STUDY OF KILLER CELL IMMUNOGLOBULIN-LIKE RECEPTOR GENES AND HLA C LIGANDS IN HEMATOPOIETIC STEM CELL TRANSPLANTATION PAIRS IN VOJVODINA

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Objective: The aim of the study was to analyse KIR/HLA profiles and to create the predictive probabilities for the selection of the most suitable Hematopoietic Stem Cell Transplantation (HSCT) donor.

Materials and Methods: The study was conducted on 92 patients with malignant hematological diseases and 181 their first degree relatives, from the region of Vojvodina. HLA and KIR genotyping was performed by polymerase chain reaction-sequence specific primers (PCR-SSP) assay. The analysis included the degree of HLA matching between transplant pairs, number of missing ligands for inhibitory KIR genes, existence of GvH / HvG ligand-ligand mismatches (specific for C1, C2 or Bw4 ligands) and distribution of C1/C1, C1/C2, C2/C2 HLA ligand groups in patients.

Results: There was no significant differences in HLA frequencies between donors and recipients as analyzed by pairwise comparison, the probability of finding HLA identical donor is only 0.154, the probability of finding the donor with ≥ 1 KIR-ligand mismatch is 0.939, the probability of finding the donor with KIR-ligand mismatch for the KIR
Conclusion: The results of our study could be used as a basis for the HSCT outcome prediction representing a powerful tool for choosing the most suitable donor.

Keywords: Hematopoietic Stem Cell Transplantation; Human Leukocyte Antigen; Killer cell Immunoglobulin-like Receptor genes

INTRODUCTION

Killer immunoglobulin–like receptors (KIRs) are members of the immunoglobulin superfamily expressed on the surface of natural killer (NK) cells and a subset of T cells (COOK et al., 2004). They are encoded by highly polymorphic genes located on chromosome 19q13.4 in a region known as the leukocyte receptor cluster (LRC) (LANIER, 1998; WENDE et al., 1999). KIRs are present in 2 main forms, delivering either an inhibitory or an activating signal following ligation. Inhibitory receptors possess a cytoplasmic tail bearing immunoreceptor tyrosine-based inhibitory motifs (ITIMs) (WILSON et al., 2000; UNKELESS and JIN, 1997), whereas activating KIRs lack a cytoplasmic tail, requiring an adaptor protein (DAP12) to generate intracellular signals via activating motifs (ITAMs) on the adaptor protein (UNKELESS and JIN, 1997; LANIER et al., 1998).

KIRs can ligate with specific human leukocyte antigen (HLA) class I molecules and other unknown ligands on target cells with the help of conserved lectin-like receptors CD94-NKG2A and CD94-NKG2C and lead to either inhibition or activation of cytotoxic cells (LANIER, 1998; VALIANTE et al., 1997). The large number of interactions between KIRs and their ligands will affect the activity of NK cells. Therefore, KIRs may play a significant role in the control of immune responses (RAULET et al., 2001). KIRs have been found to be implicated in susceptibility to diseases, including celiac disease (JABRI et al., 2000), rheumatoid arthritis (WARRINGTON et al., 2001), systemic lupus erythematosus (HOU et al., 2010), and infectious diseases (ZHI-MING et al., 2007), in the process of pregnancy (MALE et al., 2010), in the potentially beneficial graft versus leukemia responses after allogeneic transplantation (RUGGERI et al., 1999), and in the HLA matched hematopoietic stem cell transplantation (SHILLING et al., 2003).

Killer cell immunoglobulin-like receptor (KIR) ligand mismatches have been associated with a significant increase in overall survival, as well as better engraftment and a reduced incidence of graft-versus-host disease (GvHD) in patients with AML. Donor NK cells mediate an antileukemic effect in HSCT recipients when inhibitory KIRs are mismatched for HLA type in transplants, since these cells will recognize the recipient leukemia cells as foreign. The mismatched donor NK cells can decrease the rate of relapse; however, the mismatched transplant also has an increased risk of GvHD (RUGGERI et al., 1999). The two dominant HLA-C-encoded epitopes recognized by inhibitory KIR are designated C1 and C2 and are present on all known HLA-C alleles in a mutually exclusive way. Notably, selection of a HLA-C ligand-mismatched donor improves event-free survival (EFS) in haploidentical allogeneic stem cell transplantation in patients with Acute Myeloid Leukemia (AML) (VELARDI, 2008; FISCHER et al., 2012). In haploidentical transplantations that are KIR ligand mismatched in the graft-versus-host (GvH) direction, functional donor NK cells that express as their sole inhibitory receptor for self a KIR for the HLA class I group, which is absent in the recipient, sense the missing expression of the self class I ligand on allogeneic targets and mediate alloreactions (“missing self” recognition).
The importance of a specific inhibitory KIR to the HSCT outcome is also evident. Cumulative incidence analysis of aGvHD in patients undergoing HLA-identical sibling hematopoietic stem cell transplantation in the study of Ludajić at coworkers demonstrated an increased incidence of severe aGvHD in patients lacking HLA ligand for donor-inhibitory KIR2DL1 (Ludaic et al., 2009). Recent transplant strategies based on KIR-ligand mismatch to predict NK cell alloreactivity have resulted in less relapse, less GvHD and better overall survival in patients with Acute Myeloid Leukaemia (AML). NK cell alloreactivity could be predicted and directed in GvH and HvG direction specific for HLA C1, C2 or Bw4 ligand group. The incidence of chronic graft versus host disease (GvHD) was significantly lower in C1 or C2 homozygotes than in C1/C2 heterozygotes (p = 0.000). Higher overall survival (OS) and disease-free survival (DFS) rates were observed in C1 or C2 homozygotes than in C1/C2 heterozygotes (Wang et al., 2013).

Previous reviews have grouped NK alloreactivity studies in four models: (1) KIR-ligand incompatibility, or ligand-ligand model (Ruggeri et al., 2002); (2) receptor-ligand model (Leung et al., 2011); (3) KIR gene-gene (receptor-receptor or haplotype) model (initially described by Nantes group, actually is similar to the Stanford model) (Gagne et al., 2009; Parham et al., 2005; McQueen et al., 2007); (4) missing ligand model (retrospective model actually similar to the receptor-ligand model but neither the donor KIR nor HLA is considered for donor selection) (Beksac and Dalva, 2012).

This paper will summarize the impact of KIRs and their HLA ligands on stem cell transplantation outcome. The ultimate goal is based on the analysis of KIR/HLA profiles to create the probabilities that can serve as predictive tool for the most suitable donor selection.

MATERIALS AND METHODS

Study subjects

Blood samples were collected from 92 patient suffering from hematological malignant diseases (median age: 34.5 years and males/females: 39 vs 53) and their 181 healthy relatives (median age: 28.5 years and males/females: 92 vs 89), who have been analyzed for the HLA gene frequencies, moreover related potential hematopoietic stem cell donors were analyzed for the presence or absence of 16 KIR genes including two pseudogenes. Informed written consent and Local Ethics Committees’ approval were obtained.

DNA isolation and genotyping

Genomic DNA from the investigated subjects was isolated by silica-based extraction method, using the GeneJET Genomic DNA Purification Kit (Thermo Fisher Scientific Inc., Vilnius, Lithuania) from 200 μl of buffy-coat obtained from 3 ml of blood collected with EDTA. KIR and HLA genotyping was performed by using the commercially available KIR-Ready Gene kit (Inno-Train Diagnostik GmbH, Kronberg, Deutschland) and HLA-Ready Gene ABC low and HLA-Ready Gene DRDQ low (Inno-Train Diagnostik GmbH, Kronberg, Deutschland) based on polymerase chain reaction-sequence specific primers (PCR-SSP) assay. PCR-SSP was performed following the manufacturer’s instructions. Briefly, 26μl of DNA at a concentration of 25-100ng/μl with A260/A230 ratio between 1.6-1.9 was mixed with 84μl of Ready PCR Buffer, 2.2μl of Taq polymerase and 168μl of distilled water for KIR genotyping of related donors, while 102μl of DNA was mixed with 312μl of Ready PCR Buffer, 8.3μl of Taq polymerase and 624μl of distilled water for HLA A,B,C low resolution genotyping and 35μl of DNA was mixed with
111μl of Ready PCR Buffer, 3,0μl of Taq polymerase and 222μl of distilled water for HLA DRB1/DQB1 low resolution genotyping, respectively.

Ten μl of this mixture was used for each reaction. The reaction was amplified by a MASTERCYCLER Gradient (Eppendorf, Germany) PCR system under the thermal and time conditions recommended by the manufacturer, which started with a heating temperature of 96°C for 2 min, followed by 10 cycles of 15 s at 96°C, 60 s at 65°C and 20 cycles of 15 s at 96°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 an UV transilluminator and photographed. The typing was interpreted by a worksheet for specific amplification patterns, as well as by SCORE™ evaluation software (Inno-Train Diagnostik GmbH, Kronberg, Germany).

**Statistical analysis**

The percentage of the studied subjects positive for KIR (related donors) and HLA genes (patients and related donors) (carrier frequency) was determined by direct counting, according to equation: A = n/N, where n is number of persons with a given gene and N is total number of persons studied (BUBNOVA et al., 2008; MATEI et al., 2012). The degree of HLA matching among donors and patients was determined as well as the distribution of HLA C genotypes among the patients. The HLA-C genotype was defined in terms of Group C1 or Group C2 as recognized by NK cells through the KIR receptors. The analysis included the determination of missing ligands for the inhibitory KIR genes, KIR/HLA mismatches amongst the individuals within the corresponding pairs, mismatches in relation to the specific inhibitory KIR genes and KIR-ligand mismatches directed in GvH and HvG direction specific for HLA C1, C2 or Bw4 ligand groups. Search of mismatches between KIR ligands is enabled by research tool that is being available at following website: https://www.ebi.ac.uk/ipd/kir/ligand.html.

**RESULTS**

We firstly compared the carrier frequencies of the HLA -A, -B, -C, -DRB1 and -DQB1 genes in the group of patients with frequencies in the group of their first degree relatives. Analysis of HLA gene frequencies revealed no significant differences in frequencies between donors and recipients as analyzed by pairwise comparison (Table 1). Degree of HLA matching was evaluated for low resolution level mismatches across five loci HLA-A, -B, -C, -DRB1 and -DQB1. HLA matching groups were clustered upon the number of matched alleles between patients and their corresponding donors (Table 2.) Beside 28 patients who have 10/10 HLA compatible donors (identical siblings), 3 of patients lacking an HLA-identical sibling have a two-antigen–mismatched related donor, while 12 of patients have three-antigen-mismatched donor.

KIR-ligand mismatch between donor-recipient pairs were analysed according to “missing ligand model”(donors possess inhibitory KIR and patients lack a specific HLA C ligand).The analysis revealed that there were 76 pairs with one KIR-ligand mismatch, 67 pairs with two KIR-ligand mismatches, 27 pairs with three KIR-ligand mismatches and 11 pairs with no KIR-ligand mismatches. The analysis of KIR-ligand mismatches towards specific inhibitory KIRs showed that 54 patients lack HLA ligands for KIR 2DL1, 18 patients lack HLA ligands for KIR 2DL2, 29 patients lack HLA ligands for KIR 2DL3, 69 patients lack HLA ligands for KIR 3DL1 and nearly 72% of patients lack HLA ligands for KIR 3DL2, respectively (Table 3).
Table 1. Distribution of HLA-A, -B, -C, -DRB1 and -DQB1 frequencies in patients and their relatives

<table>
<thead>
<tr>
<th></th>
<th>A locus</th>
<th>B locus</th>
<th>C locus</th>
<th>D locus</th>
<th>DRB1 locus</th>
<th>DQB1 locus</th>
</tr>
</thead>
<tbody>
<tr>
<td>*01</td>
<td>0.198</td>
<td>0.141</td>
<td>*07</td>
<td>0.160</td>
<td>0.173</td>
<td>0.138</td>
</tr>
<tr>
<td>*02</td>
<td>0.519</td>
<td>0.510</td>
<td>*08</td>
<td>0.143</td>
<td>0.108</td>
<td>0.209</td>
</tr>
<tr>
<td>*03</td>
<td>0.176</td>
<td>0.184</td>
<td>*13</td>
<td>0.077</td>
<td>0.076</td>
<td>0.110</td>
</tr>
<tr>
<td>*23</td>
<td>0.066</td>
<td>0.054</td>
<td>*14</td>
<td>0.066</td>
<td>0.097</td>
<td>0.237</td>
</tr>
<tr>
<td>*24</td>
<td>0.265</td>
<td>0.260</td>
<td>*15</td>
<td>0.060</td>
<td>0.010</td>
<td>0.077</td>
</tr>
<tr>
<td>*25</td>
<td>0.082</td>
<td>0.076</td>
<td>*18</td>
<td>0.143</td>
<td>0.173</td>
<td>0.171</td>
</tr>
<tr>
<td>*26</td>
<td>0.149</td>
<td>0.130</td>
<td>*27</td>
<td>0.147</td>
<td>0.119</td>
<td>0.436</td>
</tr>
<tr>
<td>*30</td>
<td>0.033</td>
<td>0.021</td>
<td>*37</td>
<td>0.022</td>
<td>0.0 1</td>
<td>0.303</td>
</tr>
<tr>
<td>*31</td>
<td>0.038</td>
<td>0.054</td>
<td>*38</td>
<td>0.099</td>
<td>0.119</td>
<td>0.022</td>
</tr>
<tr>
<td>*32</td>
<td>0.116</td>
<td>0.152</td>
<td>*39</td>
<td>0.071</td>
<td>0.065</td>
<td>0.082</td>
</tr>
<tr>
<td>*33</td>
<td>0.044</td>
<td>0.054</td>
<td>*40</td>
<td>0.088</td>
<td>0.097</td>
<td>0.016</td>
</tr>
<tr>
<td>*66</td>
<td>0.005</td>
<td>0.0 1</td>
<td>*41</td>
<td>0.038</td>
<td>0.032</td>
<td>0.005</td>
</tr>
<tr>
<td>*68</td>
<td>0.049</td>
<td>0.010</td>
<td>*44</td>
<td>0.165</td>
<td>0.141</td>
<td>0.018</td>
</tr>
<tr>
<td>*69</td>
<td>0.005</td>
<td>0.010</td>
<td>*45</td>
<td>0.005</td>
<td>0 0</td>
<td>0 0</td>
</tr>
</tbody>
</table>

D= donors (n=181), P= patients (n=92)

Table 2. Degree of HLA matching among patients and their corresponding relatives

<table>
<thead>
<tr>
<th></th>
<th>10/10</th>
<th>9/10</th>
<th>8/10</th>
<th>7/10</th>
<th>6/10</th>
<th>5/10</th>
<th>4/10</th>
<th>3/10</th>
<th>2/10</th>
<th>1/10</th>
<th>0/10</th>
</tr>
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<tbody>
<tr>
<td>28</td>
<td>0</td>
<td>3</td>
<td>12</td>
<td>33</td>
<td>74</td>
<td>4</td>
<td>9</td>
<td>11</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>0.154</td>
<td>0</td>
<td>0.016</td>
<td>0.066</td>
<td>0.182</td>
<td>0.408</td>
<td>0.022</td>
<td>0.049</td>
<td>0.060</td>
<td>0.011</td>
<td>0.027</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Number of KIR/HLA mismatches towards the specific inhibitory KIR

<table>
<thead>
<tr>
<th>KIR 2DL1</th>
<th>KIR 2DL2</th>
<th>KIR 2DL3</th>
<th>KIR 3DL1</th>
<th>KIR 3DL2</th>
</tr>
</thead>
<tbody>
<tr>
<td>54</td>
<td>18</td>
<td>29</td>
<td>69</td>
<td>130</td>
</tr>
<tr>
<td>0.298</td>
<td>0.099</td>
<td>0.160</td>
<td>0.381</td>
<td>0.718</td>
</tr>
</tbody>
</table>

Search of mismatches between KIR ligands according to “ligand-ligand model” (for example, a ligand-ligand mismatch in GvH direction, is possible if the donor has a ligand that is absent in the recipient) was determined on the basis of the amino-acid substitutions in residues.
76–83 of the α₁ helix of the HLA class I heavy chain (C₁, C₂ and Bw4 epitopes). The patients were sorted into two groups; ligand-ligand-mismatched in GvH (D⁺R⁻) direction and ligand-ligand-mismatched in HvG (D⁻R⁺) direction in relation to a specific epitope motifs (C₁, C₂ Bw4), respectively. Our analysis revealed that there were two times 17 transplant pairs with mismatches for the HLA-C₁ group of ligands that will be (mis)matched in the both GvH and HvG direction, 24 transplant pairs with mismatches for the HLA-C₂ group of ligands that will be (mis)matched in the GvH and 30 in HvG direction and 23 transplant pairs with mismatches for the HLA-Bw4 group of ligands that will be (mis)matched in the GvH and 29 in HvG direction (Table 4).

**Table 4. Number of KIR/HLA mismatches in GvH and HvG direction for a specific ligand groups**

<table>
<thead>
<tr>
<th>MM</th>
<th>GvH (D⁺R⁻)</th>
<th>C₁</th>
<th>C₂</th>
<th>Bw4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17</td>
<td>24</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>HvG (D⁻R⁺)</td>
<td>17</td>
<td>30</td>
<td>29</td>
<td></td>
</tr>
</tbody>
</table>

We next assessed the distribution of C₁/C₁ ligands (i.e., C₁ epitope present on both HLA-C alleles), C₂/C₂ ligands (i.e., C₂ epitope present on both HLA-C alleles) and C₁/C₂ ligands (i.e., C₁ and C₂ epitope are present at the same time as heterozygous) in patients, respectively. Our analysis of HLA C ligands distributed in the patient group revealed that there were 39.13% patients homozygous for C₁, 17.39% homozygous for C₂, and 43.47% have C₁/C₂ heterozygous genotype (Table 5).

**Table 5. Distribution of C₁/C₁, C₁/C₂ and C₂/C₂ HLA ligand groups in patients**

<table>
<thead>
<tr>
<th></th>
<th>C₁/C₁</th>
<th>C₁/C₂</th>
<th>C₂/C₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>36</td>
<td>40</td>
<td>16</td>
</tr>
<tr>
<td>39.13%</td>
<td>43.47%</td>
<td>17.39%</td>
<td></td>
</tr>
</tbody>
</table>

Among all investigated transplant pairs with ≥1 KIR-ligand mismatch, there were eight HLA identical pairs with C₁/C₁ genotype, six HLA identical pairs with C₂/C₂ genotype, one with C₂/C₂ genotype and 8/10 HLA matched, two times three pairs 7/10 HLA matched (of which one group with C₁/C₁ and another with C₂/C₂ genotype), eight pairs 6/10 HLA matched with C₁/C₁ and three with C₂/C₂ genotype and twenty-two haploidentical pairs with C₁/C₁ and thirteen with C₂/C₂ genotype, respectively.

**DISCUSSION**

It is widely accepted that HLA disparity has been associated with graft failure, delayed immune reconstitution, graft-versus-host disease (GvHD), and mortality. Also, both activating and inhibitory KIR genes have a fundamental role in HSCT outcome. However, NK cell activation/function largely depends upon interactions between combinations of activating and inhibitory KIRs and their HLA receptor-ligands (Cooley et al., 2010; Symons et al., 2010; Franceschi et al., 2011; Parham et al., 2012). Donor KIR genotype influenced transplantation outcomes for patients with AML but not for those with ALL.
Compared to donors without KIR mismatches, donors having KIR mismatches showed reduced incidences of relapse and improved disease-free survival. Furthermore, KIR-ligand incompatibility in the graft-versus-host direction in haplotype-mismatched transplants suggests a possible clinical benefit as it may allow early recovery of donor alloreactive NK cells with enhanced antileukemia activity in AML (RUGGERI et al., 2002; PARK et al., 2015; PARK et al., 2012). In transplants that are KIR-ligand mismatched in the graft-versus-host (GvH) direction, donor NK cells expressing inhibitory KIRs, which do not recognize ligand(s) on recipient targets, are released from HLA inhibition and mediate alloreactions leading to clinically significant graft-versus-leukemia effects. Clinical studies in haploidentical and in some (un)related donor transplants showed that KIR-ligand incompatibilities in GvH direction are associated with a decreased incidence of relapse and improved disease-free and overall survival (OS) after HSCT (WILLEMZE et al., 2009).

Our study including relevant predictive factors for outcome of HSCT revealed that among studied patients and their potential first degree relative donors, there were 15.4% HLA identical pairs, while 40.8% were haploidentical. This finding is in accordance to the previous study (PENNINGS et al., 2002), due to the increasing tendency towards small families in Western countries, resulting in chance of having an HLA-identical sibling no greater than 15%. In contrast, in large families such as in Saudi Arabia, with an average of 5.03 children per family and high rate of consanguinity (57.7%), the chance of finding a matching sibling was 43% in patients aged birth to 5 years, compared with 68% in those aged ≥20 years (JAWDAT et al., 2009).

As in the presence of KIR-ligand mismatch between donor-recipient pairs, improved engraftment and a decrease in relapse rates were observed (RUGGERI et al., 2002; PARHAM, 2005; LEUNG, 2011), our study included the analysis of type and number of present KIR-ligand mismatches among the studied transplant pairs. There were only 6% or 11 transplant pairs without any of KIR-ligand mismatches, indicating to a relatively high probability of mismatches: 0.419 with one mismatch, 0.370 with two and 0.149 with three mismatches, respectively. Also, nearly 30% (0.298) patients lack ligands for KIR 2DL1 gene with previously described unfavorable effect to the incidence of severe aGvHD.

Search of mismatches between KIR ligands showed that in the whole group of analysed pairs, there are more ligand-ligand mismatches in HvG direction than in GvH direction (30 vs 24 for C2 epitopes, 29 vs 23 for Bw4 epitopes), while there were 17 mismatches for C1 epitopes in both of directions. Analysis by the ligand calculator enables prediction of ligand mismatches for every patient (and their corresponding donor(s)) independently, providing a prediction of possible rejection or GvH reaction in a given case. Our analysis of the HLA C ligand group distribution among patients revealed that overall probability of possessing favorable, either C1/C1 or C2/C2 ligands is 0.565 (0.391 for C1/C1 vs 0.173 for C2/C2), while overall probability of possessing unfavorable C1/C2 ligands is 0.434.

CONCLUSIONS

The result of our study could be used as a predictive tool for the assessment of HSCT outcome and for creation of individual and general calculating model of the probability of HSCT complications such as GvHD or relapse development. It represents a powerful tool in donor search strategy by enabling us to choose the most suitable donor.
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REFERENCES


STUDIJA O GENIMA IMUNOGLOBULINA SLIČNIM RECEPTORIMA PRIRODNIH ČELIJA UBICA I HLA C LIGANDIMA U PAROVA ZA TRANSPLANTACIJU MATIČNIH ČELIJA HEMATOPOEZE U VOJVDINI

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Izvod

Cilj: Cilj studije je bio da se analiziraju KIR/HLA geni i izračuna verovatnoća za izbor najpovoljnijeg donora za transplantaciju matičnih čelija hematopoeze (MČH).

Materijal i metode: Studija je sprovedena na 92 pacijenta sa malignim hematološkim bolestima i 181 njihovih srodnih donora, iz regiona Vojvodine. HLA and KIR genotipizacija je vršena testom lančane reakcije polimeraze-sekvenciono specifičnim prajmerima (PCR-SSP). Analiza je obuhvatala određivanje stepena HLA podudarnosti između parova za transplantaciju, broj nedostajućih HLA liganada za inhibitorne KIR gene u pacijenata, postojanje GvH/HvG ligand-ligand neusaglašenosti (specifičnih za C1, C2 ili Bw4 grupe liganada) i distribuciju C1/C1, C1/C2, C2/C2 HLA ligand grupa u pacijenata. Rezultati: Nisu utvrđene značajne razlike u HLA frekvencijama između davalaca i primalaca MČH koje su analizirane uporednim poređenjem, verovatnoća nalaženja HLA identičnog donora iznosi samo 0.154, verovatnoća pronalaženja donora sa ≥ 1 KIR-ligand neusaglašenosti je 0.939, verovatnoća pronalaženja donora sa KIR-ligand neusaglašenosti za KIR 2DL1 gen je 0.298, verovatnoća posedovanja povoljnih C1/C1 i C2/C2 HLA grupa liganada je 0.565. Zaključak: Rezultati istraživanja KIR/HLA gena se mogu koristiti kao osnova za predviđanje ishoda transplantacije MČH i predstavljaju sredstvo za izbor odgovarajućeg donora.

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