Published in final edited form as:
Hum Immunol. 2008 December ; 69(12): 826–832. doi:10.1016/j.humimm.2008.10.003.

A Structurally Based Epitope Analysis of MICA Antibody Specificity Patterns

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Abstract

Recent studies have suggested a clinical significance to the detection of anti-MICA antibodies in transplantation. We have developed an eplet-based version of the HLAMatchmaker algorithm to assess the epitope specificity of these antibodies. Molecular viewing of the MICA structure and the determination of amino acid sequence differences between MICA alleles has yielded a repertoire of 38 potentially immunogenic MICA eplets. These eplets are based on the functional epitope structure that considers a configuration of amino acids within a three-Ångstrom radius of an antibody-accessible polymorphic residue on the molecular surface.

MICA-reactive sera were screened in Luminex assays with single MICA allele panels and analyzed with HLAMatchmaker. We have identified reactivity patterns that correspond to eplet-specific antibodies to identify of unacceptable MICA mismatches including those alleles that have not been tested with the serum.

HLAMatchmaker is a useful algorithm to analyze the reactivity patterns of anti-MICA antibodies and the determination of MICA mismatch acceptability at the structural level.

Keywords

MICA; HLAMatchmaker; Eplet; Epitope Structure; Anti-MICA Antibodies

Introduction

The Major Histocompatibility Complex class I-related chain A (MICA) antigens are stress-inducible cell-surface proteins encoded by genes on chromosome 6 mapping close to HLA-B and HLA-C [1-3]. They have a molecular structure similar to class I HLA but they do not associate with β2-microglobulin nor do they bind peptide. MICA can serve as a ligand for the activating natural killer cell receptor NKG2D also expressed on CD8αβ T-cells and γδ T-cells [4-6].

Increased MICA expression in tissues subjected to stress or injury may trigger these cellular immune processes [7]. MICA antigens have been detected on endothelial cells [2] and

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following transplantation, MICA up-regulation correlates with histological evidence of severe rejection [8,9]. Conversely, anti-MICA antibodies can block NKG2D-mediated NK cell activity [7]. It is possible that antibodies against epitopes nearby the contact site of MICA and NKG2D might have the strongest effect The MICA system is highly polymorphic and exposure to mismatched MICA antigens can trigger alloantibody responses that are associated with transplant failure [10-14]. Pretransplant anti-MICA antibodies represent significant risk factors for allograft rejection and lower graft survival [8,15,16]. Also, the development of anti-MICA antibodies post-transplant is associated with more rejection and more graft failure [17-19].

Anti-MICA antibodies can be expected to react with epitopes defined by amino acid polymorphisms of MICA antigens in a similar way as anti-HLA antibodies react with structurally defined epitopes on the HLA molecular surface. More than fifty MICA alleles have been identified with different amino acid sequences and there is now detailed information about the molecular structure the MICA protein [20,21]. This report describes a model for structurally defined epitopes on MICA antigens. It is based on the previously reported concept that an HLA epitope is represented by a configuration of a polymorphic surface residue with other residues within a radius of about three Ångstroms [22,23]. We have applied the computer algorithm HLAMatchmaker to determine MICA compatibility at the structural level and to analyze the reactivity patterns of antibodies with structurally defined MICA epitopes.

Materials and Methods

Structural modeling of the MICA epitope repertoire

The Entrez Molecular Modeling Database (MMDB) of the National Center for Biotechnology Information (NCBI) website http://www.ncbi.nlm.nih.gov/Structure has stereochemical models of two crystalline structures of MICA: MICA-001 (PDB code 1B3J ([20] and MICA-001 bound to the NKG2D receptor (PDB code 1HYR [21]). The Cn3D molecular viewer identifies the locations of selected residues and the “space fill” command shows their exposure on the molecular surface [24]. Figure1 shows three views of the surface positions with more common residue polymorphisms of MICA antigens. They do not include polymorphic positions limited to very rare MICA alleles not found in European-Americans and African-Americans [25]; positions 90 (A*050), 105 (A*036), 124 (A*033), 142 (A*029), 176 (A*006), 230 (A*056), 256 (A*043) and 268 (A*054. The remaining 23 polymorphic positions are widely distributed on the molecular surface.

