Research Article

Distribution of HLA epitope frequencies in Turkish population

Abstract

Objectives: The antibodies interact with the “Human Leukocyte Antigen (HLA) antigens” at specific epitopes. “Epitopes” are present on a single HLA or shared by multiple antigens. In this study, we aim to determine the frequency of prevalent epitopes common in the Turkish population.

Methods: Non-related 644 healthy volunteers were recruited, and The “HLA-A, -B, -C, -DR -DQ”s were typed using the “Next Generation Sequencing”. The provisional and confirmed epitopes were identified using the “HLA Epitope Registry databases, HLA Epitopia Maps and Immucor Epitope databases” dated 07.02.2018. Epitope frequencies were calculated by counting the shared epitopes in the total number of shared HLA Class epitopes in our sample database.

Results: Class I HLA’s had 298 epitopes that repeated a total of 158,117 times with frequencies ranging between 0.0006 and 2.03%, and the most frequent epitope was 170RY found on 119 different alleles. Class II HLA’s had 193 epitopes that repeated a total of 93,082 times with frequencies ranging between 0.002 and 1.36%, and the most frequent epitope was 108P found on 42 different alleles.

Conclusions: Our findings summarize both the provisional, and confirmed epitope frequencies in the Turkish population and may help clinicians and immunogeneticists develop a better understanding of HLA epitope mismatches.

Keywords: allele; epitope; eplet matching; HLA; transplantation.

Öz

Amaç: Antikorlar, spesifik epitoplarda “Human Leukocyte Antigen (HLA) antijenleri” ile etkileşime girer. “Epitoplar” tek bir HLA üzerinde bulunur veya birden fazla antijen tarafından paylaşılır. Bu çalışmada, Türk popülasyonunda yaygın olan epitopların sikliğini belirlemeyi amaçladık.

Gereç ve Yöntemler: Akıba olmuyan 644 sağlıklı katılımcı “Human Leukocyte Antigen (HLA) antijenleri” ile etkileşime girer. “Epitoplalar” tek bir HLA üzerinde bulunur veya birden fazla antijen tarafından paylaşılır. Bu çalışmada, Türk popülasyonunda yaygın olan epitopların sikliğini belirlemeyi amaçladık.

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veritabanları” kullanılarak tanımlanmıştır. Epitop fre-
kansları, örnek veri tabanımızda paylaşılan HLA Smfı
epitoplarını toplam sayısunları paylaşılan epitopları
sayarak hesaplandı.

**Bulgular:** Smf I HLA’lar, % 0.0006–2.03 arasında değişen
frekanslardır, toplam 158.117 kez tekrarlanan 298 epitopa
sahip ve en sık görülen epitop, 119 farklı alelede bulunan
170RY idi. Smf II HLA, % 0.002–1.36 arasında değişen fre-
kansları toplam 93.082 kez tekrarlanan 193 epitopu sahipti
ve en sık görülen epitop 42 farklı alelede bulunan 108P idi.

**Sonuç:** Bulgularımız, Türk popülasyonundaki hem geçici,
hem de doğrudan epitop frekanslarını özetlemektedir.
Ve bu bulguların gerek klinisyenlerin gerekse immüno-
genetikçilerin HLA epitop uymusuzluklarını daha iyi
anlamalarına yardımcı olabileceğini düşündüzeyiz.

**Anahtar Kelimeler:** HLA; epitop; transplantasyon; eplet
eşleştirme; alel.

**Introduction**

The human leukocyte antigen (HLA) system is considered
as the most polymorphic region in the human genome.
More than 100 genes were suggested to have immunolog-
cal functions [1, 2]. The HLA system is recognized with its
associations in infectious diseases [3], autoimmune dis-
ases [4], and studies of diversity in populations [5] and its
importance in transplantation [6]. Recently, there is also a
growing field of study identifying associations between
particular HLA polymorphisms and increased risk for
adverse drug reactions [7, 8].

From a clinical point of view, the primary goal of
detecting HLA antibodies in recipient blood is to find po-
tential donors with non-perfect but acceptable HLA
matching. The presence of donor specific anti-HLA anti-
bodies (DSA) is a strong predictor for tissue and graft
rejection. The antibodies specifically target certain epi-
topes found on the surface of the HLA molecule.

