Distribution of KIR genes in the Lur population of Iran

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Abstract

Background: Killer-cell Immunoglobulin-like Receptors (KIR) are the members of inhibitory and activating receptors expressed mainly on the natural killer cells. KIR genes family is polymorphic strongly and its genomic diversity results in gene content and allelic polymorphism. The aim of this study was to report the distribution of the KIR genes in the Lur population for the first time. **Materials and Methods:** In this study, 100 unrelated healthy Lur individuals were KIR typed by polymerase chain reaction-sequence specific primers genotyping assay. Finally, Lur KIR genes distribution was compared with other Iranian populations. **Results:** Twenty-two different genotypes were found in the Lur population. The most common non-framework genes were KIR2DP1 and KIR2DL1 with a frequency of 98% and KIR3DL1 and KIR2DS4 with a frequency of 96% in the Lur population. The most common observed KIR genotype (AA genotype) consisted of six inhibitory genes, one activating gene and two pseudogenes, was occurred with a frequency of 29% in the Lur population. **Discussion:** The results show that KIR genes distribution in the Lur population has similar features with other Iranian populations studied before, but it is still unique because of decrease or increase in some loci frequencies.

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1. Introduction

Killer-cell immunoglobulin-like Receptors (KIRs) are regulator molecules expressed on the Natural Killer (NK) cells and some of the T lymphocyte subsets. These polymorphic receptors interact with specific motifs of human leukocyte antigen (HLA) class I molecules and modulate cytolytic activity of the NK cells. Some KIRs interact with HLA-C, HLA-BW4, HLA-A3/A11, and HLA-G molecules of target cells. However, for some KIRs the corresponding ligands are still unknown (1-3).

The KIR genes locate on chromosome 19 in the leukocyte receptor complex. These receptors are divided into two groups based on the number of their extracellular immunoglobulin domains (3D or 2D). Those with long (L) cytoplasmic tails bearing immune receptor tyrosine-based inhibitory motifs (ITIMs) are inhibitory receptors (3DL and 2DL), While those with short (S) cytoplasmic tails bearing no ITIMs are activating receptors (3DS and 2DS). To date, 14 KIR genes and 2 pseudogenes have been described. Seven genes of KIR3DL1-3, KIR2DL1-3 and KIR2DL5 encode for the inhibitory KIR (iKIR), six genes of KIR3DS1 and KIR2DS1-5 encode for activating KIRs (aKIR), one gene encodes for KIR2DL4 with both inhibitory and activating functions, and two genes of KIR2DP1 and KIR3DP1 are pseudogenes that do not encode a functional KIR molecule (4-7). Haplotypes A and B are the two basic haplotypes that have been defined on the basis of gene content (8-12).

Given the significant racial (13-31) and ethnic (32, 33) differences in the distribution of the KIR genes as well as association of KIR genes with diseases (34), the aim of this preliminary study was to determine the frequency of KIR genes in the Lur population living in the Lorestan province of Iran. We also compare the data so obtained with those previously described in other Iranian populations.

2. Materials and methods

2.1. Population samples

One hundred unrelated healthy Lur individuals 18-35 years old, male and female each 50, were randomly selected for this study. Lur people live in the Lorestan province of Iran and speak Luri, a dialect of Persian language. All participants were confirmed to have parents of the same ethnic group, and those with mixed parentage were excluded. In addition, none of the individuals had a personal or family history of cancer or autoimmune diseases. Whole blood samples were collected with the written consent of the individuals. The study was reviewed and approved by the ethics committee of the Lorestan University of Medical Sciences.

2.2. KIR genotyping

Genomic DNA was extracted from peripheral blood leukocytes by EXTRA GENE I kit (BAG, Germany) according to the manufacturer's instructions and DNA concentration and the ratio (OD260/OD280) were evaluated. DNA samples were genotyped for the presence or absence of 16 KIR genes by KIR TYPE kit (BAG, Germany), based on polymerase chain reaction-sequence specific primers (PCR-SSP) assay.

