

Predicting the Immunogenicity of Human Leukocyte Antigen Class I Alloantigens Using Structural Epitope Analysis Determined by HLAMatchmaker

Vasilis Kosmoliaptis,^{1,2} J. Andrew Bradley,² Linda D. Sharples,³ Afzal Chaudhry,⁴ Timothy Key,¹ Reyna S. Goodman,¹ and Craig J. Taylor^{1,5}

Background. Human leukocyte antigen (HLA) matching strategies for kidney transplantation assign equal weighting to mismatches at a particular locus and take no account of variation in immunogenicity according to recipient HLA type. We examined the ability of intra- and interlocus analysis of amino-acid polymorphisms at continuous (triplet) and discontinuous positions (eplet) defined by the HLAMatchmaker program to predict alloantigen immunogenicity. **Methods.** Sera from highly sensitized patients were screened for HLA class-I alloantibodies and mismatched combinations were analyzed using HLAMatchmaker to determine the number of triplet or extended-triplet and eplet mismatches. **Results.** Logistic regression analysis revealed a strong correlation between the number of triplet or extended-triplet and eplet mismatches and both the presence and magnitude of alloantibody to mismatched HLA-A and -B specificities. The additional structural information provided by eplet analysis gave increased discrimination of mismatched-HLA specificities for alloantigens with greatest sequence disparity but this did not further improve the ability of triplet analysis to predict alloantigen immunogenicity. High antibody levels were observed for several mismatched-HLA combinations with zero triplet or eplet mismatches indicating that self triplets or eplets expressed in different conformations do not always predict nonimmunogenic epitopes. **Conclusion.** Analysis of recipient HLA type and mismatched-HLA alloantigens using the HLAMatchmaker algorithm allows prediction of immunogenic donor HLA types.

Keywords: HLAMatchmaker, HLA immunogenicity, Triplet mismatches, Eplet mismatches.

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Human leukocyte antigen (HLA) matching has a beneficial effect on kidney transplant outcome and limiting the number of mismatches at HLA-A, -B, and -DR is an integral component of national organ allocation policies (1–6). Con-

ventional HLA-matching algorithms are based on several mismatches at each HLA locus, but a potential drawback of this approach is that all mismatches within a given locus are assigned equal weighting, regardless of structural or amino-acid sequence differences between donor and recipient HLA types. It is well known that mismatched-donor HLA specificities vary in immunogenicity from those with potential to cause graft rejection to those that are nonimmunogenic and have been designated as permissible (acceptable) mismatches (7–11). The immunogenicity of a mismatched-donor HLA specificity likely depends on the number and biochemical nature of the HLA polymorphisms compared with the recipient HLA type.

Triplet HLAMatchmaker is a computer algorithm that compares HLA compatibility at the structural level, determined by polymorphic triplet amino-acid sequences in antibody accessible positions of HLA molecules that have potential to induce humoral immune responses (12–14). The HLAMatchmaker algorithm considers each HLA specificity as multiple linear triplet-defined epitopes and performs intra- and interlocus comparisons to identify the number of shared and nonshared triplets between donor and recipient. The number of triplet amino-acid mismatches between donor and recipient HLA has been shown to correlate with renal allograft survival (15, 16) and the likelihood of HLA alloantibody formation (17, 18). However, the linear definition of

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¹ Tissue Typing Laboratory, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge, United Kingdom.

² Department of Surgery, University of Cambridge, Addenbrooke's Hospital, Cambridge, United Kingdom.

³ MRC Biostatistics Unit, Institute of Public Health, Cambridge, United Kingdom.

⁴ Department of Renal Medicine, Dialysis Centre, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge, United Kingdom.

⁵ Address correspondence to: Craig J. Taylor, Ph.D., FRCPath, Tissue Typing Laboratory (Box 209), Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 0QQ, United Kingdom.

E-mail: craig.taylor@addenbrookes.nhs.uk

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triplet amino-acids provides an incomplete assessment of conformational epitopes resulting from folding of amino-acid chains in the tertiary HLA molecule. To address this, Duquesnoy extended the original triplet algorithm to include polymorphic amino acid residues at discontinuous sequence positions that cluster together to form potential immunogenic epitopes (designated “eplets”) on the surface of the HLA molecule (19, 20). This approach has been proposed to better reflect serologically defined epitopes and provide a better assessment of HLA compatibility.

