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6 MICA: Standardized IMGT allele nomenclature, polymorphisms and diseases

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Abstract

The MICA protein is encoded by the MICA gene localized on chromosome 6 at 6p21.3, in the MHC locus, head-to-head and 46.4 kb centromeric to the HLA-B gene. The MICA protein comprises a transmembrane MHC-I-alpha-like (I-ALPHA-LIKE) chain and belongs to the MHC superfamily (MhcSF), by its groove-like domain made up of two G-LIKE-DOMAINs, and to the immunoglobulin superfamily (IgSF), by its C-LIKE-DOMAIN. In contrast to the MHC-I proteins, the MICA chain has not been found

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associated to the beta-2-microglobulin. The MICA chain is stress-induced and expressed on the basolateral membrane of intestinal epithelium cells and in epithelium-derived tumors, and its receptor is the NKG2D homodimer. We describe MICA genomics, genetics and three-dimensional (3D) data according to the IMGT Scientific chart rules based on the IMGT-ONTOLOGY concepts. This includes standardized IMGT allele names (CLASSIFICATION concept), standardized IMGT labels for the domains and regions (DESCRIPTION concept), standardized amino acid positions according to the IMGT unique numbering (NUMEROTATION concept). We provide two-dimensional (2D) representations or IMGT Colliers de Perles of the MICA G-LIKE-DOMAINs, G-ALPHA1-LIKE and G-ALPHA2-LIKE, based on the IMGT unique numbering for G-DOMAIN and G-LIKE-DOMAIN, and IMGT Colliers de Perles of the MICA C-LIKE-DOMAIN, based on the IMGT unique numbering for C-DOMAIN and C-LIKE-DOMAIN. We provide a standardized description and classification of the MICA alleles, and based on that standardization, a review on the MICA sequence and microsatellite allele frequencies described in the literature in relation with diseases. MICA data are available in the IMGT Repertoire (related proteins of the immune system RPI section) of IMGT, the international ImMunoGeneTics information system®, http://imgt.cines.fr.

Introduction

IMGT, the international ImMunoGeneTics information system®, http://imgt.cines.fr [1,2], created in 1989 at Montpellier, France (Université Montpellier II and CNRS), is the international reference in immuno-informatics and immunoinformatics. IMGT provides a standardized analysis of the immunoglobulins (IG), T cell receptors (TR), major histocompatibility complex (MHC) and related proteins of the immune system (RPI) [1,2]. The RPI section includes the immunoglobulin superfamily (IgSF) proteins other than IG and TR, defined as having at least one V-LIKE-DOMAIN or one C-LIKE-DOMAIN, and the MHC superfamily (MhcSF) proteins other than MHC, defined as having a groove-like domain made up of two G-LIKE-DOMAINs [2]. IMGT data are described according to the IMGT Scientific chart rules based on the IMGT-ONTOLOGY concepts [3]. This includes standardized IMGT gene and allele names (CLASSIFICATION concept), standardized IMGT labels for the receptors, chains, domains and regions (DESCRIPTION concept), standardized amino acid positions according to the IMGT unique numbering (NUMEROTATION concept) [4-8]. By its detailed specific annotations, IMGT is a unique resource of expertise on domains of the IgSF and MhcSF proteins. Two-dimensional (2D)

representations or IMGT Colliers de Perles [5-10] are available for the IgSF domains, based on the IMGT unique numbering for V-DOMAIN and V-LIKE-DOMAIN [5] and on the IMGT unique numbering for C-DOMAIN and C-LIKE-DOMAIN [7], and for the MhcSF domains, based on the IMGT unique numbering for G-DOMAIN and G-LIKE-DOMAIN [8]. By the presence of two G-LIKE-DOMAINs and one C-LIKE-DOMAIN, the MICA protein belongs to both the MhcSF and IgSF.

In this paper, we review the organization of the MICA gene and protein and we provide the IMGT Colliers de Perles of the MICA domains. We provide a standardized description and classification of the MICA genes and alleles and, based on that standardization, a review on the MICA sequence and microsatellite allele frequencies described in the literature in relation with diseases.

1. MICA, a member of the MhcSF and IgSF

MICA (previously designated as PERB11.1) is a member of the « major histocompatibility complex (MHC) class I chain-related genes » or MIC family. In human, six MIC genes were identified, two of them (MICA and MICB) are functional, and four others are pseudogenes.

The MIC genes are highly conserved and are present in most mammals except in rodents [11]. They are localized on chromosome 6 at 6p21.3 in the MHC locus. The MICA gene is located head-to-head and 46.4 kb centrometric to the human leukocyte antigen B (HLA-B) gene [12] (Figure 1). The MICA gene is in a FORWARD orientation, and the HLA-B gene in REVERSE orientation, according to the IMGT concept of ORIENTATION (IMGT Index, http://imgt.cines.fr). The MICB gene is at 70 kb from the MICA gene, centromeric to it, and in the same orientation [11].

The MICA gene encodes a protein that belongs to the MhcSF and to the IgSF. This protein is a transmembrane MHC-I-alpha-like (I-ALPHA-LIKE) chain, which comprises three extracellular domains, two distal G-LIKE-DOMAINs, G-ALPHA1-LIKE [D1] and G-ALPHA2-LIKE [D2], and a C-LIKE-DOMAIN [D3] proximal to the cell membrane, and three regions, a CONNECTING-REGION, a TRANSMEMBRANE-REGION and a CYTOPLASMIC-REGION (labels according to the IMGT Scientific Chart [2], http://imgt.cines.fr). The MICA mature protein is made up of 360 to 366 amino acids owing to a microsatellite polymorphism in the transmembrane region and has a relative molecular mass of about 43kDa [11]. The MICA protein is highly glycosylated with eight potential glycosylation sites, two in G-ALPHA1-LIKE, one in G-ALPHA2-LIKE and five in the C-LIKE-DOMAIN [11].

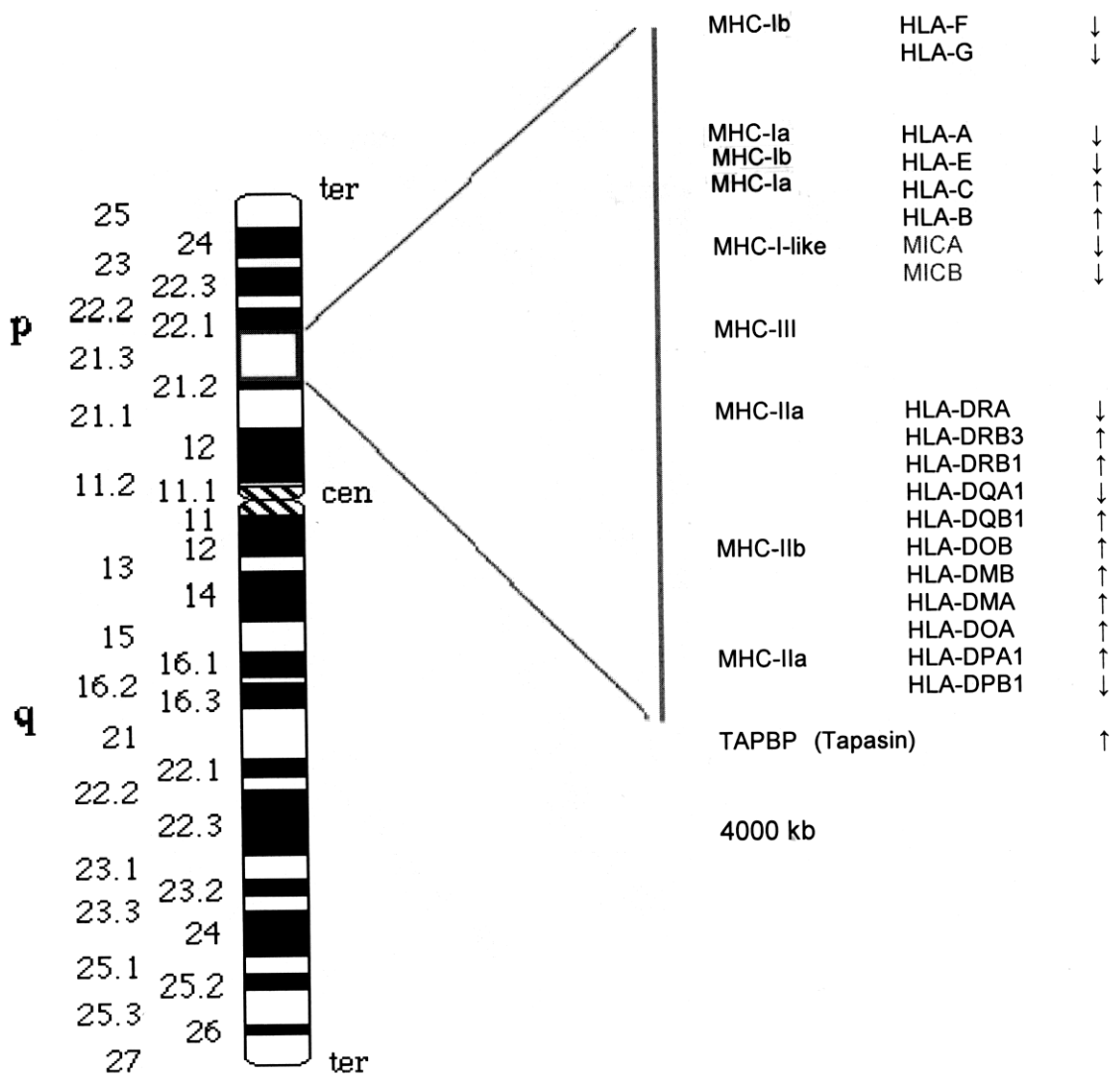

Figure 1. Chromosomal localization of the human MICA gene. The MICA gene is localized on chromosome 6 at band 6p21.3, head-to-head and 46.4 kb centrometric to the HLA-B gene. The MICA gene is in a FORWARD orientation, and the HLA-B gene in REVERSE orientation, according to the IMGT concept of ORIENTATION (IMGT Index, http://imgt.cines.fr). The MICB gene is at 70 kb from the MICA gene, centromeric to it, and in the same orientation [11]. The classical MHC-I (MHC-Ia) and MHC-II (MHC-IIa), the non-classical MHC-I (MHC-Ib) and MHC-II (MHC-IIb) genes are shown. Gene orientation is shown by arrows.

In contrast to the MHC-I proteins, in which the alpha (I-ALPHA) chain is associated to the beta-2-microglobulin (B2M), the MICA I-ALPHA-LIKE chain has not been found associated to B2M. The only identified receptor of MICA in human is the C-type lectin-like activating immunoreceptor NKG2D, a homodimer made of two monomers, designated [A] and [B] (Figure 2).

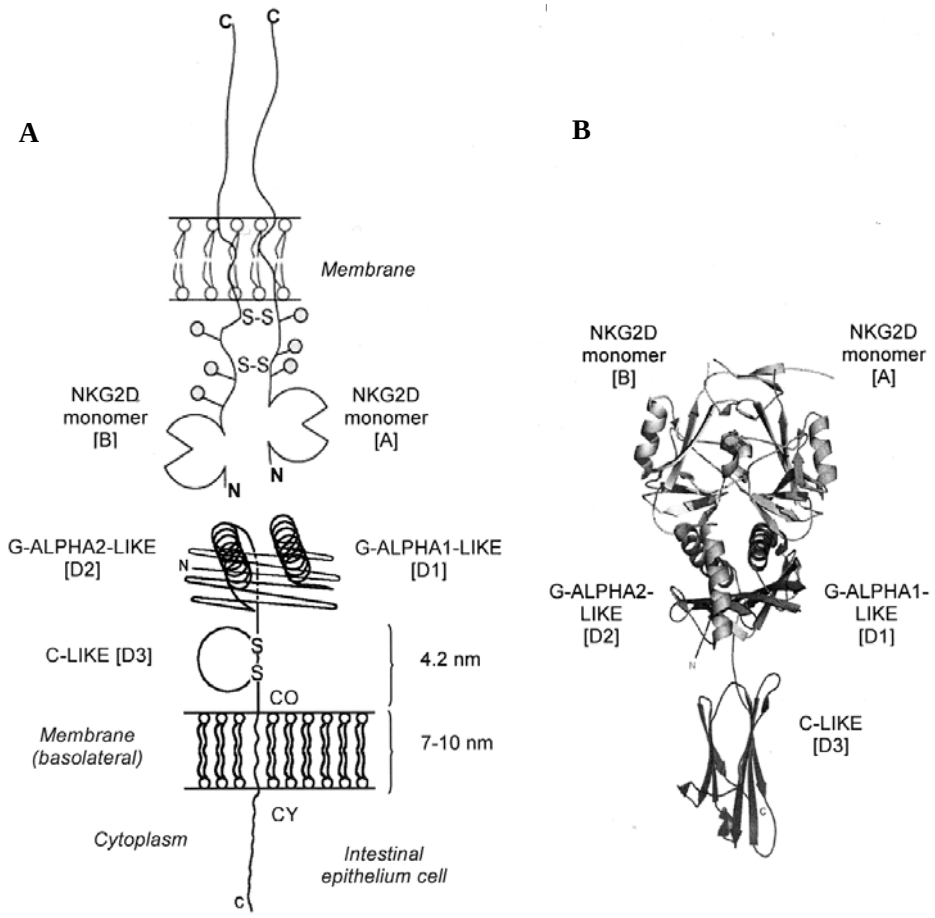

Figure 2. MICA protein with its receptor NKG2D. (A) Schematic representation of the MICA/NKG2D complex. (B) Three-dimensional (3D) structure of the MICA/NKG2D complex (code 1hyr in PDB [116] and in IMGT/3Dstructure-DB, http://imgt.cines.fr [10]). The MICA I-ALPHA-LIKE chain comprise three extracellular domains, the two G-LIKE-DOMAINs, G-ALPHA1-LIKE [D1] and G-ALPHA2-LIKE [D2], that make up the groove, and one C-LIKE-DOMAIN [D3], and three regions, a connecting region (CO), a transmembrane region (TM) and a cytoplasmic region (CY). The three regions are not present in the 3D structure (B). Note that in free MICA (code 1b3j), the C-LIKE-DOMAIN is at an angle of 96 degrees, owing to a great flexibility between [D2] and [D3] [114, 115]. Ribbon representation was obtained with PyMOL (http://pymol.sourceforge.net/). N: N-terminal end, C: C-terminal end, nm: nanometer.