Analogous to HLA epitope structure, a polymorphic residue on the molecular surface represents an essential component of a functional epitope that comprises all residues within a radius of about three Ångstroms [22]. The “select by distance” command of the Cn3D program can identify the amino acids around each polymorphic residue. These patches comprise 4-6 residues but only one or two of them are polymorphic (data not shown). The term “eplet” is used to describe a potential functional epitope and the eplet notation lists only polymorphic residues.

Table 1 shows the polymorphic positions of MICA eplets. The majority resides in the α2 and α3 domains. Most of them have single residues and in five cases two polymorphic residues are close to each other. These pairs are in positions 25, 123, 174, 206 and 214. Cn3D viewing suggested the residue exposure on the molecular surface as prominent (++), readily visible (+) and somewhat visible (-/+).

For each eplet position in Table 1 we determined the amino acid residue composition from sequence data of 56 MICA alleles listed on the Anthony Nolan Research Institute website http://www.anthonynolan.org.uk/HIG/data.html [26]. This was done with a Microsoft Excel Macro program developed for HLA eplets by Grzegorz Dudek (Medigen Molecular

Diagnostics, Warsaw, Poland) [22]. Table 2 shows a total of 50 MICA eplets and the alleles that carry them. Eplets are designated by their sequence position and amino acids are shown with the standard one-letter code. The notation “non” means all alleles except the ones listed. Almost all positions have a pair of eplets, except positions 25, 156, 174 and 251 which have three eplets.

Considering the high degree of structural homology between MICA and MICB molecules [27], we have also compared the amino acid compositions of the 3-Ångstrom patches defined by MICA eplets with MICB patches in the same sequence positions. Twelve MICA eplets have patches with identical amino acid composition as all MICB alleles; they have been marked with an asterisk at the bottom of Table 2. These eplets are inter-locus matches and according to the HLAMatchmaker concept they cannot elicit MICA-specific alloantibodies. The remaining 38 MICA eplets are considered as potential epitopes that can induce specific antibodies.

Eplet frequencies were calculated from MICA allele frequencies in 1245 European-Americans and 605 African-Americans as reported by Gao et al [25]. The 38 potentially immunogenic eplets have been sorted in Table 1 according to their random chance of being exposed as a mismatch which can be calculated with the following formula: $(1\text{-}Ep_{freq}) \times Ep_{freqmix}$ whereby Ep_{freq} represents the eplet frequency in European-Americans or African-Americans and $Ep_{freqmix}$ represents the eplet frequency in a population mixture of 2/3 European-Americans and 1/3 African-Americans. It can be readily seen that about one-third of the eplets have a low chance of being a mismatch because they have either very high (>95%) or very low (<5%) frequency in European-Americans and/or African-Americans. Such eplets seem less likely involved with specific antibody responses.

Many eplets are shared by very similar groups of MICA alleles. For instance, 36C, 129M, 206GW, and 215S are shared by the same group of fifteen MICA alleles reported in North-American populations: A*001, A*002, A*007, A*011, A*012, A*015, A*017, A*018, A*021, A*030, A*041, A*043, A*045, A*046 and A*047. These eplets have the same random chance of being a mismatch, namely 24.0% in European-Americans and 20.1% in African-Americans and this combination of eplets is referred to as the CMGWS “supereplet” and is also present on other alleles not detected in these North-American groups: A*014, A*020, A*023, A*026, A*029, A*036, A*040, A*050, A*052 and A*055. Alternatively, 25AY, 129V and 173E (referred to as the AYVE supereplet) are shared by another group of nine North-American MICA alleles: A*004, A*006, A*008, A*009, A*010, A*016, A*019, A*024 and A*044. Their random chance of being a mismatch is 20.1% in European-Americans and 28.2% in African-Americans. Other alleles have also AYVE, namely A*027, A*028, A*033, A*048, A*049, A*054 and A*056. Table 1 shows also two eplet pairs 213T-251Q and 213I-251R that are shared by distinct groups of MICA alleles.