We previously reported that the use of triplet amino acid differences between mismatched HLA-A and -B specificities and recipient HLA class I type correlated strongly with the likelihood of antibody formation and allowed prediction of acceptable (nonimmunogenic) mismatches in patients awaiting renal transplantation (18). Here, we examine the extent to which the additional structural information provided by polymorphisms at discontinuous amino acid positions (eplets) enables prediction of acceptable mismatches and the magnitude of the antibody response as defined by antibody screening using the full repertoire of single-antigen HLA class I specificities in highly sensitized patients (HSP) awaiting renal transplantation.

MATERIALS AND METHODS

Study Design

As a strategy for detecting unacceptable (immunogenic) HLA mismatches, we examined sera from HSP (exposed to multiple HLA mismatches and displaying alloantibodies to a broad repertoire of HLA class I specificities) to determine the HLA alloantigens (using single-antigen HLA antibody detection beads) that had evoked a specific alloantibody response. Patient HLA class I types and each mismatched-HLA specificity represented on the single antigen beads were entered into the HLAMatchmaker program to determine the number of triplet, extended triplet, and eplet mismatches. The qualitative and quantitative relationship between alloantibody levels to each HLA specificity and the number of triplet and eplet mismatches was then examined.

Selection of Highly Sensitized Patient Sera

Serum samples routinely obtained at bimonthly intervals from patients on the waiting list for deceased donor renal transplantation at Addenbrooke’s Hospital, Cambridge were tested for IgM and IgG HLA class I and class II specific antibodies by a combination of complement-dependent cytotoxicity against an HLA-typed lymphocyte panel and solid-phase binding assays (Enzyme-Linked Immunosorbent Assay and Luminex) using purified HLA class I and II, as previously described (18). Of 488 patients on the transplant waiting list, 34 (7%, 14 men and 20 women, with a median age of 45 years [range 24–62]) were identified as being highly sensitized (defined as $\geq 85\%$ IgG lymphocytotoxic panel reactivity) and were selected for this study. The most common cause of HLA sensitization in the 34 HSP was a combination of blood transfusion and a failed renal transplant ($n=16$); followed by a combination of blood transfusion and pregnancy ($n=7$); or pregnancy, blood transfusion, and a failed renal transplant ($n=5$). The remaining six patients had become sensitized by

blood transfusion alone ($n=5$) or a previous failed transplant alone ($n=1$). Sequential serum samples from the 34 HSP (29 white European Caucasian, 2 Asian, and 3 black African) representing peak periods of sensitization were analyzed using single-antigen beads to determine individual HLA specificities that were antibody negative (acceptable mismatches) or antibody positive (immunogenic) and the levels of antibody binding to determine the magnitude of the antibody response as an indicator of high- and low-alloantigen immunogenicity.

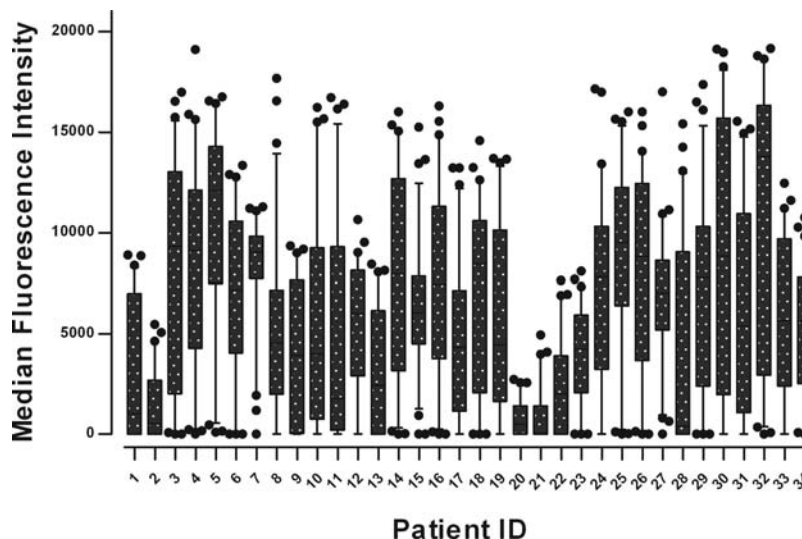
Characterization of Human Leukocyte Antigen Specific Antibodies Using Single-Antigen Human Leukocyte Antigen Class I Antibody Detection Beads

