotide sequencing was correlated with multiplex PCR-SSP and PCR-RFLP methods.

Various methods have been used to investigate the polymorphism of HLA-E alleles such as PCR and sequencing [10], PCR-SSP [11], multiplex PCR [31], PCR-RFLP [32], PCR-SSCP [33] and PCR-SSOP [34]. In this study, a multiplex PCR-SSP technique was used as the main method, due to the specificity of primers. Additionally, PCR-RFLP method was used to resolve ambiguities.

We found that AG genotype (HLA-E*01:01/ HLA-E*01:03) was the most frequent at both normal and high blood sugar groups. In addition, in healthy group GG (HLA-E*01:03/ HLA-E*01:03) genotype was higher than AA. On the contrary, in high blood sugar group, AA (HLA-E*01:01 and HLA-E*01:01) genotype was frequent although no significant difference was observed. The prevalence of HLA-E*01:01

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and HLA-E*01:03 alleles at healthy group were 48.9% and 51.1%, and in high blood sugar group were 50.6% and 49.4%, respectively. In comparing between two groups, no significant differences were observed. Despite the relationship between HLA-E expression with diabetes disease [28], our study did not show a relationship between the polymorphism of the studied alleles of HLA-E and high blood sugar.

The frequency of HLA-E alleles in the studied healthy population showed the similarity to the French (HLA-E*01:01=50% and HLA-E*01:03=50%) [31] and South Korean population (HLA-E*01:01=49.1% and HLA-E*01:03= 50.9%) [22]. Whereas, higher differences in HLA-E allele frequencies were reported in some other populations such as Japan (HLA-E*01:01=32% and HLA-E*01:03=68%) [16], southern Chinese Han population (HLA-E*01:01=32.29% and HLA-E*01:03=67.71%) [11] and Mexico (HLA-E*01:01=58.62% and HLA-E*01:03=36.49%) population [35]. It was known that the frequency of HLA alleles was associated with the ethnicity and the geographical location of the population, but the association of HLA-E alleles (HLA-E*01:01 and HLA-E*01:03) with ethnicity was not seen. For example, the results for African people (Zimbabwe) (HLA-E*01:01=50.93% and HLA-E*01:03=49.07%) [31] were similar to French and Korean people. So, in some unrelated ethnic groups, such as France, Korea and Africa (Zimbabwe), the frequencies of these alleles were similar wherase in other close populations such as the Afro-Caribbean (HLA-E*01:01=53.3% and HLA-E*01:03=46.7%) [36] and Zimbabwe, these alleles were less similar. At present, the relationship between HLA-E alleles and the ethnicities can not be explained. The discovery of new alleles of HLA-E may make it possible to explain the association between HLA-E alleles and the ethnicities in different populations.

Conclusions

It was shown that HLA-E*01:03 was the frequent allele in Iranian population. The relationship between these alleles with high blood sugar was not statistically significant. However, in the high-blood sugar group, the HLA-E*01: 01 allele was more frequent. Our results showed similarities in HLA-E allele frequencies between Iranian healthy people and French and Korean population.

Conflict of Interest

There is no potential conflict of interest to declare.

Acknowledgements

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