2. MICA gene exon/intron organization

The first complete published genomic sequence of the MICA gene was reported in 1994 [13]. In that sequence, the MICA gene comprises a coding region of 1,155 nucleotides that encodes 385 amino acids (corresponding to the allele *04 (A6), as described later). The complete nucleotide sequence encompasses 11,506 base pairs (bp) from the initiation codon to the stop codon. The MICA exon/intron organisation is similar to that of the MHC class I genes [8], but with only six exons (EX1 to EX6) (Figure 3). The total length

of the six exons vary from 1,149 to 1,167 nucleotides owing to a microsatellite polymorphism by insertion/deletion of nucleotide triplets in EX5. The precursor protein therefore encodes from 383 to 389 amino acids, with a leader-peptide (L-REGION) of 23 amino acids.

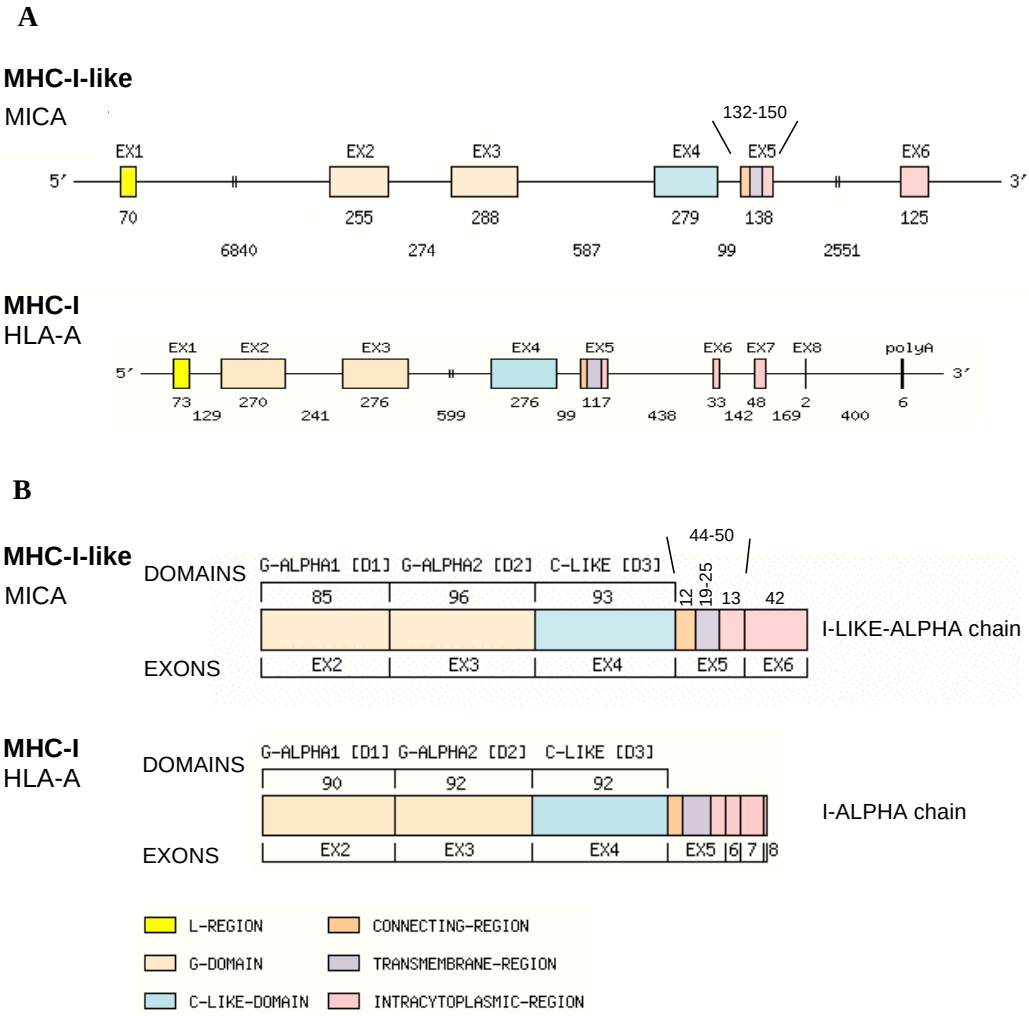

Figure 3. Gene exon/intron organization and correspondence between exons and domains for MICA. (A) Exon/intron organization of the *Homo sapiens* MICA gene (this paper) and, for comparison, of the HLA-A gene [8]. Intron and exon lengths are in base pairs (bp) (EMBL/GenBank/DDBJ accession numbers, MICA*04 (A6) X92841 [13], HLA-A K02883). Introns indicated with ⎮⎮ are not at scale. (B) Domains of the *Homo sapiens* MICA I-LIKE-ALPHA chain (this paper) and, for comparison, domains of the HLA-A I-ALPHA chain [8]. Lengths of the domains are in number of amino acids. In MICA, EX2 and EX3 encode the G-ALPHA1-LIKE [D1] and G-ALPHA2-LIKE [D2] domains [8], respectively. EX4 encodes the C-LIKE-DOMAIN [D3] [7]. The length of the EX5 (132 to 150 bp, 44 to 50 amino acids) depends on the polymorphism of a microsatellite in the transmembrane region of EX5 [15] (see section 6.1). A length of 138 bp for EX5 (46 amino acids) corresponds to an A6 allele. Colors are according to IMGT Color menu for regions and domains (http://imgt.cines.fr).

A

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   1 atgggctgg gcccggtctt cctgcttctg gctggcatct tccctttgc acctccggga
  61 gctgctgctg agccccacag tcttcgttat aacctcacgg tgctgtcctg ggatggatct
 121 gtgcagtcag ggtttctcac tgaggtacat ctggatggtc agcccttcct gcgctgtgac
 181 aggcagaaat gcagggcaaa gccccaggga cagtgggcag aagatgtcct gggaaataag
 241 acatgggaca gagagaccag agacttgaca gggaacggaa aggacctcag gatgaccctg
 301 gctcatatca aggaccagaa agaaggcttg cattccctcc aggagattag ggtctgtgag
 361 atccatgaag acaacagcac caggagctcc cagcatttct actacgatgg ggagctcttc
 421 ctctcccaaa acctggagac taaggaatgg acaatgcccc agtcctccag agctcagacc
 481 ttggccatga acgtcaggaa tttcttgaag gaagatgcca tgaagaccaa gacacactat
 541 cacgctatgc atgcagactg cctgcaggaa ctacggcgat atctaaaatc cggcgtagtc
 601 ctgaggagaa cagtgccccc catggtgaat gtcacccgca gcgaggcctc agagggcaac
 661 attaccgtga catgcagggc ttctggcttc tatccctgga atatcacact gagctggcgt
 721 caggatgggg tatctttgag ccacgacacc cagcagtggg gggatgtcct gcctgatggg
 781 aatggaacct accagacctg ggtggccacc aggatttgcc aaggagagga gcagaggttc
 841 acctgctaca tggaacacag cgggaatcac agcactcacc ctgtgccctc tgggaaagtg
 901 ctggtgcttc agagtcattg gcagacattc catgtttctg ctgttgctgc tgctgctatt
 961 tttgttatta ttattttcta tgtccgttgt tgtaagaaga aaacatcagc tgcagagggt
1021 ccagagctcg tgagcctgca ggtcctggat caacacccag ttgggacgag tgaccacagg
1081 gatgccacac agctcggatt tcagcctctg atgtcagatc ttgggtccac tggctccact
1141 gagggcgcct ag
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B

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   1 MGLGPVFLLL AGIFPFAPPG AAAEPHSLRY NLTVLSWDGS VQSGFLTEVH LDGQPFLRCD
  61 RQKCRAKPQG QWAEDVLGNK TWDRETRDLT GNGKDLRMTL AHIKDQKEGL HSLQEIRVCE
 121 IHEDNSTRSS QHFYYDGELF LSQNLETKEW TMPQSSRAQT LAMNVRNFLK EDAMKTKTHY
 181 HAMHADCLQE LRRYLKSGVV LRRTVPPMVN VTRSEASEGN ITVTCRASGF YPWNITLSWR
 241 QDGVSLSHDT QQWGDVLPDG NGTYQTWVAT RICQGEEQRF TCYMEHSGNH STHPVPSGKV
 301 LVLQSHWQTF HVSAVAAAAI FVIIIFYVRC CKKKTSAAEG PELVSLQVLD QHPVGTSDHR
 361 DATQLGFQPL MSDLGSTGST EGA★
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Figure 4. Coding region sequence of MICA*01 (A4). (A) Nucleotide sequence. (B) Deduced amino acid sequence. The nucleotide sequence of MICA*01 (A4) was extracted from the accession number L14848 sequence in the EMBL/GenBank/DDBJ databases). The amino acid sequence is the translation of the nucleotide sequence. The CODING-REGION starts from the initiation codon INIT-CODON ATG (encoding the amino acid Methionine, M) and ends to the STOP-CODON TAG (not included and indicated with an asterisk in (B)). The last nucleotide of each exon in (A) and the amino acids resulting from the splicing in (B) are in bold and purple (the five splicing sites are of the codon_start3 type, IMGT Aide-mémoire, http://imgt.cines.fr). The eight N-glycosylation sites (and the corresponding codons) are underlined. The four Alanine of the A4 microsatellite allele (and the corresponding GCT codons) are double-underlined. Depending on the alleles, the number of Alanine (and codons GCT) varies from four to ten (microsatellite alleles or STR alleles A4 to A10) (see section 6.1). Colors are according to the IMGT color menu for regions and domains (http://imgt.cines.fr).

The first exon EX1 (70 bp) that encodes the L-REGION is followed by an unusually large intron of 6,840 bp. EX2 (255 bp) and EX3 (288 bp) encode the extracellular G-ALPHA1-LIKE (85 amino acids) and G-ALPHA2-LIKE (96 amino acids), respectively, and are separated by an intron of 274 bp. EX4 (279 bp) encodes the extracellular C-LIKE-DOMAIN (93 amino acids) and is preceded by an intron of 587 bp and followed by an intron of 99 bp. The delimitation of the three extracellular domains, G-ALPHA1-LIKE [D1], G-ALPHA2-LIKE [D2] and C-LIKE-DOMAIN [D3], is based on the limits of the corresponding exons, EX2, EX3 and EX4, respectively. The EX5 length varies from 132 to 150 bp (44 to 50 amino acids), depending on a microsatellite polymorphism that corresponds to the presence of 4 to 10 GCT triplets encoding 4 to 10 Alanine (microsatellite alleles A4 to A10) (see section 6.1). EX5 encodes a CONNECTING-REGION of 12 amino acids, a TRANSMEMBRANE-REGION of 19 to 25 amino acids depending on the microsatellite alleles and an INTRACYTOPLASMIC-REGION of 13 amino acids. It is followed by a large intron of 2,551 bp. EX6 (125 bp) encodes an INTRACYTOPLASMIC-REGION of 42 amino acids and is followed by an 3' untranslated (3'UTR) sequence. The MICA*01 (A4) sequence, from the initiation codon ATG to the stop codon TAG, and the deduced amino acid sequence are shown in Figure 4 with the domain and region delimitations, according to the standardized rules of the IMGT Scientific Chart [2].

3. MICA domains and IMGT Colliers de Perles

IMGT Colliers de Perles are IMGT standardized two-dimensional (2D) graphical representations [5-10]. The IMGT Colliers de Perles for the MICA G-LIKE-DOMAINs, G-ALPHA1-LIKE and G-ALPHA2-LIKE (Figure 5), are based on the IMGT unique numbering for G-DOMAIN and G-LIKE-DOMAIN [8]. Correspondence between the IMGT unique numbering for the MICA G-ALPHA1-LIKE and G-ALPHA2-LIKE domains and the numbering of these domains in the mature MICA I-ALPHA chain is given in Table 1A. Each MICA G-LIKE-DOMAIN, G-ALPHA1-LIKE and G-ALPHA2-LIKE (Figure 5), includes a sheet of four antiparallel beta strands ("floor" of the groove or platform) and a long helical region ("wall" of the groove). The floor of the two domains are structurally similar with the A-STRAND of fourteen amino acids (positions 1 to 14), the AB-TURN of three [D1] or two [D2] amino acids (positions 15 to 17, 17 being unoccupied in G-ALPHA2-LIKE), the B-STRAND of eleven amino acids (positions 18 to 28), the BC-TURN of two amino acids (positions 29 and 30), the C-STRAND of eight amino acids (positions 31 to 38), the CD-TURN of one amino acid (positions 39 to 41, 40 and 41 being unoccupied), the D-STRAND of eight amino acids in G-ALPHA1-LIKE (positions 42 to 49) and thirteen amino acids in G-ALPHA2-LIKE owing to five additional positions (49.1-49.5) (Table 2A and Figure 5).