HLA epitopes are the specialized portions of HLA
molecules that bind with antibodies or paratopes of T-cell
receptors (TCR). The paratope consists of three light chains
and three heavy chain (CDR: Complementarity Deter-
mining Regions) regions (CDR-L1, -L2, -L3, -H1, -H2, and
-H3). The structural epitope consists of 12–22 amino acids
and contains the binding site for antibodies. The functional
epitope in the middle of these amino acid residues is 2–5
amino acids long. The “functional epitope” regions interact
with CDR-H3, which has several residues localized in the
center and play a dominant role in epitope specificity.
Functional epitope specificity is responsible for structural
epitope avidity and increases the stability of the antigen-
antibody complex [9].

Current guidelines for kidney transplantation recom-
mand matching based on the allele sequencing. However,
recent evidence suggests that an epitope-based approach
may be more efficient [10, 11].

Studies have shown that analyzing the epitope speci-
ficities may be useful in desensitization protocols [12].
Although such protocols are not totally effective, in
some cases, it may be possible to eliminate an antibody
specific to an epitope altogether through sequestration.
HLA matching at the epitope level has been shown to be
tightly linked to graft survival, and antibody development
in several studies [12–24].

As the mismatched eplets can be determined with great
ease using the free “HLA Eplet Matching” excel sheet
available at “epitopes.net”, these findings may soon have
practice changing implications. The mismatched epitope
load may be considered as a risk factor for antibody-
mediated rejection. This is also considered useful infor-
mation for clinical protocols that aim immune tolerance [25].

In this study, we aimed to determine the epitope fre-
quencies in the Turkish population to form a basis for
future studies.

**Materials and methods**

HLA typing was performed at EFI-accredited HLA Laboratory in
Istanbul University Istanbul Faculty of Medicine using Illumina MiSeq
Sequencing System. The following loci: HLA-A, HLA-B, HLA-C, HLA-
DRB1, HLA-DQB1, were typed by “Next Generation Sequencing (NGS)”
methods using commercially available kits: Omixon Holotype HLA™
assay and Omixon HLA Twin™ software.

**Sample population**

Six hundred and forty four healthy volunteer Turkish citizens aged
between 18 and 55 years without known first- or second-degree family
ties to one another were enrolled in the study.

**Statistical analyses**

HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 allele frequencies
(in the meaning of how common an allele is in a population) were
calculated by counting the repeated alleles in the total number of
alleles for each HLA loci. The Hardy–Weinberg Equilibrium (HWE)
were performed by Arlequin software package, version 3.5.2.2
(Excoffier and Lischer, 2010), and the p-values are considered signif-
ificant at the 0.05 level. Principal Component Analysis (PCA) was per-
formed based on HLA-A, HLA-B, HLA-C, HLA-DRB1 and HLA-DQB1
allele frequencies using SPSS v21.0 software.
Frequency of an allele  
\[ \text{Frequency} = \frac{\text{Number of copies of an allele}}{\text{Total number of copies of alleles in population}} \]

Both provisional and confirmed epitopes were identified using the HLA Epitope Registry databases from "epiregistry.com.br", HLA Epitopia Maps from "epitopes.net" and 07.02.2018 datemucor Epitope databases dated 07.02.2018. Epitope frequencies (in the meaning of how common a shared epitope is in a population) were calculated by counting the shared epitopes in the total number of shared HLA Class epitopes in our sample database.

Frequency of an epitope  
\[ \text{Frequency} = \frac{\text{Number of copies of a shared epitope}}{\text{Total number of copies of shared epitopes in population}} \]

## Results

Population genetics analyses were done on Arlequin v.3.5.2.2. Genotype frequencies at all loci HLA-A, -B, -C, -DRB1 were in Hardy-Weinberg Equilibrium (HWE) (p>0.05) except the HLA-DQ6B1 genes. Also, when assessed by the inbreeding coefficient (Fis), observed and expected heterozygosity did not differ at any loci (p>0.40). Ewens-Watterson tests of selective neutrality tests did not indicate any statistically significant selection (p=0.99).

The analysis of the HLA class I, and II allele frequencies of a total of 644 volunteers showed that the first three most frequent alleles were HLA-A*02:01, *04:01, *01:01, HLA-B*51:01, *35:01, *18:01, HLA-C*04:01, *07:01, *12:03, HLA-DRB1*07:01, *11:01, *11:04, HLA-DQ6B1*03:01, *03:02, *05:02 (Table 1).