A total of 85 sera obtained from 34 HSP (median 2 sera per patient, range 1–6) representing peak periods of sensitization were screened using single-antigen HLA antibody detection beads (LABScreen, One Lambda Inc., Canoga Park, CA) according to the manufacturer’s instructions. The single-antigen HLA antibody detection beads identified the following specificities: HLA-A1, 2, 3, 11, 23–26, 29–34, 36, 43, 66, 68, 69, 74, 80 and HLA-B7, 8, 13, 18, 27, 35, 37–39, 4005, 41, 42, 44–65, 67, 71–73, 75–78, 81, 82. Data acquisition was carried out using a LABScan 100 Luminex platform. The level of IgG antibody binding to each single HLA-A and -B specificity was assessed from the median fluorescence intensity (MFI) signal for each bead population after subtraction of the background MFI for control beads lacking HLA. In addition, a negative control serum (pooled human AB serum obtained from nontransfused males) was included for each test batch to establish the background MFI values for individual single antigen bead populations and the values obtained were also subtracted from the corresponding MFI values using patient sera. In patients where multiple serum samples were screened, the highest value recorded for antibody binding to individual HLA specificities was used to represent the maximum response to a given antigen. For the purposes of this study, MFI values less than 1500 after subtraction of background were considered negative. This level was chosen based on our clinical experience over the preceding 2 years of Luminex-based HLA-specific antibody screening for the renal transplant program and is approximately one to two doubling dilutions below that detectable by flow cytometric crossmatching.

Determination of Triplet and Eplet Amino Acid Mismatches Using HLAMatchmaker

The HLA-A, -B, and -C types of the 34 HSP were determined by low resolution polymerase chain reaction using sequence specific primers and each assigned to the most common corresponding four digit HLA allele according to Duquesnoy (13) with the exception of HLA-B39 (B*3901), -B13 (B*1301) and additional HLA-Cw alleles; HLA-Cw*1203, *1402, *1502, *1601 (linked to B*44), 1602 (linked to B*51), *1701, *1802. The resulting data along with the allelic data for each mismatched HLA-A and -B specificity represented by the single antigen beads were then entered into the “triplet” and “eplet” versions of the HLAMatchmaker algorithm to determine the number of triplet, extended triplet (including additional polymorphisms in the 97 amino acid residue alpha-3 domain of the HLA class I heavy chain), and eplet mismatches for each mismatched specificity. The selection of HSP for this

FIGURE 1. Levels of HLA-specific antibody binding to single-antigen HLA-A and -B antibody detection beads. Alloantibody binding was measured by Luminex and is depicted as median fluorescence intensity (MFI) for each HLA specificity. The results shown for each of the 34 HSP are the highest value recorded for antibody binding to individual HLA specificities from sequential sera. The plot shows the observed medians and middle 50% of antibody levels (represented by the boxes). Prepared using GraphPad Prism 5 (GraphPad Software, San Diego, CA).



study was based on HLA-A and -B specific antibody screening, and because sera displayed relatively low reactivity to HLA-C, -DR, and -DQ specificities these loci were of limited value for identifying unacceptable (antibody positive) mismatches and were not included in the analysis.

Statistical Analysis

Statistical analysis was performed using Splus version 7.0 (MathSoft International, Seattle, WA). The number of mismatches and the differences in the numbers of mismatches between triplets, extended triplets, and eplets were plotted on bar-charts. Bland-Altman analyses were also investigated to examine the relationship between triplets, extended triplets, and eplets. The Wilcoxon signed rank test was used to compare the number of mismatches between different methods and Spearman rank correlation was used to explore the relationship between the average number of mismatches and the difference. To assess the relationship between HLA-specific antibody binding to single-antigen beads and the number of mismatches a series of logistic regression models were fitted, with antibody reactivity as the dependent variable and the log (number of mismatches + 1) as the independent variable. A log transformation was chosen because the proportion of patients with positive antibody reactivity is expected to plateau in the range of the number of mismatches and one is added because log (0) is not defined. Informal comparison of fit for the triplets, extended triplets, and eplets were compared using the residual deviances. Because the antibody response was skewed, median regression was used to assess the relationship between the number of mismatches; the same log transformation was used for triplets, extended triplet, and eplet mismatches. In all analyses, the patients were included as fixed effects with a different intercept to model the potential dependency between measurements made on the same patient. Linear normal random effects models were used to investigate interpatient variation in both intercept and slope (corresponding models for median regression are not available). Separate median regression equations on log (triplets + 1) for each patient were also investigated.