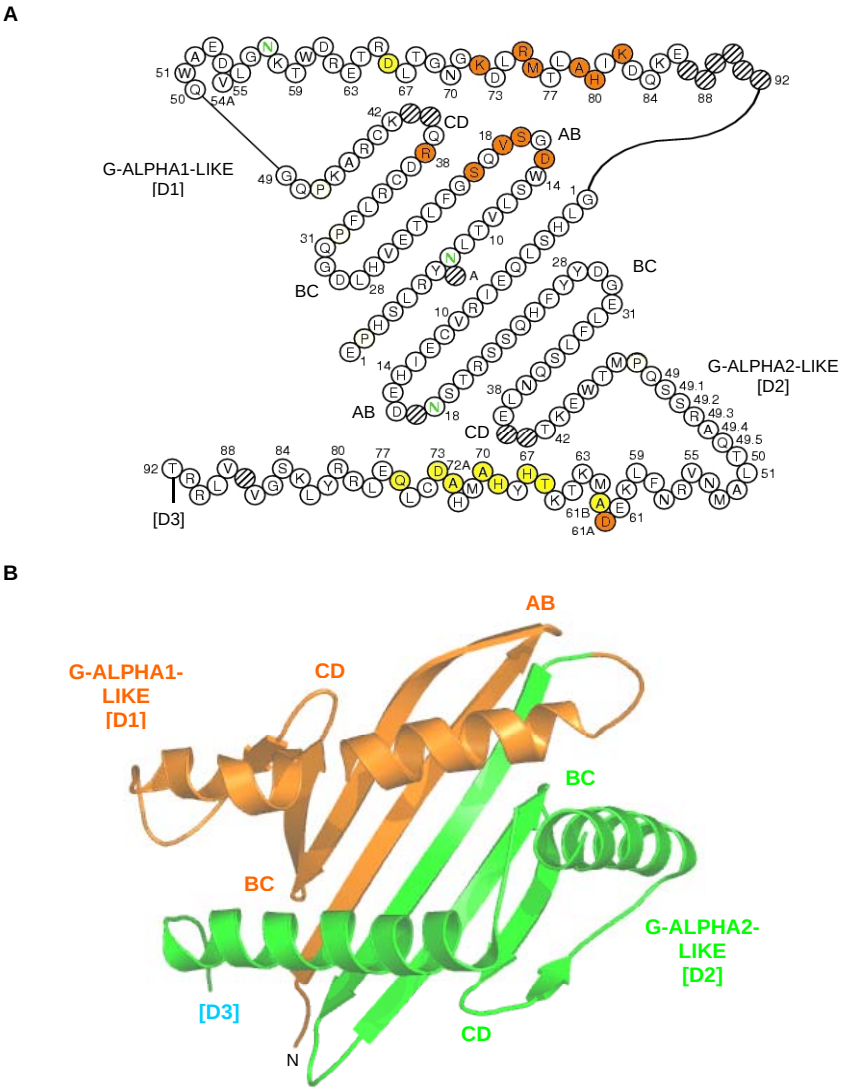


Figure 5. IMGT Colliers de Perles and 3D structure of the MICA G-ALPHA1-LIKE and G-ALPHA2-LIKE domains. (A) IMGT Colliers de Perles. The G-ALPHA1-LIKE domain (85 amino acids) comprises a groove floor of 47 amino acids and an helix of 38 amino acids. The G-ALPHA2-LIKE domain (96 amino acids) comprises a groove floor of 51 amino acids and an helix of 45 amino acids. MICA amino acids that interact with NKG2D [A] are in orange. MICA amino acids that interact with NKG2D [B] are in yellow. MICA [D1] amino acids have contacts with the NKG2D [A] monomer, except for MICA [D1] D66 that creates a salt bridge with NKG2D [B] K197. MICA [D2] amino acids have contacts with the NKG2D [B] monomer, except for MICA [D2] D61A that creates a salt bridge with NKG2D [A] K197. Amino acid numerotation is according to the IMGT unique numbering for G-DOMAIN and G-LIKE-DOMAIN [8]. Hatched circles correspond to missing positions according to that numbering. Asparagine (N) that belong to potential N-glycosylation sites are in green (N8 and N57 in [D1], N18 in [D2]). (B) Three-dimensional (3D) structure. G-ALPHA1-LIKE [D1] is orange, G-ALPHA2-LIKE [D2] domain is green. Code 1hyr from PDB [116] and from IMGT/3Dstructure-DB [10] (http://imgt.cines.fr). Ribbon representation was obtained with PyMOL (http://pymol.sourceforge.net/). The breaks in the helices correspond to disordered regions in free MICA (discussed in section 4 for the G-ALPHA2-LIKE helix).

Table 1. IMGT numbering for the MICA domains. Correspondence, for [D1] and [D2], with the mature chain numbering (A), and for [D3], with the exon numbering (B).

A - MICA G-ALPHA1-LIKE [D1] and G-ALPHA2-LIKE [D2] domains

IMGT labels	IMGT unique numbering for G-DOMAIN and G-LIKE-DOMAIN [8]	MICA*01	
		G-ALPHA1-LIKE [D1] domain	G-ALPHA2-LIKE [D2] domain
A-STRAND	**1**	1 (g)ag (GLU) (E)	86 (g)gc (GLY) (G)
	2	2 ccc PRO P	87 ttg LEU L
	3	3 cac HIS H	88 cat HIS H
	4	4 agt SER S	89 tcc SER S
	5	5 ctt LEU L	90 ctc LEU L
	6	6 cgt ARG R	91 cag GLN Q
	7	7 tat TYR Y	92 gag GLU E
	7A	--- --- -	--- --- -
	8	8 aac ASN N	93 att ILE I
	9	9 ctc LEU L	94 agg ARG R
	10	10 acg THR T	95 gtc VAL V
	11	11 gtg VAL V	96 tgt CYS C
	12	12 ctg LEU L	97 gag GLU E
	13	13 tcc SER S	98 atc ILE I
	14	14 tgg TRP W	99 cat HIS H
AB-TURN	**15**	15 gat ASP D	100 gaa GLU E
	16	16 gga GLY G	101 gac ASP D
	17	17 tct SER S	--- --- -
B-STRAND	**18**	18 gtg VAL V	102 aac ASN N
	19	19 cag GLN Q	103 agc SER S
	20	20 tca SER S	104 acc THR T
	21	21 ggg GLY G	105 agg ARG R
	22	22 ttt PHE F	106 agc SER S
	23	23 ctc LEU L	107 tcc SER S
	24	24 act THR T	108 cag GLN Q
	25	25 gag GLU E	109 cat HIS H

Table 1. Continued

	26	26 gta VAL V	110 ttc PHE F
	27	27 cat HIS H	111 tac TYR Y
	28	28 ctg LEU L	112 tac TYR Y
BC-TURN	**29**	29 gat ASP D	113 gat ASP D
	30	30 ggt GLY G	114 ggg GLY G
C-STRAND	**31**	31 cag GLN Q	115 gag GLU E
	32	32 ccc PRO P	116 ctc LEU L
	33	33 ttc PHE F	117 ttc PHE F
	34	34 ctg LEU L	118 ctc LEU L
	35	35 cgc ARG R	119 tcc SER S
	36	36 tgt CYS C	120 caa GLN Q
	37	37 gac ASP D	121 aac ASN N
	38	38 agg ARG R	122 ctg LEU L
CD-TURN	**39**	39 cag GLN Q	123 gag GLU E
	40	--- --- -	--- --- -
	41	--- --- -	--- --- -
D-STRAND	**42**	40 aaa LYS K	124 act THR T
	43	41 tgc CYS C	125 aag LYS K
	44	42 agg ARG R	126 gaa GLU E
	45	43 gca ALA A	127 tgg TRP W
	46	44 aag LYS K	128 aca THR T
	47	45 ccc PRO P	129 atg MET M
	48	46 cag GLN Q	130 ccc PRO P
	49	47 gga GLY G	131 cag GLN Q
	49.1	--- --- -	132 tcc SER S
	49.2	--- --- -	133 tcc SER S
	49.3	--- --- -	134 aga ARG R
	49.4	--- --- -	135 gct ALA A
	49.5	--- --- -	136 cag GLN Q
Helix	**50**	48 cag GLN Q	137 acc THR T
	51	49 tgg TRP W	138 ttg LEU L

Table 1. Continued

	52	50 gca ALA A	139 gcc ALA A
	53	51 gaa GLU E	140 atg MET M
	54	52 gat ASP D	141 aac ASN N
	54A	53 gtc VAL V	--- --- -
	55	54 ctg LEU L	142 gtc VAL V
	56	55 gga GLY G	143 agg ARG R
	57	56 aat ASN N	144 aat ASN N
	58	57 aag LYS K	145 ttc PHE F
	59	58 aca THR T	146 ttg LEU L
	60	59 tgg TRP W	147 aag LYS K
	61	60 gac ASP D	148 gaa GLU E
	61A	--- --- -	149 gat ASP D
	61B	--- --- -	150 gcc ALA A
	62	61 aga ARG R	151 atg MET M
	63	62 gag GLU E	152 aag LYS K
	64	63 acc THR T	153 acc THR T
	65	64 aga ARG R	154 aag LYS K
	66	65 gac ASP D	155 aca THR T
	67	66 ttg LEU L	156 cac HIS H
	68	67 aca THR T	157 tat TYR Y
	69	68 ggg GLY G	158 cac HIS H
	70	69 aac ASN N	159 gct ALA A
	71	70 gga GLY G	160 atg MET M
	72	71 aag LYS K	161 cat HIS H
	72A	--- --- -	162 gca ALA A
	73	72 gac ASP D	163 gac ASP D
	74	73 ctc LEU L	164 tgc CYS C
	75	74 agg ARG R	165 ctg LEU L
	76	75 atg MET M	166 cag GLN Q
	77	76 acc THR T	167 gaa GLU E
	78	77 ctg LEU L	168 cta LEU L

Table 1. Continued

	79	78 gct ALA A	169 cgg ARG R
	80	79 cat HIS H	170 cga ARG R
	81	80 atc ILE I	171 tat TYR Y
	82	81 aag LYS K	172 cta LEU L
	83	82 gac ASP D	173 aaa LYS K
	84	83 cag GLN Q	174 tcc SER S
	85	84 aaa LYS K	175 ggc GLY G
	86	85 gaa GLU E	176 gta VAL V
	87	--- --- -	--- --- -
	88	--- --- -	177 gtc VAL V
	89	--- --- -	178 ctg LEU L
	90	--- --- -	179 agg ARG R
	91	--- --- -	180 aga ARG R
	92	--- --- -	181 aca THR T
	92A	--- --- -	--- --- -

B - MICA C-LIKE-DOMAIN [D3]

IMGT labels	IMGT unique numbering for C-DOMAIN and C-LIKE DOMAIN [7]	MICA*01 C-LIKE-DOMAIN [D3] (exon numbering)
A-STRAND	**1.1**	1 (g)tg (VAL) (V)
	1	2 ccc PRO P
	2	3 ccc PRO P
	3	4 atg MET M
	4	5 gtg VAL V
	5	6 aat ASN N
	6	7 gtc VAL V
	7	8 acc THR T
	8	9 cgc ARG R
	9	10 agc SER S

Table 1. Continued

	10	11 gag GLU E
	11	12 gcc ALA A
	12	13 tca SER S
	13	14 gag GLU E
	14	--- --- -
	15	--- --- -
AB-TURN	**15.1**	--- --- -
	15.2	--- --- -
	15.3	--- --- -
B-STRAND	**16**	--- --- -
	17	15 ggc GLY G
	18	16 aac ASN N
	19	17 att ILE I
	20	18 acc THR T
	21	19 gtg VAL V
	22	20 aca THR T
	23	21 tgc CYS C
	24	22 agg ARG R
	25	23 gct ALA A
	26	24 tct SER S
BC-LOOP	**27**	25 ggc GLY G
	28	26 ttc PHE F
	29	27 tat TYR Y
	30	28 ccc PRO P
	31	--- --- -
	32	--- --- -
	33	29 tgg TRP W
	34	30 aat ASN N
	35	31 atc ILE I
	36	32 aca THR T

Table 1. Continued

C-STRAND	**39**	33 ctg LEU L
	40	34 agc SER S
	41	35 tgg TRP W
	42	36 cgt ARG R
	43	37 cag GLN Q
	44	38 gat ASP D
	45	39 ggg GLY G
CD-STRAND	**45.1**	40 gta VAL V
	45.2	41 tct SER S
	45.3	42 ttg LEU L
	45.4	43 agc SER S
	45.5	44 cac HIS H
	45.6	45 gac ASP D
	45.7	--- --- -
D-STRAND	**77**	46 acc THR T
	78	47 cag GLN Q
	79	48 cag GLN Q
	80	49 tgg TRP W
	81	50 ggg GLY G
	82	51 gat ASP D
	83	52 gtc VAL V
	84	53 ctg LEU L
DE-TURN	**84.1**	54 cct PRO P
	84.2	55 gat ASP D
	84.3	56 ggg GLY G
	84.4	57 aat ASN N
	84.5	--- --- -
	84.6	--- --- -