PCR-SSP was performed following the manufacturer's instructions. Briefly, 52 µl of DNA at a concentration of 25-40 ng/µl with ratio>1.5 was mixed with 26 µl of 10x PCR Buffer, 2.1 µl of Taq polymerase and 180 µl of distilled water. Ten µl of this mixture was used for each reaction. The reaction was amplified by a MYCYCLER (BioRad, USA) PCR system under the thermal and time conditions recommended by the manufacturer, which started with a heating temperature of 94°C for 2 min, followed by 10 cycles of 15 s at 94°C, 50 s at 65°C and 45 s at 72°C and 20 cycles of 15 s at 94°C, 50 s at 61°C and 30 s at 72°C.

The PCR products were analyzed in 2% agarose gel stained with ethidium bromide. The DNA separation was performed at 200 volts for 20 minutes. The amplification was checked on a UV transilluminator and photographed. The typing was interpreted by a worksheet. Samples containing at least one of the KIR B loci including KIR2DL2, KIR2DL5, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS5 or KIR3DS1 were assigned to the Bx genotype. Samples lacking all of the B loci were assigned to the AA genotype (35).

2.3. Statistical analysis

The percentage of the population positive for KIR genes and genotypes was determined by direct counting. Differences between the Lur population and other Iranian populations in the distribution of KIR genes were determined by the chi-squared test with Yate's correction, assuming the existence of the Hardy-Weinberg equilibrium. All presented P values are uncorrected and labeling with (a) indicates values which remain significant after correction ($Pc<0.05$). Principal component analysis (PCA) was performed using SPSS 18 software to determine genetic affinities according to KIR locus data from 6 different Iranian populations, i.e. the Lur population described in this study and 5 populations described elsewhere (32, 33).

3. Results

The frequencies of KIR genes in 100 unrelated healthy Lur individuals are shown in Table 1. The KIR2DL4, KIR3DL2, and KIR3DL3 framework genes and the KIR3DP1 pseudogene were founded in the Lur population with a frequency of 100%. The most frequent non-framework genes were KIR2DL1 and KIR2DP1 with a frequency of 98% and KIR3DL1 and KIR2DS4 with a frequency of 96%. The KIR2DS3 and KIR2DS5 activating KIR genes had the lowest frequency in the Lur population (34% and 40%, respectively).

The representation of KIR genotypes in 100 unrelated healthy Lur individuals is shown in Figure 1. We identified 22 different KIR genotypes in the Lur population. All of the genotypes contained 9 to 16 KIR genes. The simplest KIR genotype (number 1) included 9 KIR genes. The most complex genotype (number 5) comprised of 16 KIR genes. The most frequent genotype (number 1), observed in all populations, was occurred in 29% of the Lur population. This genotype bearing six inhibitory genes, one activating gene and two pseudogenes was consistent with the AA genotype. Other analyzed individuals (71%) had more than one activating gene and thus were assigned as Bx genotypes (Figure 1 and Table 1). In the present study, eleven genotypes had a frequency of 1%.

All observed genotypes had either KIR2DL2 or KIR2DL3 gene, which encodes receptors with HLA-C1 specificity. However, 42% of the Lur individuals had both KIR2DL2 and KIR2DL3. Seventeen genotypes, including five common genotypes, carried each four specific inhibitory KIR genes KIR2DL1, KIR2DL2/3, KIR3DL1, and KIR3DL2 for class I HLA and were represented in 94% of the Lur population. Also, 6% of the Lur individuals lacked either KIR2DL1 or KIR3DL1 gene, which encodes receptors with HLA-C2 and HLA-Bw4 specificities, respectively.

4. Discussion

In this study, 16 KIR genes were tested in 100 unrelated healthy Lur individuals. The frequency of KIR genes in the Lur population and some other Iranian populations are indicated in Table 1, which also shows any significant differences. The frequency of inhibitory KIR genes KIR2DL1, KIR2DL3, KIR2DL4, KIR3DL1, KIR3DL2, and KIR3DL3, pseudogenes KIR2DP1 and KIR3DP1, and activating gene KIR2DS4 were high in all of the Iranian populations, including the Lur population.

