

Killer Cell Immunoglobulin-Like Receptor Genes Distribution in Southeastern Anatolia Population in Turkey

D. Mihcioglu^{a, *}, F. Ozbas Gerceker^b, E. Tufioglu^b, and T. Yilmaz^b

^a *Department of Nutrition and Dietetics, Faculty of Health Science, SANKO University, Gaziantep, 27090 Turkey*

^b *Department of Biology, Faculty of Arts and Science, Gaziantep University, Gaziantep, 27310 Turkey*

**e-mail: denizmihcioglu@hotmail.com*

Received October 12, 2022; revised July 26, 2023; accepted July 31, 2023

Abstract—Killer cell immunoglobulin-like receptor (KIR) molecules on the surface of Natural Killer cells HLA class I by interacting directly with their molecules, they cause inhibition or triggering of cytokine synthesis. The KIR gene family, plays an important role in the regulation of the immune response, is located in the 19q13.4 region in humans and consists of 15 homologous genes. Inhibitory KIR (iKIR) genes are 2DL1, 2DL2, 2DL3, 2DL4, 2DL5, 3DL1, 3DL2, 3DL3, activating KIR (aKIR) genes are KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DS1; two KIR pseudogenes are KIR2DP1 and KIR3DP1. There is not enough data on the KIR gene profile of the Turkish population. It was aimed to determine the genotype distribution of KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DS1, KIR2DL1-5, KIR3DL1-3) genes in the Southeastern Anatolia Region (SAR). In the present study 200 unrelated healthy individuals were included. Polymerase-chain reaction with sequence-specific primers method (PCR-SSP) were performed. 3DL3 had the highest (99.5%) frequency and the lowest frequency among the inhibitory KIR genes was obtained for 2DL2 (56.5%). The highest frequency among the activator KIR genes was obtained for 2DS4 (93.5%) and the lowest was for 2DS5 (28%). It can be concluded that the SAR population has similar KIR gene features to the Caucasians. But studies with more extensive sample groups are needed to understand the relationship between KIR gene distribution and similarities between populations.

Keywords: KIR genes, PCR-SSP, Southeastern Anatolia population

DOI: 10.1134/S1062359022602439

INTRODUCTION

Killer cell immunoglobulin-like receptors (KIR) are glycoproteins expressed on the exterior face of natural killer (NK) cells (Tajik et al., 2009). One of the most important components of innate immunity, NK cells play a significant part in protecting against viral infections as well as infectious illnesses (Purdy and Campbell, 2009; Shi et al., 2013). NK cells are lymphocytes originating in the bone marrow and consisting of 10–15% of circulating lymphocytes (Varbanova et al., 2016). KIRs are recognized as CD158, located on chromosome 19q13.4 and a subgroup of T cells (Machado-Sulbaran et al., 2017). There is an interaction of certain KIRs with HLA-C (C1 group, KIR2DL2/3 and KIR2DS2/3; C2 group, KIR2DL1 and KIR2DS1), HLA-Bw4 (KIR3DL1), HLA-A3/A11 (KIR3DL2) and HLA-G (KIR2DL4) molecules of target cells (Tajik et al., 2009). KIR moderates the mission of NK cells through reactions with human leukocyte antigen (HLA) class I molecules (Tajik et al., 2009). According to the interplay with HLA class I molecules, KIR regulates NK cells function as

an inducer or a suppressor (Ozturk et al., 2012). The classification of KIR genes as activating or inhibiting is based on the tail length of the intracellular domains (Tajik et al., 2009). The cytoplasmic tails of inhibitory KIR (iKIR) genes are long, whereas the cytoplasmic tails of activating KIR (aKIR) genes are short. While aKIR lacks an immunoreceptor tyrosine-based inhibitory motif (ITIM), iKIR does have at least one ITIM (Martin et al., 2000). iKIRs consisted of eight genes as 2DL1, 2DL2, 2DL3, 2DL4, 2DL5, 3DL1, 3DL2, 3DL3; aKIRs consisted of six genes as KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DS1; two KIR pseudogenes are KIR2DP1 and KIR3DP1 (Bolarín et al., 2021). A and B haplotypes are the two groups into which KIR haplotypes are divided (Hiby et al., 2010). Inhibitory KIR3DL3, KIR2DL3, KIR2DL1, KIR2DL4, KIR3DL1, KIR3DL2 genes, pseudogens KIR2DP1, KIR3DP1 and activating KIR2DS4 constitute haplotype A that is identified with a stable content. Conversely, haplotype B has 5 different aKIRs. The genes with the highest diversity in haplotype A are located in the telomeric