It can be expected that serum screening with panels selected from the twenty-four North-American MICA alleles listed above cannot determine which eplets are specifically recognized by antibodies reacting with the CMGWS or AYVE supereplet. Other MICA alleles are needed to determine antibody specificity against individual eplets in these configurations. For instance, A*022 and A*053 would be informative for antibodies against 36C because these alleles do not have the other eplets of the CMGWS supereplet. Similarly, A*025 and A*051 would be informative for antibodies against 25AY whereas A*014 and A*036 would be informative for antibodies against 173E of the AYVE supereplet. These alleles are rather uncommon and may not be informative if the serum has additional MICA antibody specificity.

Serum screening for MICA antibodies

The analysis of anti-MICA antibodies was performed using the single antigen MICA provided in the LSA-MIC product (Tepnel Lifecodes, Stamford, CT) according to the manufacturer's instructions. In brief, an aliquot of a mixture of Luminex microspheres, each coated with a single MICA antigen, was incubated with a small volume of test serum sample and washed to remove unbound antibody. Anti-Human IgG antibody conjugated to phycoerythrin was added and after incubation the bead mixture was diluted for analysis with the Luminex instrument and Lifematch software (Tepnel Lifecodes).

The presence of anti-MICA antibody in a serum sample was determined by comparing the median fluorescence intensity (MFI) of the beads containing the individual MICA antigens to the signal intensities of the positive and negative control beads included in the bead mixture. These data were used to determine the relative amount of antibody bound to the beads and whether the single antigen beads were positive or negative for anti-MICA antibody.

HLAMatchmaker analysis of MICA antibody reactivity patterns

The MICA eplet repertoire (Table 2) has become the basis for developing a new version of the HLAMatchmaker program to analyze serum antibody patterns with single MICA alleles on the Luminex platform. The program can be downloaded free of charge from the http://www.HLAMatchmaker.net website. The analysis can be done in five easy steps. First record the alleles of the panel on the "Panel" worksheet and if possible, enter the MICA types of antibody producer and immunizer on the "Enter Data" sheet. Second, enter the serum reactivity with the panel. The easiest way is to copy and paste the MFI values from the XML files generated by the commercial vendor's Luminex data analysis programs. Third, determine whether the self-MICA alleles of the antibody producer give low MFI values in relation to the negative controls and the rest of the panel. Although no MICA typing information was available for the vast majority of cases in this study, one can expect that at least one allele in the panel must be "self" and therefore should give a low MFI value. Fourth, record the negative alleles in the "Enter Data" sheet and HLAMatchmaker removes their corresponding eplets. Fifth, record the eplets shared by the reactive alleles in the panel in the "Enter Data" sheet. The program has a "Results" sheet that summarizes the information about the antibody specificity pattern and the listing of MICA alleles as acceptable or unacceptable mismatches.

Results

Sera with anti-MICA antibody reactivity were tested with Luminex panels of single MICA alleles. These sera came primarily from patients who had become sensitized after transplantation. MICA typing information was available for only few patients and fewer transplant donors. Nevertheless, our HLAMatchmaker-based analysis revealed generally consistent antibody reactivity patterns that correlate with the presence of specific eplets. Figure 2 shows three examples whereby the serum reactivity with a MICA allele panel seems to involve a single antibody specificity pattern.

Serum 1 reacted with all three 25TC-positive alleles A*001, A*012 and A*018 but none of the 25TC-negative alleles and was therefore considered to be specific for 25TC. All 25TC-positive alleles can be considered as unacceptable mismatches including A*021 not tested in the panel.

Serum 2 reacted with only the14G-positive alleles in this panel and was therefore considered specific for 14G. All 14G-positive alleles can be considered as unacceptable mismatches including thirteen untested alleles, namely A*013, A*014, A*020, A*022, A*023, A*034, A*035, A*036, A*041, A*044, A*047, A*052 A*053 and A*055.

