

SIGNIFICANCE AND DISTRIBUTION OF THE MIC A/B ALLELES AMONG THE WORLDWIDE POPULATIONS

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ABSTRACT

The Major histocompatibility complex chain 1(MIC) genes are recently studied upon their association with various infections, Autoimmune and Inflammatory diseases, various cancers and Graft rejections. The expression of these genes mediates numerous key cellular and immunological pathways. Numerous alleles are reported for these genes across the worldwide populations. This report utilizes the public domain data in effectively analyzing the various MIC allelic distributions in different population subgroups in the light of previous reports and established hypotheses in the context of clinical and population genetics.

KEY WORDS

HLAs, Allele frequencies, Racial Admixture and Genetic predisposition.

1. INTRODUCTION:

Antigen presenting systems such as the Major histocompatibility complex (MHC) are relatively primitive innate immune mechanisms and are conserved across numerous species [1-10]. The human leukocyte antigens (HLAs) are human MHC and are present in the short arm region of Chromosome 6. They are reported to be mediating a plethora of immune regulations. The genetic variations of this region were studied for decades, in respect to tissue transplantation and association with various clinical complications and autoimmune and infectious diseases [11-16]. HLAs are also highly polymorphic and reported to be ethnicity-specific, hence studied in the context of human evolution and ethno-specific susceptibility or resistance towards diseases [17-23].

Another interesting group of genes mapped in the Chromosome 6, called the Major histocompatibility complex class 1 chain-related (MIC) genes (**Figure A**), are recently reported [24], in the similar context as that of HLAs. The MIC comprises MHC class I

polypeptide-related sequence A (MICA) and MHC class I polypeptide-related sequence B (MICB). The sequence of MICA is highly polymorphic with more than 100 identified alleles as reported in <http://www.ebi.ac.uk/ipd/imgt/hla/>.

The products of these genes, the MIC A/B proteins are expressed in the gastrointestinal epithelium [25]. They are ligands to the NKG2D receptor of natural killer (NK) cells and are primarily regulated by the NF- κ B [26,27]. This receptor-ligand interaction result in the production of cytokines and subsequent cytolysis of target cells. The mechanism of shedding of these ligands by the tumour cells, in order to escape cytolysis is an intriguing phenomenon. Hence, various approaches were devised to upregulate the MIC expression in the target cells, which would in turn increase the cytotoxicity in tumors [28].

Recently, the polymorphisms and expression of the MHC class I chain(MICA/B)-related alleles are reported to be associated with various complications such as Psoriasis [29], Ocular toxoplasmosis[30], Behçet's disease [31], Alcoholic

Liver disease [32], Liver fibrosis [33], Ankylosing spondylitis [34], Celiac disease [35], HIV infections [36], Autoimmune diseases[37-39], and importantly, with Graft rejection [40, 41], and numerous cancers[42-47].

Such MIC variations are widely reported in worldwide populations such as Chinese [33, 48, 49, 50], Indian [51], Iranian [52, 53], Swedish [54], Finnish [55], Korean [56, 57], Spanish [58], Bolivian [59], and Algerian [60].

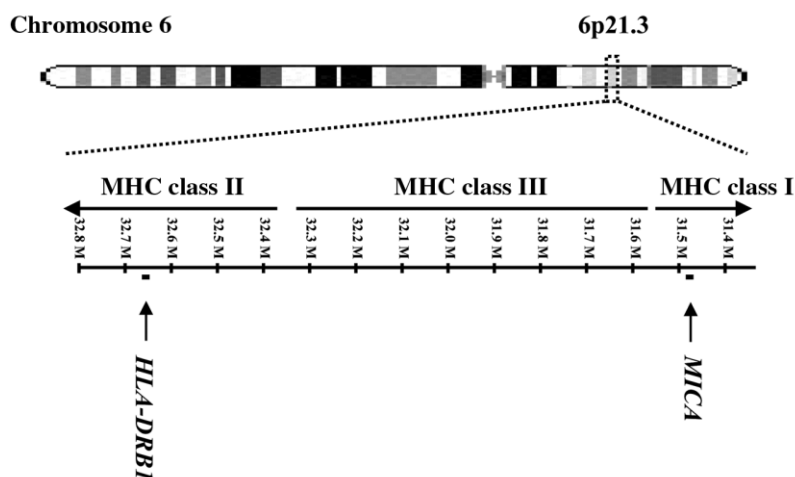


Figure A: Genetic arrangement of the MIC genes within the MHC genes.

2. DATA SELECTION AND ANALYSES:

The allelic frequency data of various MIC genes for around 30 worldwide populations were collected from the public open-access database www.Allelerequencies.net (Tables 1-7). The frequencies of individual alleles to the corresponding populations were calculated using MS-Excel. Neighbor Joining (NJ) Tree (Figure: 32A) and Principal component analysis (PCA) (Figure: 32B) were performed to identify possible clustering among the populations using the PAST (Paleontological statistics) software [61]. Self organizing maps (SOM) were constructed using the unsupervised heuristic approaches to find the presence of possible hidden patterns. For this purpose, we used the R package 'kohonen'[62]. Only informative alleles were considered. 16 nodes (neurons) were used. Number of Iterations=1000. n.hood=Circular. alpha=Guessing statistical parameter (FIGURES:33-61).

3. RESULTS AND DISCUSSION:

All the allelic frequencies of both MICA/B gene (Columns) against the corresponding populations (Rows) are depicted in the matrix plot (Figure

1). According to their class, the alleles were tabulated with their respective populations (Figure 2-29).

In this study, various Asian, South American and African and Afro-American populations are observed to be completely devoid of all the A group (A4-A10) alleles (Figures: 1 and 2-5). The Asian study populations, except the Japanese, comprised the MICB alleles (MICB*001 to MICB*029), which are completely absent in all other world populations (Figures: 1 and 6-13). In addition, the alleles MICA *007:02, MICA *013 and MICA *014 are observed to be totally absent in all the study populations (Figures: 1 and 14-21).

The A5 allele is widely distributed across the various Asian, Middle-East and Southern European populations (Figures: 1 and 2-5). This allele is reported to be associated with Liver fibrosis in Chinese communities [33]. Meanwhile, the Malaysian Chinese community is reported to be susceptible to Nasopharyngeal Carcinoma due to the MICA variations [64].

The MHC SNPs rs76546355, rs2848713, rs76546355 and rs2848713 which are in close proximity with MICA are associated with Behcet's

disease in the Iranian community [52]. In addition, the *MICB* expression is reported to be associated with susceptibility towards Multiple sclerosis in this population [53]. Interestingly, this current study does not indicate any presence of *MICA/B* allelic variations in Iranian population.

The *MICA* *011 allele is reported [59] to be associated with protection against Chronic Chagas Disease among the Bolivian subjects. Even though, this study does not include Bolivian subjects, the neighbor communities could be considered for possible presence of this allele. Evidently, the USA Caucasian population 2, Brazilian, Argentinean and the Spanish Majorca Chueta populations (**Figures: 1 and 18-21**) possess this allele, albeit in low frequencies.

MICA *009 alleles are associated, though in statistically insignificant levels, with Cutaneous malignant melanoma in South eastern Spanish communities [58]. This present study involves the *MICA* *009 alleles with two other subtypes, *MICA* *009:01 and *MICA**009:02. The *MICA* *009 allele is observed in Majorca Chueta Spanish, North East Thais, USA Caucasian population 2 and Japanese populations (**Figures: 1 and 14-17**). Meanwhile, the *MICA* *009:01 allele is found to be in Baotou Han Chinese and various South American populations. It is found in the Brazilian subgroups such as Mato Grosso do Sul Nandeva, Parana Kaingang, Parana Guarani M'byá, Mato Grosso do Sul Kaiowa and Limao Verde- Corrego Reserve Terena, and in the Argentinean subgroups such as Formosa Wichí and Formosa Toba. The Moroccan subgroup Nador Metalsa also has this allele in high frequency (**Figures: 1 and 14-17**). The *MICA**009:02 is observed in the Formosa Toba Argentinean, Moroccan Nador Metalsa Moroccan, Nigerian subgroups such as South Efik and South Yoruba and in the USA Boston Afro-American subgroups (**Figures: 1 and 14-17**). The Baotou Han Chinese is the only Asian community with both *MICA**009:01 and *MICA**009:02.