For Class I, a total of 298 unique epitopes were observed in our population database corresponding to a total number of 158,117 counted epitopes. The frequency of any given epitope ranged between 0.0006 and 2.03%. The top 10 most frequent epitopes listed were 170RY, 99Y, 142TQ, 163T, 102DV, 163TEW, 11SV, 156L, 97R, 194V, and are shown in the table (Table 2). We also observed that the first three of the most shared Class I epitopes (170RY, 99Y, 142TQ) and the first three of the most frequent epitopes in our population database were same as shown in the table (Table 3).

For HLA class II, a total of 193 unique epitopes were observed in our population database, corresponding to a total number of 93,082 counted epitopes. The frequency of any given epitope ranged between 0.002 and 1.36%. The top 10 most frequent epitopes listed were 108P, 23R, 189R, 112H, 85V, 40F, 56P, 130R, 16H, 3S, and were shown in the

### Table 1: HLA class I and II allele frequencies (first 10 most frequent alleles shown here).

| HLA-A | Freq | HLA-B | Freq | HLA-C | Freq | HLA-DRB1 | Freq | HLA-DQ6B1 | Freq |
|-------|------|-------|------|-------|------|----------|------|-----------|------|
| 02:01 | 20.19% | 051:01 | 10.64% | 04:01 | 17.70% | 07:01 | 9.47% | 03:01 | 25.47% |
| 24:02 | 13.82% | 35:01 | 7.84% | 07:01 | 11.72% | 11:01 | 9.39% | 03:02 | 9.32% |
| 01:01 | 13.04% | 18:01 | 7.14% | 12:03 | 11.41% | 11:04 | 8.93% | 05:02 | 9.24% |
| 03:01 | 9.47% | 35:03 | 4.89% | 06:02 | 9.70% | 03:01 | 8.15% | 02:01 | 8.23% |
| 11:01 | 7.07% | 44:02 | 4.66% | 02:02 | 6.37% | 16:01 | 6.60% | 05:01 | 8.00% |
| 26:01 | 6.29% | 38:01 | 4.43% | 07:02 | 6.37% | 15:01 | 6.37% | 02:02 | 7.69% |
| 23:01 | 4.27% | 69:01 | 4.35% | 01:02 | 4.43% | 04:03 | 5.51% | 05:03 | 7.69% |
| 68:01 | 4.11% | 08:01 | 4.11% | 15:02 | 3.42% | 01:01 | 4.81% | 06:03 | 5.12% |
| 32:01 | 3.96% | 07:02 | 4.11% | 03:04 | 2.87% | 13:01 | 4.43% | 06:02 | 4.89% |
| 03:02 | 2.64% | 13:02 | 3.49% | 12:02 | 2.87% | 14:54 | 4.43% | 06:01 | 3.18% |

### Table 2: Class I epitope frequencies.

| Class I epitope | Count | Freq |
|----------------|-------|------|
| 170RY          | 3,217 | 2.03%|
| 99Y            | 2,879 | 1.82%|
| 142TQ          | 2,581 | 1.63%|
| 163T           | 2,180 | 1.38%|
| 102DV          | 2,087 | 1.32%|
| 163TEW         | 1,947 | 1.23%|
| 115V           | 1,870 | 1.18%|
| 156L           | 1,862 | 1.18%|
| 97R            | 1,837 | 1.16%|
| 194V           | 1,831 | 1.16%|

### Table 3: Most shared epitope list by class I alleles.

| Class I epitope | Total alleles | HLA-A | HLA-B | HLA-C |
|----------------|---------------|-------|-------|-------|
| 170RY          | 119           | 37    | 57    | 25    |
| 99Y            | 114           | 34    | 61    | 19    |
| 142TQ          | 108           | 20    | 63    | 25    |
| 102DV          | 87            | 37    | 47    | 3     |
| 9Y(ABC)        | 79            | 15    | 49    | 15    |
| 156L           | 78            | 18    | 49    | 11    |
| 193P1          | 72            | 15    | 57    | 0     |
| 156LA          | 71            | 17    | 43    | 11    |
| 97R            | 69            | 14    | 34    | 21    |
| 72QTD          | 67            | 29    | 25    | 13    |
We also observed that the first three of the most shared Class II epitopes (112H, 25R, 40F) and the first three of the most frequent epitopes in our population database were different but the most frequent epitope 108P was the most shared epitope between the HLA-DRB1 alleles (Table 5).

### Discussion

Epitope matching has become an important issue in organ transplants. Recent studies discuss whether epitope matching can replace allele matching. Currently, HLA laboratories receive epitope matching requests, and there are even recommendations based on epitope matching in the UNOS organ allocation algorithm. Continuous advances in the identification and mapping of functional HLA epitopes or eplets make the use of epitope matching almost indispensable in assessing immunological risk. While determining the number of eplet mismatches for each donor recipient pair is not a practical approach, it should be considered for highly sensitized patients and young transplant candidates who may need repeat transplantation. Thus, maximum survival rate can be achieved in the first kidney transplant, and the risk of allosensitivity after transplantation can be minimized [26].

HLA mismatches predispose to the development of DSA that are strongly associated with antibody mediated rejection (AMR) and late allograft loss [27, 28]. The presence of DSAs is often a barrier to transplantation, and highly sensitized patients experience a longer waiting time for a suitable donor kidney than non-sensitized patients. In kidney transplantation, graft survival rates were similar for transplants from fully HLA matched donors, and low HLA matched donors, and the researchers focused on areas where HLA epitopes interact with antibody (eplet regions) [29].

Experimentally defining of eplets and epitopes:

1. **Step 1** – The monoclonal antibody or alloantibody isolated from the prepared serum is tested with single antigen beads (SAB Test) for each possible single allele.

2. **Step 2** – Positive results show that the related antibody targets a unique epitope on the positive allele bead and negative results show that no antigen-antibody binding for current related antibody.

3. **Step 3** – Alignment of the amino acid sequences of all positive and negative alleles shows that all positive alleles share the same amino acid changes at the same positions.

4. **Step 4** – Amino acid positions of positive antibodies can be visualized using molecular structure visualization software to evaluate and understand the binding site specifications for the antigen-antibody binding relation. If more than one amino acid defines an epitope, the distance between any two amino acids stays within the binding range of the antibody [30].

Studies have shown that in cases of equal numbers of HLA antigen mismatches, lower eplet mismatch numbers are associated with a lower incidence of DSA formation, and a lower incidence of AMR compared to higher eplet mismatch numbers [31, 32].

However, not all eplet mismatches are equally immunogenic and can result in different antibody responses. Therefore, not all epitope or eplet mismatches can provoke anti-HLA antibody homogeneously [9]. Therefore, considering immunogenic eplet mismatches instead of the total number of eplet mismatches can provide more effective results when assessing risk during the transplant procedure.

The level of eplet mismatch of a donor is determined by the eplet repertoire of the recipient’s HLA allele phenotype.

### Table 4: Class II epitope frequencies.

| Class II epitope | Count | Freq |
|-----------------|-------|------|
| 108P            | 1,262 | 1.36%|
| 23R             | 1,254 | 1.35%|
| 189R            | 1,246 | 1.34%|
| 112H            | 1,241 | 1.33%|
| 85V             | 1,232 | 1.32%|
| 40F             | 1,230 | 1.32%|
| 56P             | 1,224 | 1.31%|
| 130R            | 1,216 | 1.31%|
| 16H             | 1,215 | 1.31%|
| 3S              | 1,215 | 1.31%|

### Table 5: Most shared epitope list by class II alleles.

| Class II epitope | Total | HLA-DRB1 | HLA-DQB1 | Other class II |
|-----------------|-------|----------|----------|----------------|
| 112H            | 50    | 41       | 0        | 9              |
| 25R             | 49    | 41       | 0        | 8              |
| 40F             | 49    | 41       | 0        | 8              |
| 78Y             | 49    | 39       | 0        | 10             |
| 108P            | 48    | 42       | 0        | 6              |
| 58A             | 47    | 37       | 0        | 10             |
| 85V             | 47    | 38       | 0        | 9              |
| 4R              | 45    | 38       | 0        | 7              |
| 16H             | 45    | 35       | 0        | 10             |
| 33N             | 45    | 35       | 0        | 10             |
This type of analysis can easily be done using special software. The HLA Matchmaker program (http://www.epitopes.net) is a computer algorithm that determines the HLA compatibility between donors and recipients by evaluating the 3D molecular modeling of the epitope-paratope interfaces of antigen-antibody complexes [33]. That is, by evaluating foreign and shared eplets between donors and recipients, it can calculate the number of eplet mismatches for each donor-recipient pair and significantly expand the potential donation pool for highly sensitive recipients.

HLA Matchmaker is not the only method available for predicting epitope matching. Another method is the Predicted Indirectly Re-Cognizable HLA Epitopes PIRCHE score. It probably explains the recognition of HLA polymorphisms corresponding to epitopes by the recipient CD4 + T cell and has often been studied in the context of class II molecules [34]. HLA Matchmaker and PIRCHE are examples of complex computational algorithms designed to predict epitopes found in HLA, but these algorithms cannot determine which epitopes are truly antigenic (capable of binding to antibody) or immunogenic (capable of inducing antibody production in response to antigen-antibody interaction) [35].

For the clinical purposes targeted in the transplantation process, it is important that the transplantation program focuses on alleles in the relevant population. Due to the global increase of racial and ethnic heterogeneity in all world populations, such alleles cause more mismatches independent of rare alleles.

High resolution HLA typing of new HLA alleles with high prevalence from different populations and their incorporation into the HLA Matchmaker will enable more accurate identification and calculation of immunogenic mismatched eplets.

The http://www.hlamatchmaker.net program was used to define the discrepancies between the donors and recipients, and for estimating the donor specific de novo antibody risk in the study of Udeme et al. Acute rejection, allograft fibrosis, and antibody mediated rejection were retrospectively investigated in this study [36].

DSA were detected in 20 out of 42 (48%). The antibody against HLA-DQ81 * 02 was associated with acute rejection, and DQ epitope mismatch was found higher in recipients with class II DAS. DSA were detected to have developed in recipients in case when the DQ epitope mismatch was higher than 5 or 6. The eplet mismatches of 4Q, 45GE, 52PQ, and 52PL were suggested to be the immunodominant epitopes in many recipients. The data of the epitope discrepancies were suggested to be possibly helpful for transplant physicians in developing immunosuppression strategies between recipients, and donors [36].

Our current study shows that “HLA-A*02:01, *24:02, *01:01, HLA-B*51:01, *35:01 and *18:01, HLA-C*04:01, *07:01, *12:03, HLA-DRB1*07:01, *11:01, *11:04, HLA-DQB1*03:01, *03:02, *05:02” allele frequencies, revealed similarities with previous studies of the Turkish population [37, 38]. Uyar and Kaya et al. [37, 38]. It is of interest that the DQB1, showed the greatest deviation from HWE, which is consistently less polymorphic than the other loci. Certainly, other explanations for the deviation from HWE, including nonrandom mating patterns with regard to admixed individuals within the ethnic group, must also be considered, as significant deviations from HWE are also seen in our population [39].

This is the first study demonstrating the most frequently detected HLA antigens in our population. The first 10 epitopes detected for Class I, and Class II HLA were 170RY, 99Y, 142ITQ, 163T, 102DV, 163TEW, 97R, 194V, 156L, 156LA as HLA Class I epitopes, and 108P, 189R, 23R, 112H, 85V, 40F, 16H, 56P, 38V, 3S, respectively as HLA Class II epitopes.

We suggest that the first comprehensive HLA epitope data on the Turkish population will help clinicians and immunogenetics researchers in determining the HLA-epitope frequencies and mismatches in their population of interest and will be useful for further antibody related transplant studies.

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Author contributions: Fatma Savran Oguz provided the concept, design, interpretation of the data, drafting of the paper, and gave final approval. Suleyman Rustu Oguz contributed to the concept and design, assembled the data, and helped with the data analysis. Tanju Sedat Karadeniz conducted the study design and gave final approval. Suleyman Rustu Oguz contributed to the assembly of data with technical support. Sule Karatas and Demet Kivanc provided technical support. Hayriye Senturk Ciftci helped with assembly of data with technical support. Filiz Aydin contributed to the study design and gave final approval.

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Ethical approval: This study was approved by the Ethics Committee of the Istanbul University Faculty of Medicine (Ethics no: 470) and in accordance with the standards of the Declaration of Helsinki.
Data availability: The data that support the findings of this study are available on request from the corresponding author, [Oguz FS].

References

1. Thorsby E. A short history of HLA. Tissue Antigens 2009;74:101–16.
2. Beck S, Geraghty D, Inoko H, Rowen L, Aguado B, Bahram S, et al. Complete sequence and gene map of a human major histocompatibility complex. Nature 1999;401:921–3.
3. Blackwell JM, Jamieson SE, Burgner D. HLA and infectious diseases. Clin Microbiol Rev 2009;22:370–85.
4. Thorsby E, Lie BA. HLA associated genetic predisposition to autoimmune diseases: genes involved and possible mechanisms. Transpl Immunol 2005;14:175–82.
5. Shiina T, Hosomichi K, Inoko H, Kulsiki JK. The HLA genomic loci map: expression, interaction, diversity and disease. J Hum Genet 2009;54:35–39.
6. Claas FH, Duquesnoy RJ. The polymorphic alloimmune response in clinical transplantation. Curr Opin Immunol 2008;20:566–7.
7. Alfrevic A, Pirmohamed M. Drug induced hypersensitivity and the HLA complex. Pharmaceuticals 2010;4:69–90.
8. Yip VL, Marson AG, Jorgensen AL, Pirmohamed M, Alfrevic A. HLA genotype and carbamazepine-induced cutaneous adverse drug reactions: a systematic review. Clin Pharmacol Ther 2012;92:757–65.
9. Kramer C, Heidt S, Claas FJH. Towards the identification of the relative immunogenicity of individual HLA antibody epitopes. Hum Immunol 2019;80:218–20.
10. Claas FJH, Bankers MK, Oudshoorn M, van Rood JJ, Mulder A, Roelen DL, et al. Differential immunogenicity of HLA mismatches in clinical transplantation. Transpl Immunol 2005;14:187–91.
11. Doxiadis II, Duquesnoy RJ, Claas FH. Extending options for highly sensitized patients to receive a suitable kidney graft. Curr Opin Immunol 2005;17:536–40.
12. Walton DC, Hillo SJ, Cantwell LS, Divinye MB, Wright ST, Snell GI, et al. HLA matching at the eplet level protects against chronic lung allograft dysfunction. Am J Transplant 2016;16:2695–703.
13. Goodman RS, Taylor CJ, O'Rourke CM, Lynch A, Bradley JA, Key T. Utility of HLAMatchmaker and single-antigen HLA-antibody detection beads for identification of acceptable mismatches in highly sensitized patients awaiting kidney transplantation. Transplantation 2006;81:1331–6.
14. Kosmoliaptis V, Bradley JA, Sharples LD, Chaudhry A, Key T, Goodman RS, et al. Predicting the immunogenicity of human leukocyte antigen class I alloantigens using structural epitope analysis determined by HLAMatchmaker. Transplantation 2008;85:1817–25.
15. Duquesnoy RJ, Awadalla Y, Lomago J, Jelinek L, Howe J, Zern D, et al. Retransplant candidates have donor-specific antibodies that react with structurally defined HLA-DR,DQ,DP eplets. Transpl Immunol 2008;18:352–60.
16. Kosmoliaptis V, Chaudhry AN, Sharples LD, Halsall DJ, Dafforn TR, Bradley JA, et al. Predicting HLA class I alloantigen immunogenicity from the number and physiochemical properties of amino acid polymorphisms. Transplantation 2009;88:791–8.
17. Duquesnoy RJ, Marrari M. Detection of antibodies against HLA-C eplets in patients with rejected kidney transplants. Transpl Immunol 2011;24:164–71.
18. Höniger G, Foroaro I, Granado C, Tiercy J-M, Hüsli I, Schaub S. Frequency and determinants of pregnancy-induced child-specific sensitization. Am J Transplant 2013;13:746–53.
19. Wiebe C, Nickerson P. Posttransplant monitoring of de novo human leukocyte antigen donor-specific antibodies in kidney transplantation. Curr Opin Organ Transplant 2013;18:470–7.
20. Wiebe C, Nevins TE, Robiner WN, Thomas W, Matas AJ, Nickerson PW. The synergistic effect of class II HLA eplet-mismatch and nonadherence on acute rejection and graft survival. Am J Transplant 2015;15:2197–202.
21. Filippone EJ, Farber JL. Humoral immunity in renal transplantation: eplets, Cw and DP, and complement-activating capability - an update. Clin Transplant 2015;29:729–87.
22. Sapir-Pichhadze R, Tinkham K, Quach K, Logan AG, Laupacis A, John R, et al. HLA-DR and -DQ eplet mismatches and transplant glomerulopathy: a nested case-control study. Am J Transplant 2015;15:137–48.
23. Singh P, Filippone EJ, Colombe BW, Shah AP, Zhan T, Harach M, et al. Sensitization trends after renal allograft failure: the role of DQ eplet mismatches in becoming highly sensitized. Clin Transplant 2016;30:71–80.
24. Sullivan PM, Warner P, Kemna MS, Albers EL, Law SP, Weiss NS, et al. Molecular epitope mismatching and long-term graft loss in pediatric heart transplant recipients. J Heart Lung Transplant 2015;34:950–67.
25. Duquesnoy RJ. HLA epitopes and tolerance induction protocols. Am J Transplant 2014;14:2667.
26. Tambur AR. HLA-epitope matching or eplet risk stratification: the devil is in the details. Front Immunol 2018;9:2010.
27. Lefaucheur C, Loupy A, Hill GS, Andrade J, Nochy D, Antoine C, et al. Preexisting donor-specific HLA antibodies predict outcome in kidney transplantation. J Am Soc Nephrol 2010;21:1398–406.
28. Wiebe C, Gibson IW, Blydt-Hansen TD, Karpinski M, Ho J, Storsley LJ, et al. Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. Am J Transplant 2012;12:1157–67.
29. Lucas DP, Leffell MS, Zachary AA. Differences in immunogenicity of HLA alleles and the impact of cross-reactivity on the humoral response. Transplantation 2015;99:77–85.
30. El-Awar N, Jucaud V, Nguyen A. HLA epitopes: the targets of monoclonal and alloantibodies defined. J Immunol Res 2017;2017:1–16.
31. Tafuro S, Malheiro J, Santos S, Dias L, Almeida M, Martins S, et al. Degree of HLA class II eplet mismatch load improves prediction of antibody-mediated rejection in living donor kidney transplantation. Hum Immunol 2019;80:966–75.
32. Wiebe C, Rush DN, Nevins TE, Birk PE, Blydt-Hansen T, Gibson IW, et al. Class II eplet mismatch modulates tacrolimus trough levels required to prevent donor-specific antibody development. J Am Soc Nephrol 2017;28:3353–62.
33. Duquesnoy RJ, Marrari M. HLAMatchmaker: a molecularly based algorithm for histocompatibility determination. II. Verification of the algorithm and determination of the relative immunogenicity of amino acid triplet-defined epitopes. Hum Immunol 2002;63:353–63.
34. Otten HG, Calis JJA, Keşmir C, van Zuijen AD, Spierings E. Predicted indirectly recognizable HLA epitopes presented by HLA-DR correlate with the de novo development of donor-specific HLA IgG antibodies after kidney transplantation. Hum Immunol 2013;74:290–6.

35. Duquesnoy RJ. Human leukocyte antigen epitope antigenicity and immunogenicity. Curr Opin Organ Transplant 2014;19:428–35.

36. Ekong UD, Antala S, Bow L, Sese D, Morotti R, Rodriguez-Davalos M, et al. HLA, non-HLA antibodies, and eplet mismatches in pediatric liver transplantation: observations from a small, single-center cohort. Exp Clin Transplant 2019;1:6–17.

37. Uyar FA, Dorak MT, Saruhan-Direkeneli G. Human leukocyte antigen-A, B and -C alleles and human leukocyte antigen haplotypes in Turkey: relationship to other populations. Tissue Antigens 2004;64:180–7.

38. Kaya Z, Gönen S, Caliskan B, Kemer Z, Ünal AB, Değirmenci E. HLA genotypes in Turkish hematopoietic cell recipients and likelihood of finding a matched donor through family searches. Exp Clin Transplant 2017;17:813–8.

39. Chen JJ, Hollenbach JA, Trachtenberg EA, Just JJ, Carrington M, Rønningen KS, et al. Hardy-Weinberg testing for HLA class II (DRB1, DQA1, DQB1, and DPB1) loci in 26 human ethnic groups. Tissue Antigens 1999;54:533–42.