Table 1. Continued

	84.7	--- --- -
	85.7	--- --- -
	85.6	--- --- -
	85.5	--- --- -
	85.4	58 gga GLY G
	85.3	59 acc THR T
	85.2	60 tac TYR Y
	85.1	61 cag GLN Q
E-STRAND	**85**	62 acc THR T
	86	63 tgg TRP W
	87	64 gtg VAL V
	88	65 gcc ALA A
	89	66 acc THR T
	90	67 agg ARG R
	91	68 att ILEU I
	92	69 tgc CYS C
	93	70 caa GLN Q
	94	--- --- -
	95	--- --- -
	96	--- --- -
EF-TURN	**96.1**	--- --- -
	96.2	--- --- -
F-STRAND	**97**	71 gga GLY G
	98	72 gag GLU E
	99	73 gag GLU E
	100	74 cag GLN Q
	101	75 agg ARG R
	102	76 ttc PHE F
	103	77 acc THR T
	104	78 tgc CYS C

Table 1. Continued

FG-LOOP	**105**	79 tac TYR Y
	106	80 atg MET M
	107	81 gaa GLU E
	108	82 cac HIS H
	109	83 agc SER S
	110	--- --- -
	111	--- --- -
	112	--- --- -
	113	--- --- -
	114	84 ggg GLY G
	115	85 aat ASN N
	116	86 cac HIS H
	117	87 agc SER S
G-STRAND	**118**	88 act THR T
	119	89 cac HIS H
	120	90 cct PRO P
	121	91 gtg VAL V
	122	92 ccc PRO P
	123	93 tct SER S

Unoccupied positions according to the IMGT unique numbering for G-DOMAIN and G-LIKE-DOMAIN [8] and to the IMGT unique numbering for C-DOMAIN AND C-LIKE-DOMAIN [7] are shown with dashes. The codon encoding the amino acid at position 1 of [D1], [D2] and [D3], according to the IMGT unique numbering, results from the splicing between EX1 and EX2, EX2 and EX3, and EX3 and EX4, respectively. This codon and the nucleotide from the preceding exon are shown between parentheses (see codon_start3 splicing type in IMGT Aide-mémoire, http://imgt.cines.fr). EMBL/GenBank/DDBJ accession number of MICA*01: L14848.

The alpha helix of the G-ALPHA1-LIKE comprises thirty-eight amino acids (positions 50 to 92, 87-92 being unoccupied) that include an additional position at 54A. The alpha helix of the G-ALPHA2-LIKE comprises forty-five amino acids (positions 50 to 92, 87 being unoccupied) that include three additional positions at 61A, 61B and 72A (Table 2A and Figure 5).

The IMGT Collier de Perles for the MICA C-LIKE-DOMAIN (Figure 6) is based on the IMGT unique numbering for C-DOMAIN and C-LIKE-

DOMAIN [7]. Correspondence between the IMGT unique numbering for the MICA C-LIKE-DOMAIN [D3] and the exon numbering is given in Table 1B (corresponding to amino acids 182 to 274 in the mature MICA I-ALPHA chain). The C-LIKE-DOMAIN (93 amino acids) (Figure 6) is composed by the A-STRAND of fourteen amino acids (positions 1.1, 1 to 15, 14 and 15 being unoccupied), the B-STRAND of ten amino acids (positions 16 to 26, 16 being unoccupied), the BC-LOOP of eight amino acids (positions 27 to 36), 31 and 32 being unoccupied, the C-STRAND of seven amino acids (positions 39 to 45), the CD-STRAND of six amino acids (positions 45.1 to 45.6), the D-STRAND of eight amino acids (positions 77 to 84), the DE-TURN of eight amino acids (positions 84.1 to 84.4 and 85.4 to 85.1), the E-STRAND of nine amino acids (positions 85 to 93, 94 to 96 being unoccupied), the F-STRAND of eight amino acids (positions 97 to 104), the FG-LOOP of nine amino acids (positions 105 to 117, 110 to 113 being unoccupied), and the G-STRAND of six amino acids (positions 118 to 123) (Table 2B and Figure 6).

Table 2. Lengths of the strands, turns and helices in the MICA domains. Lengths in number of amino acids (aa) are according to the IMGT unique numbering for G-DOMAIN and G-LIKE-DOMAIN [8] (A), and according to the IMGT unique numbering for C-DOMAIN and C-LIKE-DOMAIN [7] (B).

A - MICA G-ALPHA1-LIKE [D1] and G-ALPHA2-LIKE [D2] domains

IMGT labels	Lengths	
	G-ALPHA1-LIKE [D1] domain (85 aa)	G-ALPHA2-LIKE [D2] domain (96 aa)
A-STRAND	14	14
AB-TURN	3	2
B-STRAND	11	11
BC-TURN	2	2
C-STRAND	8	8
CD-TURN	1	1
D-STRAND	8	13
Helix	38	45

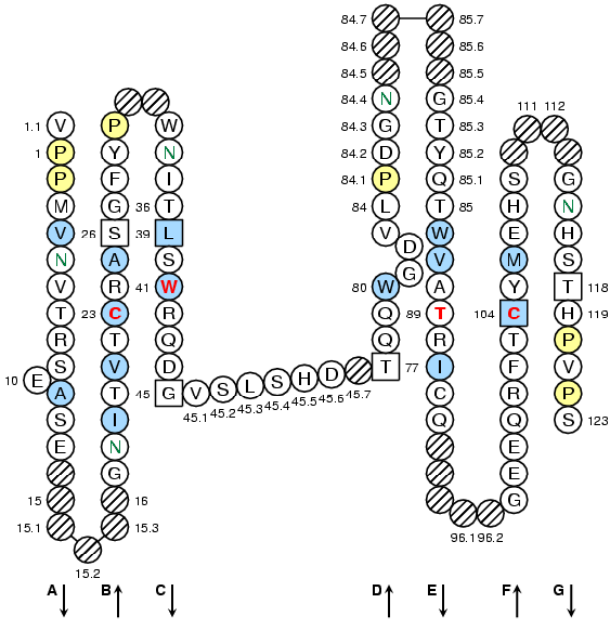
Table 2. Continued

B - MICA C-LIKE-DOMAIN [D3]

IMGT labels	Lengths
	C-LIKE-DOMAIN [D3] (93 aa)
A-STRAND	14
B-STRAND	10
BC-LOOP	8
C-STRAND	7
CD-STRAND	6
D-STRAND	8
DE-TURN	8
E-STRAND	9
F-STRAND	8
FG-LOOP	9
G-STRAND	6

Figure 6

A



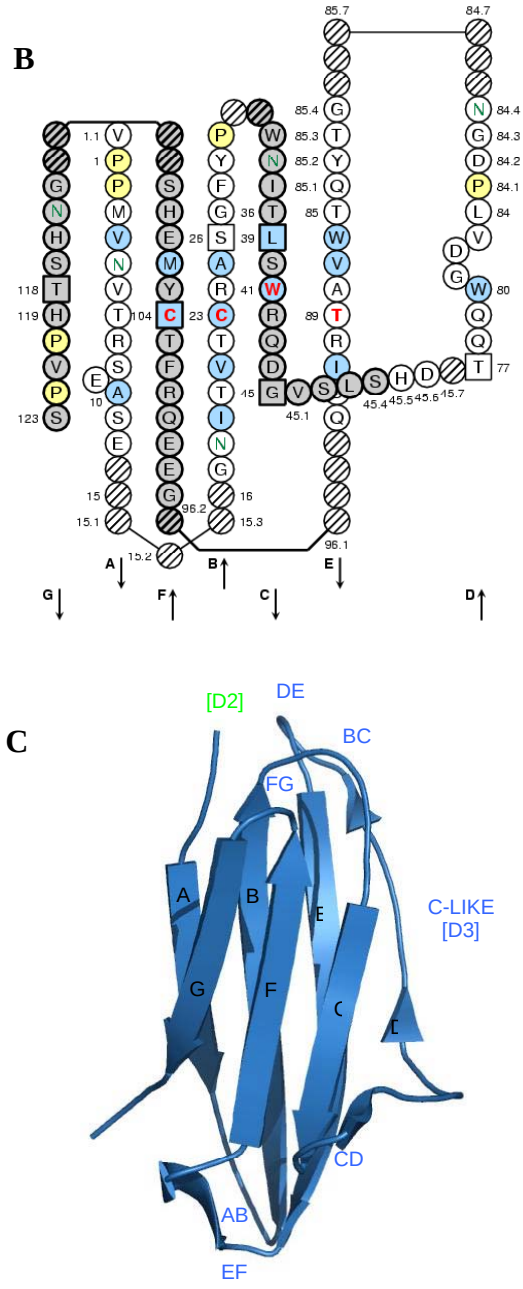


Figure 6. IMGT Colliers de Perles and 3D structure of the MICA C-LIKE-DOMAIN. (A) IMGT Collier de Perles on one layer. (B) IMGT Collier de Perles on two layers. (C) Three-dimensional (3D) structure. The C-LIKE-DOMAIN comprises 93 amino acids. Amino acid numerotation is according to the IMGT unique numbering for C-DOMAIN and C-LIKE-DOMAIN [7]. Hatched circles correspond to missing positions according to that numbering. Arrows indicate the direction of the beta strand and their different designations in 3D structures. In (B), the GFC strands are on the forefront, the ABED strands are on the back. Asparagine (N) that belong to potential N-glycosylation sites are in green (positions 5, 18, 34, 84.4 and 115). Code 1hyr from PDB [116] and from IMGT/3Dstructure-DB [10] (http://imgt.cines.fr). Ribbon representation in (C) was obtained with PyMOL (http://pymol.sourceforge.net/).

4. MICA three-dimensional structure

4.1. Free MICA

In 1999, Li *et al*. [114] determined the crystal structure of the MICA I-ALPHA-LIKE chain (MICA*01, code 1b3j, in the Protein Data Bank PDB [116] and in IMGT/3Dstructure-DB http://imgt.cines.fr [10]), at 2.8 Å resolution, by multiple isomorphous replacement. The three-dimensional (3D) structure comprises the two groove domains, G-ALPHA1-LIKE [D1] and G-ALPHA2-LIKE [D2], and the C-LIKE-DOMAIN [D3]. In the helix of the G-ALPHA2-LIKE [D2] domain of free MICA, amino acids 63 to 73 (according to the IMGT unique numbering for G-DOMAIN and G-LIKE-DOMAIN [9]) are disordered and presumed to form an extended flexible loop [114] (Figure 5B). The residues 88 to 92 (according to the IMGT unique numbering) of G-ALPHA2-LIKE [D2] that link that domain with the C-LIKE-DOMAIN [D3] are in an extended conformation that permits a considerable interdomain flexibility [114].

4.2. MICA/NKG2D complex

In 2001, Li *et al.* [115] determined the 3D structure of the complex between MICA and its receptor NKG2D (code 1hyr, in PDB [116] and in IMGT/3Dstructure-DB [10]). NKG2D is a homodimer, composed by two monomers, designated as [A] and [B]. When MICA is in complex with the NKG2D homodimer, the residues 63 to 73 of MICA [D2] are ordered, adding almost two turns of helix. These fostered contacts with NKG2D create a small pocket (roughly 6 Å wide x 6 Å deep x 14 Å long) [115]. The two monomers of NKG2D equally contribute to interactions with MICA (Table 3). Indeed, seven positions in each monomer (152 Tyr, 182 Ileu, 184 Met, 185 Gln, 197 Lys, 199 Tyr, 207 Asn) interact with MICA, the seven positions of NKG2D [A] contacting the MICA [D1] helix and the seven positions of NKG2D [B] contacting the MICA [D2] helix. In addition, four positions of NKG2D [A] and four positions of NKG2D [B] make “specific” interactions with MICA [D1] and [D2], respectively: 183 Glu, 186 Lys, 201 Glu and 205 Thr from NKG2D [A] interact with MICA [D1], whereas 150 Lys, 181 Ileu, 191 Leu and 195 Ser from NKG2D [B] interact with MICA [D2].

The MICA positions that interact with the NKG2D receptor are shown in Figure 5 and Table 3. Eleven positions of the MICA [D1] interact with NKG2D [A]: 15 (Asp), 17 (Ser), 18 (Val), 20 (Ser), 38 (Arg), 72 (Lys), 75 (Arg), 76 (Met), 79 (Ala), 80 (His) and 82 (Lys) (according to the IMGT unique numbering [8]). The “specific” contacts between MICA [D1] and NKG2D [A] include hydrogen bonds between MICA 15 (Asp) and 17 (Ser) and NKG2D 186 (Lys), MICA 20 (Ser) and NKG2D 205 (Thr), MICA 82 (Lys) and NKG2D 183 (Glu), whereas the MICA arginine at position 75 creates

Table 3. Contacts between MICA (ligand) and NKG2D homodimer (receptor) amino acids. The numbering for the MICA amino acids is according to the IMGT unique numbering for G-DOMAIN and G-LIKE-DOMAIN [8]. Contacts between MICA and NKG2D amino acids are detailed in *IMGT/3Dstructure-DB Residue@Position contacts* in IMGT/3Dstructure-DB (http://imgt.cines.fr). Contact types are from *Li et al.* [115] (code 1hyr in PDB [116] and in IMGT/3Dstructure-DB [10]).