Serum 3 reacted strongly with only MICA alleles that had the CMGWS supereplet representing the combination of 36C, 129M, 206GW and 215S. Although further testing with informative alleles in the panel may provide information which eplets are actually recognized by antibodies in this serum, these data show already that besides the reactive alleles in the panel, all other untested CMGWS-positive alleles (A*014, A*020, A*021, A*023, A*026, A*036, A*040, A*041, A*045, A*047, A*050, A*052 and A*055) should be considered as unacceptable mismatches.

This serum analysis yielded also more complex reactivity patterns and Figure 3 shows three examples. Serum 4 reacted with all 14W-positive alleles but the highest MFI values were seen with alleles that also have the AYVE supereplet, It seems likely that this high reactivity is due to an additive effect of anti-14W and anti-AYVE antibodies binding to A*004, A*006, A*008, A*009, A*016, A*019 and A*033.

Serum 5 showed weak reactions with seven AYVE-positive alleles and somewhat stronger reactions with three 25TC-positive alleles. This serum can be considered to have anti-AYVE and anti-25TC antibodies.

Serum 6 reacted with all CMGWS-positive alleles but the highest MFI values were seen for alleles that also had 14W. On the other hand, this serum did not react with any of the seven 14W-positive, CMGWS-negative alleles and this rules out the presence of 14W-specific antibodies. In accordance with a previous report [28], the most likely explanation of this reactivity pattern is that 14W functions as a critical contact site for an antibody specific against a component of the CMGWS supereplet.

Discussion

This report describes how the concept that HLA antibodies react with structurally defined epitopes can be applied to the analysis of anti-MICA antibodies. We have determined a repertoire of 38 potentially immunogenic MICA eplets from the molecular structure and amino acid sequence differences between MICA alleles. These eplets are based on the functional epitope structure that considers a configuration of amino acids within a three-Ångstrom radius of an antibody-accessible polymorphic residue on the molecular surface. Twelve MICA eplets have three-Ångstrom patches that are shared with all alleles of the structurally similar MICB and as inter-locus matches they are not considered immunogenic.

Although MICA and HLA class I α chains are similar molecules, it has been noted that almost none of the polymorphic residues are shared between these groups [29]. Therefore, MICA can be considered as a separate alloantigenic system and a MICA eplet-based HLAMatchmaker program can determine the specificity of anti-MICA antibodies in allosensitized patients.

The HLAMatchmaker-based analysis of serum screens with single MICA allele panels can identify reactivity patterns that correspond to eplet-specific antibodies and this permits the identification of unacceptable mismatches including those alleles that have not been tested with the serum. Although anti-MICA antibodies are associated with transplant rejection, there is little information whether the avoidance of unacceptable MICA mismatches benefits transplant outcome. Nevertheless, a better understanding of MICA antibody specificity patterns may help in the interpretation of transplant outcomes in the clinical setting.

Our analysis of serum reactivity with single MICA alleles is still in progress and a detailed characterization of epitope specificity of antibodies requires information about the MICA types of antibody producer and immunizer and serum absorption/elution analyses with informative allele panels. Nevertheless, our experience so far has identified several eplets that are commonly recognized by MICA-reactive sera. These include the supereplets CMGWS

(combination of 36C, 129M, 206GW, and 215S) and AYVE (combination of 25AY, 129V and 173E) as well as 25TC, 14W, 14G and 122V.

At present, there is little information about anti-MICB alloantibody responses [30]. With about six more common polymorphic residue positions among its 20 alleles the MICB system is less polymorphic than MICA and about 12 MICB eplets seem possible.

Acknowledgements

This study is supported by grant AI-55933 from the National Institutes of Health

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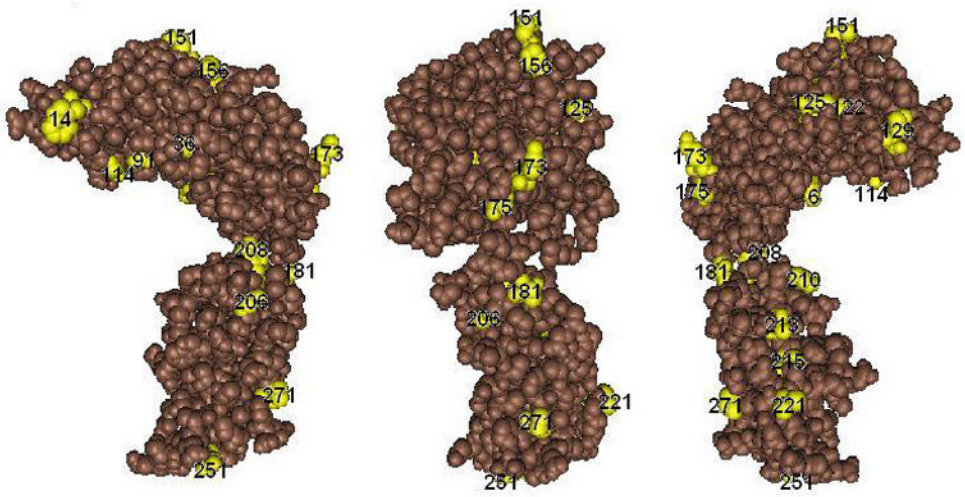

Figure 1.
Three views of polymorphic residue positions on the MICA molecule. They are based on the stereochemical modeling of the crystalline structure of MICA-001 (PDB code: 1HYR [21]).