The allele *MICA* *012:01 is observed only in the Brazilian Parana Kaingang population subgroup (**Figures: 1 and 19**). Meanwhile, the SOMs of both *MICA* *12:01(**Figure: 46**) and *MICA* *16 (**Figure: 48**)

exhibit similar pattern. Another pattern is shared among the alleles *MICA* *17(**Figure: 49**), *MICA**19 (**Figure: 51**), *MICA* *52 (**Figure: 56**) and *MICB* *13(**Figure: 60**). In addition, the alleles *MICB* *02.1.1 (**Figure: 57**) and *MICB* *009N (**Figure: 59**) also exhibit similar SOM pattern.

The *MICA* *027 allele is found to be absent in all populations, but observed only in the Spanish Murcia and various Brazilian and Argentinean communities (**Figures: 1 and 22-25**). One possibility for this interesting distribution (**Figure: 30**) could be the admixture of Spaniards with the South American natives during the discovery of the Americas. The allele *MICA* *046 is observed only among the Morocco Nador Metalsa and Spain Murcia populations (**Figures: 1 and 26-29**). The Morocco Nador Metalsa is also the only population with the *MICA* *035 allele (**Figures: 1 and 27**).

Strikingly, the *MICA* *041 allele is observed only among the native African and Afro-American populations such as Nigerian South Yoruba, USA African-American pop 2, Nigerian South Igbo, Nigerian South Efik and USA Boston African-American (**Figures:1,26-29 and 31**). This allele is observed among no other world populations. This allele seems much restricted to the African ethnicity and not shared among the other populations, despite the 400 years of racial admixture, since the discovery of the New World.

In the PCA analysis, almost all the Asian populations were observed to be clustered together. Also clustered were the groups of Middle-Eastern, Southern European, African and Afro-American and South American populations. Interestingly, the USA Caucasian population (Pop 2) is found to be clustered along with the Asian populations. The ungrouped populations were found to be the Chinese Baotou Han, Spanish Murcia and Spanish Majorca Chueta populations (**Figure 32B**). Almost similar groupings were observed in the NJ tree analysis (**Figure 32A**).

The allele *MICA* *002 is reportedly involved with Ocular Taxoplasmosis [30]. In this study, the *MICA* *02 is observed among the Spanish subgroups such as Murcia, Majorca (high frequencies) and Majorca Chueta, the USA Caucasian pop2 and

Asian communities such as the North East Taiwanese subgroup and the Japanese (**Figures:1 and 14-17**). The allelic subtype *MICA* *002:01 is observed to be widely distributed among the Brazilian subgroups such as Parana Kaingang, Parana Guarani M'byá, Mato Grosso do Sul Kaiowa, Limao Verde and Corrego Reserve Terena, Argentinean communities such as Formosa Wichi, and Formosa Toba, Nigerian subgroups such as South Efik and South Igbo and South Yoruba, Moroccan Nador Metalsa, the USA Boston African American and the USA African American pop 2 (**Figures:1 and 14-17**). Another subtype *MICA* *02:02 is observed among the Baotou Han Chinese and the Mato Grosso do Sul Nandeva Brazilian (high frequencies) subgroups (**Figures:1 and 14-17**).

The allele *MICA* *007 is associated with the elicitation of inflammatory cascade via fibroblasts [37]. An allelic subtype *MICA**007:01 is also implicated in the pathogenesis of Ankylosing Spondylitis in both Caucasian and Chinese subjects [34]. In this study, the *MICA* *007 allele is observed among the Spanish subgroups such as Murcia, Majorca and Majorca Chueta, the USA Caucasian population 2 and the Japanese. The subtype *MICA**007:01 is observed among the Baotou Han Chinese, South American communities such as Mato Grosso do Sul Nandeva Brazilian, and Formosa Wichi Argentinean and the Nador Metalsa Moroccan subgroups (**Figures:1 and 14-17**).

The allele *MICA* *008 is reported to be associated with Inflammatory bowel disease (IBD) and Peripheral Arthropathy [64], Allosensitization in Kidney transplants[41] and fibroblast inflammatory pathways[37]. This current study details the presence of this allele among the Spanish communities such as Murcia, Majorca and Majorca Chueta, North East Thais, USA Caucasian population 2 and the Japanese communities. The subtype, *MICA* *008:01 is observed among the Baotou Han Chinese, Brazilian subgroups such as Mato Grosso do Sul Nandeva, Parana Kaingang, Parana Guarani M'byá, Mato Grosso do Sul Kaiowa

and Limao Verde and Corrego Reserve Terena, Nador Metalsa Moroccan, South Efik Nigerian, Formosa Toba Argentinean and the USA Boston African American communities. Another subtype, *MICA* *008:02- Baotou Han Chinese, USA Boston African American, USA African American population 2 and Nigerian communities such as South Efik, South Yoruba and South Igbo (**Figures:1 and 14-17**).

The allele *MICA* *17 confers protection against HIV infections[36]. This allele is observed among the Spanish subgroups such as Murcia and Majorca Chueta, Nador Metalsa Moroccan, and North East Thais in this study (**Figures:1 and 18-21**).

The allele *MICA**019 is associated with the risk of Ankylosing spondylitis in Chinese populations[34]. This allele is also reportedly associated with the onset of inflammation via fibroblasts[37]. This allele is observed among the Mato Grosso do Sul Nandeva Brazilian, Majorca Chueta Spanish, Nador Metalsa Moroccan, North East Thais and the Japanese communities. Interestingly, no Chinese populations are observed to be possessing this allele in this present study (**Figures: 1 and 18-21**).

4 .LIMITATIONS:

One of the obvious limitations is that the MIC alleles are yet to be reported in larger cohorts in evolutionarily informative populations such as Indian, Scandinavian, Native American, Spanish Basque, Andamanese and Taiwanese, etc. Studies with other minor populations such as Korean, Western European, Turkish and Slavic communities also could facilitate effective inferences. These MIC alleles are reportedly more effective when present as haplotypes with HLAs and other key genes, rather than acting alone. This is the primary limitation of the present study, as it considers only the distribution of MIC alleles alone among the world populations. This analysis is also statistically limited by the different sample numbers of the populations, the allele frequencies were calculated from.

	A4	A5	A5.1	A6	A9	A10
China Baotou Han	0.115	0.293	0.236	0.178	0.139	
China Guangzhou Han	0.132	0.288	0.264	0.146	0.17	
China Hui	0.091	0.307	0.239	0.17	0.193	
China Hunan Province Han	0.147	0.376	0.265	0.076	0.118	0.006
China North Han	0.094	0.281	0.266	0.156	0.203	
China Uygur	0.071	0.163	0.225	0.337	0.204	
Brazil Mato Grosso do Sul Nandeva						
Spain Murcia						
Spain Majorca	0.163	0.069	0.252	0.342	0.171	
Japan Tokyo	0.161	0.292	0.123	0.258	0.166	
Brazil Parana Kaingang						
Spain Majorca Chueta	0.199	0.117	0.16	0.289	0.192	
Greece Athens	0.148	0.111	0.223	0.407	0.111	
Brazil Parana Guarani M'byá						
Brazil Mato Grosso do Sul Kaiowa						
Morocco Nador Metalsa						
Iran Tehran	0.083	0.167	0.167	0.472	0.111	
Italy Rome	0.096	0.212	0.115	0.404	0.173	
Argentina Formosa Wichi						
Thailand North East						
Brazil Limao Verde and Corrego Reserve Terena						
Nigeria South Efik						
Argentina Formosa Toba						
USA Caucasian pop2						
Kazakhstan	0.131	0.237	0.224	0.224	0.184	
USA Boston African American						
Saudi Arabia Riyadh	0.056	0.083	0.222	0.5	0.139	
Japan						
Nigeria South Yoruba						
USA African American pop 2						
Nigeria South Igbo						
China Zhangjiajie Tujias						
China Zhejiang Han						
Thailand North East pop 2						

Table 1: World populations with the respective allele frequency values for *MIC* genes A4 to A10. Blank cells indicate the absence of studied conducted.