MICA (ligand)				NKG2D (receptor)			Contact types between MICA and NKG2D amino acids [115]
DOMAIN	IMGT labels	Amino acid		Amino acid		Monomers	
		IMGT unique numbering [8]	Name	Name	Position		
G-ALPHA1-LIKE [D1]	AB-TURN	15	ASP D	LYS K	186	[A]	H bond
		17	SER S	LYS K			
	B-STRAND	18	VAL V	MET M	184		H bond
							Hydrophobic
				GLN Q	185		H bond
		20	SER S	THR T	205		H bond
	C-STRAND	38	ARG R	ASN N	207		
	Helix	66	ASP D	LYS K	197	[B]	Salt bridge
		72	LYS K	TY R Y	152	[A]	Hydrophobic
		75	ARG R	TYR Y	152		H bond
				MET M	184		Hydrophobic
				GLU E	201		Salt bridge
		76	MET M	TYR Y	152		Hydrophobic
				TYR Y	199		
		79	ALA A	MET M	184		

Table 3. Continued

		80	HIS H	ILE I	182		
				TYR Y	199		H bond
		82	LYS K	GLU E	183		
G-ALPHA2-LIKE [D2]	Helix	61 A	ASP D	LYS K	197	[A]	Salt bridge
		61B	ALA A	LYS K	150	[B]	H bond
		66	THR T	LEU L	191		Hydrophobic
			THR T	ASN N	207		H bond
		67	HIS H	TYR Y	152		Hydrophobic
		69	HIS H	MET M	184		Hydrophobic
				GLN Q	185		H bond
		70	ALA A	TYR Y	152		Hydrophobic
				TYR Y	199		
		72A	ALA A	ILE I	182		
				MET M	184		
		73	ASP D	TYR Y	199		H bond
			ASP D	SER S	195		H bond
		76	GLN Q	ILE I	181		H bond
			GLN Q	ILE I	182		Hydrophobic

H bond: Hydrogen bond

a salt bridge with NKG2D 201 (Glu). Eight positions of the MICA [D2] interact with the NKG2D [B]: 61B (Ala), 66 (Thr), 67 (His), 69 (His), 70 (Ala), 72A (Ala), 73 (Asp), 76 (Gln). Interestingly, six of these amino acids (positions 66, 67, 69, 70, 72A, 73) are in the disordered loop of free MICA. The "specific" contacts between MICA [D2] and NKG2D [B] include hydrogen bonds between MICA positions 61B (Ala), 73 (Asp) and 76 (Gln) and the NKG2D [B] positions 150 (Lys), 195 (Ser) and 181 (Ile), respectively, whereas, the MICA threonine at position 66 establishes hydrophobic interactions with NKG2D 191 (Leu) (Table 3).

Owing to the position of the NKG2D receptor on top of the MICA chain, the amino acid 66 (Asp) in MICA [D1] interacts with NKG2D [B] and the amino acid 61A (Asp) in MICA [D2] interacts with NKG2D [A] (Figure 5A).

5. MICA function

MICA gene encodes a cell surface highly glycosylated protein that is expressed exclusively in the basolateral membrane of intestinal epithelium cells [101] and epithelium-derived tumours [102]. This expression does not require peptide or beta-2-microglobulin (B2M) [101].

The presence of MICA at the basolateral membrane depends on a Leu-Val and Val-Leu (EX6 positions 2-3 and 7-8) dihydrophobic tandem motif in the cytoplasmic tail, that is absent in A5.1 alleles described in the next section. In polarized cells, the shorter A.5.1 MICA protein of 309 amino acids (instead of 361 amino acids for an A5 protein) and without intracytoplasmic region, is not sorted to the basolateral membrane but is transported to the apical surface [103].

MICA is preferentially concentrated in lipid rafts (cholesterol and sphingolipid-rich plasma membrane microdomains). Like other proteins associated with lipid rafts, MICA is S-acylated (two juxtaposed cysteines encoded by EX5, codons 33-34 to 39-40 depending on the microsatellite allele). *In vitro* mutation in the S-acylation site, in which the cysteine codon at position 39 of an A10 allele is replaced by a stop codon, leads to a truncated form of MICA that is unable to activate NK cells [108]. MICA is a stress-inductible ligand for NKG2D, a C-type lectin-like activating immunoreceptor, expressed on most NK cells, CD8+ αβ T cells, macrophages and γδ T cells [104-106, 110]. As shown above, a NKG2D homodimer interacts with a single MICA protein [107]. MICA is stress-induced and its regulation depends on heat shock motifs in the promoter sequence, at the 5'end of the gene, similar to those found in HSP70 genes [101, 104]. An oxidative stress with H_2O_2 can also induce MICA expression [102]. MICA expression is increased on cultured endothelial cells and fibroblasts infected by human cytomegalovirus (CMV). The cytolytic and cytokine responses by CMV-specific CD8+ αβ T cells is potentially augmented following engagement of the NKG2D receptor on T cells with the MICA ligand induced on CMV infected cells [101]. *Mycobacterium tuberculosis* infection also induces MICA cell surface expression and enhances the effector function of TRGV9-TRDV2 γδ T cells [111]. Bacteria of the *Escherichia coli* diarrheagenic group increase MICA expression mediated by the specific interaction between bacterial adhesion AfaE and its cellular receptor (CD55) [112]. Owing to MICA role in stress and immune response, regulation of the MICA expression is the subject of many studies. Recently, it has been shown that the large intron 1 contains a NF-κB site that binds p65 (RelA)/p50 heterodimers and p50/p50 homodimers of the

NF-κB transcription family and that NF-κB plays an important role in the regulated expression of the stress-induction of MICA [113].

6. MICA polymorphisms

6.1. MICA allele identification

Seventy-three MICA alleles have been so far identified for the sequence polymorphism of the coding region of the mature protein. The IMGT nomenclature for MICA alleles follows the standardized rules of the IMGT Scientific Chart [2]. Sequences have been defined for each allele based on one, or whenever possible, several of the following IMGT criteria: first sequence published, longest sequence, mapped sequence. IMGT allele names are identified by the gene name followed by an asterisk and a 2-digit number (MICA alleles in the text below are IMGT allele names) (Table 4). Polymorphisms by insertion/deletion of trinucleotide repeats are designated as A5 to A10 and refered to as microsatellite alleles (see below).

Five MICA alleles (MICA*01 to MICA*05) were first described by Bahram *et al*. [11] in 1994 with a total of 18 nucleotide substitutions and 14 amino acid changes. Eleven new alleles (MICA*06 to MICA*16) were described two years later by Fodil *et al*. [14] with nine nucleotide substitutions and eight amino acids changes. In 1997, Mizuki *et al*. [15] showed that the exon 5 harbours a polymorphic microsatellite (or Short Tandem Repeat "STR"). This STR showed a variable number of trinucleotide GCT repeats that encodes 4, 5, 6 or 9 Alanine (A, Ala). These STR or microsatellite alleles were designated as A4, A5, A6 and A9. There is also an A5.1 allele that contains five triplet repeats plus one additional nucleotide "g". This insertion leads to a frameshift and results in a stop codon and a premature termination.

Forty-one new alleles were described by different groups in 1999 [16-20], that correspond, in the IMGT nomenclature (Table 4) to MICA*17 to MICA*19, MICA*21 to MICA*45, MICA*52 to MICA*57, MICA*66 to MICA*72. In 2000, Perez-Rodriguez *et al*. [21] reported an A10 allele (MICA*20) with ten GCT repeats in EX5. A compilation of MICA alleles from the literature, published in 2001 [23], comprised fifty-one alleles (that correspond in the IMGT nomenclature to MICA*01, MICA*02, MICA*04 to MICA*46, MICA*52 to MICA*57). The same year, Obuchi *et al*. [24] found 2 new alleles (MICA*48, MICA*49) and Ban *et al*. [25] described four MICA alleles in exon 4 (MICA*61 to MICA*64). In 2002, Perez-Rodriguez *et al*. [22] reported two new MICA alleles (MICA*46 and MICA*47). In 2003, Rueda *et al*. [26], Tian *et al*. [45] and Zwirner *et al*. [27] described three new alleles (MICA*50, MICA*59, MICA*65, respectively). In 2004, Quiroga *et al*. [28] identified three new alleles (MICA*51, MICA*58, MICA*60). Eight other sequences were found in EMBL/GenBank/DDBJ by the IMGT annotators and were named MICA*66 to MICA*73.

Table 4. MICA alleles. IMGT reference alleles and other sequences from the literature.

A. IMGT reference alleles. Seventy-three MICA sequence alleles have been identified so far. EX5 microsatellite alleles (A4 to A10) could be assigned to 35 of them.

IMGT MICA allele names	Other alleles names[a,b]		Gene functionality[c]	IMGT reference sequences			EX 5 microsatellite alleles[d]
	(a)	(b)		Exons	Accession numbers	Molecule type	
MICA*01	*001	*001	F	EX 1-6	L14848	cDNA	A4
MICA*02	*00201	*002	F	EX 2-5, EX6	AF336063, AF336064 (AH010545)	gDNA	A9
MICA*03[e]		*003	F	EX 2-4	U56942	gDNA	
MICA*04	*004	*004	F	EX 1-6	X92841	gDNA	A6
MICA*05	*005	*005	F	EX 2-4	U56944	gDNA	
MICA*06	*006	*006	F	EX 2-5, EX6	AF336065, AF336066 (AH010526)	gDNA	A6
MICA*07	*00701	*007	F	EX 1-6	AY750850	cRNA	A4
MICA*08	*00801	*008	ORF	EX 2-5, EX6	AF336067, AF336068 (AH010568)	gDNA	A5.1
MICA*09	*00901	*009	F	EX 2-5, EX6	AF336069, AF336070 (AH010569)	gDNA	A6
MICA*10	*010	*010	F	EX 2-5, EX6	AF336071, AF336072 (AH010532)	gDNA	A5
MICA*11	*011	*011	F	EX 2-5, EX6	AF336073, AF336074 (AH010546)	gDNA	A6
MICA*12	*01201	*012	F	EX 2-5, EX6	AF336081, AF336082 (AH010562)	gDNA	A4

Table 4. Continued

MICA*13	*013	*013	F	EX 2-4	U56952	gDNA	
MICA*14	*014	*014	F	EX 2-4	U56953	gDNA	
MICA*15	*015	*015	F	EX 2-3, EX 4-5, EX 6	AF264738, AF264739, AF264740 (AF264738)	gDNA	A9
MICA*16	*016	*016	F	EX 2-5, EX6	AF336075, AF336076 (AH010560)	gDNA	A5
MICA*17	*017	*017	F	Ex 2-3, EX 4-5, EX 6	AF264735, AF264736, AF264737 (AH010819)	gDNA	A9
MICA*18	*01801	*018	F	EX 2-5, EX6	AF336077, AF336078 (AH010561)	gDNA	A4
MICA*19	*019	*019	F	EX 2-5, EX6	AF336079, AF336080 (AH010587)	gDNA	A5
MICA*20	*020		F	EX 2-5	AJ249394	gDNA	A10
MICA*21	*021	*021	F	EX 2-4	Y18110	gDNA	
MICA*22	*022	*022	F	EX 2-4	Y16804	gDNA	
MICA*23	*023		ORF	EX2, EX3, EX4, EX5	AF085039, AF085040, AF085041, AF085042 (AH008143)	gDNA	A5.1
MICA*24	*024	*024	F	EX 2-4	Y16807	gDNA	
MICA*25	*025	*025	F	EX 2-4	Y16808	gDNA	
MICA*26	*026		F	EX2, EX3, EX4, EX5	AF085051, AF085052, AF085053, AF085054 (AH008146)	gDNA	A6
MICA*27	*027		F	EX 2-5	AJ250802	gDNA	A5
MICA*28	*028	*028	ORF	EX2,	AF011829,	gDNA	A5.1

Table 4. Continued

				EX3, EX4, EX5	AF011830, AF011831, AF093115 (AH007167)		
MICA*29	*029	*029	F	EX 2-4	Y18112	gDNA	
MICA*30	*030	*036	F	EX2, EX3, EX4	AF079422, AF079423, AF079424 (AH006333)	gDNA	
MICA*31	*031	*037	F	EX2, EX3, EX4	AF011838, AF011839, AF011840 (AH007170)	gDNA	
MICA*32	*032	*038	F	EX2, EX3, EX4	AF011841, AF011842, AF011843 (AH007170)	gDNA	
MICA*33	*033	*039	F	EX 2-5	AJ250505	gDNA	A5
MICA*34	*034	*040	F	EX2, EX3, EX4	AF011847, AF011848, AF011849 (AH007173)	gDNA	
MICA*35	*035	*041	F	EX2, EX3, EX4	AF011850, AF011851, AF011852 (AH007174)	gDNA	
MICA*36	*036	*043	F	EX2, EX3, EX4	AF011859, AF011860, AF011861 (AH007176)	gDNA	
MICA*37	*037	*044	F	EX2, EX3, EX4	AF011862, AF011863, AF011864 (AH007177)	gDNA	
MICA*38	*038	*045	F	EX2, EX3, EX4	AF011865, AF011866, AF011867 (AH007178)	gDNA	

Table 4. Continued

MICA*39	*039	*046	F	EX2, EX3, EX4	AF011868, AF011869, AF011870 (AH007179)	gDNA	
MICA*40	*040	*047	F	EX2, EX3, EX4	AF011871, AF011872, AF011873 (AH007180)	gDNA	
MICA*41	*041	*048	F	EX 2-5	AJ271789	gDNA	A9
MICA*42	*042	*049	F	EX2, EX3, EX4	AF106635, AF106636, AF106637 (AH007473)	gDNA	
MICA*43	*043	*050	F	EX 2-3, EX 4-5	AJ250990, AJ250991	gDNA	A4
MICA*44	*044	*051	F	EX2, EX3, EX4	AF106641, AF106642, AF106643 (AH007475)	gDNA	
MICA*45	*045	*052	F	EX 2-3, EX 4-5	AJ250506, AJ250507	gDNA	A4
MICA*46	*046		F	EX 2-3, EX 4-5	AJ250501, AJ250502	gDNA	A9
MICA*47	*047		F	EX 2-3, EX 4-5	AJ295250, AJ295251	gDNA	A6
MICA*48	*048		F	EX2-3, EX4-5, EX6	AF264741, AF264742, AF264743 (AH010820)	gDNA	A5
MICA*49	*049		F	EX2-3, EX4-5, EX6	AF264744, AF264746, AF264747 (AH010821)	gDNA	A6
MICA*50	*050		F	EX 2-5	AY095537	gDNA	A7
MICA*51	*051		F	EX 2-4	AJ563426	gDNA	
MICA*52	*00202	*042	F	EX2, EX3,	AF011877, AF011878,	gDNA	

Table 4. Continued

				EX4	AF011879 (AH007182)		
MICA*53	*00702	*023	F	EX2-4	Y16805	gDNA	
MICA*54	*00802	*026	ORF	EX 2-3, EX 4-5	AJ250499, AJ250500	gDNA	A5.1
MICA*55	*00803	*054	F	EX2, EX3, EX4	AF106653, AF106654, AF106655 (AH007479)	gDNA	
MICA*56	*00902	*020	F	EX 2-5, EX6	AY029762, AY029763 (AH010740)	gDNA	A6
MICA*57	*01202	*053	F	EX2, EX3, EX4	AF106647, AF106648, AF106649 (AH007477)	gDNA	
MICA*58	*01802		F	EX 2-5	AJ580805	gDNA	A4
MICA*59	*MICA*CHAH*		F	EX2, EX3, EX4	AF411923, AF411924, AF411925 (AH011062)	gDNA	
MICA*60	*00703		F	EX 2-5	AJ580806	gDNA	A4
MICA*61	*MICA-040*		F	EX 4	AF302792	gDNA	
MICA*62	*MICA-041*		F	EX 4	AF303446	gDNA	
MICA*63	*MICA-042*		F	EX 4	AF305055	gDNA	
MICA*64	*MICA-043*		F	EX 4	AF305056	gDNA	
MICA*65	*MICA*001 variant*		F	EX 1-6	AY204547	cDNA	A5
MICA*66	*MUC-28*	*027	F	EX 2-4	Y16811	gDNA	
MICA*67	*MUC-31*	*030	F	EX 2-4	Y18113	gDNA	
MICA*68	*MUC-32*	*031	F	EX 2-4	Y18114	gDNA	
MICA*69	*MUC-33*	*032	F	EX 2-4	Y18115	gDNA	
MICA*70	*MUC-34*	*033	F	EX 2-4	Y18116	gDNA	
MICA*71	*MUC-35*	*034	F	EX 2-4	Y18117	gDNA	
MICA*72	*MUC-36*	*035	F	EX 2-4	Y18118	gDNA	
MICA*73			F	EX 1-6	BC016929	cDNA	A4

Table 4. Continued

B. Other sequences from literature.

MICA IMGT allele names	Other allele names[a]	Gene functionality[c]	IMGT reference sequences		
			Exons	Accession numbers	Molecule type
MICA*01	*001	F	EX2, EX3, EX4, EX5	AF085059, AF085060, AF085061, AF085062	gDNA
			EX 2-5, EX6	AF336085, AF336086	
			EX 2-4	U56940	
				L29406, U69965	
MICA*02	*00201	F	EX2, EX3, EX4, EX5	AF085043, AF085044, AF085045, AF085046	gDNA
			EX 2-4	U56941	
			EX 2-4, EX6	AF336083, AF336084	
MICA*04	*004	F	EX2, EX3, EX4, EX5	AF085031, AF085032, AF085033, AF085034	gDNA
			EX 2-4	U56943	
MICA*05	*005	F	EX 2-4	U56944	gDNA
MICA*06	*006	F	EX2, EX3, EX4, EX5	AF085023, AF085024, AF085025, AF085026	gDNA
			EX 2-5, EX6	AF336065, AF336066	
MICA*07	*00701	F	EX2, EX3, EX4, EX5	AF085047, AF085048, AF085049, AF085050	gDNA
MICA*08	*00801	ORF	EX2, EX3, EX4, EX5	AF085015, AF085016, AF085017, AF085018	gDNA
			EX 2-4	U56947	
			EX 1-3	L29411	
				L29409	
				U69624, U69625, U69628	
				U69970, U69976, U69977	

Table 4. Continued

MICA*09	*00901	F	EX2, EX3, EX4, EX5	AF085019, AF085020, AF085021, AF085022	gDNA
			EX 2-4	U56948	
				U69626, U69971	
MICA*10	*010	F	EX2, EX3, EX4, EX5	AF085055, AF085056, AF085057, AF085058	gDNA
			EX 2-4	U56949	
				Y16801, L29408, U69629, U69969, U69974	
MICA*11	*011	F	EX2, EX3, EX4, EX5	AF085035, AF085036, AF085037, AF085038	gDNA
			EX 2-4	U56950	
				U69630, U69975	
MICA*12	*01201	F	EX 2-4	U56951	gDNA
			EX 2-3, EX5	U69627, U69972	
MICA*15	*015	F	EX 2-4	U56954	gDNA
MICA*16	*016	F	EX2, EX3, EX4, EX5	AF085027, AF085028, AF085029, AF085030	gDNA
			EX 2-4	U56955	
				Y16802, U69623, U69966	
MICA*17	*017	F	EX2, EX3, EX4	AF079413, AF079414, AF079415	gDNA
			EX 2-4	AF097403	
			EX 2-4	Y16810	
			EX 2-5	AJ250803	
MICA*18	*01801	F	EX2, EX3, EX4	AF011874, AF011875, AF011876	gDNA
			EX2, EX3, EX4	AF079425, AF079426, AF079427	
			EX5	AF093116	
			EX 2-4	AF097404	
			EX 2-4	Y16806	
			EX 2-5	AJ250805	

Table 4. Continued

MICA*19	*019	F	EX2, EX3, EX4	AF011835, AF011836, AF011837	gDNA
			EX2, EX3, EX4	AF079416, AF079417, AF079418	
			EX5	AF093113	
			EX 2-4	AF097405	
			EX 2-5	AJ250804	
				AB015600	
MICA*22	*022	F	EX2, EX3, EX4	AF011856, AF011857, AF011858	gDNA
MICA*24	*024	F	EX2, EX3, EX4	AF011832, AF011833, AF011834	gDNA
MICA*25	*025	F	EX2, EX3, EX4	AF011853, AF011854, AF011855	gDNA
MICA*27	*027	F	EX2, EX3, EX4, EX5	AF085011, AF085012, AF085013, AF085014	gDNA
MICA*28	*028	F	EX 2-4	Y18111	gDNA
MICA*29	*029	F	EX 2-3, EX 4-5	AJ250503, AJ250504	gDNA
MICA*33	*033	F	EX2, EX3, EX4	AF011844, AF011845, AF011846	gDNA
			EX5	AF093114	
MICA*41	*041	F	EX2, EX3, EX4	AF106632, AF106633, AF106634	gDNA
MICA*43	*043	F	EX2, EX3, EX4	AF106638, AF106639, AF106640	gDNA
MICA*45	*045	F	EX2, EX3, EX4	AF106644, AF106645, AF106646	gDNA
MICA*47	*047	F	EX2	AF286732	gDNA
MICA*53	*00702	F	EX2, EX3, EX4	AF011880, AF011881, AF011882	gDNA
MICA*54	*00802	ORF	EX2, EX3, EX4	AF011883, AF011884, AF011885	gDNA
			EX2, EX3, EX4	AF106650, AF106651, AF106652	
			EX 2-4	Y16809	
MICA*56	*00902	F	EX2, EX3, EX4	AF011886, AF011887, AF011888	gDNA
			EX2, EX3, EX4	AF079419, AF079420, AF079421	
			EX 2-4	Y16803	
				AF097406	

[a] (a) Allele names from http://www.ebi.ac.uk/imgt/hla/index.html or, in italics, from publications.
[b] (b) Allele names from http://mhc-x.u-strasbg.fr/human.htm
[c] F: FUNCTIONAL, ORF: Open Reading Frame. Functionality is according to the IMGT Scientific chart rules [2,3]. Four sequence alleles (MICA*08, MICA*23, MICA*28, MICA*54) correspond to the A5.1 microsatellite allele and encode a truncated protein of 309 amino acids (instead of 361 for a mature A5 protein). Indeed, the insertion of one nucleotide between positions 59 and 60 (between codons 20 and 21) of EX5 of the A5.1 allele leads to a frameshift, the last fifteen amino acids (295-309) of A5.1 (codons 21-35 of EX5) are in an unusual reading frame and there is a stop codon at position 310 (EX5 of A5.1 encodes 35 amino acids, instead of 45 amino acids in the A5 alleles). Moreover, the A5 protein also comprises the 42 amino acids encoded by EX6. As the A5.1 truncated protein is expressed but is not functional, the allele sequences of A5.1 are considered as ORF.
[d] The EX5 microsatellite alleles correspond to the sequence tandem repeat (STR) described in the text.
[e] MICA*03 : This allele described in ref. [14], needs to be confirmed. Indeed, Single-Strand Conformation Polymorphism (SSCP) patterns and Polymerase Chain Reaction (PCR) sequence identical to those of the MICA*04 allele were found when PITOUT human tumour cell line (HTCL) was reanalysed [19]. However, although PITOUT is described as an homozygous cell line for HLA, the possibility that it is heterozygous for the MICA gene remains.

6.2. MICA sequence and microsatellite allele frequencies

Frequencies of the MICA alleles for the sequence polymorphisms and for the microsatellite have extensively been studied. However, the results of the studies have rarely been correlated. In this section we provide a synthesis of these analyses using the standardized IMGT allele nomenclature.

In 1999, Pedersdorf *et al*. [17] found, in five families with different ethnic background, that MICA*08 is the most frequent allele in Caucasians, Non-Caucasians (Hispanic American, African American, Native American and Asian American) and Unknown race with gene frequencies of 55, 40 and 42%, respectively. MICA*02 (13, 17 and 11%) and MICA*04 (13, 17 and 6%) are the two other alleles more represented. Also in 1999, Komatsu-Wakui *et al.* [19] observed the frequency of MICA among 114 healthy Japanese subjects: MICA*08 is the most frequent (25.2%) followed by MICA*09, MICA*02, MICA*10, MICA*04 and MICA*12 (18.4, 12.5, 12.5, 11.1, 10.9%, respectively). In addition, they found a blank allele that corresponds to a deletion of the entire MICA gene (6.7%). This deletion might be coupled with a MICB null allele (MICB*18) and are considered to form a conservative haplotype in Japanese population (3.8%).

In 2001, Tian *et al*. [29] showed than MICA*08 (A5.1), MICA*04 (A6) and MICA*02 (A9) are the most frequent alleles in 29 African-American families, with a frequency of 28.2, 26.4 and 25%. In 2002, Zhang *et al.* [30]

found, in South American Indians (North-eastern Argentina) that MICA*02 (A9) is the most frequent allele. MICA*02 (A9), MICA*27 (A5) and MICA*10 (A5) accounted for more than 90% of all the MICA alleles in this population. In 2003, Pyo *et al*. [31] observed the frequency of MICA alleles in the Korean population: MICA*08 (A5.1) is the most frequent one (24.4%) followed by MICA*10 (A5) and MICA*02 (A9) (18.3 and 17.8%). Zhang *et al.* [32] found among 201 African Americans that MICA*02 (A9) and MICA*08 (A5.1) are the two most frequent MICA alleles (27.9 and 26.9%, respectively) followed by MICA*04 (A6), MICA*54 (A5.1), MICA*09 (A6) (18.7, 5.5 and 4.2%, respectively). Tian *et al*. [45], studied MICA variation in groups of sub-Saharan African (three Nigerian tribal populations and two African-American populations) and found that MICA*02 (A9), MICA*04 (A6), MICA*08 (A5.1) are conserved in all groups, but there are differences between the Nigerian tribes and between those tribes and the African-American populations.

In 2004, Marin *et al*. [33] found, in the Sao Paulo population (Brazil) that MICA*08 is predominant (47%). Nishiyama *et al*. [34] reported that MICA*09 have the higher frequency among Indonesians. Novota *et al*. [96] found, in Czech population, that the most frequent STR allele is A5.1 (59.3%) and the less frequent is A5 (20.0%). A7, A8 and A10 STR alleles were not identified in that study.

In several studies, polymorphisms are only studied at the microsatellite level. In those cases, the EX5 STR polymorphism that is observed may correspond to either one sequence allele (for A7 and A10) or to several possible sequence alleles (four for A5.1, five for A9, seven for A5, eight for A6, and nine for A4), as described in Table 4 and summarized below:

- A4: nine alleles (MICA*01, MICA*07, MICA*12, MICA*18, MICA*43, MICA*45, MICA*58, MICA*60, MICA*73).
- A5: seven alleles (MICA*10, MICA*16, MICA*19, MICA*27, MICA*33, MICA*48, MICA*65).
- A5.1 : four alleles (MICA*08, MICA*23, MICA*28, MICA *54).
- A6: eight alleles (MICA*04, MICA*06, MICA*09, MICA*11, MICA*26, MICA*47, MICA*49, MICA*56).
- A7: one allele (MICA*50).
- A9: five alleles (MICA*02, MICA*15, MICA*17, MICA*41, MICA*46).
- A10: one allele (MICA*20).

More sequence alleles may correspond to these STR polymorphisms, as EX5 has not yet been sequenced in the thirty-eight other alleles, and as new alleles will certainly be identified and sequenced. Moreover, it is not excluded that an A8 STR allele may also been found.

7. MICA polymorphisms and diseases

It has frequently been suggested that MICA may to be involved in susceptibility in several diseases (Table 5). However as the MICA polymorphisms (sequence and EX5 microsatellite alleles) are, in most studies, not clearly associated with diseases, it has been suggested that this association may be secondary and owned to linkage disequilibrium with HLA-B alleles. As a large number of publications with different results has been devoted to Behçet's disease, these studies are detailed below. The other diseases are reported in Table 5.

7.1. Behçet's disease

In 1997, Mizuki *et al*. [12] demonstrated that there is a strong linkage disequilibrium between the MICA microsatellite alleles and the HLA-B, with association between MICA (A4) and HLA-B18 and -B17, MICA (A5) and HLA-B62, MICA (A5.1) and HLA-B7, -B8 and -B60, MICA (A6) and HLA-B44, -B51 and -B52, MICA (A9) and HLA-B35. They found that all of the HLA-B51 (reported to be associated to the Behçet's disease) positive patients possessed an A6 allele (one with the higher frequency in the patient group). Thus, they concluded that MICA is a possible candidate gene for the Behçet's disease. In 1999, Mizuki *et al*. [35] showed that HLA-B51 is the gene involved in the development of Behçet's disease in Japanese patients. The important increase of MICA*09 in the patient groups results secondarily from a strong linkage disequilibrium with HLA-B51. The same year, Yabuki *et al*. [36] found the same association between the A6 polymorphism and Behçet's disease in Greek patients. Gonzalez-Escribano *et al.* [37] found among 58 Spanish patients with Behçet's disease, that HLA-B51 is more closely associated to Behçet's susceptibility than MICA microsatellite alleles. Wallace *et al*. [38] also found that the A6 polymorphism and MICA*09 may be markers for additional risk factors and HLA-B51 may be the most significant factor in the Middle Eastern group of Behcet's disease patients.

In 2000, Mizuki *et al*. [39] showed, in three different populations (Greek, Japanese and Italian), that HLA-B51 is the unique pathologic gene of Behçet's disease. In 2001, Mizuki *et al*. [40] also showed, in Jordanian patients, that the pathogenic gene in Behçet's disease is HLA-B51 not MICA. In another study among Italian patients, Salvarini *et al*. [41] also found that the association with the A6 MICA alleles is secondary to the strong linkage disequilibrium with HLA-B51 in Behçet's disease. Similarly, in 2002, in a study among Arab and non-Ashkenazi Jewish patients in Israel, Cohen *et al.* [42] concluded that the most probably implicated gene in the development of Behçet's disease is HLA-B51 even if they found a strong association between the disease and the A6 MICA alleles in Israeli Arabs. However, the same year, Park *et al*. [43],

Table 5. MICA polymorphisms (sequence alleles and EX5 microsatellite alleles) and diseases. Sequence alleles refer to nucleotide sequences alleles identified in the coding region of the mature protein (see IMGT Scientific chart, http://imgt.cines.fr [2]). EX5 microsatellite alleles refer to MICA EX5 Short Tandem Repeat (STR).

Diseases	MICA alleles		Populations		Ref
	Sequence alleles	EX5 microsatellite alleles	Ethnic group	Country	
Behçet's disease		A6			12
	MICA*09		Oriental	Japan	35
		n.s.	Caucasoid	Greece	36
		n.s.	Caucasoid	Spain	37
	MICA*09	A6	Arab	Palestine	38
		n.s.	Caucasoid	Greece, Italy and Japan	39
			Oriental	Japan	
			Arab	Jordania	40
			Caucasoid	Italy	41
			Arab	Israel	42
		A6	Oriental	Korea	43
			Caucasoid	Italy	97
		A5/A6	Oriental	Mongolia	44

Table 5. Continued

Insulin-dependant diabetes mellitus (T1DM or IDDM)		A9	Oriental	Taiwan	46
		A5	Caucasoid	Italy	47
		A4	Oriental	Japan	48
		A5.1			
		A6 (protective haplotype)			
		A4	Oriental	Korea	49
		A6 (protective haplotype)			
		A5 (in children)	Caucasoid	Italia	50
		A5.1 (in adults)			
		A9 (protective haplotype)	Caucasoid (Basque)	Spain	51
		A4			
		A5	Oriental	India	52
		A5	Caucasoid	Sweden	53
		A6 (protective haplotype)		Spain	64
		A5.1			
		A9 (protective haplotype)			

Table 5. Continued

Addison's disease (ADD)		A5.1/A5.1	Caucasoid	Italy	54
		A5.1			
		A6 (protective haplotype)			
		A5.1	Caucasoid	USA	55
		A5.1/A5.1		Spain	64
		A5.1			
		A9 (protective haplotype)			
Psoriasis	MICA*02	A9	Caucasoid	Spain	56, 61
		A5.1	Oriental	Korea, China	57, 59
	PERB11.1*06		Caucasoid	Australia	58
		A9	Jewish	Spain	60
		A4	Caucasoid	Croatia	62
	MICA*02, MICA*08, MICA*10, MICA*17		Oriental	Thailand	63
Ankylosing spondylitis (AS)		A4	Caucasoid		65, 67
	MICA*07, MICA*10		Oriental	Japan	66
		ns	African, Asian and Caucasoid		68
		A4	Caucasoid	Sardinia and Italy	69

Table 5. Continued

Systemic lupus erythematosus (SLE)		A5	Caucasoid	Italy	70
		A5.1			
		A9 (protective haplotype)			
		n.s.	Oriental	China	78
Coeliac disease (CD)		A5.1	Caucasoid	Spain	64, 71, 72, 75, 76
		A9 (protective haplotype)			64
		A5.1	Arab Saharawi	Sahara occidental	73
			Caucasoid	Italy	74
				Finland	77
Ulcerative colitis (UC)		A6	Oriental	Japan	79, 80
		n.s.	Caucasoid	Germany	81
		A5.1		Spain	82
		A5			
Oral submucous fibrosis (OSF)		A6	Oriental	Taiwan	83
Graves' disease		A5	Oriental	Taiwan	84

Table 5. Continued

Primary sclerosing cholangitis (PSC)		A5.1		Norway	85
	MICA*02 (protective allele)			England	86
	MICA*08/MICA*08				
Familial Mediterranean fever (FMF)		A9		France	87
		n.s.		Lebanon	88
Takayasu's arteritis (TA)		n.s.	Oriental	India	89
		A6		Japan	90
Buerger's disease		A4	Oriental	Japan	90
		n.s.		India	91
Acute anterior uveitis		A4	Oriental	Japan	92, 93
Latent autoimmune diabetes in adults (LADA)		A5.1	Caucasoid	Finland	94
				Sweden	95
Mixed connective tissue disease (MCTD)		A5.1/A5.1	Caucasoid	Sweden	98
		A4			
Oral squamous cell carcinoma (OSCC)		A6	Oriental	Taiwan	99
Hepatitis B	MICA*15			USA	100
Hepatitis C					

n.s.: not significant

among Korean patients with Behçet's disease, suggested that the A6 MICA alleles rather than HLA-B51 is strongly associated with the disease, and that this allele is a useful susceptibility marker of Behçet's disease, especially in the HLA-B51 negative patients. In 2003, Chung *et al.* [44] reported a Mongolian patient with Behçet's disease who has A5/A6 MICA alleles.

7.2. Other diseases

Other diseases that may be associated with MICA polymorphisms are listed in Table 5.

Conclusion

As new MIC alleles are described, a standardized description and classification is required to compare data from different laboratories, different ethnic groups and to analyse their relationship with diseases.

By providing a simple and precise definitions of the sequence alleles, by establishing a correlation between sequence and STR microsatellite alleles and by bridging the gap between sequences, and 2D structures with the IMGT Colliers de Perles, IMGT provides the necessary framework for extensive studies of the MICA alleles, interactions of the MICA protein with its receptor NKG2D and its function in pathological situations.

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References

1. Lefranc M-P, Giudicelli V, Kaas Q, Duprat E, Jabado-Michaloud J, Scaviner D, Ginestoux C, Clément O, Chaume D and Lefranc G. IMGT, the international ImMunoGeneTics information system®. Nucl. Acids Res., 2005; 33:D593-D597.
2. Lefranc M-P, Clément O, Kaas Q, Duprat E, Chastellan P, Coelho I, Combres K, Ginestoux C, Giudicelli V, Chaume D and Lefranc G. IMGT-Choreography for immunogenetics and immunoinformatics. *In Silico* Biology 5, 0006, 2004. Epub <http://www.bioinfo.de/isb/2004/05/0006/>. *In Silico* Biology, 2005; 5:45-60.
3. Giudicelli, V and Lefranc, M-P. Ontology for Immunogenetics: IMGT-ONTOLOGY. Bioinformatics, 1999; 15:1047-1054.

4. Pommié C, Levadoux S, Sabatier R, Lefranc G and Lefranc M-P. IMGT standardized criteria for statistical analysis of immunoglobulin V-REGION amino acid properties. J. Mol. Recognition 2004; 17:17-32.
5. Lefranc M-P, Pommié C, Ruiz M, Giudicelli V, Foulquier E, Truong L, Thouvenin-Contet V and Lefranc G. IMGT unique numbering for immunoglobulin and T cell receptor variable domains and Ig superfamily V-like domains. Dev. Comp. Immunol., 2003; 27:55-77.
6. Duprat E, Kaas Q, Garelle V, Giudicelli V, Lefranc G and Lefranc M-P. IMGT standardization for alleles and mutations of the V-LIKE-DOMAINs and C-LIKE-DOMAINs of the immunoglobulin superfamily. Recent Res. Devel. Human Genet. 2004; 2:111-136.
7. Lefranc M-P, Pommié C, Kaas Q, Duprat E, Bosc N, Guiraudou D, Jean C, Ruiz M, Da Piedade I, Rouard M, Foulquier E, Thouvenin V and Lefranc G. IMGT unique numbering for immunoglobulin and T cell receptor constant domains and Ig superfamily C-like domains. Dev. Comp. Immunol. 2005; 29:185-203.
8. Lefranc M-P, Duprat E, Kaas Q, Tranne M, Thiriot A and Lefranc G. IMGT unique numbering for MHC groove G-DOMAIN and MHC superfamily (MhcSF) G-LIKE-DOMAIN. Dev. Comp. Immunol. 2005; 29:917-938.
9. Kaas Q, Duprat E, Le Tourneur G and Lefranc M-P. IMGT standardization for molecular characterization of the T cell receptor/peptide/MHC complexes. Springer (in press).
10. Kaas Q, Ruiz M and Lefranc M-P. IMGT/3Dstructure-DB and IMGT/StructuralQuery, a database and a tool for immunoglobulin, T cell receptor and MHC structural data. Nucl. Acids Res. 2004; 32:D208-D210.
11. Bahram S, Bresnahan M, Geraghty DE and Spies T. A second lineage of mammalian major histocompatibility complex class I genes. Proc Natl Acad Sci U S A. 1994; 91:6259-6263.
12. Mizuki N, Ota M, Kimura M, Ohno S, Ando H, Katsuyama Y, Yamazaki M, Watanabe K, Goto K, Nakamura S, Bahram S and Inoko H. Triplet repeat polymorphism in the transmembrane region of the MICA gene: A strong association of six GCT repetitions with Behçet disease. Proc Natl Acad Sci U S A. 1997; 94:1298-1303.
13. Bahram S, Mizuki N, Inoko H and Spies T. Nucleotide sequence of the human MHC class I MICA gene. Immunogenetics. 1996; 44:80-81.
14. Fodil N, Laloux L, Wanner V, Pellet P, Hauptmann G, Mizuki N, Inoko H, Spies T, Theodorou I and Bahram S. Allelic repertoire of the human MHC class I MICA gene. Immunogenetics. 1996; 44:351-357.
15. Fodil N, Pellet P, Laloux L, Hauptmann G, Theodorou I and Bahram S. MICA haplotypic diversity. Immunogenetics 1999; 49:557-560.
16. Mitsuishi Y. 1999, accession numbers AF106632 to AF106655 (AH007472 to AH007479) in EMBL/GenBank/DDBJ databases.
17. Petersdorf EW, Shuler KB, Longton GM, Spies T and Hansen JA. Population study of allelic diversity in the human MHC class I-related MIC-A gene. Immunogenetics. 1999; 49:605-612.
18. Visser CJ, Tilanus MG, Tatari Z, van der Zwan AW, Bakker R, Rozemuller EH, Schaeffer V, Tamouza R and Charron D. Sequencing-based typing of MICA

reveals 33 alleles : a study on linkage with classical HLA genes. Immunogenetics. 1999; 49:561-566.
19. Komatsu-Wakui M, Tokunaga K, Ishikawa Y, Kashiwase K, Moriyama S, Tsuchiya N, Ando H, Shiina T, Geraghty DE, Inoko H and Juji T. MIC-A polymorphism in Japanese and a MIC-A-MIC-B null haplotype. Immunogenetics. 1999; 49:620-628.
20. Yao Z, Volgger A, Helmberg W, Keller E, Fan LA, Chandanayingyong D and Albert ED. Definition of new alleles of MIC-A using sequencing-based typing. Eur J Immunogenet. 1999; 26:225-232.
21. Perez-Rodriguez M, Corell A, Arguello JR, Cox ST, McWhinnie A, Marsh SG and Madrigal JA. A new MICA allele with ten alanine residues in the exon 5 microsatellite. Tissue Antigens. 2000; 55:162-165.
22. Perez-Rodriguez M, Arguello JR, Fischer G, Corell A, Cox ST, Robinson J, Hossain E, McWhinnie A, Travers PJ, Marsh SG and Madrigal JA. Further polymorphism of the MICA gene. Eur J Immunogenet. 2002; 29:35-46.
23. Robinson J, Perez-Rodriguez M, Waller MJ, Cuillerier B, Bahram S, Yao Z, Albert ED, Madrigal JA and Marsh SG. MICA Sequences 2000. Immunogenetics. 2001; 53:150-169.
24. Obuchi N, Takahashi M, Nouchi T, Satoh M, Arimura T, Ueda K, Akai J, Ota M, Naruse T, Inoko H, Numano F and Kimura A. Identification of MICA alleles with a long Leu-repeat in the transmembrane region and no cytoplasmic tail due to a frameshift-deletion in exon 4. Tissue Antigens. 2001; 57:520-535.
25. Ban GH, Chu JY, Xu SB, Yang ZQ, Qian YP, Yu JK, Na JB, Liu XJ and Zhang SZ. Distribution of MICA microsatellite in 13 population groups of China. Yi Chuan Xue Bao. 2001; 28:1085-1092.
26. Rueda B, Pascual M, Lopez-Nevot MA, Gonzalez E and Martin J. A new allele within the transmembrane region of the human MICA gene with seven GCT repeats. Tissue Antigens. 2002; 60:526-528
27. Zwirner NW, Molinero LL, Fuertes MB and Fainboim L. 2003 accession number AY204547 in EMBL/GenBank/DDBJ databases.
28. Quiroga I, Sweeney D, Sutton PM, Chapple SD, Souto-Grando JP, Barnardo MC and Fuggle SV. Identification of a novel MICA allele: MICA*051. Tissue Antigens. 2004; 63:466-469.
29. Tian W, Boggs DA, Ding WZ, Chen DF and Fraser PA. MICA genetic polymorphism and linkage disequilibrium with HLA-B in 29 African-American families. Immunogenetics. 2001; 53:724-728.
30. Zhang Y, Lazaro AM, Zou Y, Lavingia B, Moraes EM, Moraes RJ and Stastny P. MICA polymorphism in South American Indians. Immunogenetics. 2002; 53:900-906.
31. Pyo CW, Hur SS, Kim YK, Choi HB, Kim TY and Kim TG. Distribution of MICA alleles and haplotypes associated with HLA in the Korean population. Hum Immunol. 2003; 64:378-384.
32. Zhang Y, Han M, Vorhaben R, Giang C, Lavingia B and Stastny P. Study of MICA alleles in 201 African Americans by multiplexed single nucleotide extension (MSNE) typing. Hum Immunol. 2003; 64:130-136.

33. Marin ML, Savioli CR, Yamamoto JH, Kalil J and Goldberg AC. MICA polymorphism in a sample of the Sao Paulo population, Brazil. Eur. J. Immunogenet. 2004; 31:63-71.
34. Nishiyama M, Takahashi M, Manaka KC, Roosihermiatie B, Kuriyama T and Nakae K. Research report: Frequencies of mica gene polymorphism: a comparison between Indonesians on Bacan Island and suburban Japanese. Southeast Asian J Trop Med Public Health. 2004; 35:195-201.
35. Mizuki N, Ota M, Katsuyama Y, Yabuki K, Ando H, Goto K, Nakamura S, Bahram S, Ohno S and Inoko H. Association analysis between the MIC-A and HLA-B alleles in Japanese patients with Behcet's disease. Arthritis Rheum. 1999; 42:1961-1966.
36. Yabuki K, Mizuki N, Ota M, Katsuyama Y, Palimeris G, Stavropoulos C, Koumantaki Y, Spyropoulou M, Giziaki E, Kaklamani V, Kaklamani E, Inoko H and Ohno S. Association of MICA gene and HLA-B*5101 with Behcet's disease in Greece. Invest. Ophthalmol. Vis. Sci. 1999; 40:1921-1926.
37. Gonzalez-Escribano MF, Rodriguez MR, Aguilar F, Alvarez A, Sanchez-Roman J and Nunez-Roldan A. Lack of association of MICA transmembrane region polymorphism and Behcet's disease in Spain. Tissue Antigens 1999; 54:278-281.
38. Wallace GR, Verity DH, Delamaine LJ, Ohno S, Inoko H, Ota M, Mizuki N, Yabuki K, Kondiatis E, Stephens HA, Madanat W, Kanawati CA, Stanford MR and Vaughan RW. MIC-A allele profiles and HLA class I associations in Behcet's disease. Immunogenetics 1999; 49:613-617.
39. Mizuki N, Ota M, Yabuki K, Katsuyama Y, Ando H, Palimeris GD, Kaklamani E, Accorinti M, Pivetti-Pezzi P, Ohno S and Inoko H. Localization of the pathogenic gene of Behcet's disease by microsatellite analysis of three different populations. Invest. Ophthalmol. Vis. Sci. 2000; 41:3702-3708.
40. Mizuki N, Yabuki K, Ota M, Verity D, Katsuyama Y, Ando H, Onari K, Goto K, Imagawa Y, Mandanat W, Fayyad F, Stanford M, Ohno S and Inoko H. Microsatellite mapping of a susceptible locus within the HLA region for Behcet's disease using Jordanian patients. Hum Immunol. 2001; 62:186-190.
41. Salvarani C, Boiardi L, Mantovani V, Olivieri I, Ciancio G, Cantini F, Salvi F, Malatesta R, Molinotti C, Govoni M, Trotta F, Filippini D, Paolazzi G and Viggiani M. Association of MICA alleles and HLA-B51 in Italian patients with Behcet's disease. J. Rheumatol. 2001; 28:1867-1870.
42. Cohen R, Metzger S, Nahir M and Chajek-Shaul T. Association of the MIC-A gene and HLA-B51 with Behcet's disease in Arabs and non-Ashkenazi Jews in Israel. Ann. Rheum. Dis. 2002; 61:157-160.
43. Park SH, Park KS, Seo YI, Min DJ, Kim WU, Kim TG, Cho CS, Mok JW, Park KS and Kim HY. Association of MICA polymorphism with HLA-B51 and disease severity in Korean patients with Behcet's disease. J. Korean Med. Sci. 2002; 17:366-370.
44. Chung YL, Bang DS, Lee ES, Lee SN, Mok JW and Park KS. Behcet's disease: the first Mongolian case in literature showing HLA B51, MICA gene type *5/*6. Yonsei Med. J. 2003; 44:935-938.
45. Tian W, Boggs DA, Uko G, Essiet A, Inyama M, Banjoko B, Adewole T, Ding WZ, Mohseni M, Fritz R, Chen DF, Palmer LJ and Fraser PA. MICA, HLA-B

haplotypic variation in five population groups of sub-Saharan African ancestry. Genes Immun. 2003; 4:500-505.
46. Lee YJ, Huang FY, Wang CH, Lo FS, Tsan KW, Hsu CH, Huang CY, Chang SC and Chang JG. Polymorphism in the transmembrane region of the MICA gene and type 1 diabetes. J. Pediatr. Endocrinol. Metab. 2000; 13:489-496.
47. Gambelunghe G, Ghaderi M, Cosentino A, Falorni A, Brunetti P, Falorni A and Sanjeevi CB. Association of MHC Class I chain-related A (MIC-A) gene polymorphism with Type I diabetes. Diabetologia 2000; 43:507-514.
48. Kawabata Y, Ikegami H, Kawaguchi Y, Fujisawa T, Hotta M, Ueda H, Shintani M, Nojima K, Ono M, Nishino M, Taniguchi H, Noso S, Yamada K, Babaya N and Ogihara T. Age-related association of MHC class I chain-related gene A (MICA) with type 1 (insulin-dependent) diabetes mellitus. Hum. Immunol. 2000; 61:624-629.
49. Park Y, Lee H, Sanjeevi CB and Eisenbarth GS. MICA polymorphism is associated with type 1 diabetes in the Korean population. Diabetes Care 2001; 24:33-38.
50. Gambelunghe G, Ghaderi M, Tortoioli C, Falorni A, Santeusanio F, Brunetti P, Sanjeevi CB and Falorni A. Umbria Type 1 Diabetes Registry. Two distinct MICA gene markers discriminate major autoimmune diabetes types. J. Clin. Endocrinol. Metab. 2001; 86:3754-3760.
51. Bilbao JR, Martin-Pagola A, Calvo B, Perez de Nanclares G, Gepv-N and Castano L. Contribution of MIC-A polymorphism to type 1 diabetes mellitus in Basques. Ann. N. Y. Acad. Sci. 2002; 958:321-324.
52. Sanjeevi CB, Kanungo A, Berzina L, Shtauvere-Brameus A, Ghaderi M and Samal KC. MHC class I chain-related gene a alleles distinguish malnutrition-modulated diabetes, insulin-dependent diabetes, and non-insulin-dependent diabetes mellitus patients from eastern India. Ann. N. Y. Acad. Sci. 2002; 958:341-344.
53. Gupta M, Nikitina-Zake L, Zarghami M, Landin-Olsson M, Kockum I, Lernmark A and Sanjeevi CB. Association between the transmembrane region polymorphism of MHC class I chain related gene-A and type 1 diabetes mellitus in Sweden. Hum. Immunol. 2003; 64:553-561.
54. Gambelunghe G, Falorni A, Ghaderi M, Laureti S, Tortoioli C, Santeusanio F, Brunetti P and Sanjeevi CB. Microsatellite polymorphism of the MHC class I chain-related (MIC-A and MIC-B) genes marks the risk for autoimmune Addison's disease. J. Clin. Endocrinol. Metab. 1999; 84:3701-3707.
55. Park YS, Sanjeevi CB, Robles D, Yu L, Rewers M, Gottlieb PA, Fain P and Eisenbarth GS. Additional association of intra-MHC genes, MICA and D6S273, with Addison's disease. Tissue Antigens 2002; 60:155-163.
56. Gonzalez S, Martinez-Borra J, Torre-Alonso JC, Gonzalez-Roces S, Sanchez del Rio J, Rodriguez Perez A, Brautbar C and Lopez-Larrea C. The MICA-A9 triplet repeat polymorphism in the transmembrane region confers additional susceptibility to the development of psoriatic arthritis and is independent of the association of Cw*0602 in psoriasis. Arthritis Rheum. 1999; 42:1010-1016.
57. Choi HB, Han H, Youn JI, Kim TY and Kim TG. MICA 5.1 allele is a susceptibility marker for psoriasis in the Korean population. Tissue Antigens 2000; 56:548-550.

58. Tay GK, Hui J, Gaudieri S, Schmitt-Egenolf M, Martinez OP, Leelayuwat C, Williamson JF, Eiermann TH and Dawkins RL. PERB11 (MIC): a polymorphic MHC gene is expressed in skin and single nucleotide polymorphisms are associated with psoriasis. Clin. Exp. Immunol. 2000; 119:553-558.
59. Cheng L, Zhang SZ, Xiao CY, Hou YP, Li L, Luo HC, Jiang HY and Zuo WQ. The A5.1 allele of the major histocompatibility complex class I chain-related gene A is associated with psoriasis vulgaris in Chinese. Br. J. Dermatol. 2000; 143:324-329.
60. Gonzalez S, Brautbar C, Martinez-Borra J, Lopez-Vazquez A, Segal R, Blanco-Gelaz MA, Enk CD, Safriman C and Lopez-Larrea C. Polymorphism in MICA rather than HLA-B/C genes is associated with psoriatic arthritis in the Jewish population. Hum. Immunol. 2001; 62:632-638.
61. Gonzalez S, Martinez-Borra J, Lopez-Vazquez A, Garcia-Fernandez S, Torre-Alonso JC and Lopez-Larrea C. MICA rather than MICB, TNFA, or HLA-DRB1 is associated with susceptibility to psoriatic arthritis. J. Rheumatol. 2002; 29:973-978.
62. Grubic Z, Peric P, Eeeuk-Jelicic E, Zunec R, Stingl K, Curkovic B and Kerhin-Brkljacic V. The MICA-A4 triplet repeats polymorphism in the transmembrane region confers additional risk for development of psoriatic arthritis in the Croatian population. Eur. J. Immunogenet. 2004; 31:93-98.
63. Romphruk AV, Romphruk A, Choonhakarn C, Puapairoj C, Inoko H and Leelayuwat C. Major histocompatibility complex class I chain-related gene A in Thai psoriasis patients: MICA association as a part of human leukocyte antigen-B-Cw haplotypes. Tissue Antigens 2004; 63:547-554.
64. Bilbao JR, Martin-Pagola A, Perez De Nanclares G, