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Clinical Impact of KIR2DS3 and KIR2DL3 Genes in Neuroblastoma Patients

Gülay Sezgin[a] Özlem Görüroğlu Öztürk[b] Ayşe Özkan[a] Serhan Küpeli[a] İbrahim Bayram[a]

[a]Division of Pediatric Oncology/Pediatric BMT Unit, Çukurova University Medical School, Adana, Turkey;
[b]Department of Medical Biochemistry,Çukurova University Medical School, Adana, Turkey

Highlights of the study

- We report a role for KIR2DS3 and KIR2DL3 in development of neuroblastoma.
- We observed lower activating KIR2DS3 and increased inhibitory KIR2DL3 in patients compared to the control group.
- Activating KIR2DS3 was increased in early stages (stage 1, 2, 3, and 4S), while inhibitory KIR2DL3 was higher in patients with stage 4 neuroblastoma.

Keywords
Neuroblastoma · Killer immunoglobulin-like receptor genes · KIRs · Natural killer cells

Abstract
Objective: Neuroblastoma is a common fatal tumor of childhood. Natural killer (NK) cells can exert direct cytotoxicity on tumor cells. The killer immunoglobulin-like receptor (KIR) family of NK cell receptors is involved in activation/inhibition of NK cells. In the KIR gene cluster, six of them (3DS1, 2DS1–5) encode receptors triggering activation, while seven of them (3DL1–3, 2DL1–3, 2DL5) encode receptors triggering inhibition. We aimed to assess the distribution of genetic polymorphisms of KIRs on the clinical course of neuroblastoma and provide guidance on potential therapeutic options. ***Methods:*** Our study group included 50 neuroblastoma patients and 100 healthy children as controls. Twenty-eight patients were boys, and twenty-two were girls; median age was 36 months. Fourteen patients had stage 1, 2, 3, or 4S disease, and 36 patients had stage 4 disease. Isolated DNA from the peripheral blood was amplified for sequence-specific oligonucleotide probe analysis of 16 KIR genes. The Fisher's exact test was used to evaluate the variation of KIR gene distribution. ***Results:*** All patients had a lower frequency of KIR2DS3 compared to the control group ($p = 0.005$). Evaluation of individual KIR genes/genotypes in patients with early stages (stage 1, 2, 3, and 4S) versus stage 4 disease revealed that the frequency of KIR2DS3 was increased in early stages ($p = 0.023$). Inhibitory KIR2DL3 was increased in the patient group compared to controls ($p = 0.038$). Furthermore, the frequency of KIR2DL3 was higher in stage 4 neuroblastoma patients compared to the patients with early stages ($p = 0.023$). ***Conclusion:*** Our data suggest a role for KIR2DS3 and KIR2DL3 in development of neuroblastoma. Thus, modulation of KIR2SD3 and/or KIR2DL3 expression or function might present a novel therapeutic strategy for neuroblastoma.

Karger@karger.com
www.karger.com/mpp

Correspondence to:
Gülay Sezgin, gsezgin@cu.edu.tr

Introduction

Neuroblastoma is the most common fatal tumor of childhood. It arises from neural crest cells of the sympathetic nervous system. In infants, these tumors may regress spontaneously or mature into a benign ganglioneuroma. Older children usually present with advanced disease, and their prognosis for survival is very poor. Therefore, understanding the molecular basis, pathogenesis, and clinical behavior is important for the developing therapeutic approaches.

Neuroblastomas are staged according to the International Neuroblastoma Staging System (INSS) and recently according to the International Neuroblastoma Risk Group Staging System [1] (INRGSS) to allow uniformity for treatment and assessment of the patients all over the world. In the INSS staging, stages 1, 2, 3, and 4S are nonmetastatic forms, and stage 4 is the metastatic form. In stage 4S (special neuroblastoma) patients, the original tumor is located where it originated (as in stage 1, 2A, or 2B) and has spread only to the skin, liver, and/or bone marrow in infants less than 1 year of age. The spread to the bone marrow is minimal (usually less than 10% of cells examined show cancer). These infants commonly experience spontaneous disease regression.

