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Specific "intra-allele" and "intra–broad antigen" human leukocyte antigen alloantibodies in kidney graft transplantation

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ABSTRACT

Human leukocyte antigen (HLA) antibodies are epitope specific and not antigen specific. This work presents a case of intra-allele (IA) sensitization. A 40-year-old-man underwent transplantion with identical "broad" DR. He was apparently not sensitized to HLA antigens by complement-dependent cytotoxicity (CDC), with one previous transplantation 15 years previously. In post-transplantation monitoring, we detected an "intra–broad antigen" (IBA) anti-DRB1*13 DSA by Luminex. We performed post-transplantation B-cell cross-matching (CM) by CDC, this being completely negative. We detected allele-specific antibodies by single antigens (SA), anti-DRB1*1303 (IBA), -DQB1*0301 (IA), -DRB1*1101, -DRB3*0101, anti-DPB1*0202, and anti-DRB1*0103. These antibodies originated from the first transplantation, HLA-DR6+ homozygous and serologically broad matched, but retrospectively typed as DRB1*1401, **1303*; DRB3*0101, *0202; DQB1**0301*, *0503; DPB1*0401, **0202* (mismatches in italics). However the second donor was DRB1*1301, *1401 (DR6+ homozygous); DRB3*0202; DQB1*0603, *0503; DPB1*0401 (mismatches in italic). Therefore, the stronger antibodies generated in the first transplantion (anti-DRB1*1303 and -DQB1*0301) were not specific for the specific subtypes (DRB1*1301 and -DQB1*0603) on the second transplantation. Finally, it was possible to exactly define the potential immunizing epitopes the recognition of which determined antibody production. Therefore, our patient had low titers of pretransplantation IBA and IA antibodies that were not prospectively detected by CDC. Post-transplantation with Luminex, we detected these alloantibodies, but as they were not IA and IBA DSA, they did not cause allograft injury.

1. Introduction

In renal transplantation, donor–recipient HLA-matching is performed considering compatibility for human leukocyte antigen (HLA) broad antigens. On the contrary, the use of the new HLA-specific solid-phase techniques to characterize alloantibodies in sera from sensitized patients has shown production of antibodies specific for HLA-A, -B, -C, -DR, -DQ, and -DP molecules [1]. In this sense, recent articles have demonstrated that HLA antibodies are epitope specific and not antigen specific [2,3]. In fact, it has been demonstrated that the patient who lost a kidney graft developed a wide antibody pattern specific for all of the HLA molecules sharing the donor mismatched epitope. Particularly, in HLA class II antibody screening, newer serum screening methods such as enzyme-linked immunosorbent assay, flow cytometry, and Luminex technology have greatly enhanced the detection and specificity analysis of anti–HLA class II antibodies in sensitized patients [4,5]. In addition, a relatively recent breakthrough in HLA antibody research was the development of HLA single antigens (SA) beads [6,7]. SA Flow or Luminex bead technology assists not only in the identification of antibody specificities but also in the identification of potential antibody epitopes.

Moreover, the high polymorphism of the MHC is not reflected in the number of HLA antigens. In fact, DNA-based techniques identified a great number of HLA alleles due to one or more amino acid substitutions in the sequence of an HLA molecule. Thus any unique single–amino acid residue or a combination of several amino acid residues (or residue combinations) are positively targeted, whereas alleles without it are not recognized by testing antibody or serum.

This work presents a very interesting clinical case with respect to intra-allele sensitization of a patient. This allele-specific but not antigen-specific sensitization could have an important role in clinical transplant outcome.

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Table 1
HLA class I and II typing of the patient and organ donors

Locus	HLA-A	HLA-B	HLA-DRB1	HLA-DRB3	HLA-DQB1	HLA-DPB1
Patient	*26, *29	*38, *44	*0901, *1401	*0202	*0303, *0503	*0401, *0501
Donor 1	*68*, *29	*44, *53*	*1303*, *1401	*0101*, *0202	*0301*, *0503	*0202*, *0401
Donor 2	*11*, *25	*18*, *35*	*1301*, *1401	*0202	*0603*, *0503	*0401

Mismatches are marked in italics.