region, while in haplotype B they are located in the centromeric region (Pyo et al., 2010). KIR genes are very important in determining the susceptibility of individuals to diseases, as each KIR-ligand interaction may cause different effects on NK cells (Alomar et al., 2017; Hollenbach et al., 2009; Shastry et al., 2008; Tozkır et al., 2016). Since the KIR and HLA gene regions are highly polymorphic, they are also very valuable tools for anthropological studies to understand the history of human populations, migrations, mixing, or pathogen outbreaks (Parham and Moffett, 2013). Anatolia is geographically located between the Caucasus, Central Asia, the Levant, and Eastern Europe (Kuhn, 2002). Turkey consists of seven geographical regions. One of these regions is the Southeastern Anatolia Region (SAR). The SAR, located in Upper Mesopotamia, hosted many civilizations throughout history and therefore has ethnic diversity. Population studies to determine the genotype/haplotype distribution of KIR genes are increasing day by day, but there is still a lack of information for some populations. There is limited data on the KIR gene profile of the Turkish population in the Allele Frequency Net Database (www.allelefrequencies.net/) (Ozturk et al., 2012). The goal of this study was to determine the genotype distribution of activating and inhibitory KIR genes (KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DS1, KIR2DL1-5, KIR3DL1-3) in healthy volunteers in the SAR Population of Turkey.

MATERIALS AND METHODS

Study Group

The study included 200 unrelated healthy volunteers, 100 females and 100 males, ranging in age from 20 to 65 years. Subjects were randomly selected from the provinces of the SAR; Gaziantep ($n = 36$), Kilis ($n = 12$), Sanliurfa ($n = 36$), Siirt ($n = 4$), Batman ($n = 12$), Diyarbakir ($n = 32$), Sirnak ($n = 22$), Adiyaman ($n = 16$), Mardin ($n = 30$) (Fig. 1), they had no history of a genetic disorder. This study was approved by the Ethics Committee of Clinical Research at Gaziantep University (February 23, 2015, 20|5162).

DNA Isolation

Blood samples were taken into EDTA tubes and DNA isolation was performed using the salting-out method (Miller et al., 1988). After qualification and quantification analyses, all DNA samples were stored at -80°C until genotyping.

KIR Genotyping

The genotype distribution of eight inhibitory KIR genes (KIR2DL1, KIR2DL2, KIR2DL3, KIR2DL4, KIR2DL5, KIR3DL1, KIR3DL2, KIR3DL3) and six activating KIR genes (KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DS1) were determined by the polymerase-chain reaction with sequence-specific primers method (PCR-SSP). This method was worked out for detecting the absence or



Fig. 1. Distribution of the samples ($n = 200$) from nine geographic location of the Southeastern Anatolia Region of Turkey marked as white and black colour.

Table 1. Primer sets for PCR-SSP analysis of KIR genes

Gene name	Primer sequence	PCR product, bp
KIR2DL1	FP 5'-ttggtcagatgtcatgtttgaa-3'*	143
	RP 5'-tcctgccaggtcttgcg-3'**	
KIR2DL2	FP 5'-aaaccttctctcagccca-3'	142
	RP 5'-gccctgcagagaacctaca-3'	
KIR2DL3	FP 5'-acaagacctcagagggtga-3'	160
	RP 5'-gcaggagacaactttggatca-3'	
KIR2DL4	FP 5'-tcaggacaagccctctgc-3'	130
	RP 5'-gacaggacccccatcttc-3'	
KIR2DL5	FP 5'-atctatccaggaggaggag-3'	148
	RP 5'-tcatagggtgagtcagag-3'	
KIR3DL1	FP 5'-tgagcacttcttctgcacaa-3'	129
	RP 5'-taggtccctgcaaggga-3'	
KIR3DL2	FP 5'-aaaccttctctgtctccc-3'	134
	RP 5'-tggagatgggacgtggc-3'	
KIR3DL3	FP 5'-gcaatgttggtcagatgcag-3'	199
	RP 5'-agccgacaactcataggta-3'	
KIR2DS1	FP 5'-gtaggctcccgcaggga-3'	148
	RP 5'-acaagcagtggtcacttgac-3'	
KIR2DS2	FP 5'-ctgcacagagagggaagta-3'	177
	RP 5'-cagagggtcactgggagc-3'	
KIR2DS3	FP 5'-acctgtctctgcagctct-3'	160
	RP 5'-agcatctgtagttctctct-3'	
KIR2DS4	FP 5'-cagctcccggagctcta-3'	224
	RP 5'-tgacggaacaagcagtgga-3'	
KIR2DS5	FP 5'-cagagaggggacgtaacc-3'	174
	RP 5'-tccagagggtcactgggc-3'	
KIR3DS1	FP 5'-tccatcggttccatgatgcg-3'	111
	RP 5'-gaccacgatgtccaggga-3'	

* FR: forward primer, ** RP: reverse primer.

presence of KIR genes loci. Primer sets designed specifically for each gene were used for the amplification of KIR genes (Table 1) (Tajik et al., 2009). In order to ensure the reliability of the PCR process; primers designed specifically for the non-polymorphic region of the growth hormone gene were added to each PCR reaction as a positive internal control. PCR mix; totally of 15 μ L was prepared, containing 100 ng of DNA, gene-specific primers (0.1–0.8 mM) and inter-

nal control primers (0.2 Mm), 200 mM dNTP, 10 \times PCR buffer, 2 mM MgCl₂, and 0.5 u Taq Polymerase. Reaction condition, heating temperature 94°C for 2 min, 94°C for 10 s and 65°C for 60 s (10 cycles); 94°C for 10 s, 61°C for 50 s and 72°C for 30 s (20 cycles).

PCR products were separated in a 2% agarose gel stained with ethidium bromide and bands were visualized by using an ultraviolet transilluminator.

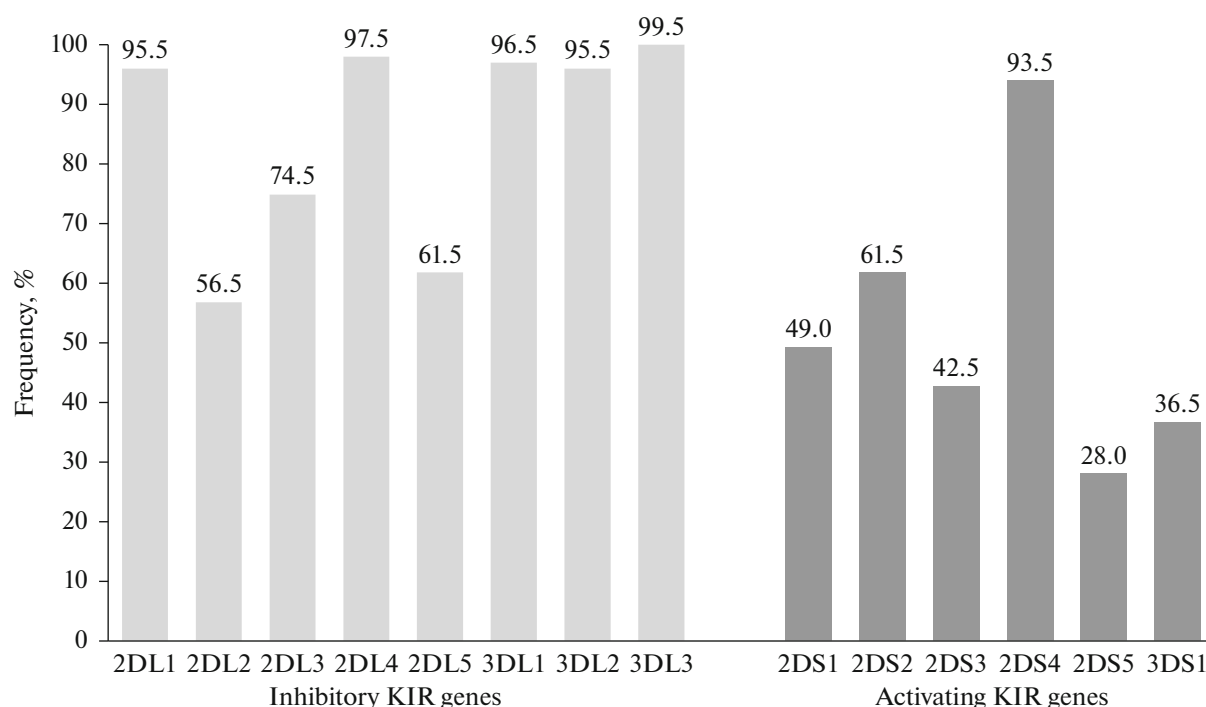


Fig. 2. Distribution of KIR genes frequencies in Southeastern Anatolia population ($n = 200$).

Statistical Analysis

After determining the presence or absence of KIR genes in each individual, the genotype frequency for each gene was determined by the direct counting method. Other populations' data were obtained from the Allele Frequency Net Database (www.allelefrequencies.net/) (Suzuki et al., 2004; Majorczyk et al., 2007; Norman et al., 2007; Tajik et al., 2009; Velickovic et al., 2009; Ozturk et al., 2012; Prakash et al., 2013; Spiroski et al., 2013; Osman et al., 2014) and compared to the current study's data. The percentages in the country populations were calculated by the Comparison of Two Independent Proportions. Using KIR locus data from 12 distinct populations as well as the Southeastern Anatolia population, principal component analysis (PCA) was used to identify genetic relationship. The SPSS statistical software package version 22.0 was used for analysis. Statistical significance was accepted at the $p < 0.05$ level.