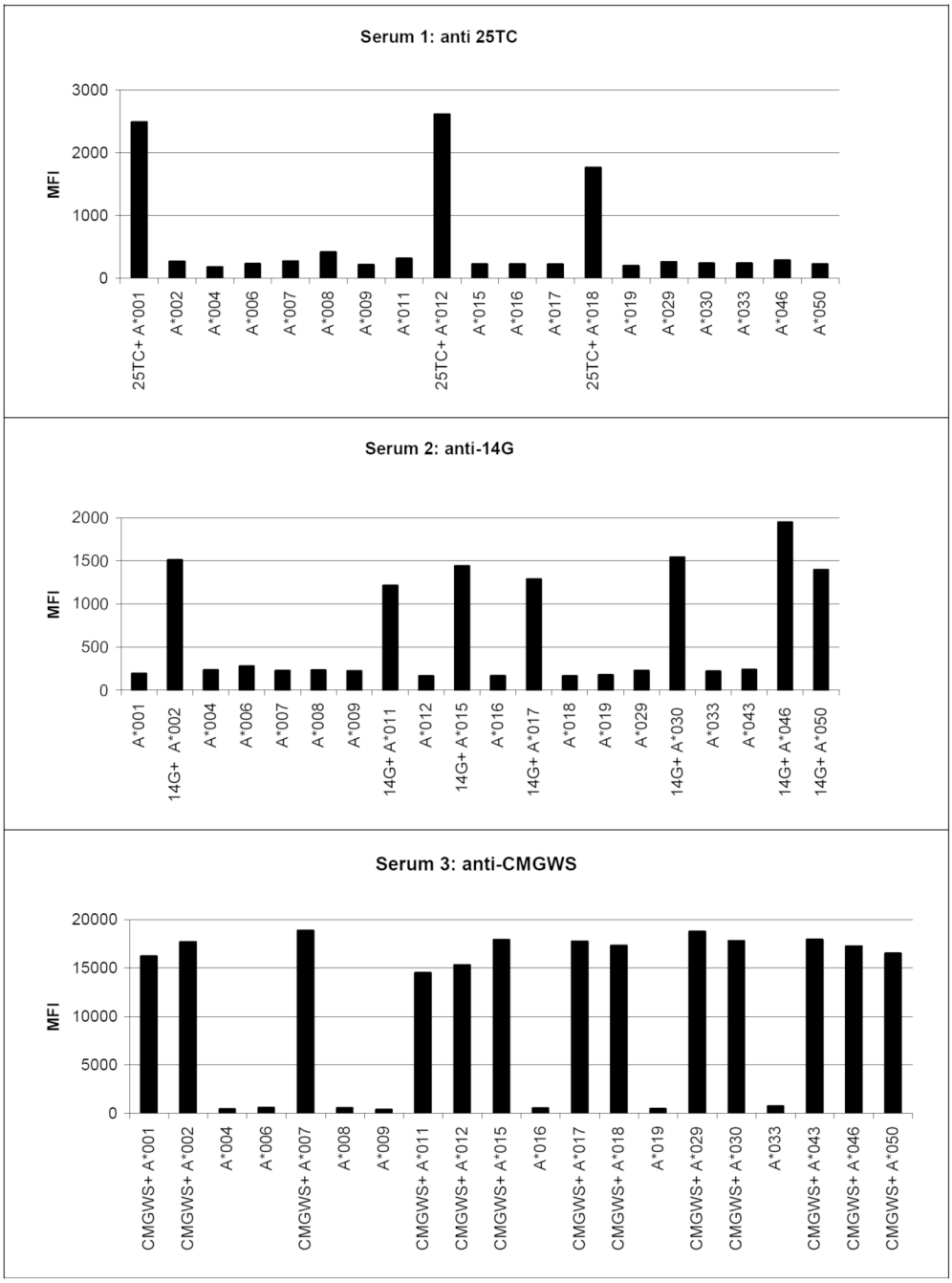

Figure 2.
Examples of serum reactivity associated with one MICA eplet.