Natural killer (NK) cells are innate lymphocytes that can mediate direct cytotoxicity on tumor cells and virus-infected cells. NK cell receptors that regulate NK cell function are genetically very diverse. The killer immunoglobulin-like receptor (KIR) family of NK cell receptors are a family of membrane glycoproteins. KIRs contain two or three extracellular immunoglobulin-like domain molecules (D) with a long (L) or short (S) cytoplasmic tail [2]. Sixteen KIR genes have been discovered: 6 genes encoding activating KIR (2DS1-5 and 3DS1), 7 genes encoding inhibitory KIR (2DL1-3, -5 and 3DL1-2), KIR2DL4, which has both inhibitory and activating activity, and 2 pseudogenes (2DP1 and 3DP1). In addition, KIR3DL3, KIR3DP1, KIR2DL4, and KIR3DL2 are framework genes which are always present in the genome [3].

KIRs are very polymorphic and regulate NK cell function via balanced transmission of activating or inhibitory signals. NK cell function is affected by inherited KIR and KIR ligand repertories and their interactions. NK cell cytotoxicity requires the presence of an activating signal in addition to the absence of inhibitory KIR ligand on target cells [2–4]. KIRs recognize target cells via MHC class I molecules. When inhibitory KIRs are bound to their matched MHC class I ligands, inhibitory intracellular signals are sent, and autoreactivity is circumvented. Conversely, when MHC class I is absent or downregulated (e.g., in cancerous, virus-infected, or transformed cells), inhibitory signaling are not received, and NK cells then become cytotoxic [2]. KIR mismatch that results in decreased inhibitory NK cell phenotype are beneficial in the treatment of neuroblastoma [5–8]. However, the Children's Oncology Group (COG) study, ANBL0032, found that patients with genes for inhibitory KIR and KIR ligands (KIR-L) had the greatest improvement in survival after immunotherapy [9]. Also, the baseline expression of other activating NK receptors has been shown to be important for survival. In one study that compared the progression-free survival of high-risk neuroblastoma patients, those with the activating NKp30 isoform NKp30B had better progression-free survival when compared to patients with an inhibitory NKp30 isoform, NKp30c [10].

The early development of neuroblastoma suggests contribution of genetic factors, and genetic variations in KIRs might be associated with susceptibility to neuroblastoma. The aim of this study was to ascertain whether specific KIRs are related to the pathogenesis and stage of neuroblastoma.

Subjects and Methods

Subjects

The study group consisted of 50 neuroblastoma patients followed at the Pediatric Oncology Clinic of Çukurova University Medical School. Blood samples were withdrawn from the patients at the time of diagnosis. The control group consisted of 100 healthy children. All individuals included in this study were from the Çukurova region of Turkey and were all matched for ethnicity. They were also unrelated and randomly selected. The enrolled subjects had no serological evidence of hepatitis C virus, hepatitis D virus, and HIV infections and had no other diseases, such as diabetes, malignant tumor, or autoimmune diseases. The study was conducted according to the principles of Helsinki Declaration. Informed written consent was obtained from families of participants, and the study was approved by Çukurova University Ethics Committee.

KIR Genotyping

DNA from venous blood samples was extracted by the DNA isolation kit (QIAamp DNA Blood Mini Kit, cat no: 51104, QIAGEN Vertriebs GmbH, Vienna, Austria). Genotyping of KIR genes was performed using the KIR-SSO multiplex typing kit from Tepnel Lifecodes Corporation (Stamford, Connecticut, CT, USA). This product consists of a mixture of locus-specific oligonucleotide probes coupled to color-coded microspheres (Luminex Corp, Austin, TX, USA) and two PCR reactions for the amplification of KIR-exons 4, 5, 7, 8, and 9. To type each sample, PCR was performed, and the product was hybridized with the SSO-probe mixture using the manufacturer's protocol. After hybridization, the sample plate was placed in a Luminex instrument (Luminex Corporation) for multiplex assay for analysis.

Table 1. Demographic characteristics of the neuroblastoma patients and controls.

	Patients ($N = 50$)	Controls ($N = 100$)
Age, months, median (range)	36 (3–113)	72 (36–144)
Sex		
Female	22	54
Male	28	46
Tumor stage		
Nonmetastatic (stage 1, 2, 3, 4S)	14	–
Metastatic (stage 4)	36	–

Prediction of Group-A/-B KIR Haplotypes

Frequencies of group-A and -B KIR haplotypes were deduced from the genotype data. Individuals carrying only KIR3DL3, 2DL3, 2DL1, 2DP1, 3DP1, 2DL4, 3DL1, 2DS4, and 3DL2, a fixed gene content characteristic of group-A haplotypes, were considered carrying two copies of group-A KIR haplotypes (AA genotypes). If any of the genes KIR2DL2, 2DL5, 3DS1, 2DS1, 2DS2, 2DS3, and/or 2DS5 were present, then the genotype was considered as having the B haplotype (Bx) [11–13].