RESULTS

Genotyping of KIR genes was performed using the PCR-SSP method in a total of 200 unrelated individuals from the SAR. The frequencies (%) of eight inhibitory and six activating KIR genes are given in Fig. 2.

When the frequencies of activating and inhibitory genes were compared, it was observed that the frequencies of inhibitory KIR genes were generally

higher than those of activating genes. Among the inhibitory KIR genes, 3DL3 had the highest (99.5%) frequency, which was followed by 2DL4 (97.5%), 3DL1 (96.5%), 3DL2 (95.5%), and 2DL1 (95.5%). The lowest frequency among the inhibitory KIR genes was obtained for 2DL2 (56.5%). The frequencies of 2DL3 and 2DL5 were 74.5 and 61.5%, respectively. The highest frequency among the activator KIR genes was obtained for 2DS4 (93.5%) and the lowest was for 2DS5 (28%). The gene frequencies of the remaining activating KIR genes were; 2DS2 (61.5%), 2DS1 (49%), 2DS3 (42.5%), and 3DS1 (36.5%).

The KIR gene profiles of the Southeastern Anatolia population and other selected 12 populations were compared (Table 2). The KIR2DL1 frequency was similar to the other populations except Indonesian ($p < 0.05$) and particularly North Indian ($p < 0.01$). The KIR2DL2 frequency was close to the Iranian, Polish and Moscow (Russia) populations, while there was significantly difference between the Swedish, and Japanese ($p < 0.05$), North Indian, and Indonesian ($p < 0.01$) populations. The distribution of KIR2DL3 was similar to the populations of Saudi Arabian, South Turkey, and North Indian, compared to the other nine populations. The frequency of KIR2DL4 SAR was close to other populations except Polish, Macedonian, North Indian, and the Iranian population. The frequency of KIR2DL5 was found to be the close in the Iranian population and SAR. KIR3DL1 frequency

Table 2. The distribution of KIR genes profile in Southeastern Anatolia population compared with other populations

KIR genes	Poland <i>n</i> = 690	Iran <i>n</i> = 200	Georgia <i>n</i> = 188	Uzbekistan <i>n</i> = 67	Macedonia <i>n</i> = 214	Russia Moscow <i>n</i> = 84	Saudi Arabia <i>n</i> = 148	South Turkey <i>n</i> = 200	North India <i>n</i> = 512	Sweden <i>n</i> = 102	Japan <i>n</i> = 50	Indonesia <i>n</i> = 45
2DL1	0.558	0.610	0.535	0.078	0.776	0.404	0.206	0.430	<0.001**	0.274	0.127	0.031*
2DL2	0.565	1.000	0.287	0.69	0.622	0.793	0.027	0.483	<0.001**	0.019*	<0.001**	0.025*
2DL3	<0.001**	0.003*	0.004*	<0.001**	<0.001**	0.003*	0.055	0.19	0.422	<0.001**	<0.001**	<0.001**
2DL4	0.002*	0.025*	0.109	0.192	0.02*	0.144	0.053	0.253	<0.001**	0.379	0.26	0.285
2DL5	0.034*	1.000	0.615	<0.001**	<0.001**	0.217	0.517	0.476	0.001*	0.038*	<0.001**	0.496
3DL1	0.071	0.036*	0.187	0.071	0.219	0.359	0.345	0.023*	<0.001**	0.056	0.866	0.288
3DL2	<0.001**	<0.001**	<0.001**	<0.001**	<0.001**	<0.001**	<0.001**	<0.001**	<0.001**	<0.001**	<0.001**	<0.001**
3DL3	0.063	0.317	1.000	0.563	0.301	0.517	0.390	1.000	0.110	0.615	0.618	0.635
2DS1	0.154	0.484	0.288	0.149	0.855	0.093	0.346	0.027*	0.260	0.332	0.008	0.271
2DS2	0.045*	0.416	0.062	0.261	0.302	0.389	0.025*	0.087	0.067	<0.001**	<0.001**	0.002*
2DS3	0.002*	0.359	0.040*	0.068	0.176	0.382	0.896	0.050	0.715	0.007*	<0.001**	0.156
2DS4	0.456	0.448	<0.001**	0.156	0.701	0.854	0.717	0.563	<0.001**	0.187	0.897	0.239
2DS5	0.642	0.011*	0.133	0.036*	0.592	0.760	0.002*	0.020*	<0.001**	0.539	0.252	0.688
3DS1	0.644	0.104	0.154	0.747	0.558	0.749	0.893	0.261	<0.001**	0.149	0.096	0.072

The KIR gene frequencies of the Southeastern Anatolia population were compared to the frequencies of 12 populations. Population's frequency data were obtained from <http://www.allelefrequencies.net> database. * 0.01 ≤ *p* < 0.05; ** 0.001 ≤ *p* ≤ 0.01.

was similar to other populations except populations of Iran, South Turkey ($p < 0.05$) and North India ($p < 0.01$). Remarkably, frequency of KIR3DL2 was significantly different than the other 12 populations. When considering the frequency of KIR3DL3, interestingly there was no significant difference between SAR and all other populations.

The frequency of KIR2DS1 in SAR was significantly different from the South Turkey population ($p < 0.05$). KIR2DS2 frequency in SAR was different from Polish, Indonesian, Saudi Arabian ($p < 0.05$) and Swedish, Japan populations ($p < 0.01$), while it was close to other populations. The frequency of KIR2DS3 was significantly different from Polish, Georgian, Swedish, and Japanese populations ($p < 0.05$). The KIR2DS4 gene frequency in the studied population differed significantly from the Georgian and North Indian populations. KIR2DS5 gene profile was found to be significantly different from populations in Iran, Uzbekistan, Saudi Arabia, South Turkey, and North India. The frequency of KIR3DS1 in SAR was significantly different from the North Indian population ($p < 0.01$).

DISCUSSION

The innate immune system's NK cells are an essential part of the system. They compose the initial line of defense against infections and tumors. KIR receptors regulate the cytotoxic activity of NK cells by recognizing the HLA class I ligand on target cells (Machado-Sulbaran et al., 2017). Considerable genetic diversity reported in KIR genes leads to genotype differences in populations from various geographical regions and ethnic origins.

In the present study, we investigated the genotype distribution of activating and inhibitory KIR genes (KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DS1, KIR2DL1-5, KIR3DL1-3) in the Southeastern Anatolia population. We performed the PCR-SSP method for investigating the KIR gene distribution in 200 healthy volunteers. Although there were a limited number of studies about Turkey population in the database, this was the first one for KIR gene profiling in the SAR. The results of this study were compared with other population data obtained from the database. Generally speaking, the most significant difference in both inhibitory and activating KIR gene distribution was found between the studied population and the North Indian population. According to our results, the KIR gene profile of SAR was found to be similar to other Caucasoid populations. Considerable similarities with other populations were found for certain KIR genes: KIR2DL1, KIR2DL2, KIR2DL4, KIR3DL3 (Poland, Iran, Macedonia populations), KIR2DL5 (Iran), KIR3DL1 (Japan), KIR2DS1 (Iran and Macedonia), KIR2DS2 (Iran, Macedonia and Russia-Moscow), KIR2DS3 (Saudi Arabia and North India), KIR2DS4 (Poland, India, Saudi Arabia and South Turkey), KIR2DS5 (Poland and Russia-Moscow), KIR3DS1 (Poland, Uzbekistan and Macedonia). On the other hand, KIR3DL2 was found to be significantly different from all other populations.

Principal component (PC) maps of activatory and inhibitory genes were composed separately according to Table 2. According to the PC map of inhibitory KIR genes (Fig. 3), North India population is found to be very far from Caucasian populations, including SAR, in accordance with the study done in the Iranian population (Tajik et al., 2009). The PC map of activating

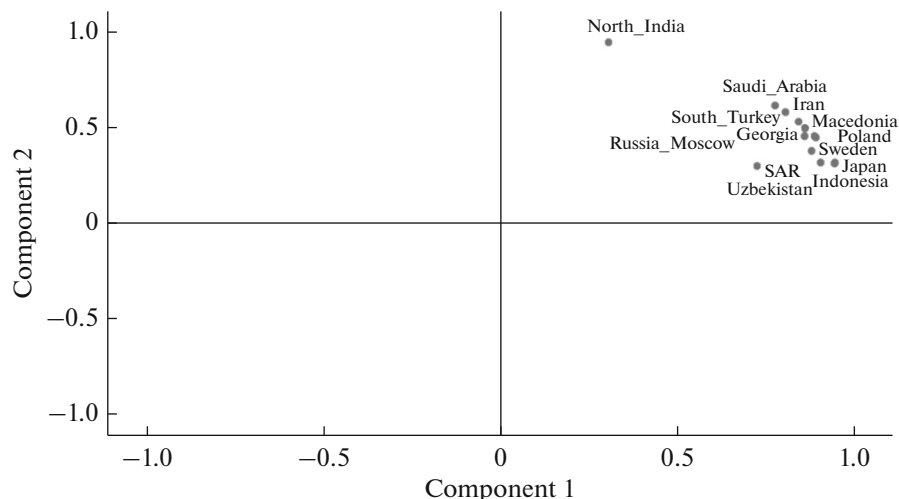


Fig. 3. Principal component map of inhibitory KIR genes data from present study and 12 populations.

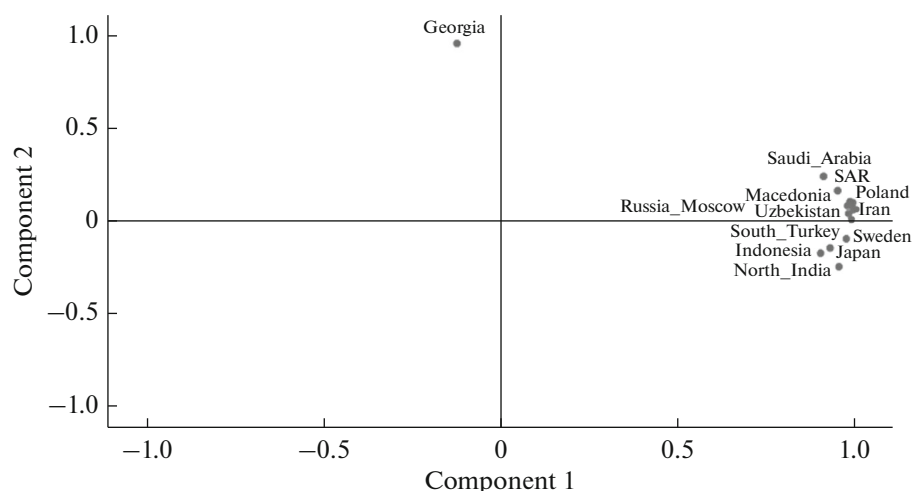


Fig. 4. Principal component map of activatory KIR genes data from present study and 12 populations.

KIR genes (Fig. 4) indicates the relationship of SAR to other analyzed populations and Georgia population was found to have the most different activating KIR gene profile.

Due to its central geographical location, Anatolia has been a connection point by interacting with other parts of the Near East and Europe during and after the Neolithic Age (Omrak et al., 2016). The Ottoman state annexed Macedonia in the 14th century and Turks from Anatolia settled in the Balkans (Günşen, 2013) Turkish groups such as Azerbaijan Turks, Turkmens, Kashkays, Khorasan Turks, Halaçs, Sungurs, Ebiverdis, Kazakhs, and Uzbeks live in certain regions of Iran (Gökdağ, 2013). The SAR has been exposed to many migrations throughout history and has hosted different civilizations. According to our results, the KIR gene profile of SAR was found to be close to other Caucasoid populations.

CONCLUSIONS

In conclusion, this was the first study focusing on the KIR gene profile in the SAR of Turkey. This study also confirmed that the PCR-SSP method could still be used for KIR genotyping in different populations. Our study showed that the SAR population has similar KIR gene features to the Caucasians in general. The KIR gene distribution in this community and the genetic relationship between communities will be better understood with additional research using a bigger sample size and new populations.

FUNDING

This study was supported by Gaziantep University Scientific Research Projects Coordination Unit (Project no. FEF.YLT.16.02 and FEF.YLT.16.04).

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of Clinical Research at Gaziantep University (February 23, 2015, 20|5162).

CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

REFERENCES

- Alomar, S.Y., Alkhuriji, A., Trayhyrn, P., Alhetheel, A., Al-Jurayyan, A., and Mansour, L., Association of the genetic diversity of killer cell immunoglobulin-like receptor genes and HLA-C ligand in Saudi women with breast cancer, *Immunogenetics*, 2017, vol. 69, no. 2, pp. 69–76. <https://doi.org/10.1007/s00251-016-0950-x>
- Bolarin, J., Pérez-Cárceles, M., Luna, A., Minguela, A., Muro, M., and Legaz, I., Killer cell immunoglobulin-like receptors (KIR) genes can be an adequate tool in forensic anthropological studies: evaluation in a wide Caucasian Spanish population, *Aust. J. Forensic Sci.*, 2021, pp. 1–23. <https://doi.org/10.1080/00450618.2021.1930156>
- Gökdağ, B.A., İran Türkleri, *Yeni Türkiye*, 2013, vol. 54, pp. 2203–2213.
- Günşen, A., Pomaks as a Balkan community and evidence of Turkishness in their perceptions of identity, *Balkan Araştırma Enstitüsü Dergisi-Trakya Üniversitesi*, 2013, vol. 2, no. 1, pp. 35–54.
- Hiby, S.E., Ashrafian-Bonab, M., Farrell, L., Single, R.M., Balloux, F., Carrington, M., and Moffett, A., Distribution of killer cell immunoglobulin-like receptors (KIR) and their HLA-C ligands in two Iranian populations, *Immunogenetics*, 2010, vol. 62, no. 2, pp. 65–73. <https://doi.org/10.1007/s00251-009-0408-5>
- Hollenbach, J.A., Ladner, M.B., Saetern, K., Taylor, K.D., Mei, L., Haritunians, T., McGovern, D., Erlich, H.A., Rotte, J.I., and Trachtenberg, E.A., Susceptibility to Crohn's disease is mediated by KIR 2DL2/KIR 2DL3 heterozygosity and the HLA-C ligand, *Immunogenetics*, 2009,