2. Subjects and methods

A 40-year-old Caucasian man with end-stage renal disease (renal polyquistosis) underwent kidney retransplantation in our hospital with a deceased 42-year-old donor kidney. Before transplantation, cross-matching (CM) of the patient's serum and the unseparated donor's lymphocytes by standard complement-dependent cytotoxicity (CDC) assay was apparently negative.

The maintenance immunosuppressive regimen consisted of prednisone, mycophenolate mofetil, and tacrolimus, as previously published [4].

Our patient was apparently not sensitized to HLA antigens, with a panel-reactive antibody (PRA) level approaching 0% by standard CDC technique, without previous blood transfusion history and with one previous transplantation 15 years previously. With respect to this first transplantation, the patient presented with transplant glomerulopathy in 2007 (time of allograft survival, 13 years), the diagnosis of which was based on the presence of duplication of the glomerular basement membrane (Banff cg (chronic lesions in the glomeruli) score >0) detected by light microscopy using silver-methenamine staining in the absence of evidence of recurrent glomerulonephritis and thrombotic microangiopathy. The result of the C4d staining by immunofluorescence was negative. The patient required dialysis and was not nefrectomized.

In the routine post-transplantation monitoring (3 months after second transplantation), we detected anti-HLA class II antibodies (IgG) by Luminex technology (Labscreen Mix, One Lambda, Canoga Park, CA). With the Luminex analyzer, reporter fluorescence of the beads was determined and expressed as median fluorescence intensity (MFI), which is directly proportional to the amount of antibody bound to the microspheres. The pretransplantation serum (second transplantation) was also positive by Luminex technology (retrospective study). Anti–HLA class I and anti-MHC class I chain-related A antibodies screenings were totally negative.

Second, we detected a possible intra–broad antigen DSA anti-DRB1*13 antibody (donor's typing had DRB1*13) in the specificities analysis (Labscreen PRA, One Lambda, Canoga Park, CA). With these facts, nephrologists in our hospital indicated a renal biopsy, the results of which were completely normal, without any evidence of C4d deposits and the current creatinine of <1 mg/dl. The rest of the post-transplantation course was uncomplicated.

We performed post-transplantation B-cell (from donor's frozen spleen) CM by CDC assay with the pre- and post-transplantation sera (second transplantation), and results were completely negative. This CM test (with extended times for more sensitivity) was performed as previously published [4].

In this second transplantation, the broad HLA matching between donor-recipient was 1A+2DR antigens; thus with identical broad DR [donor: *A11*, 10 [25]; *B18, 35*; DR6 [13,14]; recipient: A10 [26], 29; B38, 44; DR6 [14], 9; marked MMs in cursive]. HLA-A, -B, -DRB1, and -DQB1 genotyping was performed by allele specific PCR-SSP method (One Lambda, Canoga Park, CA), as previously published [8].

To study in depth this interesting case, high-resolution HLA class II typing of our recipient was also performed with the following result: DRB1*0901, *1401; DRB3*0202; DRB4*0103; DQB1*0303, *0503, DPB1*0401, *0501 (Table 1).

The SA bead assay by Luminex technology allow the fine identification of allele-specific antibodies [6]. Thus we performed SA analysis for class II antibodies (LSA01, lot 006, One Lambda, Canoga Park, CA). We detected several antibodies allele-specific, anti-DRB1*1303 (intra–broad antigen) and -DQB1*0301 (intra-allele) in high titer (MFI, ~7000), and anti-DRB1*1101 and DRB3*0101 (intra-allele) in moderate titer (MFI, ~3000), and anti-DPB1*0202 and -DRB1*0103 and in low titer (MFI, <1500). These SA results were consistently confirmed in another serum after 3 and 6 month intervals and in the pretransplantation serum (second transplantation). Unfortunately, serum obtained before the first transplantation was not available. The MFI data are shown in Table 2.

These alloantibodies originated in the first transplantation, HLA-DR6+ homozygous and serologically broad matched, but retrospectively DNA typed as DRB1*1401, *1303*; DRB3*0101, *0202; DQB1*0301*, *0503; DPB1*0401, *0202* (marked allele mismatches in italics). This donor's sample fortunately was obtained from our archives in liquid nitrogen (frozen lymphocytes from our investigation projects on liver transplantation).