Comparing the results of the present study with those of Ashouri et al (32) and Hiby et al (33) studies in the other Iranian populations, proved high similarity in KIR gene frequencies in the Lur, Bakhtiari, and Jonobi populations (Table 1). Among neighboring populations, the most similar to the Lur population in distribution of KIR genes, was the Bakhtiari population, and this can be confirmed on the common ancestral origin of these populations. Also, the comparison of the results of this study with

those of Tajik et al (31) study in 200 unrelated healthy individuals from across Iran showed that the KIR gene frequencies in the Lur population has no significant difference with the general Iranian population. On the other hand, in the Lur population, considerable differences with the other Iranian populations were found for some of the KIR loci (Table 1): KIR2DS1, KIR2DS5, and KIR3DS1 with Persian population, KIR2DS2 with Azari population, and KIR2DS3 with Arab and Azari populations. Two activating KIR genes, KIR2DS3 and KIR2DS5, had the lowest observed frequencies in the Lur population. However, the frequency of KIR2DS5 gene was higher than that observed in the other Iranian populations. In addition, major differences were observed between the Lur population and the Azari and Persian populations. For example, KIR2DS1 and KIR2DS5 frequencies in the Persian population were lower than that observed in the Lur population (35% and 25.4% vs. 48% and 40%, respectively). In contrast, KIR2DS2 and KIR3DS3 frequencies were higher in the Azari population than that observed in the Lur population (70.2% and 53.5% vs. 55% and 34%, respectively).

PCA mapping using KIR locus data from the Lur population and five previously described Iranian populations (32, 33) showed relationship of the Lur population with the Bakhtiari and Jonobi populations and difference between this population and the Persian, Azari and Arab populations (Figure not shown).

In the present study, 22 different KIR genotypes were observed in the Lur population (Figure 1). The five most common genotypes (numbers 1-5) observed in the Lur population accounted for 65% of all present genotypes, which were also frequent in the other Iranian populations. In this study, the AA genotype with a frequency of 29% was the most common genotype in the Lur population (Table 1). In addition, the AA genotype frequency in the Lur population was higher than that observed in the other Iranian populations. In this context, major differences were observed between the Lur population and the Arab and Azari populations. Thus, the AA genotype frequency in the Lur populations (29%) was higher than Arab population (15.8%) and Azari population (14.3%). In contrast, Bx genotypes frequency in Lur population (71%) was lower than Arab population (84.2%) and Azari population (85.7%).

Table 1. The distribution of KIR genes in the Lur population and compared with other Iranian populations.

KIR Genes and Genotypes	Lur population (n=100) F (%)	Persian* population (n=248) F (%)	Bakhtiari* population (n=96) F (%)	Arab* population (n=76) F (%)	Azari* population (n=48) F (%)	Jonobi** Population (n=100) F (%)
Genes						
2DL1	**98**	98	94.8	100	98	97
2DL2	**54**	56.8	54.1	63.1	67.9	54
2DL3	**88**	91	89.6	89.5	89.2	85
2DL4	**100**	100	100	100	100	100
2DL5	**61**	58	54.1	67.1	73.8	62
3DL1	**96**	94	95.8	85.5	90.5	93
3DL2	**100**	100	100	100	100	100
3DL3	**100**	100	100	100	100	100
2DS1	**48**	**35**[(a)]	42.7	44.7	39.2	42
2DS2	**55**	54	49	56.3	**70.2**[(a)]	57
2DS3	**34**	38.3	27.1	**50**[(b)]	**53.5**[(a)]	42
2DS4	**96**	96	97.9	98.7	98.8	93
2DS5	**40**	**25.4**[(a)]	39.6	35.5	34.5	36
3DS1	**45**	**33**[(b)]	45.8	42.1	38	37
2DP1	**98**	98	96.9	98.7	100	97
3DP1	**100**	100	100	100	100	100
Genotypes						
AA	**29**	28.7	25	**15.8**[(b)]	**14.3**[(a)]	26
Bx	**71**	71.3	75	**84.2**[(b)]	**85.7**[(a)]	74

* Ashouri et al 2009; ** Hiby et al 2010

[(a)] Significant difference after correction (PC<0.05)

[(b)] Significant difference before correction (P<0.05)

KIR Genotype	KIR Genotype #	KIR Genes																			No. of individuals (n=100)
		Inhibitory KIR								Activating KIR						Pseudo gene		No. of Genes			
		2DL1	2DL2	2DL3	2DL4	2DL5	3DL1	3DL2	3DL3	2DS1	2DS2	2DS3	2DS4	2DS5	3DS1	2DP1	3DP1	Inhibitory	Activating	Pseudogene	Total	
AA	1	■		■	■		■	■	■				■			■	■	6	1	2	9	29
Bx	2	■		■	■	■	■	■	■	■			■	■	■	■	■	7	4	2	13	12
	3	■	■	■	■		■	■	■		■		■			■	■	7	2	2	11	10
	4	■	■	■	■	■	■	■	■		■	■	■			■	■	8	3	2	13	7
	5	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	8	6	2	16	7
	6	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	8	5	2	15	7
	7	■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	8	5	2	15	6
	8	■	■		■	■	■	■	■		■	■	■			■	■	7	3	2	12	4
	9	■	■		■	■	■	■	■	■	■	■	■	■	■	■	■	7	6	2	15	3
	10	■	■	■	■	■	■	■	■	■	■		■	■		■	■	8	4	2	14	2
	11		■		■	■	■	■	■	■	■		■	■			■	6	4	1	11	2
	12	■	■	■	■	■		■	■	■	■	■		■	■	■	■	7	5	2	14	1
	13	■	■		■	■		■	■	■	■	■		■	■	■	■	6	5	2	13	1
	14	■		■	■	■		■	■	■				■	■	■	■	6	3	2	11	1
	15	■	■	■	■	■		■	■	■	■			■	■	■	■	7	4	2	13	1
	16	■	■	■	■	■	■	■	■		■	■	■		■	■	■	8	4	2	14	1
	17	■		■	■	■	■	■	■	■		■	■		■	■	■	7	4	2	13	1
	18	■		■	■	■	■	■	■	■	■		■	■	■	■	■	7	5	2	14	10
	19	■		■	■	■	■	■	■	■		■	■	■	■	■	■	7	5	2	14	1
	20	■		■	■	■	■	■	■			■	■		■	■	■	7	3	2	12	1
	21	■	■		■	■	■	■	■	■	■	■	■		■	■	■	7	5	2	14	1
	22	■	■		■	■	■	■	■	■	■		■	■		■	■	7	4	2	13	1

Figure 1. Distribution of Killer cell immunoglobulin-like receptors (KIR) genotypes in 100 Lur individuals.

KIR locus data analysis could be applied for evaluation of the genetic relationships among populations from different geographic areas in anthropological studies. Moreover, the determination of KIR gene frequencies and also the distribution of those genotypes in a population may be used as a good reference for genetic studies to identify the association between KIR genes and susceptibility to specific diseases e.g. infectious diseases (36, 37), autoimmune/inflammatory disorders (38, 39), cancers (40), and reproduction (41).

In summary, in this the first study, frequencies of KIR genes and those genotypes were determined in the Lur population living in the Lorestan province of Iran. Our results showed that the Lur population possesses the previously reported general features of the other Iranian populations, with some additional interesting differences.

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References

1. Winter CC, Long EO. A single amino acid in the p58 killer cell inhibitory receptor controls the ability of natural killer cells to discriminate between the two groups of HLA-C allotypes. J Immunol 1997; 158: 4026-28.