- vol. 61, no. 10, pp. 663–671.
<https://doi.org/10.1007/s00251-009-0396-5>
- Kuhn, S.L., Paleolithic archeology in Turkey, *Evol. Anthropol.: Iss., News, Rev.*, 2002, vol. 11, no. 5, pp. 198–210.
<https://doi.org/10.1002/evan.10033>
- Machado-Sulbaran, A.C., Muñoz-Valle, J.F., Ramírez-Dueñas, M.G., Baños-Hernández, C.J., Graciano-Machuca, O., Velarde-De la Cruz, E.E., Parra-Rojas, I., and Sánchez-Hernández, P.E., Distribution of *KIR* genes and *KIR2DS4* gene variants in two Mexican Mestizo populations, *Hum. Immunol.*, 2017, vol. 78, no. 10, pp. 614–620.
<https://doi.org/10.1016/j.humimm.2017.07.010>
- Majorczyk, E., Pawlik, A., Łuszczek, W., Nowak, I., Wiśniewski, A., Jasek, M., and Kuśnierczyk, P., Associations of killer cell immunoglobulin-like receptor genes with complications of rheumatoid arthritis, *Genes Immun.*, 2007, vol. 8, no. 8, pp. 678–683.
<https://doi.org/10.1038/sj.gene.6364433>
- Martin, A.M., Freitas, E.M., Witt, C.S., and Christiansen, F.T., The genomic organization and evolution of the natural killer immunoglobulin-like receptor (KIR) gene cluster, *Immunogenetics*, 2000, vol. 51, no. 4, pp. 268–280.
<https://doi.org/10.1007/s002510050620>
- Miller, S., Dykes, D., and Polesky, H., A simple salting out procedure for extracting DNA from human nucleated cells, *Nucleic Acids Res.*, 1988, vol. 16, no. 3, p. 1215.
<https://doi.org/10.1093/nar/16.3.1215>
- Norman, P.J., Abi-Rached, L., Gendzekhadze, K., Korb, D., Gleimer, M., Rowley, D., Bruno, D., Carrington, C.V.F., Chandanayingyong, D., Chang, Y.-H., Crespi, C., Direkseneli, G.S., Fraser, P.A., Hameed, K., Kamkamidze, G., Koram, K.A., Layrisse, Z., Matamoros, N., Milà, J., Park, M.H., Pitchappan, R.M., Ramdath, D.D., Shiau, M.-Y., Stephens, H.A.F., Struik, S., Verity, D.H., Vaughan, R.W., Tyan, D., Davis, R.W., Riley, E.M., Ronaghi, M., and Parham, P., Unusual selection on the KIR3DL1/S1 natural killer cell receptor in Africans, *Nat. Genet.*, 2007, vol. 39, no. 9, pp. 1092–1099.
<https://doi.org/10.1038/ng2111>
- Omrak, A., Günther, T., Valdiosera, C., Svensson, E. M., Malmström, H., Kiesewetter, H., Aylward, W., Storå, J., Jakobsson, M., and Götherström, A., Genomic evidence establishes Anatolia as the source of the European Neolithic gene pool, *Curr. Biol.*, 2016, vol. 26, no. 2, pp. 270–275.
<https://doi.org/10.1016/j.cub.2015.12.019>
- Osman, A.E., Mubasher, M., ElSheikh, N.E., AlHarthi, H., Al Yami, A.S., Rajalingam, R., Al-Dehaimi, A., Middleton, D., and ElGhazali, G., Characterization of human killer immunoglobulin-like receptors (KIRs) among healthy Saudis, *Hum. Immunol.*, 2014, vol. 75, no. 6, pp. 536–540.
<https://doi.org/10.1016/j.humimm.2014.02.023>
- Ozturk, O.G., Polat, G., and Atik, U., Diversity of killer cell immunoglobulin-like receptor genes in Southern Turkey, *Mol. Biol. Rep.*, 2012, vol. 39, no. 2, pp. 1989–1995.
<https://doi.org/10.1007/s11033-011-0945-5>
- Parham, P. and Moffett, A. Variable NK cell receptors and their MHC class I ligands in immunity, reproduction and human evolution, *Nat. Rev. Immunol.*, 2013, vol. 13, no. 2, pp. 133–144.
<https://doi.org/10.1038/nri3370>
- Prakash, S., Alam, S., Sharma, R.K., Sonawane, A., Imran, M., and Agrawal, S., Distribution of Killer cell immunoglobulin like receptor genes in end stage renal disease among North Indian population, *Hum. Immunol.*, 2013, vol. 74, no. 10, pp. 1339–1345.