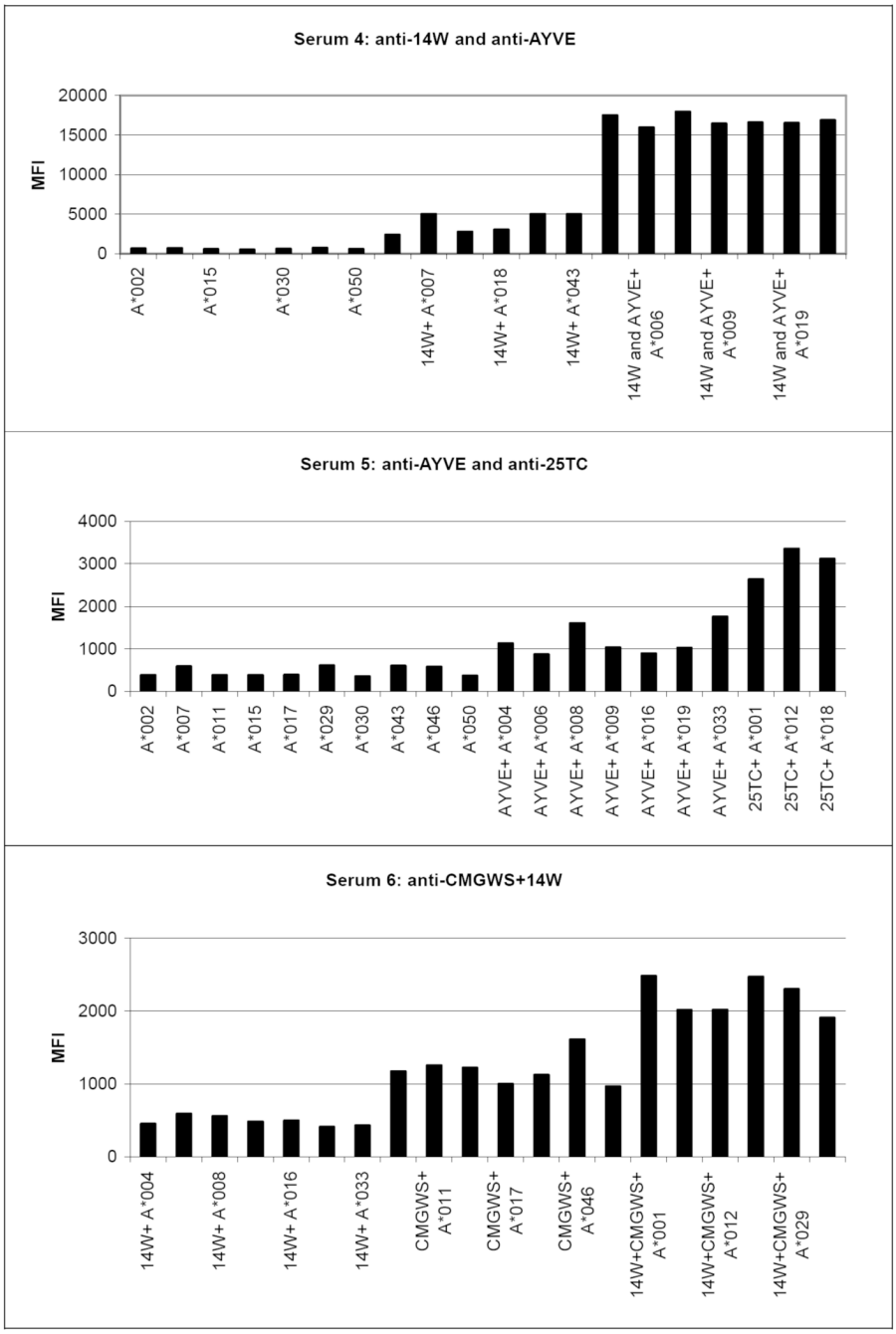

Figure 3.
Examples of MICA sera with dual reactivity patterns.

Table 1

Eplet positions on MICA molecules

Eplet Position	Domain	Surface Visibility	Polymorphic Positions
6	α1	+	6
14	α1	++	14
24	α1	±	24
25	α1	±	24 36
26	α1	+	26
36	α1	±	36
91	α2	+	91
114	α2	++	114
122	α2	+	122
123	α2	+	122 125
125	α2	++	125
129	α2	++	129
151	α2	++	151
156	α2	++	156
173	α2	++	173
174	α2	++	173 175
175	α2	+	175
181	α2	+	181
206	α3	++	206 210
208	α3	++	208
213	α3	++	213
214	α3	++	213 215
215	α3	+	215
221	α3	+	221
251	α3	++	251
271	α3	++	271

Table 2

List of MICA eplets, their frequencies and chances of being a mismatch in two North-American populations and the alleles that carry them

Eplet	Frequency in European-Americans	Mismatch Chance	Frequency in African-Americans	Mismatch Chance	MICA alleles
213T	47.7%	28.0%	65.2%	18.6%	*001*002*004*005*006*007*009*011*012*013*014*015*017*018*020*021*023*024*025*026*028*029*030*031*032*034*036*038*040*041*043*044*045*046*047*049*050*051*052*055
251Q	47.6%	27.9%	64.9%	18.7%	*001*002*004*006*007*009*011*012*014*015*017*018*020*021*023*024*025*026*028*029*030*031*032*034*036*038*040*041*043*044*046*047*049*050*051*052*055
129M	31.3%	24.0%	42.6%	20.1%	*001*002*007*011*012*014*015*017*018*020*021*023*025*026*029*030*031*032*034*035*036*037*038*039*040*041*042*043*045*046*047*050*051*052*055
36C	31.3%	24.0%	42.6%	20.1%	*001*002*007*011*012*013*014*015*017*018*020*021*022*023*026*029*030*034*035*036*037*038*039*040*041*043*045*046*047*050*052*053*055
206GW	31.2%	24.0%	42.6%	20.1%	*001*002*007*011*012*013*014*015*017*018*020*021*023*025*026*028*029*030*031*032*036*040*041*043*045*046*047*050*051*052*055
215S	31.2%	24.0%	42.6%	20.1%	*001*002*007*011*012*013*014*015*017*018*020*021*023*025*026*028*029*030*031*032*036*040*041*043*045*046*047*050*051*052*055
174EG	43.5%	22.4%	31.8%	27.0%	*008*013*014*024*027*028*048*053
213I	52.6%	22.0%	33.9%	30.7%	*008*010*016*019*022*027*033*035*037*039*042*048*053*054*056
251R	52.6%	22.0%	33.9%	30.7%	*005*008*010*013*016*019*022*027*033*035*037*039*042*048*053*054*056
25AC	24.1%	21.5%	36.8%	17.9%	*002*007*011*013*014*015*017*020*022*023*026*029*030*034*035*036*037*038*039*040*041*043*045*046*047*050*052*053*055
25AY	69.1%	20.1%	56.5%	28.2%	*004*005*006*008*009*010*016*019*024*025*027*028*031*032*033*042*044*048*049*051*054*056
129V	69.1%	20.1%	56.5%	28.2%	*004*005*006*008*009*010*013*016*019*022*024*027*028*033*044*048*049*053*054*056
173E	69.1%	20.1%	56.5%	28.2%	*004*006*008*009*010*013*014*016*019*022*024*027*028*033*036*044*048*049*053*054*056
14G	19.0%	19.7%	35.0%	15.8%	*002*011*013*014*015*017*020*022*023*030*034*035*036*041*044*046*047*050*052*053*055
175G	74.7%	18.9%	74.4%	19.1%	*001*002*005*007*008*011*012*013*014*015*017*018*020*021*023*024*025*026*027*028*029*030*031*034*035*037*038*039*040*041*042*043*045*046*047*048*050*051*052*053*055
175S	25.6%	18.8%	24.7%	19.1%	*004*006*009*010*016*019*022*032*033*036*044*049*054*056
214TT	16.5%	15.5%	22.6%	14.3%	*004*005*006*009*024*034**038*044*049
122V	16.4%	15.4%	22.6%	14.2%	*004*006*009*044*049
14W	81.3%	14.2%	64.1%	27.1%	*001*004*005*006*007*008*009*010*012*016*018*019*021*024*025*026*027*028*029*031*032*033*037*038*039*040*042*043*045*048*049*051*054*056
123LE	82.9%	13.7%	75.1%	20.0%	non*001*004*006*009*031*033*040*044*049
181R	7.6%	10.5%	19.1%	9.2%	*004*014*032*044
24A	93.1%	6.4%	93.3%	6.3%	non*001*012*018*021
25TC	7.2%	6.2%	5.8%	6.3%	*001*012*018*021
6P	5.8%	4.0%	1.2%	4.2%	*010*025*054
271A	3.1%	2.9%	2.9%	2.9%	*011*030*047
151V	2.9%	2.7%	2.6%	2.7%	*011*034
114R	0.2%	2.0%	5.6%	1.9%	*014*015
156L	2.2%	1.9%	1.4%	1.9%	*012*021*032
156H	98.1%	1.8%	97.3%	2.6%	non*012*021*032*043
221L	2.3%	1.6%	0.2%	1.6%	*016*039