However, the second donor's molecular typing was DRB1*1301, *1401 (DR6+ homozygous); DRB3*0202; DQB1*0603, *0503; DPB1*0401 (marked allele mismatches in italics). Therefore, the stronger antibodies generated in the first transplant (anti-DRB1*1303 and -DQB1*0301) were not directed against the allele-specific subtypes (HLA-DRB1*1301 and -DQB1*0603) present in the second kidney transplant. HLA class I and II molecular typing of patient and donors are summarized in Table 1.

To test the possible cytotoxicity of these IgG antibodies, we performed B-cell cross-match by CDC assay with the pre- and post-transplantation recipient sera (second transplantation) against several frozen cells, DRB1*1301$^+$, DRB1*1302$^+$ and DRB1*1401$^+$ (recipient's own HLA type), which were completely negative; in opposition to them, DRB1*1303$^+$, DRB1*1101$^+$ (cross-reacting molecule, more similar to DRB1*1303 than to DRB1*1301 and *1302 subtypes) and DQB1*0301$^+$ were moderately positive (classical serologic scores of 4–6).

Table 2
Values of SA Luminex MFI for different alleles in the studied sera

Locus	Pre-2nd Tx (0 Months) MFI	Post-2nd Tx (3 Months) MFI	Post-2nd Tx (6 Months) MFI	Post-2nd Tx (9 Months) MFI
DRB1*1303	6911	7123	7029	6921
DQB1*0301	6827	7045	6923	6837
DRB1*1101	2941	3247	3198	2910
DRB3*0101	2821	3011	2861	2766
DPB1*0202	1371	1437	1332	1299
DRB1*0103	1401	1614	1582	1389
DQB1*0401	507	562	544	497
DRB1*0802	499	432	394	401
DRB1*1501	452	441	407	386
DRB1*1301	386	358	346	361
DRB1*1601	322	339	353	317
DRB1*0801	297	301	275	268
DRB1*1502	261	230	255	242
DRB1*1602	211	235	228	204

MFI, median fluorescence intensity; Tx, transplant; SA, single-antigen.

Finally, to identify the epitope recognized by these intra-broad antigen and intra-allele alloantibodies, we compared and analyzed the aminoacids sequences of patient's HLA class II molecules to those of the HLA alleles corresponding to intra-broad antigen and intra-allele antibodies by using an online database (http://www.ebi.ac.uk/imgt/hla) (HLA Informatics group section at the Anthony Nolan Web site), and Histocheck and HLAMatchmaker software [9–11], analyzing the structure of immunizing molecule, the intra-allele antibodies and the immunizing epitopes. By comparing the amino acid sequences of a group of HLA-DRB1 alleles that are either recognized or not recognized by the alloantiserum, a likely or potential epitope was deduced. DR1 antigen (β-chain) model (http://www.ncbi.nlm.nih.gov/entrez) was used as a reference sequence to predict the localization of certain residues on the surface of specific DR antigens.

The structural polymorphisms of HLA-DR are mainly restricted to the β chains. They are readily visible on the top of the molecule adjacent to the bound peptide, and many of them involve contiguous sequences. Polymorphic residues on the side of the molecule generally comprise distinct clusters in both β1 and β2 domains [10]. A few polymorphisms are visible at the bottom part of the molecule that is nearby the cell membrane. DRB, and DQB seem to show similar numbers of polymorphic positions. DQA displays somewhat contiguous polymorphic positions on the top of the molecule near the bound peptide. Sequence comparisons of 381 most common DRB1, DRB3, DRB4, and DRB5 alleles have identified 49 polymorphic positions on the molecular surface, as previously suggested by Duquesnoy and Askar [10].

In our patient, it was possible to define exactly the potential immunizing epitopes the recognition of which determined his antibody production (Table 3). First, the major immunization was related with the broad mismatched molecule of his first transplant, DRB1*1303, whose amino acid sequence at 32–37 is YNQEEY, identical to DRB1*1101 (YNQEEY) and rather similar to DRB1*0103 (YNQEES) and different from the amino acid sequence in the recipient and the second transplant donor [DRB1*1401 (HNQEEF) and DRB1*1301 (HNQEEN)]. Thus the recognition of epitope 32Y in the DRB1*1303 molecule from the first transplantation modeled the specific antibody response of our recipient. In this sense, other detected alloantibodies with moderate and low titer, such as anti-DRB1*1101 and -DRB1*0103, shared 32Y epitope with DRB1*1303 molecule, confirming these interesting findings. This position has an underside location (*i.e.*, underneath the groove) and its molecular surface expression of this polymorphic residue has been graded as readily visible by Duquesnoy and Askar [10]. Other MFI values of molecules with similar and shared sequences are shown in Table 2.