<https://doi.org/10.1016/j.humimm.2013.06.015>
- Purdy, A.K. and Campbell, K.S., Natural killer cells and cancer: regulation by the killer cell Ig-like receptors (KIR), *Cancer Biol. Ther.*, 2009, vol. 8, no. 23, pp. 2209–2218.
<https://doi.org/10.4161/cbt.8.23.10455>
- Pyo, C.-W., Guethlein, L.A., Vu, Q., Wang, R., Abi-Rached, L., Norman, P.J., Marsh, M.S.G., Miller, J.S., Parham, P., and Geraghty, D.E., Different patterns of evolution in the centromeric and telomeric regions of group A and B haplotypes of the human killer cell Ig-like receptor locus, *PLoS One*, 2010, vol. 5, no. 12, p. e15115.
<https://doi.org/10.1371/journal.pone.0015115>
- Shastri, A., Sedimbi, S.K., Rajalingam, R., Rumba, I., Kanningo, A., and Sanjeevi, C., Different KIRs confer susceptibility and protection to adults with latent autoimmune diabetes in Latvian and Asian Indian populations, *Ann. N.Y. Acad. Sci.*, 2008, vol. 1150, no. 1, pp. 133–138.
<https://doi.org/10.1196/annals.1447.058>
- Shi, L., Zhang, H., Shen, Y., Dong, Y., Li, Y., Dong, Z., Guo, C., Shi, L., Yao, Y., and Yu, J., Distribution of KIR genes in Han population in Yunnan Province: comparison with other Han populations in China, *Int. J. Immunogenet.*, 2013, vol. 40, no. 5, pp. 361–368.
<https://doi.org/10.1111/iji.12046>
- Spiroski, M., Milenkovic, Z., Petlichkovski, A., Ivanovski, L., Topuzovska, I.K., and Djulejic, E., Killer cell immunoglobulin-like receptor genes in four human West Nile virus infections reported 2011 in the Republic of Macedonia, *Hum. Immunol.*, 2013, vol. 74, no. 3, pp. 389–394.
<https://doi.org/10.1016/j.humimm.2012.11.015>
- Suzuki, Y., Hamamoto, Y., Ogasawara, Y., Ishikawa, K., Yoshikawa, Y., Sasazuki, T., and Muto, M., Genetic polymorphisms of killer cell immunoglobulin-like receptors are associated with susceptibility to psoriasis vulgaris, *J. Invest. Dermatol.*, 2004, vol. 122, no. 5, pp. 1133–1136.
<https://doi.org/10.1111/j.0022-202X.2004.22517.x>
- Tajik, N., Shahsavari, F., Mousavi, T., and Radjabzadeh, M., Distribution of KIR genes in the Iranian population, *Tissue Antigens*, 2009, vol. 74, no. 1, pp. 22–31.
<https://doi.org/10.1111/j.1399-0039.2009.01263.x>
- Tozkır, J.D., Tozkır, H., Gürkan, H., Dönmez, S., Eker, D., Pamuk, G.E., and Pamuk, Ö.N., The investigation of killer cell immunoglobulin-like receptor genotyping in patients with systemic lupus erythematosus and systemic sclerosis, *Clin. Rheumatol.*, 2016, vol. 35, no. 4, pp. 919–925.
<https://doi.org/10.1007/s10067-016-3222-0>
- Varbanova, V., Naumova, E., and Mihaylova, A., Killer-cell immunoglobulin-like receptor genes and ligands and their role in hematologic malignancies, *Cancer Immunol., Immunother.*, 2016, vol. 65, no. 4, pp. 427–440.
<https://doi.org/10.1007/s00262-016-1806-9>
- Velickovic, M., Velickovic, Z., Panigoro, R., and Dunkley, H., Diversity of killer cell immunoglobulin-like receptor genes in Indonesian populations of Java, Kalimantan, Timor and Irian Jaya, *Tissue Antigens*, 2009, vol. 73, no. 1, pp. 9–16.
<https://doi.org/10.1111/j.1399-0039.2008.01149.x>

Publisher's Note. Pleiades Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.