RESULTS

Characterization of Sera From Highly Sensitized Patients Using Single-Antigen Beads

The 34 HSP in this study were selected on the basis of high ($\geq 85\%$ IgG) panel reactive antibodies. Their sera were screened by single-antigen beads each bearing 65 different HLA-A and -B specificities. Of the 65 HLA specificities analyzed, the number of mismatched HLA-A and -B specificities identified for each patient ranged from 61 to 63 depending on whether patients were homozygous at HLA-A or -B or both, giving a total of 2088 mismatched combinations. Antibody binding (defined as an MFI of ≥ 1500 after subtraction of background fluorescence) was positive for 1585 (76%) of HLA-mismatched combinations. There was marked variability between patients in both the number of mismatched-HLA specificities against which individual patient sera reacted (ranging 21%–100%, median 51 HLA specificities) and the level of binding to individual HLA-A and -B specificities (Fig. 1). Although it cannot be assumed that each of the different HLA specificities is expressed at the same density on different bead populations, examples of high and low binding by different sera for each of the bead populations demonstrated that most of the quantitative variability between patients was due to differences in antibody levels. Those HSP with antibodies to a relatively small number of different HLA specificities (e.g., patients 20 and 21) had antibodies to common specificities expressed in the HLA antibody screening panel used to define the level of sensitization.

Comparison of Triplet, Extended Triplet, and Eplet Mismatches Identified Using HLAMatchmaker

For each of the 34 HSP, HLAMatchmaker was used to compare the HLA-A, -B, and -C types with each of the 61 to 63 mismatched HLA-A and -B specificities represented on the single-antigen HLA antibody detection beads to determine the number of triplet, extended triplet, and eplet mismatches. The mean number (and range) of triplet, extended triplet,

and eplet mismatches present in each of the 2088 different HLA-mismatched combinations was 4.7 (0–13), 5.2 (0–14), and 6.0 (0–19), respectively. A total of 66 (3%) mismatched-HLA combinations did not have any triplet mismatches, because the polymorphic amino acids on the mismatched-HLA specificity were present on at least one of the patients HLA-A, -B, or -C antigens. Figure 2 depicts the number of triplet, extended triplet, and eplet mismatches present within mismatched-HLA specificities and shows that the number of triplet mismatches is significantly lower than the number of eplet mismatches ($P < 0.0001$). The increased number of eplet mismatches was attributable almost exclusively to those mismatched-HLA specificities with the highest number (top quartile) of triplet mismatches. This observation indicates that eplets provide additional discrimination predominantly for those HLA specificities with the greatest disparity in amino acid sequence from the patient.

Relationship between Triplets, Extended Triplet, and Eplet Mismatches and the Presence of HLA-Specific Antibody in HSP

Sera obtained from the 34 HSP were assessed for the presence or absence of antibody binding to each of the mismatched HLA-A and -B specificities expressed on the single-antigen beads. Logistic regression analysis was used to determine the relationship between the proportion of the HLA-mismatched combinations that were antibody positive and the number of triplet, extended triplet, and eplet mismatches (Fig. 3). It can be seen that an increasing number of triplet, extended triplet, and eplet mismatches was associated with the presence of a detectable antibody response to the relevant mismatched-HLA specificity. The regression models fitted to triplets, extended triplets, and eplets gave similarly good predictions, with a strong relationship between reactivity and number of mismatches for all three models ($P < 0.0001$).

In several cases, antibodies were present to mismatched-HLA specificities that had no triplet (19 of 66 [29%]), extended triplet (15 of 56 [27%]), and eplet mismatches (15 of 54 [27%]). This may indicate that intra- and interlocus comparisons of self-triplets and eplets expressed in different combinations on mismatched-HLA specificities can form potentially immunogenic epitopes that stimulate an alloantibody response. When the number of triplet, extended triplet, and eplet mismatches exceeded eight, the large majority ($\geq 84\%$) of HLA-mismatched combinations were antibody positive.

Relationship of Triplets, Extended Triplet, and Eplet Mismatches and the Level of Antibody to Mismatched-HLA Specificities

The above analysis was based solely on whether antibodies to mismatched-HLA specificities were present or absent, but does not take account of the magnitude of the antibody response. Because there are differing levels of alloantibody to individual mismatched-HLA specificities, we next considered the relationship between the number of triplets, extended triplets, and eplets and quantitative levels of antibody binding. For this analysis, the results were plotted as boxplots (Fig. 4). It can be seen that for triplets, extended triplets, and eplets, as the number of mismatches increased from zero to five there was a corresponding increase in antibody binding levels. However, when the number of mis-

mismatches exceeded five there was no further increase in the levels of antibody binding. It was apparent from this analysis that a small number of mismatched-HLA specificities had high levels of antibody binding (MFI > 5000) in the absence of any triplet, extended triplet, and eplet mismatches. In four of the 34 HSP, clinically significant antibody binding above MFI 5000 (range 5229–12,795), sufficient to cause a positive flow cytometric and lymphocytotoxic crossmatch, were observed for nine, eight, and six mismatched-HLA combinations with zero triplet, extended triplet, and eplet mismatches, respectively. To exclude the possibility that this high level of antibody binding to HLA specificities that carried no triplet or eplet mismatches was caused by amino acid sequence variation between HLA alleles, we undertook high resolution sequence-based HLA typing (four digits) and compared this with the high-resolution HLA typing of the target molecules, but found no change in the allele assignment (data not shown). Overall, the relationship between antibody binding levels and the number of mismatches identified by the different HLAMatchmaker algorithms were similar and eplet mismatches did not provide any additional discrimination over triplet mismatches.

The relationship between the levels of antibody binding and the number of triplet, extended triplet, and eplet mismatches was investigated using median regression analysis (Fig. 4). Mismatched-HLA specificities were grouped according to the number of HLAMatchmaker defined mismatches, and the median antibody reactivity was determined. The result of the regression analysis showed that all models predict an increase in the level of antibody against specificities with a high number of triplets, extended triplets, and eplet mismatches. Again, the models were equally effective for prediction of median antibody response.

We next considered the extent to which triplet, extended triplet, and eplet mismatches predicted the presence of HLA-specific antibody for individual patients to determine if the association differed between the three HLAMatchmaker models. As expected the antibody response according to triplet mismatch varied markedly between patients. When analyzed separately, 24 patients showed a statistically significant positive association between the HLA-specific antibody formation and the number of triplet mismatches, and no patients showed a significant and negative association. No individual patients showed a positive correlation between HLA-specific antibody formation and the number of triplet mismatches but a negative association using extended triplets or eplets.

DISCUSSION

The principle finding from this study is that HLAMatchmaker is a potentially valuable tool for optimizing allocation of donor kidneys to reduce humoral alloimmunity and the potential problems of allosensitization. For the first time, we considered the impact of triplet and eplet mismatches on the levels of alloantibody detected in patient serum, rather than simple assessment of the presence or absence of alloantibody alone. HLA-C locus and HLA-class II were not included in the analysis because the frequency of antibody response to these molecules in HSP is low and does not, therefore, enable evaluation of their immunogenicity.

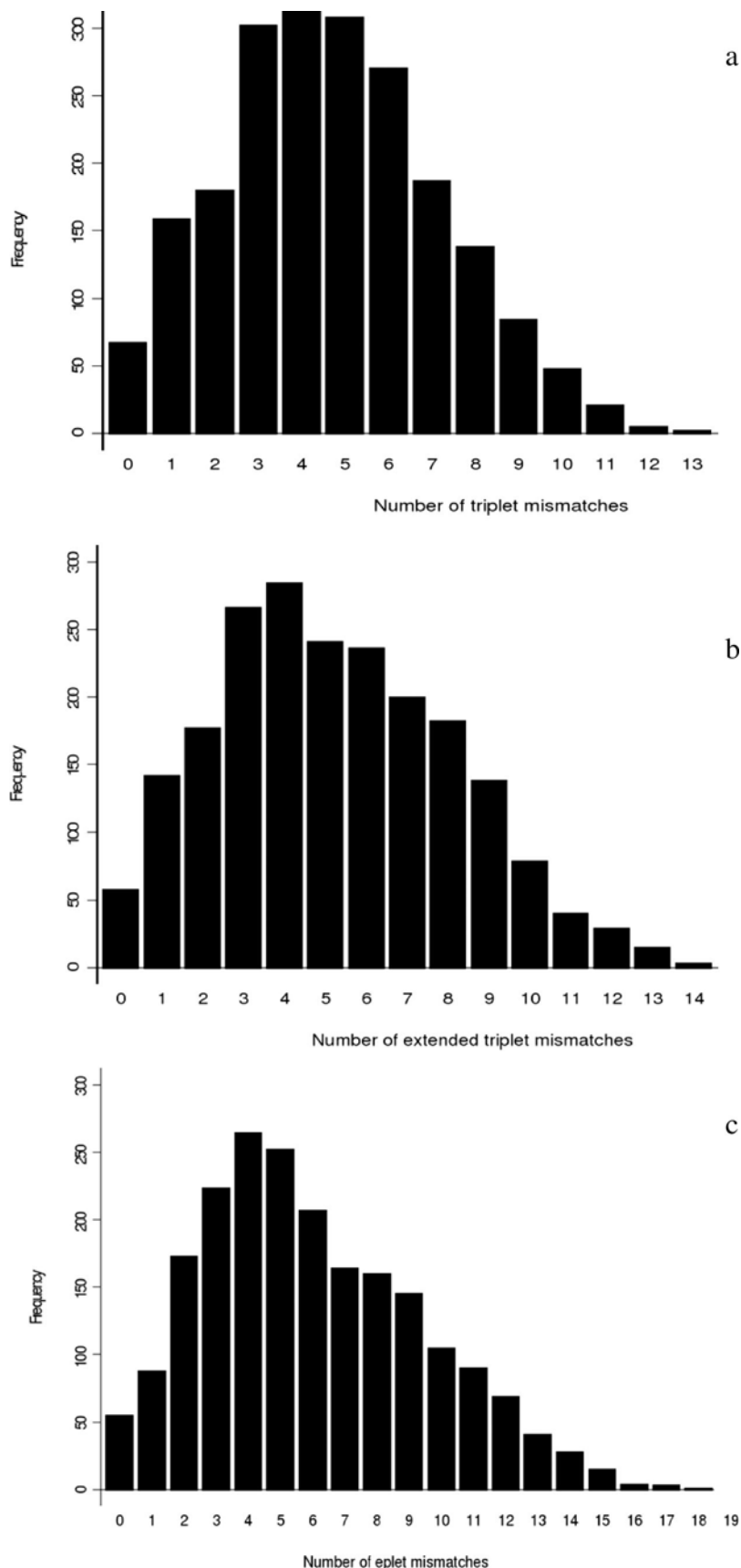


FIGURE 2. Number of triplet (panel a), extended triplet (panel b) and eplet (panel c) mismatches present within mismatched HLA-A and -B specificities. For each of the 34 HSP, the HLA-A, -B, and -C types were entered into the HLAMatchmaker program and the number of triplet, extended triplet, and eplet mismatches, for the 65 single HLA-A and -B specificities represented on single-antigen beads, calculated. The number of triplet mismatches is significantly lower than the number of eplet mismatches (Wilcoxon signed rank test, $P < 0.0001$). The correlation coefficient between the average and the difference is -0.50 ($P < 0.0001$).

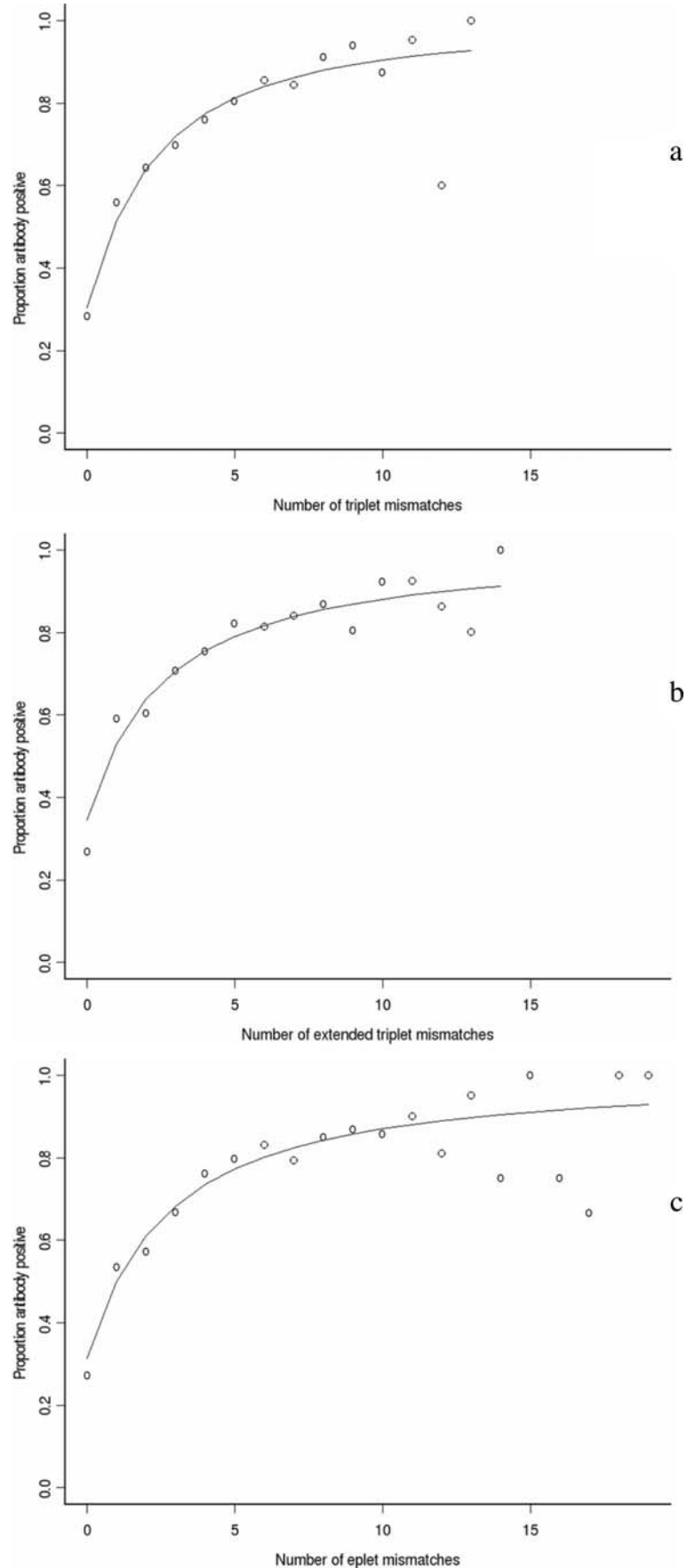


FIGURE 3. Relationship between the presence or absence of HLA-specific antibody and the number of triplet (panel a), extended triplet (panel b), and eplet (panel c) mismatches. Sera obtained from 34 HSP were assessed for the presence or absence of antibody binding to each of the mismatched HLA-A and -B specificities expressed on the single-antigen beads. Logistic regression analysis was used to determine the relationship between the proportion antibody positive and the number of triplet, extended triplet, and eplet mismatches and the relative fit of the regression curves compared. The likelihood ratio chi-squared provided a measure of the fit of each model to the data (higher values indicate a better fit). The triplet model provided the best method for predicting a positive antibody response (χ^2 [1df]=183.4) followed by eplets (161.8) and then extended triplets (147.1).

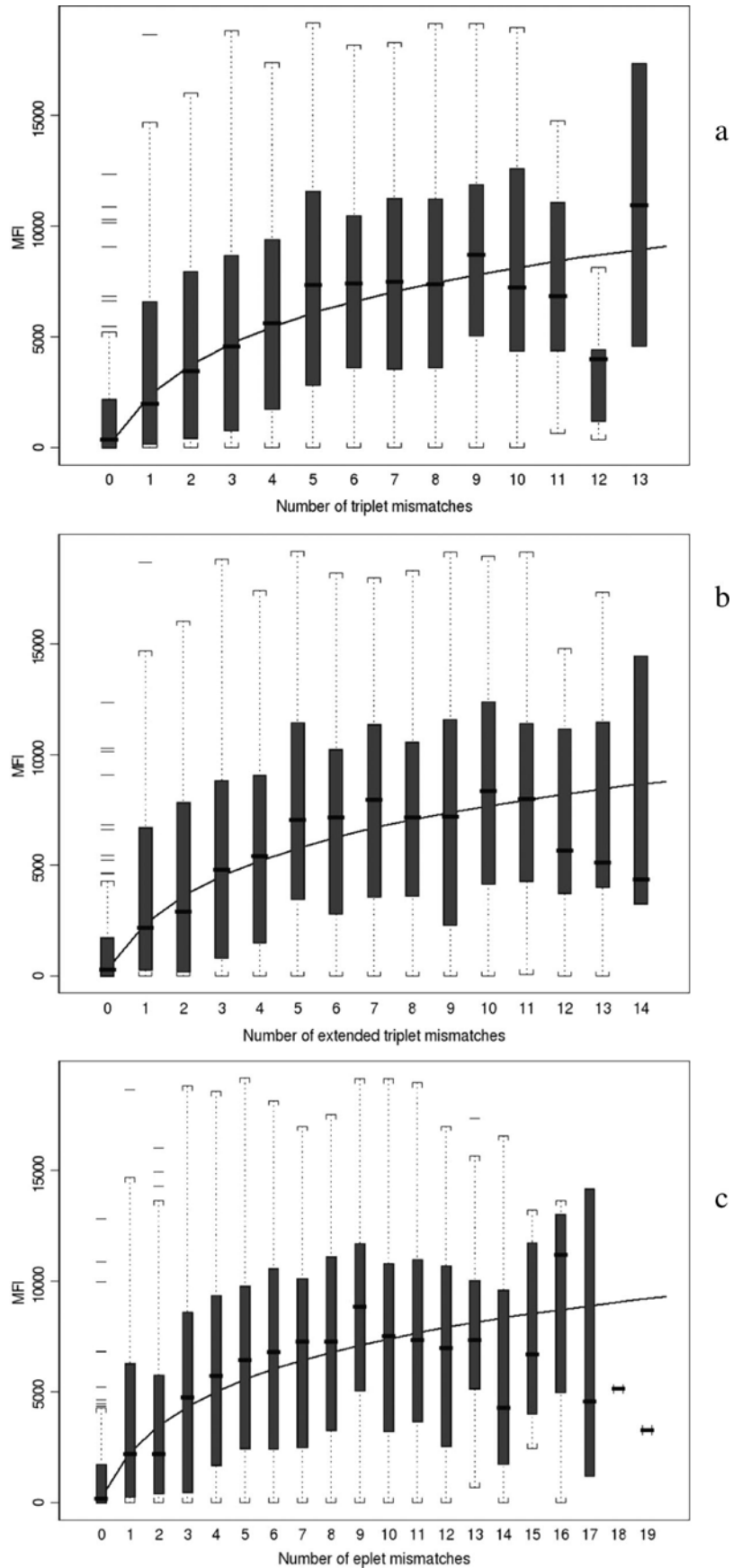


FIGURE 4. Relationship between levels of HLA-specific antibody and the number of triplet, extended triplet, and eplet mismatches. Sera from 34 HSP were assessed for levels of antibody binding (expressed as MFI) to mismatched HLA-A and -B specificities on single-antigen beads. The plots show the observed medians and middle 50% of antibody levels (represented by the boxes) for triplets (panel a), extended triplets (panel b), and eplets (panel c). Median regression analysis was used to determine the relationship between the number of triplet, extended triplet, and eplet mismatches and antibody levels.

The results obtained here confirm our earlier observation that there is a strong positive association between the number of triplet amino acid mismatches and the likelihood of a humoral response to a particular HLA class I mismatch (18). In addition, the level of alloantibody observed also correlated with the number of triplet mismatches, suggesting that triplet mismatches predict not only the presence, but also the magnitude of the alloantibody response to individual HLA-A and -B mismatches. The importance of evaluating the strength of HLA specific alloantibodies in the sera of transplant patients has recently been highlighted by Mizutani et al. (21) and our findings indicate that HLAMatchmaker is a useful tool for predicting the level of alloantibodies that arise in response to mismatched-HLA specificities.

Extended triplets take account of additional polymorphisms in the alpha-3 domain of HLA class I molecules, whereas eplets were incorporated into the HLAMatchmaker algorithm to better reflect antibody binding epitopes that include polymorphic amino acid residues at discontinuous sequence positions that cluster together in the tertiary protein molecule (19). In the present study, the additional structural information provided by extended triplets and eplets gave further discrimination between mismatched-HLA class I specificities but did not improve the ability of HLAMatchmaker to predict acceptable and unacceptable mismatches.

The use of eplets is based on the concept that alloantibody binding sites likely comprise approximately 15 to 22 amino acid residues that fold to display a functional epitope of 2 to 5 residues that are key in determining antibody specificity and affinity, with the remaining residues helping to increase the stability of antibody binding (19). In some cases, eplets constitute linear sequences that are identical to those of triplets and hence would not be expected to provide additional predictive value. In others eplets are formed by discontinuous amino acids that are brought together on folding within a radius of 3 to 3.5 Å to constitute a functional antibody-binding epitope and might be expected to provide a better prediction of epitope structure than triplets. In the present study, although there were more eplet mismatches than triplet mismatches for the HLA specificities examined, this was largely confined to mismatched-HLA specificities with the highest number of triplet mismatches and most of these were antibody positive, thereby limiting the scope for eplets to further improve prediction of immunogenicity.

In our previous analysis, we reported that only 9% of the HLA specificities with zero triplet mismatches were antibody positive and in all cases antibody binding was equivocal (18). However, in the present study, we identified four patients who showed a strong alloantibody response (MFI > 5000) to HLA-A or -B specificities that contained zero triplet or eplet mismatches. The possible explanation that this was due to the presence of unusual HLA alleles in these four patients was excluded as high resolution (four digits) DNA sequence-based HLA typing did not identify any miss-assigned alleles. HLAMatchmaker assumes that an amino acid polymorphism at a particular site on the comparator alloantigen that is shared at the same position by any one of the different host HLA molecules will not invoke an alloimmune response (13, 14). However, our results suggest that this assumption may not always be correct and that whether or not the expression of a self-amino acid sequence provides an

immunogenic epitope may be dependent in part on the tertiary conformation of the protein molecule.

In conclusion, the number of triplet amino acid mismatches between an alloantigen and the host HLA type determined using the HLAMatchmaker algorithm, correlates closely with both the development and strength of an alloantibody response. Although eplets identify additional potential epitopes the increased differentiation they provided was mainly limited to mismatched-HLA specificities with a large number of amino acid mismatches and a high antibody response. Overall HLAMatchmaker provides a valuable tool for predicting the immunogenicity of a given HLA mismatch in patients awaiting renal transplantation.

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