Statistical Analyses

The percentage of each KIR gene in the patient and control groups were determined by direct counting (individuals positive for the gene/individuals tested per population × 100). Data analysis was performed with the statistical software Minitab Version 15. Differences between two groups in the frequencies of each KIR gene were estimated by two-tailed Fisher's exact test, and $p < 0.05$ was considered to be statistically significant. The Benjamini-Hochberg-adjusted p value test was used to calculate the corrected p values.

Results

Fifty patients (28 boys and 22 girls) with neuroblastoma underwent genotyping for KIR genes. The median age was 36 months (range 3–113 months). Fourteen patients had stage 1, 2, 3, or 4S disease, and 36 patients had stage 4 disease. The control group consisted of 46 boys and 54 girls; the median age was 72 months (range 36–144 months) (Table 1).

Distribution of KIR Genes and Genotypes

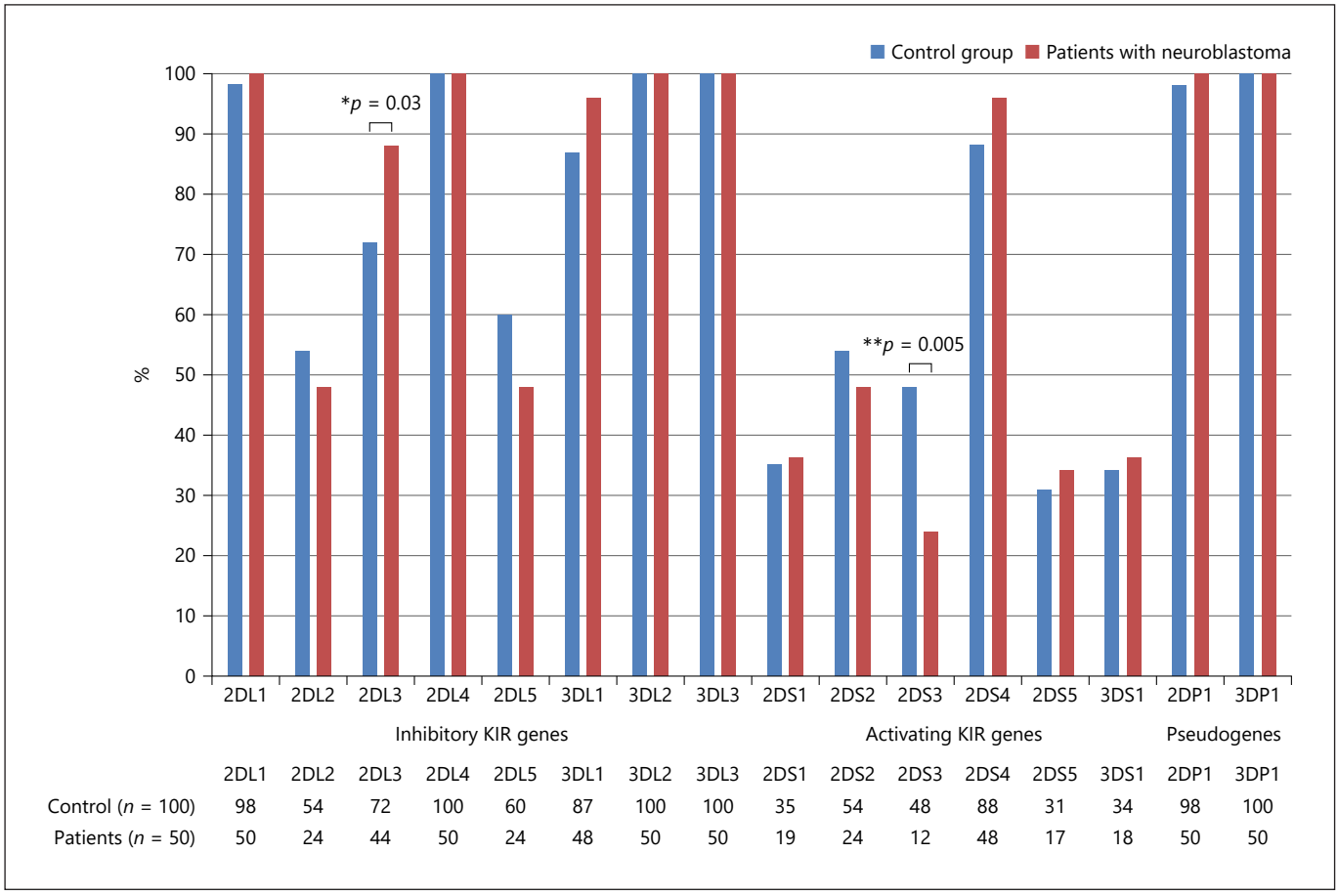
The framework genes KIR2DL4, 3DL2, 3DL3, and 3DP1 were present in all of the samples. Additionally, the KIR pseudogene KIR2DP1 was present in 100% of the patient group and 98% of the control group. The inhibitory KIR genes tended to have a higher frequency compared to activating KIR genes in all study samples. Among them, inhibitory KIR genes 2DL1 (98%) and 3DL1 (87%) had the highest frequency of all samples. With the exception of KIR2DS4, frequencies of the other activating genes were all lower than 54% (Fig. 1). Eleven different genotypes were found in 50 patients with neuroblastoma. A total of 34% of patients had AA genotypes which consists of only one activating gene, 2DS4 (Fig. 2). Other patients demonstrated the presence of more than one activating gene and thus may be considered as Bx. Of all eleven different genotypes, three of them (genotypes: Bx7, Bx8, Bx9) were observed only once (Fig. 2).