2. Thananchai H, Gillespie G, Martin MP, Bashirova A, Yawata N, Yawata M, et al. Cutting edge: allele-specific and peptide-dependent interactions between KIR3DL1 and HLA-A and HLA-B. J Immunol 2007; 178: 33-7.
3. Dohring C, Scheidegger D, Samaridis J, Cella M, Colonna M. A human killer inhibitory receptor specific for HLA-A1, 2. J Immunol 1996; 156: 3098-101.
4. Martin AM, Freitas EM, Witt CS, Christiansen FT. The genomic organization and evolution of the natural killer immunoglobulin-like receptor (KIR) gene cluster. Immunogenetics 2000; 51: 268-80.
5. Shahsavar F, Tajik N, Entezami K. Killer cell immunoglobulin-like receptors and their ligands. Qom University of Medical Sciences Journal 2010; 15: 47-62. (In Persian)
6. Trowsdale J. Genetic and functional relationships between MHC and NK receptor genes. Immunity 2001; 15: 363-74.
7. Wilson MJ, Torkar M, Haude A, Milne S, Jones T, Sheer D, et al. Plasticity in the organization and sequences of human KIR/ILT gene families. Proc Natl Acad Sci U S A 2000; 97: 4778-83.
8. Hsu KC, Chida S, Geraghty DE, Dupont B. The killer immunoglobulin-like receptor (KIR) genomic region: gene-order, haplotypes and allelic polymorphism. Immunol Rev 2002; 190: 40-52.
9. Martin AM, Kulski JK, Gaudieri S, Witt CS, Freitas EM, Trowsdale J, et al.Comparative genomic analysis, diversity and evolution of two KIR haplotypes A and B. Gene 2004; 335: 121-31.
10. Shilling HG, Guethlein LA, Cheng NW, Gardiner CM, Rodriguez R, Tyan D, et al. Allelic polymorphism synergizes with variable gene content to individualize human KIR genotype. J Immunol 2002; 168: 2307-15.
11. Vilches C, Parham P. KIR: diverse, rapidly evolving receptors of innate and adaptive immunity. Annu Rev Immunol 2002; 20: 217-51.
12. Uhrberg M. The KIR gene family: life in the fast lane of evolution. Eur J Immunol 2005; 35: 10-15.
13. Flores AC, Marcos CY, Paladino N, Capucchio M, Theiler G, Arruvito L, et al. KIR genes polymorphism in Argentinean Caucasoid and Amerindian populations. Tissue Antigens 2007; 69: 568-76.
14. Whang DH, Park H, Yoon JA, Park MH. Haplotype analysis of killer cell immunoglobulin-like receptor genes in 77 Korean families. Hum Immunol 2005; 66: 146-54.
15. Jiang K, Zhu FM, Lv QF, Yan LX. Distribution of killer cell immunoglobulin-like receptor genes in the Chinese Han population. Tissue Antigens 2005; 65: 556-63.
16. Toneva M, Lepage V, Lafay G, Dulphy N, Busson M, Lester S, et al. Genomic diversity of natural killer cell receptor genes in three populations. Tissue Antigens 2001; 57: 358-62.
17. Norman PJ, Stephens HA, Verity DH, Chandanayingyong D, Vaughan RW. Distribution of natural killer cell immunoglobulin-like receptor sequences in three ethnic groups. Immunogenetics 2001; 52: 195-205.
18. Gendzekhadze K, Norman PJ, Abi-Rached L, Layrisse Z, Parham P. High KIR diversity in Amerindians is maintained using few gene-content haplotypes. Immunogenetics 2006; 58: 474-80.
19. Lee YC, Chan SH, Ren EC. Asian population frequencies and haplotype distribution of killer cell immunoglobulin-like receptor (KIR) genes among Chinese, Malay, and Indian in Singapore. Immunogenetics 2008; 60: 645-54.
20. Denis L, Sivula J, Gourraud PA, Kerdudou N, Chout R, Ricard C, et al. Genetic diversity of KIR natural killer cell markers in populations from France, Guadeloupe, Finland, Senegal and Reunion. Tissue Antigens 2005; 66: 267-76.
21. Du Z, Gjertson DW, Reed EF, Rajalingam R. Receptor-ligand analyses define minimal killer cell Ig-like receptor (KIR) in humans. Immunogenetics 2007; 59: 1-15.
22. Niokou D, Spyropoulou-Vlachou M, Darlamitsou A, Stavropoulos-Giokas C. Distribution of killer cell immunoglobulin-like receptors in the Greek population. Hum Immunol 2003; 64: 1167-76.
23. Norman PJ, Carrington CV, Byng M, Maxwell LD, Curran MD, Stephens HA, et al. Natural killer cell immunoglobulin-like receptor (KIR) locus profiles in African and South Asian populations. Genes Immun 2002; 3: 86-95.
24. Rajalingam R, Krausa P, Shilling HG, Stein JB, Balamurugan A, McGinnis MD, et al. Distinctive KIR and HLA diversity in a panel of north Indian Hindus. Immunogenetics 2002; 53: 1009-19.
25. Santin I, de Nanclares GP, Calvo B, Gaafar A, Castano L, Bilbao JR. Killer cell immunoglobulin-like receptor (KIR) genes in the Basque population: association study of KIR gene contents with type 1 diabetes mellitus. Hum Immunol 2006; 67: 118-24.

