UCLA INTERNATIONAL MICA EXCHANGE - AN UPDATE

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Introduction:

Increased interest in MICA (MHC class I chain-related gene A) antibodies and the role they play in triggering alloimmune response in solid organ transplants emphasizes the growing need of reliable platforms for MICA genotyping. In this study, we evaluated the average percent assignment of MICA alleles among labs using various methodologies to aid in the standardization of MICA allele assignments. Along the way, new alleles were identified as well.

Table 1. MICA alleles examined from 2009 - 2024

	# times						
MICA Allele	tested	Black	Caucasian	Hispanic	Asian	Mixed	Unknown
MICA*001	14			\bigcirc			
MICA*002	40	\bigcirc	\bigcirc		\bigcirc		
MICA*004	34	\bigcirc	\bigcirc	\bigcirc	\bigcirc	\bigcirc	
MICA*006	4						
MICA*007	15						
MICA*008	53		\bigcirc				
MICA*009	22		\bigcirc	\bigcirc	\bigcirc		
MICA*010	30	\bigcirc	\bigcirc		\bigcirc		\bigcirc
MICA*011	21			\bigcirc		\bigcirc	
MICA*012	20		\bigcirc		\bigcirc		
MICA*015	17	\bigcirc					
MICA*016	13		\bigcirc		\bigcirc		
MICA*017	13		\bigcirc	\bigcirc	\bigcirc	\bullet	
MICA*018	22				ightarrow		
MICA*019	20	\circ	\bigcirc		\bigcirc		
MICA*027	22				\bigcirc		
MICA*029	3						\bigcirc
MICA*041	9			\bigcirc			
MICA*045	10				\bigcirc		
MICA*047	1					\bigcirc	
MICA*049	1						
MICA*052	2						
MICA*068	6						
MICA*072	2						
MICA*101	1						
MICA*250	1						
MICA*266	1						

Results:

From 2009 – 2024, MCA genotyping was performed on a total of 186 DNA samples. During this period, 27 different MICA alleles were examined, including MICA*101, MICA*250, and MICA*266. <u>Table 1</u> lists each of the 27 alleles examined, along with the number of times each was tested, and the ethnicity of the DNA samples examined. In some cases, the same donor DNA was tested multiple times.

MICA*008 (n = 53) was the most frequently examined allele, followed by MICA*002 (n = 40), and MICA*004 (n = 34). Some alleles, such as MICA*002, MICA*004, and MICA*008, were observed across all populations. While others, such as MICA*001 and MICA*045, were observed in only 1 or 2 ethnic populations. Figure 1 illustrates a breakdown of the ethnic makeup of the Exchange samples. Hispanics (29%) were the largest group represented, followed by Asians (26%). Selection of samples was not based simply on race, but on providing a broad range of MICA genotypes for participants to examine.

Figure 1. Breakdown of ethnic populations for MICA samples



Methods:

In 2007, the UCLA Immunogenetics Center developed a proficiency testing program for MICA genotyping. This update documents the evolution of MICA genotyping from 2009 – 2024 following the first 2 years of the program. Data collected from participants in the Exchange included MICA genotypes, typing method, and kit information.

Table 2. Average % assignment of MICA alleles, 2009 - 2024

Average % assignment of MICA alleles (n = 27)					
0-50%	51-90%	91-100%			
VICA*002 (A9)	MICA*007 (A4)	MICA*001 (A4)			
VICA*009 (A6)	MICA*008 (A5.1)	MICA*004 (A6)			
VICA*027 (A5)	MICA*010 (A5)	MICA*006 (A6)			
	MICA*012 (A4)	MICA*011 (A6)			
	MICA*041 (A9)	MICA*015 (A9)			
	MICA*049 (A6)	MICA*016 (A5)			
	MICA*068 (A9)	MICA*017 (A9)			
	MICA*101 (A6)	MICA*018 (A4)			
	MICA*266 (A4)	MICA*019 (A5)			
		MICA*029 (A4)			
		MICA*045 (A4)			
		MICA*047 (A6)			
		MICA*052 (A9)			
		MICA*072 (A9)			
		MICA*250 (A4)			

Table 2 lists the average % assignment for each of the 27 alleles examined. Fifteen alleles had an average % assignment of \geq 91%, and 9 alleles had an average % assignment of 51% – 90%. The average % assignment of MICA*002 (40%), MICA*009 (47%), and MICA*027 (50%) was relatively low, as labs were unable to resolve each from among other MICA alleles (Table 3).

Table 3. Ambiguous MICA alleles

MICA Allele	not resolved from	MICA Allele	not resolved from
	*002, *020, *055,		
	*086, *089, *090,		
MICA*002	*091	MICA*007	*026, *079
			*027, *048, *058,
MICA*009	*049	MICA*008	*070, *073
			*016, *019, *020,
			*033, *054, *055,
			*056, *065, *066,
MICA*027	*048	MICA*010	*069
			*018, *060, *061,
		MICA*012	*067
		MICA*041	*002
		MICA*049	*009
		MICA*068	*002, *020, *055
		MICA*101	*047

In general, % assignment of MICA alleles improved over the years as many labs navigated away from a SSO (sequence specific oligonucleotide) based typing method to NGS (next generation sequencing). Figure 2 illustrates the improvement in the % assignment of MICA*002 over the years. In 2009, MICA*002 was assigned by only 31% (5 of 16). At that time, 11/16 labs indicated SSO as the method type. In 2024, the % assignment of MICA*002 was much higher, increasing to 71% (12 of 17) in the latest Exchange study (Exchange 47). Among the 12 labs reporting MICA*002 in 2024, 9 labs indicated NGS as the method type.

Figure 2. Percent (%) detection of MICA*002, 2009 – 2024



An example of how the International MICA Exchange achieves its goal of improving and standardizing MICA genotyping is shown in

Two new alleles were identified in the MICA Exchange. The first, MICA*018new,

Table 4. Identification of new MICA*018 allele

	2013	2014	2024
	Sample #078	Sample #086	sample #205
	(n = 20)	((n = 17)	(n = 15)
MICA*018	65%	65%	20%
MICA*018:01	30%	29%	26%
MICA*018new	5%	6%	-
MICA*250			7%
MICA*250:01			47%

was observed in a DNA sample from a Filipino donor. As shown in Table 4, this sample was examined several times in the Exchange as sample numbers #078 (2013), #086 (2014), and #205 (2024). In the 2013 and 2014 studies, a single lab reporting by SBT identified the presence of a possible new MICA*018 allele. The lab described the new allele as differing from MICA*018:01 by a single nucleotide substitution in exon 5 at codon 279 (G \rightarrow A), which results in an amino acid change from valine to methionine. In 2024, this DNA sample was retyped once again as sample #205. By this time, the MICA*018:01 variant carried by this sample was now known as MICA*250:01. Eight labs (54%) reporting by NGS reported MICA*250:01 in 2024. MICA*250:01 was accepted to the IPD-IMGT/HLA database in 2022, 9 years after the MICA*018 variant was first identified in the MICA Exchange.

Table 6. MICA*101 standardization, 2016 - 2022

	2016	2021	2022	
	Sample #114	Sample #177	sample #186	
	(n = 17)	(n = 14)	(n = 13)	
VICA*047	100%	36%	23%	
MICA*047/*101	-	7%	8%	
VICA*101	-	57%	69%	

Table 6. DNA from a donor of mixed race (Hispanic/Caucasian) was examined several times in the Exchange as samples #114 (2016), #177 (2021), and #186 (2022). In 2016, MICA*047 was reported by all 17 labs (2 SBT, 2 SSP, 13 SSO). In 2021, however, MICA*047 was only reported by 5 labs (36%), while 8 labs (1 SBT, 7 NGS) (57%) assigned MICA*101. The following year the sample was re-examined again with the percent of labs assigning MICA*101 increasing to 69% (9/13); 8 of the 9 labs assigning MICA*101 indicated NGS as the method type. MICA*101 was accepted to the IPD-IMGT/HLA database in 2020.

Conclusion:

With an increasing number of labs performing NGS, we observed a rise in the average percent assignment of MICA alleles and a drop in the reporting of ambiguities, compared to the early years of the MICA Exchange. However, there is still room for improvement. Only 56% (15/27) of the alleles examined achieved an average percent assignment of > 90%. The UCLA International MICA Exchange continues to provide opportunities for labs to validate their typing kits, to identify limitations in the various typing methods, and to identify new alleles. For these reasons, the MICA Exchange programs is vital to improving the reliability and resolution of MICA genotyping.



For more information regarding the International MICA Exchange or any other proficiency testing programs offered by the UCLA Immunogenetics Center, please visit our website at https://www.uclahealth.org/departments/pathology/research-services/immunogeneticsuic/services-and-pricing/reference-programs.

Acknowledgment:

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Table 5. Identification of new MICA*041 allele

	2016	2020	2022	2024
	Sample #115	Sample #166	sample #190	sample #20
	(n = 17)	((n = 17)	(n = 11)	(n = 16)
MICA*002/*020/*055+	18%	16%		
MICA*002		8%	9%	
MICA*002/*041		15%	18%	13%
MICA*041	82%	61%	45%	62%
MICA*041new			27%	25%

The second new allele, a variant of MICA*041, was from a Hispanic donor. It was first examined in 2016 as sample #115 (Table 5). At the time, 14 labs (82%) assigned MICA*041. The sample was re-examined several more times as samples #166 (2020), #190 (2022), and #207 (2024). In 2022, 3 labs noted sample #190 carried a variant of MICA*041. The variant was described by labs as differing from MICA*041 by a single nucleotide substitution in exon 6 at codon 355.2 (GAT \rightarrow GCT), resulting in an amino acid change from aspartic acid to alanine. These same observations were noted once again 2 years later by 4 labs reporting by NGS in the 2024 study (Exchange 47).