Relationship of KIR Genes and Genotypes with Neuroblastoma

Frequencies of individual KIR genes were compared between patients with neuroblastoma and normal controls (Fig. 1). All sixteen KIR genes were compared by Fisher's exact test. The inhibitory KIR gene KIR2DL3 was more common in patients than that in controls ($p = 0.038$). Additionally, compared to the control group, neuroblastoma patients had a lower activating KIR gene, KIR2DS3 ($p = 0.005$). There were no statistically significant differences between the rate of AA and Bx genotypes of patient and control groups and early versus late stages ($p > 0.05$). The correction of the p values was calculated using the Benjamini-Hochberg-adjusted p value test. Although the inhibitory KIR2DL3 was not significantly different between control versus patient groups, the activating KIR2DS3 was found to be significantly different between the patient and control groups ($p = 0.025$).

Distribution of KIR Genes/Genotypes of Patients with Neuroblastoma in Different Stages

The distribution of individual KIR genes/genotypes was studied in neuroblastoma patients with early stages and stage 4. The frequency of the KIR2DS3 gene was more common in patients with early stages. A statistically significant difference was found between the patients with early stages and patients with stage 4 ($p = 0.023$). In addition, the frequencies of 2DL3 genes in the patient group with stage 4 were higher than that in the patient group with early stages. There was a statistically significant positive correlation between 2DL3 genes and development of higher stages in patients ($p = 0.044$) (Fig. 3). The corrected p values were not statistically significant for both KIR2DL3 and KIR2DS3 between early and late stages. Comparison of both the inhibitory KIR2DL3 and activator KIR2DS3 between controls versus metastatic stage patients was significant ($p = 0.005$ and 0.0002, respectively) (Fig. 4). The validation of our



	2DL1	2DL2	2DL3	2DL4	2DL5	3DL1	3DL2	3DL3	2DS1	2DS2	2DS3	2DS4	2DS5	3DS1	2DP1	3DP1
Control (n = 100)	98	54	72	100	60	87	100	100	35	54	48	88	31	34	98	100
Patients (n = 50)	50	24	44	50	24	48	50	50	19	24	12	48	17	18	50	50

Fig. 1. Comparison of frequencies of KIR genotypes in neuroblastoma patients (N = 50) and controls (N = 100) was estimated by two-tailed Fisher's exact test. A statistically significant difference was found between the patient and control groups in frequency of the inhibitory KIR2DL3 gene *p = 0.038. Activating KIR2DS3 was lower in neuroblastoma patients compared to the control group, **p = 0.005.

findings concerning the correlation of KIR2DL3 and KIR2DS3 with tumor stage in independent datasets was carried out on R2 platform (https://hgserver1.amc.nl/cgi-bin/r2/main.cgi). KIR2DL3 was found to be high, and KIR2DS3 was found to be low in all stages of neuroblastoma patients in line with our data (online suppl. File. 1; see www.karger.com/doi/10.1159/000524656 for all online suppl. material,).

Discussion

Specific KIR genes and their ligands have been reported to be associated with protection or development of leukemias and solid tumors. A significant increase in KIR2DL2 and KIR2DS2 was found in both acute and chronic myeloid and lymphoid leukemias [14, 15]. However, the frequencies of KIR2DL2 and KIR2DS2 were reported to be the same in Iranian patients with acute leukemia; on the contrary, the frequency of activating KIR2DS3 was significantly decreased in the AML group [16].

NK cells exhibit cytotoxicity against neuroblastoma. In a retrospective analysis of stage 4 neuroblastoma patients receiving autologous hematopoietic stem cell transplantation at the Memorial Sloan Kettering Cancer Center, a survival advantage was demonstrated in patients with a "missing ligand" [8]. The COG phase II trial using the hu14.18-IL-2 immunotherapy (humanized anti-GD2 monoclonal antibody linked to human IL-2) in relapsed/refractory neuroblastoma patients showed that KIR/KIR ligand mismatch was associated with response to immu-

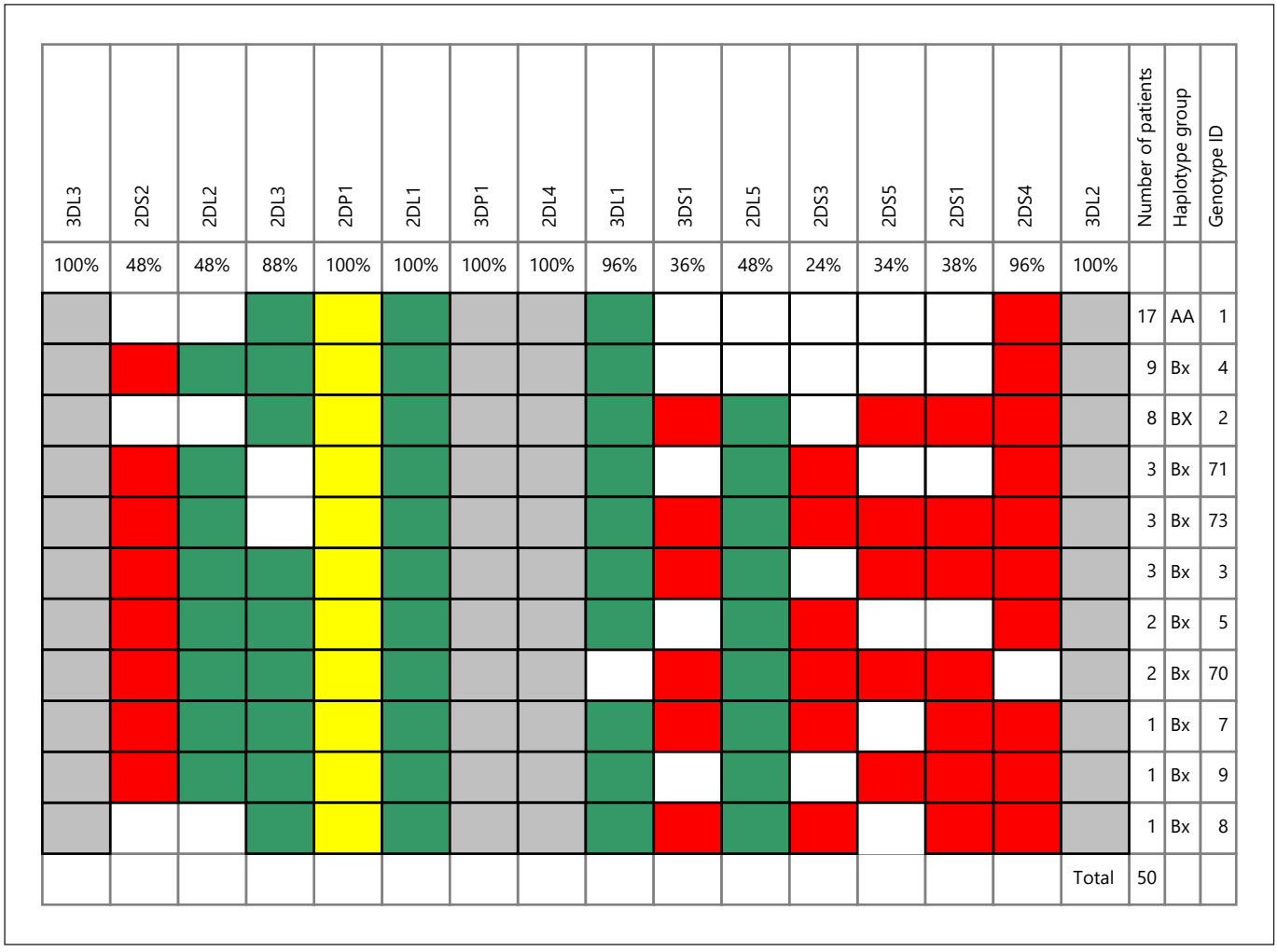


Fig. 2. KIR genotypes in neuroblastoma patients. Framework genes are in gray color, activating KIR genes are in red, inhibitory genes are in green, and pseudogenes are in yellow. The haplotype group and genotype ID and the number of patients are presented on the right side.

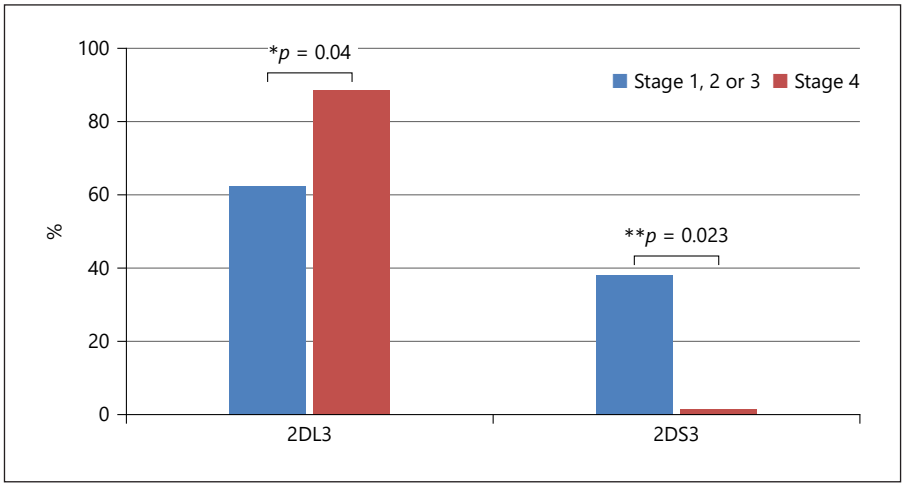
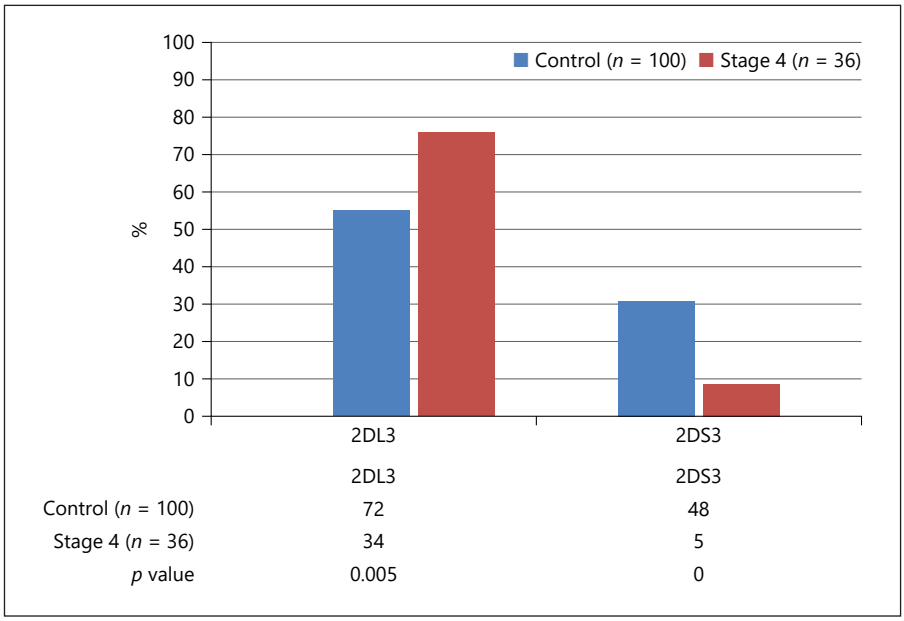


Fig. 3. Comparison of patients with early stages of neuroblastoma versus patients with stage 4 for inhibitory KIR2DL3 $*p = 0.044$ and for activator KIR2DS3, $**p = 0.023$ by two-tailed Fisher's exact test.



	2DL3	2DS3
Control (*n* = 100)	72	48
Stage 4 (*n* = 36)	34	5
p value	0.005	0

Fig. 4. Comparison of stage 4 neuroblastoma patients with controls for inhibitory KIR2DL3 and activator KIR2DS3 genes by Fisher's exact test.

notherapy [6]. Most studies on NK cell genes in neuroblastoma have focused on particular KIR gene/ligand combinations and their role in response to antibody immunotherapy [5–7]. Keating et al. [17] showed an increased frequency of both KIR2DL2 and KIR2DS2 in neuroblastoma patients as compared to healthy controls ($p = 0.019$ and $p = 0.008$, respectively). The frequencies of two further B haplotype genes, KIR2DS3 and KIR3DS1, were also increased, but these changes were not statistically significant ($p = 0.253$ and $p = 0.365$, respectively) [17]. Erbe et al. [9] genotyped 174 patients from the COG ANBL0032 phase III clinical trial and investigated the effect of KIR/KIR ligand genotypes on clinical outcomes; they found KIR2DL1, KIR2DL3, and KIR3DL1 in >92% of these neuroblastoma patients, and KIR2DL2 is found in only 51% of this study population. In contrast to previous reports, the KIR ligand-missing genotype was not associated with an improved outcome when compared with the KIR ligands-present genotype. They demonstrated that patients with certain KIR/KIR ligand genotypes namely patients with inhibitory KIR2DL2 with its ligand (HLA-C1) together with inhibitory KIR3DL1 with its ligand (HLA-Bw4) were associated with improved outcome if they received immunotherapy. However, no difference was found in the clinical outcome between the patients with the complementary KIR/KIR ligand genotypes receiving the immunotherapy versus isotretinoin alone [9]. Although the role of inhibitory KIR/KIR ligands in response to immunotherapy was studied, not much is known about the role of activating KIR/KIR ligands. Siebert et al. [18] investigated the involvement of activating KIRs and FCGR polymorphisms in patients treated with human/mouse chimeric anti-GD2 Ab ch14.18 immunotherapy. They found that patients with high-affinity FCGR2A, -3A genotypes, and genotype B/x or the presence of activating KIR2DS2 showed the strongest cellular cytotoxicity against neuroblastoma. KIR2SD2 is in linkage dysequilibrium with KIR2DL2 as previously shown [19]. The expression of KIR2SD2 was found to be in higher frequency in neuroblastoma patients compared to controls. In the absence of immunotherapy, KIR2SD2 expression did not protect from development of neuroblastoma due to the simultaneous presence of KIR2DL2 overcoming the effect of KIR2SD2. In addition, patients with KIR2DS3 genotype also had increased cellular cytotoxicity against neuroblastoma. However, no difference in cellular cytotoxicity and EFS was detected between patients with only 2DS2 compared to 2DS2- and 2DS3-positive patients [18].

In our study, the inhibitory KIR genes 2DL1 and 3DL1 had high frequencies in all samples (>87%) as shown in previous studies. All activating KIR genes were found to be decreased except KIR2SD4. It has been reported that different allelic variants of KIR2DS4 encode soluble form of the proteins which have no cytotoxic function. For example, while KIR2DS4 * 001 allele encodes the normal activating KIR2DS4 surface molecule, KIR2DS4 * 003, KIR2DS4 * 004, and KIR2DS4 * 006 are deleted variant

alleles and allelic forms that are not expressed on the NK cell surface. In individuals where these variant alleles are homozygous, it has been reported that 2DS4 gene products are dysfunctional and have no cytotoxic effect on tumor cells [20, 21]. Allelic variants of the KIRs were not examined in our study.