Second, in the analysis of intra-allele DQB1 antibodies, patient's molecule was DQB1*0303 and the originated alloantibody was anti-DQB1*0301. Only 4 amino acids of DQB1*0301 are different from DQB1*0303 molecule (A/G 13, L/Y 26, E/G 45, and 185I). The epitopes 45EV and 185I have "side" locations of the DQB1 molecule, and their molecular surface expression of these polymorphic residues has also been graded as prominently visible by Duquesnoy and Askar [10]. As the 45EV epitope has been suggested as the eplet corresponding to the serologically defined DQ7 antigen [10,12], we think that this epitope could be implicated in the development of this alloantibody in our patient.

Third, in the anti-DRB3 antibody analysis, 10 amino acids are different between DRB3*0202 (patient) molecule and DRB3*0101 (immunizing molecule in the first transplant), being very difficult to know the exact responsible epitope of alloantibody production. There are also unique eplets that distinguish DRB3*01 (12RKS and 183A) from DRB3*02 alleles. These eplets appear to correspond to the DR52 subtypes serologically defined as DR52a and DR52b. These eplet differences are clinically relevant because other authors have also shown several cases whereby a DRB3*0202- or DR52b-positive patient makes antibodies reactive with DRB3*0101 or DR52a [10], and our clinical case could confirm these facts.

Therefore, the patient had very low titers of pretransplantation intra-broad antigen and intra-allele antidonor antibodies (from his first transplantation) that were not detected prospectively by CDC assay. In the post-transplantation monitoring with Luminex technology, we detected these broad DSA alloantibodies; but as they were not intra-allele DSA, they did not cause the kidney allograft injury. In this sense, after 9 months, the patient is currently well, with a creatine level serum of $<$1 mg/dl.

4. Discussion

For more than 30 years, the CDC assay has been standard for the detection of preformed anti-HLA antibodies in the sera of potential kidney transplant recipients. This assay has been criticized for not being able to detect noncomplement binding, low affinity, or low-titer antibodies. In this respect, there are articles comparing the different methods of HLA antibodies screening [1–4] in the detection of these antibodies. Current HLA class II–matching strategies in kidney transplantation consider only the serologically defined HLA-DR antigens controlled by the DRB1 locus, although mismatching for HLA-DQ and HLA-DP appears to be associated with lower graft survival and the development of clinically relevant alloantibodies in transplant recipients) [11–13].

In our clinical case, we did not detect these antibodies pretransplantation from previous alloimmunization of our patient, but this point can be explained by a minimal level pretransplantation (sensitization event, 14 years previously) for CDC detection and later an increase by polyclonal B-cell activation by the second transplant, as previously suggested [14,15].

In this regard, the longevity of antibody responses is maintained by the presence of these long-lived plasma cells or the persistence of antigen. Long-term antibody responses, however, are maintained by nondividing, long-lived plasma cells that produce high-affinity antibody and reside mainly in the bone marrow. Survival of long-lived plasma cells is regulated through the competition of limited survival niches. Once in survival niches, the persistence of long-lived plasma cells does not require the presence of antigen [12,15].

By contrast, HLA antigens are highly polymorphic, cell-surface–expressed molecules with more than 3000 different alleles presently documented in human beings [8]. This property increases the chances of sensitization via exposure to nonself MHC or other

Table 3
Sequence protein alignments of HLA-DRB1 molecules implicated in our clinical case

DRB1*0103	10 GDTRPRFLWQ	20 LKFECHFFNG	30 TERVRLLERC	40 IYNQEESVRF	50 DSDVGEYRAV	60 TELGRPDAEY	70 WNSQKDILED	80 ERAAVDTYCR	90 HNYGVGESFT	100 VQRRVEPKVT
DRB1*110101	--------EY	STS-------	-----F-D-Y	F-----Y---	------F---	-------E--	------F--D	----------	----------	-----H----
DRB1*130101	--------EY	STS-------	-----F-D-Y	FH----N---	------F---	----------	------I--D	E---------	-----V----	-----H----
DRB1*130301	--------EY	STS-------	-----F-D-Y	F-----Y---	----------	------S---	------I--D	K---------	----------	-----H----
DRB1*140101	--------EY	STS-------	-----F-D-Y	FH----F---	----------	------A--H	---------R	---E------	-----V----	-----H----

Numbers represent positions in the corresponding DRB1 protein (100 amino acids represented).

nonself antigens, commonly through blood transfusion, pregnancy, or previous transplantation [5,16–19].

Consequently, HLA-specific antibodies found in post-transplantation patients have been shown to be strongly associated with allograft failure [6,18]. Particularly, HLA class II antigens play an important role in determining donor–recipient compatibility in solid organ and stem cell transplantation, and their mismatching elicits strong alloimmune responses that impair transplant success. In addition, preformed donor-specific anticlass II antibodies increase the risk of transplant failure [11–13,18], and the post-transplantation development of anti– class II antibodies is associated with a higher incidence of acute and chronic rejection [1,14]. Anti–HLA class II antibody levels are also related to the increase in the risk of developing transplant glomerulopathy (TG) [14]. TG is more than a glomerular process; in most cases, the disease involves the entire renal capillary network and is usually identified by light microscopy as a duplication of the glomerular basement membrane. Even when diagnosed early, TG is progressive and frequently leads to allograft failure.

During humoral immunization, the antibody producer is often exposed to multiple HLA incompatibilities, but the specificities of the antibodies are generally limited to a few epitopes [3]. Thus HLA typing differences between antibody producer and immunizer will define the mismatched residues repertoire, and this information facilitates the interpretation of antibody reactivity patterns with HLA panels [20]. The identification of reactive and nonreactive residues permits a determination of HLA mismatch acceptability for sensitized patients.

By contrast, each structural epitope has a functional epitope of approximately two or five residues that dominate the strength and specificity of binding with antibody. Functional epitopes have one or more nonself residues, and the term “eplet” is used to describe polymorphic HLA residues within 3.0 Å of each surface-exposed polymorphic position in the molecular sequence [10,12,13].

Each classical DR antigen should be viewed as a package of DR+DQ+DP antigen,s and its class epitope load depends on the patient’s DR, DQ, and DP type representing the repertoire of self-epitopes [13].

This case underlines the importance of identifying patients who are sensitized by using several fine and very sensitive allelic screening methods, emphasizing the importance of high resolution molecular typing (four-digit allelic level, including HLA-C, DRB1, DQB1, and DPB1 locus, all of which have been shown to induce specific antibody responses in transplant recipient) in solid organ transplantation in determined patients and particularly in those undergoing retransplantation. Luminex technology and single antigens have been noted to be more sensitive, safe, and preferred over other techniques for antibody detection [4,7].

In conclusion, the phenomenon of allele-specific antibody might not be infrequent and can form against single–amino acid substitutions. A recent article seems to corroborate these data [21]. Individual allele specific antibodies can often be detected only by using kits from more than one manufacturer or by using both identification and single-antigen bead kits from the same manufacturer. The occurrence of allele-specific antibodies raises issues for solid organ transplant matching, when donors are not usually typed at the allele level. Thus true non– donor allele–specific, post-transplantation antibodies may not be harmful to the allograft.

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References

[1] Terasaki PI, Ozawa M. Predicting kidney graft failure by HLA antibodies: a prospective trial. Am J Transplant 2004;4:438–43.
[2] Piazza A, Poggi E, Ozzella G, Borrelli L, Monaco PI, Scornajenghi A, et al. Public epitope specificity of HLA class I antibodies induced by failed transplant: alloantibody characterization by flow cytometric techniques. Transplantation 2006;81:1298.
[3] Piazza A, Ozzella G, Poggi E, Gennarelli D, Catalano M, Cremona R, Adorno D. Intra-broad antigens” and “intra-alleles” HLA alloantibodies. In Terasaki PI (ed): Visuals of the European Clinical Histocompatibility Workshop: Canoga Park, CA, 2008.
[4] Muro M, Llorente S, Marín L, et al. Acute vascular rejection mediated by HLA antibodies in a cadaveric kidney recipient: discrepancies between FlowPRA™, ELISA and CDC vs Luminex screening. Nephr Dial Transpl 2005;20:223–6.
[5] Muro M, Rivera J, Botella C, Campillo JA, Ferrer F, Álvarez-López MR. HLA-DR antibodies in transfusion-related acute lung injury (TRALI): A case report. Transfus Apher Sci 2008;38:209–12.
[6] Mizutani K, Terasaki P, Hamdani E, Esquenazi V, Rosen A, Miller J, Ozawa M. The importance of anti-HLA-specific antibody strength in monitoring kidney transplant patients. Am J Transplant 2007;7:1027–31.
[7] Howell M, Mutunga M, Pengilley R, Carter V. Use of Luminex technology for identification of HLA class I allele specific antibodies-occurrence and practicalities for clinical transplantation. In Terasaki PI (ed): Visuals of the European Clinical Histocompatibility Workshop: Canoga Park, CA, 2008.
[8] Lucas D, Campillo JA, López-Hernández R, Martínez-García P, López-Sánchez M, Botella C, et al. Allelic diversity of MICA gene and MICA/HLA-b haplotypic variation in a population of the Murcia region in southeastern Spain. Hum Immunol 2008;69:655–60.
[9] Elsner HA, DeLuca D, Strub J, Blasczyk R. HistoCheck: rating of HLA class I and II mismatches by an internet-based software tool. Bone Marrow Transplant 2004;33:165–9.
[10] Duquesnoy RJ, Askar M. HLAMatchmaker: A molecularly based algorithm for histocompatibility determination. V. Eplet matching for HLA-DR, HLA-DQ, and HLA-DP. Hum Immunol 2007;68:12–25.
[11] Dankers MKA, Witvliet MD, Roelen D, de Lange P, Korfage N, Persijn GG, et al. The number of aminoacid triplet differences between patient and donor is predictive for the antibody reactivity against mismatched human leukocyte antigens. Transplantation 2004;77:1236–9.
[12] Duquesnoy RJ. Human leukocyte antigen class II antibodies and transplant outcome. Transplantation 2008;86:638–40.
[13] Duquesnoy RJ, Awadalia Y, Lomago J, et al. Retransplant candidates have donor-specific antibodies that react with structurally defined HLA-DR, DQ, DP epitopes. Transpl Immunol 2008;18:352–60.
[14] Issa N, Cosio F, Gloor J, Sethi S, Dean PG, Moore SB, et al. Transplant glomerulopathy: risk and prognosis related to anti-human leukocyte antigen class II antibody levels. Transplantation 2008;86:681–5.
[15] Vongwiwatana A, Tasanarong A, Hidalgo LG, Halloran P. The role of B cells and alloantibody in the host response to human organ allografts. Immunol Rev 2003;196:197–218.
[16] Muro M, Palacios S, Moya-Quiles MR, Candela M, Álvarez-López MR. Acute haemolytic transfusion reaction secondary to HLA alloimmunization. Int J Lab Haematol 2008;30:84–6.
[17] Suarez-Alvarez B, López-Vázquez A, González MZ, Fdez-Morera JL, Díaz-Molina B, Blanco-Gelaz MA, et al. The relationship of anti-MICA antibodies and MICA expression with heart allograft rejection. Am J Transplant 2007;7:1842–8.
[18] Muro M, Marin L, Miras M, Moya-Quiles R, Minguela A, Sánchez-Bueno F, et al. Human liver allograft recipients harbouring anti-donor preformed lymphocytotoxic antibodies exhibit a poor graft survival at the first year after transplantation. Experience of one centre. Transpl Immunol 2005;14:91–7.
[19] Marin L, Torio A, Muro M, Fernandez-Parra R, Minguela A, Bosch V, et al. Alloimmune neonatal neutropenia and thrombocytopenia associated with maternal anti HNA-1a, HPA-3b and HLA antibodies. Pediatr Allergy Immunol 2005;16:279–82.
[20] El-awar N, Akaza T, Terasaki PI, Nguyen A. Human leukocyte antigen class I epitope: updated to 103 total epitopes, including C locus. Transplantation 2007;84:532.
[21] Lomago J, Jelenik L, Zern D, Howe J, Martell J, Zeevi A, Duquesnoy RJ. How did a patient who types for HLA-B*4403 develop antibodies that react with HLA-B*4402? Hum Immunol 2010;71:176–8.