	*001	*002	*002:01	*002:02	*004	*005	*006	*007	*007:01	*007:02	*008	*008:01	*008:02	*009	*009:01	*009:02	*010
China Baotou Han		0.12			0.048				0.014			0.231	0.005		0.12	0.005	0.188
China Guangzhou Han																	
China Hui																	
China Hunan Province Han																	
China North Han																	
China Uygur																	
Brazil Mato Grosso do Sul Nandeva	0		0.375	0	0		0		0.011			0.034	0		0.017	0	0.341
Spain Murcia	0.078	0.16			0.149	0.006		0.01			0.25						0.045
Spain Majorca	0.051	0.14			0.176		0.01	0.05			0.29			0.09			0.018
Japan Tokyo																	
Brazil Parana Kaingang	0.002		0.396	0	0.02		0		0	0		0.02	0		0.002	0	0.265
Spain Majorca Chueta	0.005	0.16			0.2		0	0.68			0.17			0.08			0.005
Greece Athens																	
Brazil Parana Guarani M'byá	0		0.215	0	0		0		0	0		0.015	0		0.02	0	0.33
Brazil Mato Grosso do Sul Kaiowa	0		0.641	0	0.003		0		0	0		0.006	0		0.089	0	0.141
Morocco Nador Metalsa	0.03		0.073		0.232				0.024			0.268			0.085	0.14	
Iran Tehran																	
Italy Rome																	
Argentina Formosa Wichi	0		0.476		0				0.012			0			0.012	0	0.19
Thailand North East	0	0.18			0.035			0			0.21			0.02			0.182
Brazil Limao Verde and Corrego Reserve Terena	0		0.445		0				0			0.008			0.023	0	0.172
Nigeria South Efik			0.172		0.219							0.328	0.031				0.078
Argentina Formosa Toba	0.005		0.346		0.011				0			0.01			0.016	0.016	0.277
USA Caucasian pop2	0.03	0.13			0.06		0	0.02			0.55			0.03			0.05
Kazakhstan																	
USA Boston African American			0.3		0.233							0.183	0.075				0.033
Saudi Arabia Riyadh																	
Japan		0.15			0.092			0.01			0.3			0.17			0.108
Nigeria South Yoruba			0.331		0.27							0.142	0.068				0.007
USA African American pop 2			0.256		0.295							0.231	0.051			0	
Nigeria South Igbo			0.424		0.13							0.25	0.011			0	
China Zhangjiajie Tujias																	
China Zhejiang Han																	
Thailand North East pop 2																	

Table 2: World populations with the respective allele frequency values for *MICA* alleles *001 to *010. Blank cells indicate the absence of studied conducted.

	*011	*012	*012:01	*013	*014	*015	*016	*017	*018	*019	*020
China Baotou Han											
China Guangzhou Han											
China Hui											
China Hunan Province Han											
China North Han											
China Uygur											
Brazil Mato Grosso do Sul Nandeva			0			0.01		0	0.06	0.006	0
Spain Murcia						0.03		0.01	0.03		
Spain Majorca											
Japan Tokyo											
Brazil Parana Kaingang	0.008		0.002			0.02	0.02	0	0	0	0.17
Spain Majorca Chueta	0.016	0.084				0	0.09	0.05	0.04	0.021	
Greece Athens											
Brazil Parana Guarani M'byá	0		0			0	0.01	0	0	0	0.01
Brazil Mato Grosso do Sul Kaiowa	0		0			0.01	0	0	0	0	0
Morocco Nador Metalsa	0.03					0.02	0.02	0.02	0.02	0.012	
Iran Tehran											
Italy Rome											
Argentina Formosa Wichi	0		0				0	0	0	0	
Thailand North East	0	0.031					0	0.22	0.06	0.153	0
Brazil Limao Verde and Corrego Reserve Terena	0		0				0	0	0	0	
Nigeria South Efik											
Argentina Formosa Toba	0.005		0				0	0	0	0	
USA Caucasian pop2	0.02	0.02				0	0.02				
Kazakhstan											
USA Boston African American											
Saudi Arabia Riyadh											
Japan	0.127									0.035	
Nigeria South Yoruba											
USA African American pop 2											
Nigeria South Igbo											
China Zhangjiajie Tujias											
China Zhejiang Han											
Thailand North East pop 2											

Table 3: World populations with the respective allele frequency values for *MICA* alleles *011 to *020. Blank cells indicate the absence of studied conducted.

	*021	*022	*023	*024	*025	*026	*027	*029	*30
China Baotou Han									
China Guangzhou Han									
China Hui									
China Hunan Province Han									
China North Han									
China Uygur									
Brazil Mato Grosso do Sul Nandeva				0		0	0.14	0	
Spain Murcia							0.03		
Spain Majorca									
Japan Tokyo									
Brazil Parana Kaingang				0		0	0.01	0	0
Spain Majorca Chueta									
Greece Athens									
Brazil Parana Guarani M'byá				0		0	0.4	0	0
Brazil Mato Grosso do Sul Kaiowa				0		0	0.11	0	0
Morocco Nador Metalsa							0.01		
Iran Tehran									
Italy Rome									
Argentina Formosa Wichi							0.31		
Thailand North East						0.014			
Brazil Limao Verde and Corrego Reserve Terena							0.35		
Nigeria South Efik									
Argentina Formosa Toba							0.31		
USA Caucasian pop2									
Kazakhstan									
USA Boston African American									
Saudi Arabia Riyadh									
Japan									
Nigeria South Yoruba									
USA African American pop 2									
Nigeria South Igbo									
China Zhangjiajie Tujias									
China Zhejiang Han									
Thailand North East pop 2									

Table 4: World populations with the respective allele frequency values for *MICA* alleles *021 to *030. Blank cells indicate the absence of studied conducted.

	*30	*030	*031	*032	*033	*034	*035	*041	*043	*042	*043	*044	*045	*046	*047	*048	*049	*050	*051	*052
China Baotou Han																				
China Guangzhou Han																				
China Hui																				
China Hunan Province Han																				
China North Han																				
China Uygur																				
Brazil Mato Grosso do Sul Nandeva							0	0				0	0	0						0
Spain Murcia					0.01									0.006				0.01		0.006
Spain Majorca																				
Japan Tokyo																				
Brazil Parana Kaingang	0						0	0	0			0	0	0		0				0
Spain Majorca Chueta																				
Greece Athens																				
Brazil Parana Guarani M'byá	0						0	0	0			0	0	0		0				0
Brazil Mato Grosso do Sul Kaiowa	0						0	0	0			0	0	0		0				0
Morocco Nador Metalsa							0.006							0.012						
Iran Tehran																				
Italy Rome																				
Argentina Formosa Wichi																0				
Thailand North East																			0	0.082
Brazil Limao Verde and Corrego Reserve Terena																0				
Nigeria South Efik								0.031												
Argentina Formosa Toba																0				
USA Caucasian pop2																				
Kazakhstan																				
USA Boston African American								0.158												
Saudi Arabia Riyadh																				
Japan																				
Nigeria South Yoruba								0.02												
USA African American pop 2								0.013												
Nigeria South Igbo								0.098												
China Zhangjiajie Tujias																				
China Zhejiang Han																				
Thailand North East pop 2																				

Table 5: World populations with the respective allele frequency values for *MICA* alleles *030 to *052. Blank cells indicate the absence of studied conducted.

	*001	*002	*002:01	*002:01:01	*003	*004	*004:01	*004:01:01	*005:01	*005:02	*005:02:01	*005:03	*005:04	*005:06	*005:07	*005:08	*006	*007	*008	*009N	*010
China Baotou Han																					
China Guangzhou Han																					
China Hui																					
China Hunan Province Han																					
China North Han																					
China Uygur																					
Brazil Mato Grosso do Sul Nandeva																					
Spain Murcia																					
Spain Majorca																					
Japan Tokyo																					
Brazil Parana Kaingang																					
Spain Majorca Chueta																					
Greece Athens																					
Brazil Parana Guarani M'byá																					
Brazil Mato Grosso do Sul Kaiowa																					
Morocco Nador Metalsa																					
Iran Tehran																					
Italy Rome																					
Argentina Formosa Wichi																					
Thailand North East																					
Brazil Limao Verde and Corrego Reserve Terena																					
Nigeria South Efik																					
Argentina Formosa Toba																					
USA Caucasian pop2																					
Kazakhstan																					
USA Boston African American																					
Saudi Arabia Riyadh																					
Japan																					
Nigeria South Yoruba																					
USA African American pop 2																					
Nigeria South Igbo																					
China Zhangjiajie Tujias	0	0	0.249	0.013	0				0	0.396		0.027	0.045				0.003	0.005	0.091	0.019	
China Zhejiang Han			0.123	0.018			0.084				0.574	0.056		0.001	0.003	0.001			0.079	0.009	0.001
Thailand North East pop 2	0.36			0.005	0.123				0	0.384		0.03							0.089		

Table 6: World populations with the respective allele frequency values for *MICB* alleles *001 to *010. Blank cells indicate the absence of studied conducted.

	*011	*012	*013	*014	*016	*018	*019	*023	*024	*026	*027	*028	*029
China Baotou Han													
China Guangzhou Han													
China Hui													
China Hunan Province Han													
China North Han													
China Uygur													
Brazil Mato Grosso do Sul Nandeva													
Spain Murcia													
Spain Majorca													
Japan Tokyo													
Brazil Parana Kaingang													
Spain Majorca Chueta													
Greece Athens													
Brazil Parana Guarani M'byá													
Brazil Mato Grosso do Sul Kaiowa													
Morocco Nador Metalsa													
Iran Tehran													
Italy Rome													
Argentina Formosa Wichi													
Thailand North East													
Brazil Limao Verde and Corrego Reserve Terena													
Nigeria South Efik													
Argentina Formosa Toba													
USA Caucasian pop2													
Kazakhstan													
USA Boston African American													
Saudi Arabia Riyadh													
Japan													
Nigeria South Yoruba													
USA African American pop 2													
Nigeria South Igbo													
China Zhangjiajie Tujias	0	0.003	0	0.102	0.005				0.043				
China Zhejiang Han			0.001	0.039		0.001	0.003	0.001		0.001	0.001	0.004	0.001
Thailand North East pop 2			0.02	0.036									

Table 7: World populations with the respective allele frequency values for *MICB* alleles *011 to *029. Blank cells indicate the absence of studied conducted.

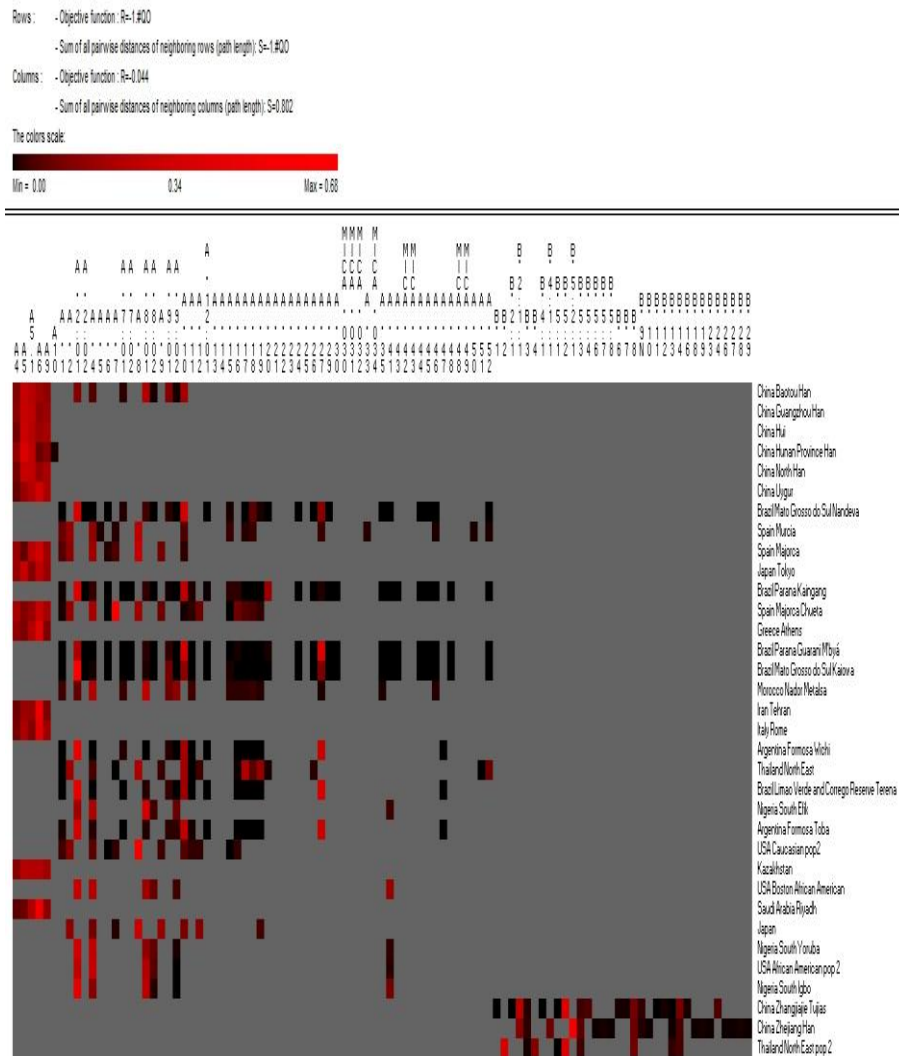


Figure 1: Matrix Plot of the MIC allelic frequencies among the worldwide populations.

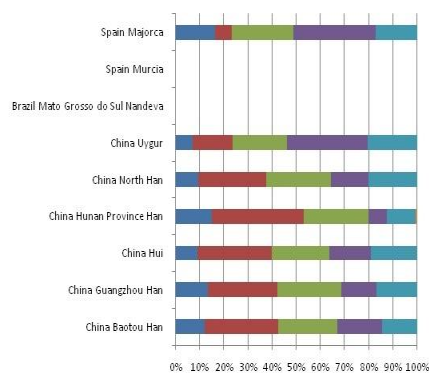


Figure 2

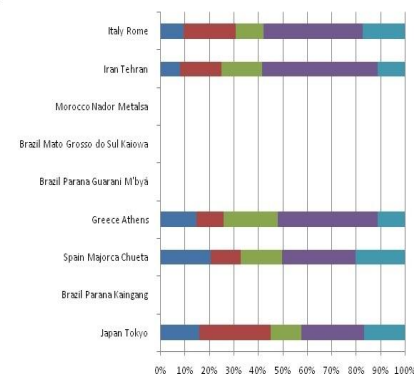


Figure 3

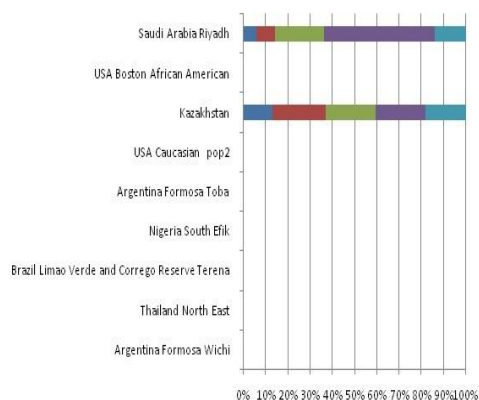


Figure 4

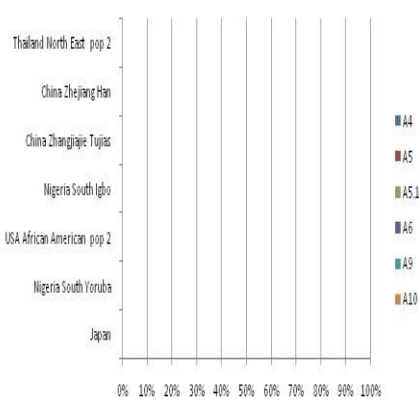


Figure 5

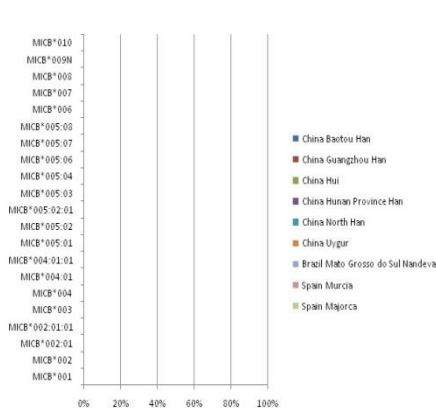


Figure 6

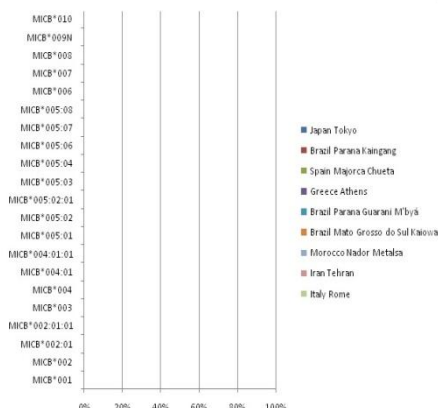


Figure 7

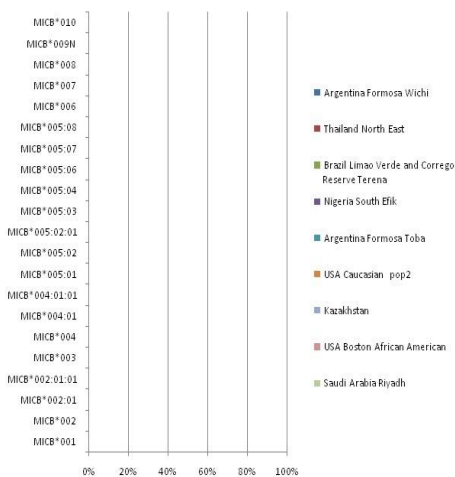


Figure 8

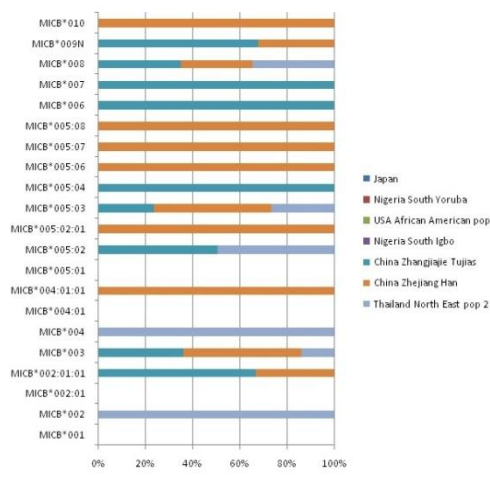


Figure 9

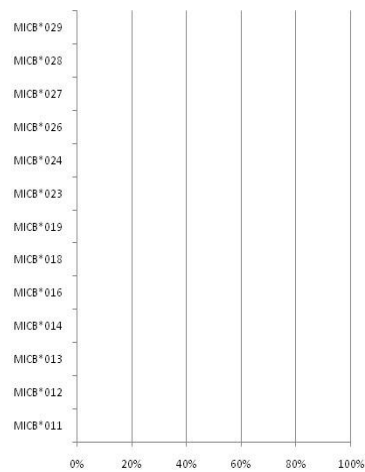


Figure 10

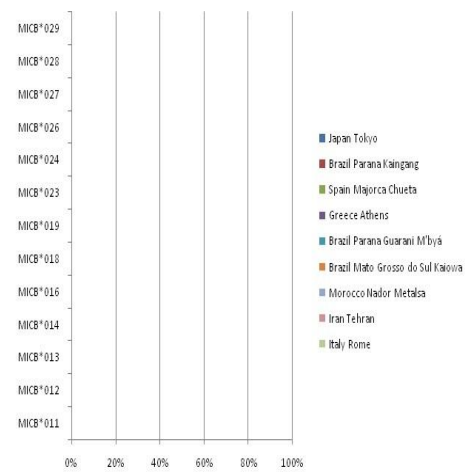


Figure 11

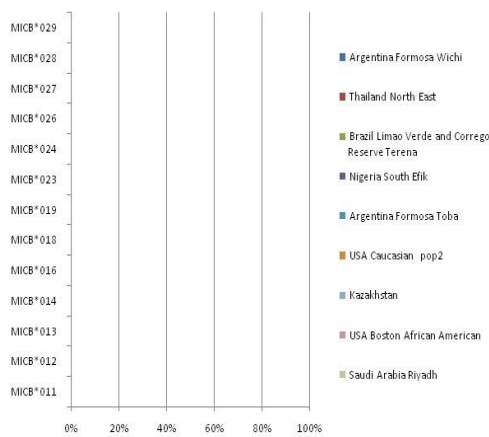


Figure 12

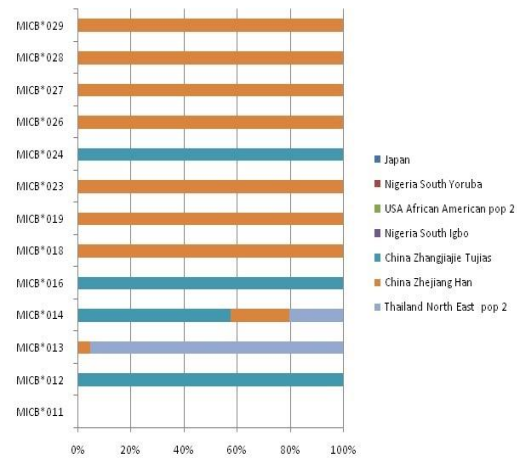


Figure 13

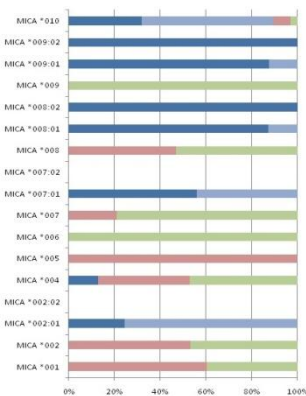


Figure 14

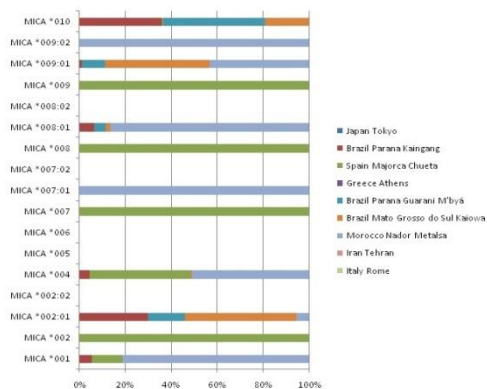
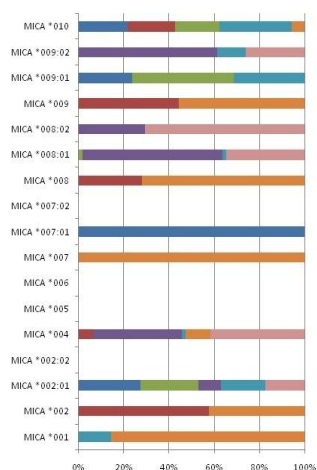
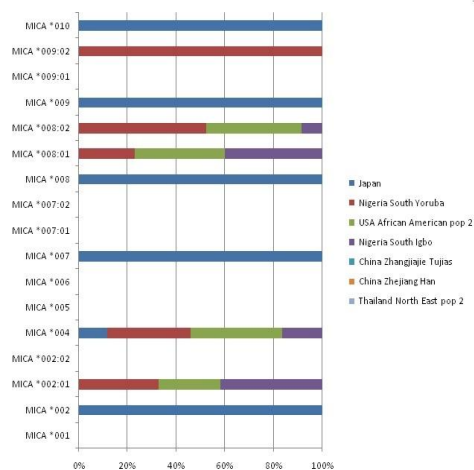
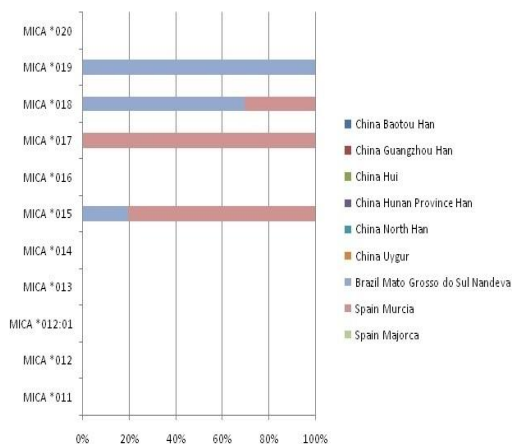
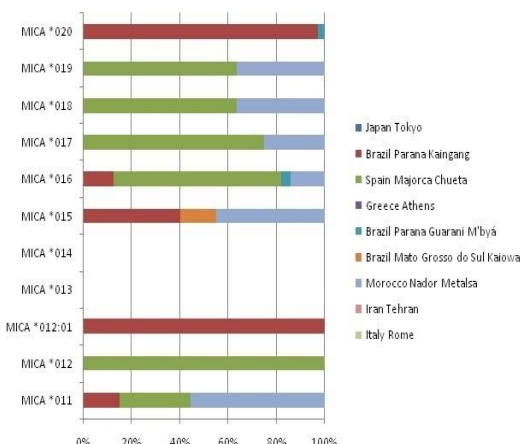
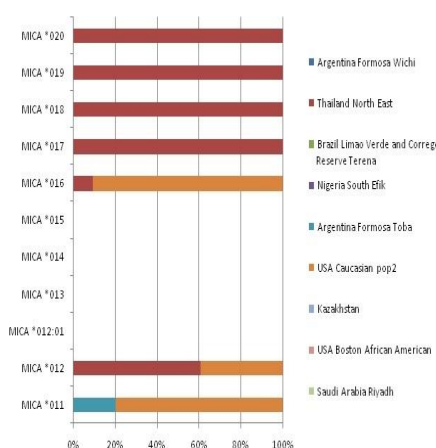
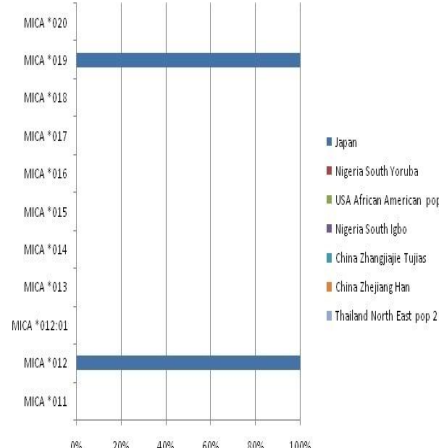


Figure 15


Figure 16

Figure 17

Figure 18

Figure 19

Figure 20

Figure 21

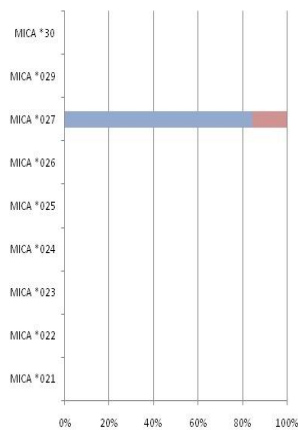


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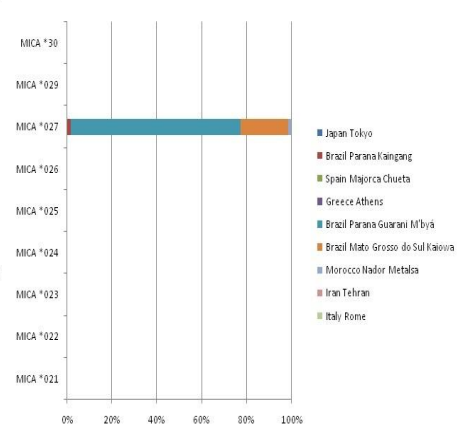


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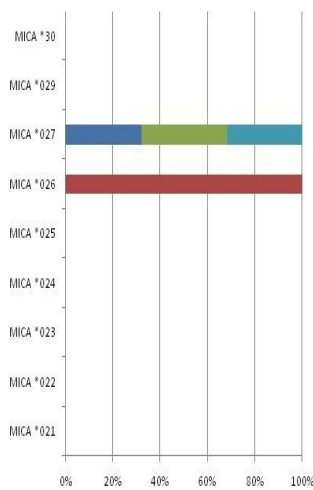


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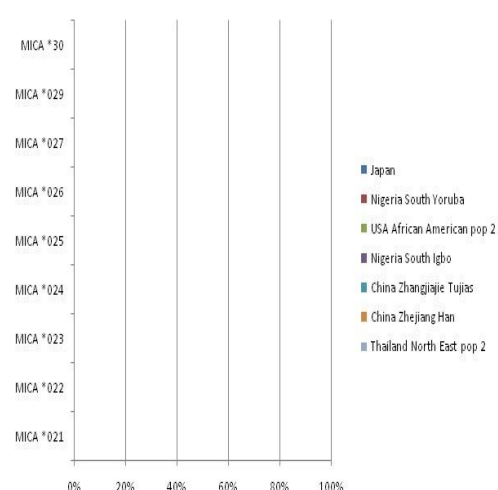


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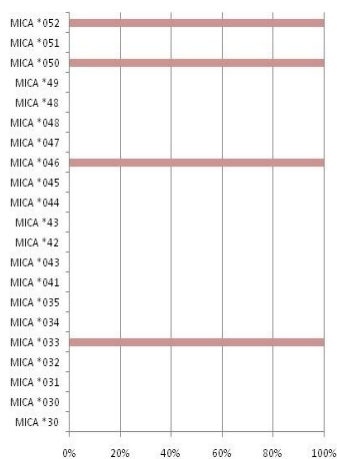


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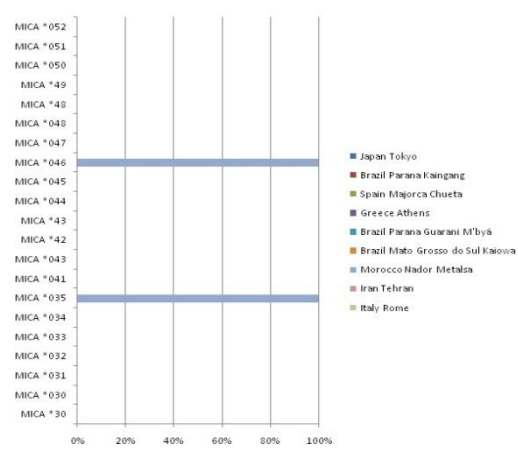


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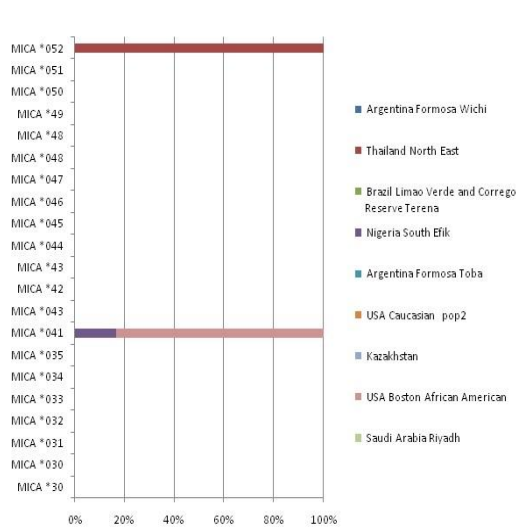


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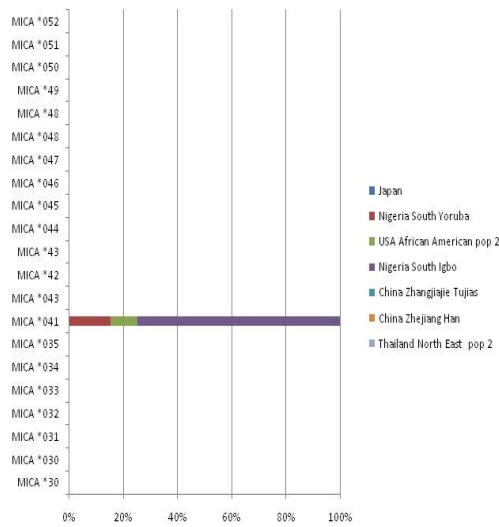


Figure 29


Figure 30: Distribution of the allele *MICA* *027 among the Spanish and South American populations.

Figure 31: Distribution of the allele *MICA* *041 among the populations of African origin.

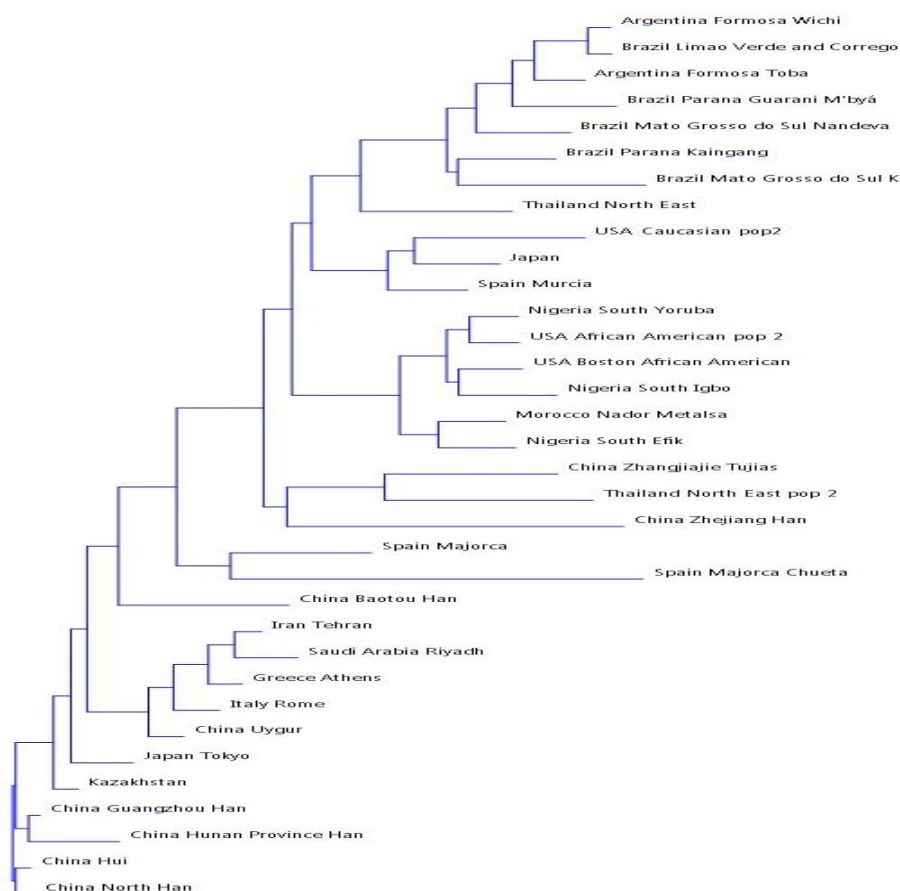


Figure 32a: Neighbor-Joining (NJ)Tree indicating the worldwide populations grouped based on the corresponding MIC A/B allele frequencies.

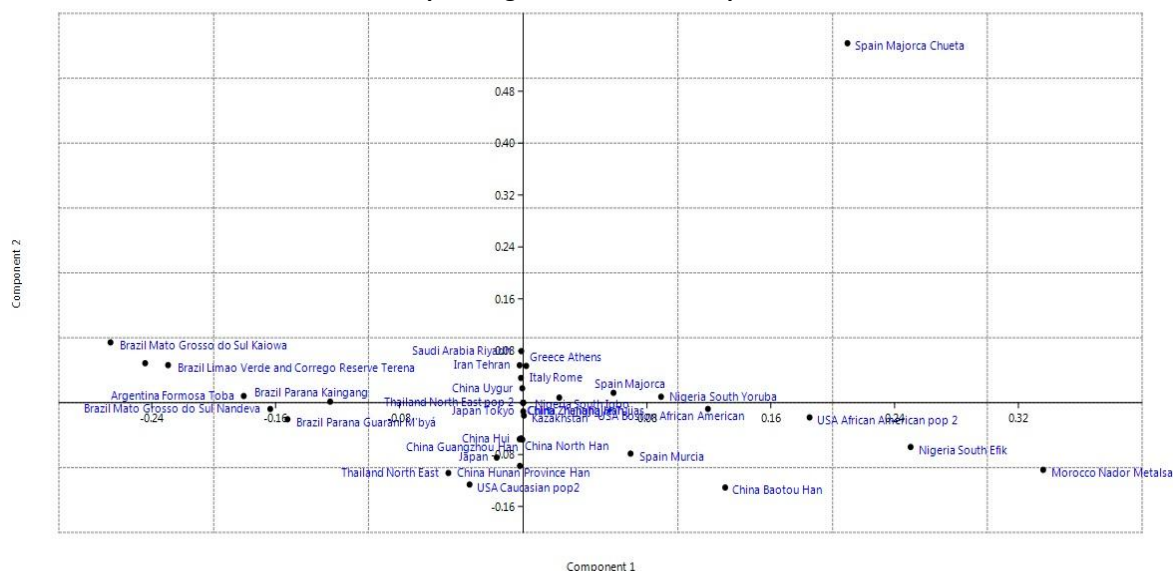


Figure 32b: The Principal component analysis (PCA) graph indicating the worldwide populations clustered based on the corresponding MIC A/B allele frequencies.

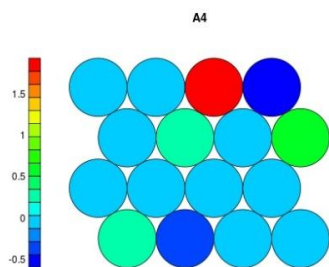


Figure 33

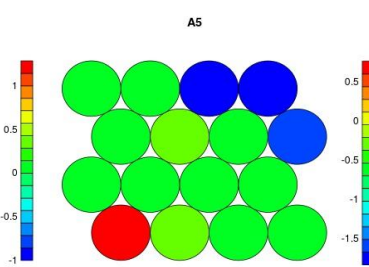


Figure 34

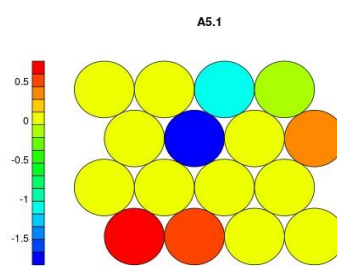


Figure 35

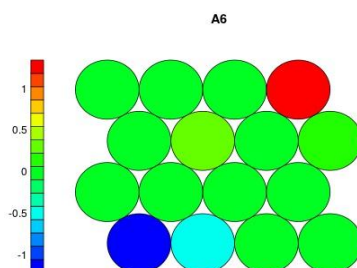


Figure 36

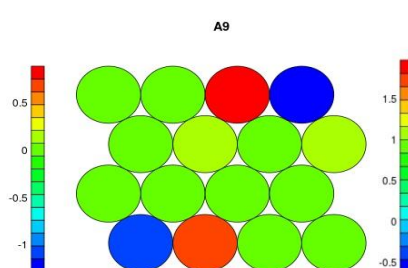


Figure 37

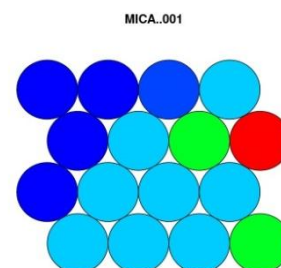


Figure 38

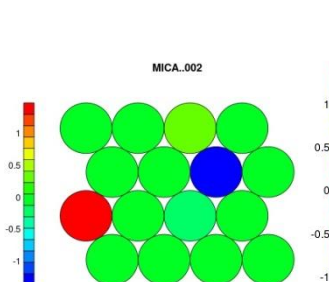


Figure 39

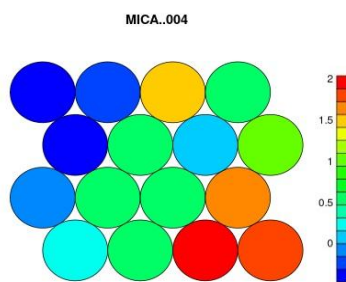


Figure 40

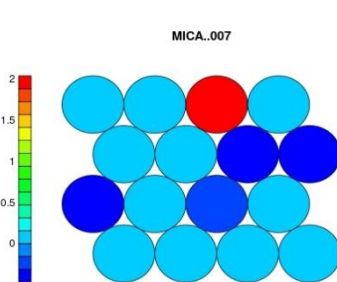


Figure 41

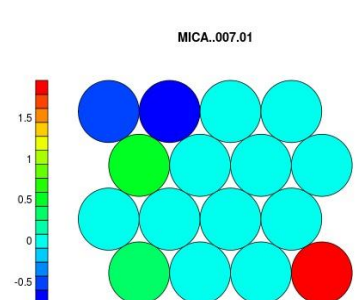


Figure 42

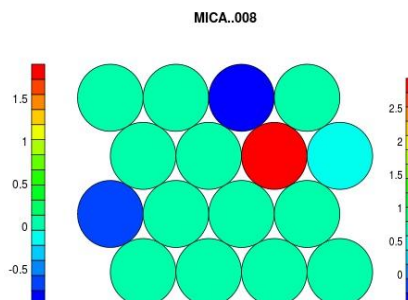


Figure 43

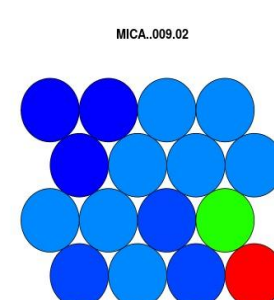


Figure 44

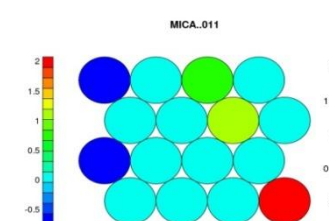


Figure 45

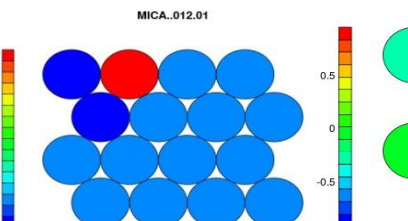


Figure 46

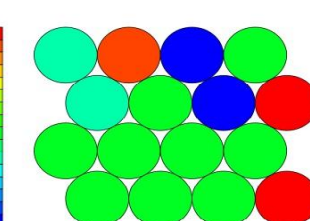


Figure 47

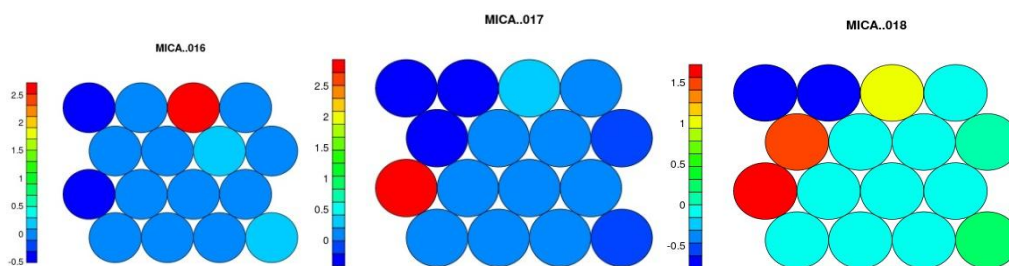


Figure 48

Figure 49

Figure 50

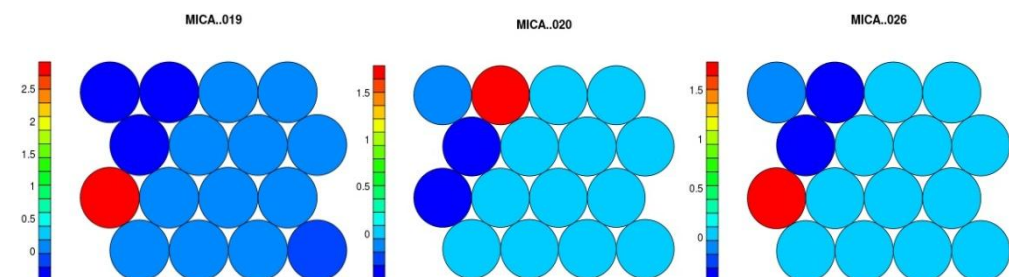


Figure 51

Figure 52

Figure 53

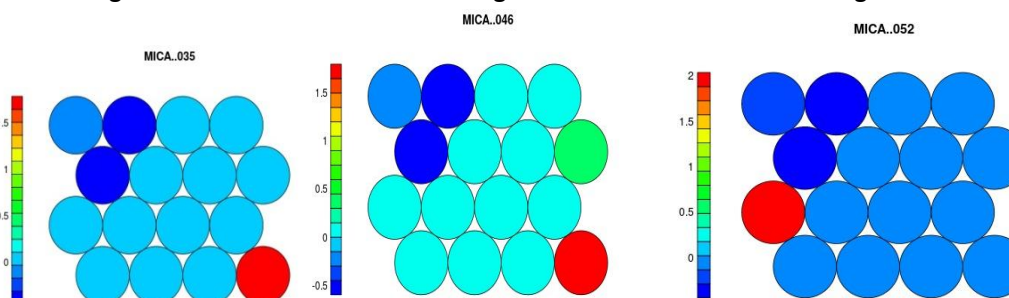


Figure 54

Figure 55

Figure 56

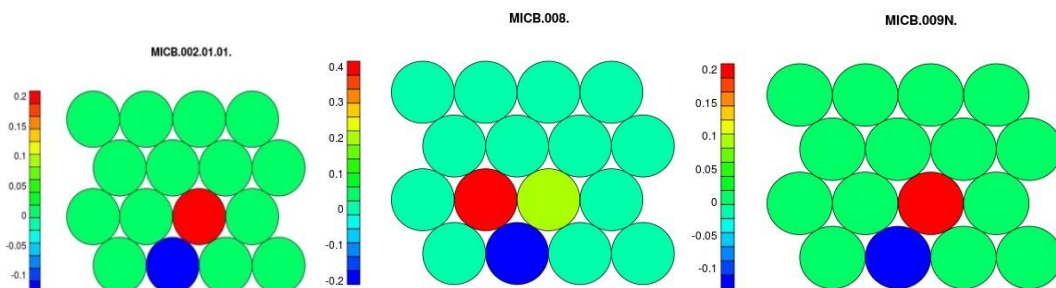


Figure 57

Figure 58

Figure 59

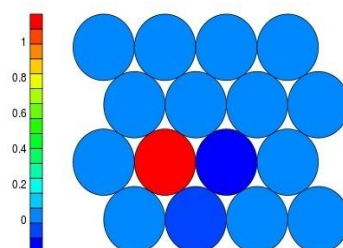


Figure 60

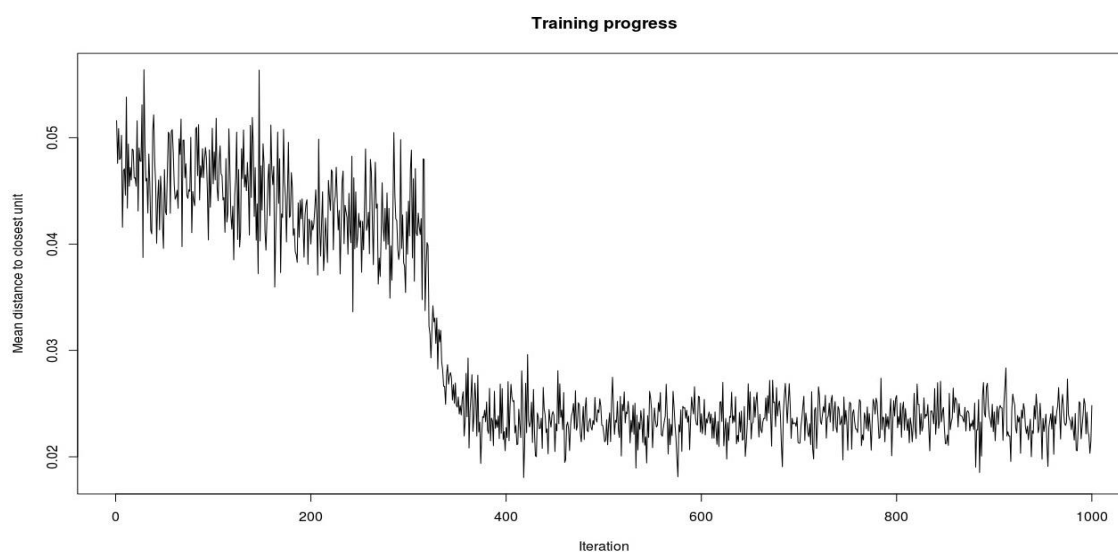


Figure 61: Training graph of the SOM maps.

5. CONCLUSION:

Altogether, this study indicates the possibility of including the MIC genes to be the markers for world-wide populations, in addition to the conventional population-genetic markers such as mtDNAs, HLAs and Y chromosomes. Yet, this study anticipates similar works with different populations, which could give a detailed picture of the distribution of MIC genes worldwide. These results could also complement other studies with genes such as that of HLAs and other markers, to understand the epidemiology of various diseases and importantly of transplantation optimizations.

CONFLICT OF INTERESTS:

The Authors declare no conflict of Interests.

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