26. Gutierrez-Rodriguez ME, Sandoval-Ramirez L, Diaz-Flores M, Marsh SG, Valladares-Salgado A, Madrigal JA, et al. KIR gene in ethnic and Mestizo populations from Mexico. Hum Immunol 2006; 67: 85-93.
27. Velickovic M, Velickovic Z, Dunckley H. Diversity of killer cell immunoglobulin-like receptor genes in Pacific Islands populations. Immunogenetics 2006; 58: 523-32.
28. Middleton D, Meenagh A, Gourraud PA. KIR haplotype content at the allele level in 77 Northern Irish families. Immunogenetics 2007; 59: 145-58.
29. Kulkarni S, Single RM, Martin MP, Rajalingam R, Badwe R, Joshi N, et al. Comparison of the rapidly evolving KIR locus in Parsis and natives of India. Immunogenetics 2008; 60: 121-9.
30. Pavlova Y, Kolesar L, Striz I, Jabor A, Slavcev A. Distribution of KIR genes in the Czech population. Int J Immunogenet 2008; 35: 57-61.
31. Tajik N, Shahsavar F, Mousavi T, Radjabzadeh MF. Distribution of KIR genes in the Iranian population. Tissue Antigens 2009; 74: 22-31.
32. Ashouri E, Farjadian S, Reed EF, Ghaderi A, Rajalingam R. KIR gene content diversity in four Iranian populations. Immunogenetics 2009; 61: 483-92.
33. Hiby SE, Ashrafian-Bonab M, Farrell L, Single RM, Balloux F, Carrington M, et al. Distribution of killer cell immunoglobulin-like receptors (KIR) and their HLA-C ligands in two Iranian populations. Immunogenetics 2010; 62: 65-73.
34. Shahsavar F, Mousavi T, Entezami K, Azargoon A. Association of KIR-HLA interactions with diseases. Yafte 2011; 49: 89-103. (In Persian)
35. Cooley S, Trachtenberg E, Bergemann TL, Saeteurn K, Klein J, Le CT, et al. Donors with group B KIR haplotypes improve relapse-free survival after unrelated hematopoietic cell transplantation for acute myelogenous leukemia. Blood. 2009; 113: 426-32.
36. Tajik N, Shah-hosseini A, Mohammadi A, Jafari M, Nasiri M, Radjabzadeh MF, et al. Susceptibility to pulmonary tuberculosis in Iranian individuals is not affected by compound KIR/HLA genotype. Tissue Antigens 2012;79(2):90-6.
37. Shahsavar F, Azargoon A, Mousavi T, Akbari S. KIR-HLA combinations and susceptibility to tuberculosis. Yafte 2013; 54: 117-27. (In Persian)
38. Mousavi T, Poormoghim H, Moradi M, Tajik N, Shahsavar F, Asadifar B. Inhibitory Killer Cell Immunoglobulin-Like Receptor KIR3DL1 in Combination with HLA-B Bw4iso Protect against Ankylosing Spondylitis. Iran J Immunol 2010; 7(2): 88-95.
39. Shahsavar F, Mousavi T, Sabooteh T. The role of balance between inhibitory and activating KIRs in determining susceptibility to Ankylosing Spondylitis. Yafte 2012; 52: 45-57. (In Persian)
40. Shahsavar F, Tajik N, Entezami K, Radjabzadeh MF, Asadifar B, Alimoghaddam K, et al. KIR2DS3 is associated with protection against acute myeloid leukemia. Iran J Immunol 2010; 7(1): 8-17.
41. Hiby SE, Regan L, Lo W, Farrell L, Carrington M, Moffett A. Association of maternal killer-cell immunoglobulin-like receptors and parental HLA-C genotypes with recurrent miscarriage. Hum Reprod 2008; 23(4): 972-6.

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