Eplet	Frequency in European-Americans	Mismatch Chance	Frequency in African-Americans	Mismatch Chance	MICA alleles
125K	1.1%	1.2%	1.4%	1.2%	*001*031*040
91R	1.1%	0.9%	0.6%	0.9%	*017
125E	99.2%	0.8%	97.7%	2.3%	non*001*031*040
208C	0.3%	0.2%	0.0%	0.2%	*046
251E	0.0%	0.1%	0.3%	0.1%	*045
156R	0.0%	0.1%	0.3%	0.1%	*043
208Y	100.0%	0.0%	99.1%	0.9%	non*046
26V	100.0%	0.0%	98.6%	1.4%	non*041*047
Monomorphic at MICB:					
6R*	94.5%	0%	97.9%	0%	non*010*025
26G*	0.0%	0%	0.5%	0%	*041*047
91Q*	99.2%	0%	98.5%	0%	non*017
114G*	99.8%	0%	93.5%	0%	non*014*015
122L*	84.0%	0%	76.5%	0%	non*004*006*009*044*049
151M*	97.4%	0%	96.5%	0%	non*011*034
173K*	31.3%	0%	42.6%	0%	*001*002*005*007*011*012*015*017*018*020*021*023*025*026*029*030*031*032*034*035*037*038*039*040*041*042*043*045*046*047*050*051*052*055
181T*	92.8%	0%	80.0%	0%	non*004*014*032*044
206SR*	69.1%	0%	56.5%	0%	*004*005*006*008*009*010*016*019*022*024*027*033*034*035*037*038*039*042*044*048*049*053*054*056
215T*	69.1%	0%	56.5%	0%	*004*005*006*008*009*010*016*019*022*024*027*033*034*035*037*038*039*042*044*048*049*053*054*056
221V*	98.0%	0%	98.9%	0%	non*016*039
271P*	97.2%	0%	98.6%	0%	non*011*030*047