Increased expression of inhibitory KIR2DL3 and decreased expression of activating KIR2DS3 in the patient group compared to controls were statistically significant. In addition, patients with early stages (stage 1, 2, 3, and 4S) had higher expression of KIR2DS3 and lower expression of KIR2DL3 compared to patients with metastatic disease (stage 4). Although when corrected *p* values are calculated, only KIR2DS3 frequency between patients and controls was found be statistically significant ($p = 0.025$). Comparison of KIR2DL3 between patients and controls, comparison of both KIR2DS3 and KIR2DL3 between early stages versus metastatic stage were found to have borderline *p* values.

KIR genes have a complex role in cancer development. Although the patient group was small, our data suggest a role for KIR2DL3 and KIR2DS3 in the development of neuroblastoma. In all the above mentioned studies including the present study, the genotype was ascertained assuming that the tumor cells are expressing their inherited ligands. Semeraro et al. [10] have demonstrated the interaction of NK receptor NKp30 and its ligand, B7-H6, in high-risk neuroblastoma patients; NKp30 expression was markedly decreased in NK cells from metastatic bone marrow, where neuroblasts and monocytes express the NKp30 ligand B7-H6. NK cells from patients with metastatic neuroblastoma exhibited deficient transcription of the activating isoforms of NKp30 (NKp30A and NKp30B) compared to patients with localized neuroblastoma and the control group. Patients with NK cells with more activating NKp30B over inhibitory NKp30C stayed in remission longer after chemotherapy and hematopoietic stem cell transplantation. Besides, depletion of the NKp30C isoform transcripts by specific small interfering RNAs restored NKp30 effector functions [10]. The discovery of miRNAs and understanding their biology in development of disease, especially in cancer, have made them an attractive tool for both diagnostics and therapeutics. Several functional studies have confirmed the role of miRNAs in pathogenesis of cancer and some miRNA-targeted therapeutics have reached clinical trials [22]. Nutalai et al. [23] identified a mechanism of functional regulation of KIR3DL3 via miRNAs. Pesce et al. [24] investigated miR-146a-5p in the regulation of KIR expression and showed that miR-146a-5p is mainly involved in the regulation of inhibitory KIRs (KIR2DL1, KIR2DL2, KIR2DL3, KIR2DL4, and KIR3DL1). By using dual-luciferase reporter assay, they have validated KIR2DL1 and KIR2DL2 as targets of miR-146a-5p. They also identified other novel miRNAs regulated in $CD56^{dim}$ and $CD56^{bright}$ NK cells that can target potential NK surface marker genes on different bioinformatics platforms. Although they did not validate KIR2DL3 as a target, miR-146a-5p is predicted as a novel regulator of KIR2DL3. Targeting by miR-146a-5p will result in inhibitory KIR downregulation, hence generate the effect of NK/KIR-mismatching against HLA-class I+ tumor cells and can increase the NK-mediated antitumor activity in metastatic neuroblastoma patients. Also miR-34a-5p, miR-373-5p, and miR-1 were predicted as novel miRNA-targeting KIR2SD3 on $CD56^{dim}$ and $CD56^{bright}$ NK cells, respectively. Modulation with these miRNAs may have therapeutic benefit in activating KIR2DS3 in bone marrow cells of neuroblastoma patients [24].

Conclusion

The presence of the activating KIR genotype may have a protective effect against development of different cancers, while increase in inhibitory KIR may provide a basis for the development of cancer. Future studies on neuroblastoma should include the assessment of KIR ligands and NK cells in tumor tissues. Further treatment by targeting miRNAs to prevent the inhibitory KIR2DL3 or to enhance the activating KIR2DS3 is worthy of research.

Statement of Ethics

The Institutional Review Board of Çukurova University in Adana, Turkey (IRB 79: July 6, 2018) approved the study.

Conflict of Interest Statementconflict

The authors declare that no competing interests exist.

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Author Contributions

Planning and conducting the study: Gülay Sezgin; collecting and interpreting the data: Gülay Sezgin, Özlem Görüroğlu Öztürk, and Ayşe Özkan; drafting/revision of the manuscript and approval of the final draft of the submitted manuscript: Gülay Sezgin, Özlem Görüroğlu Öztürk, Ayşe Özkan, Serhan Küpeli, and İbrahim Bayram.

Data Availability Statement

All data generated in this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

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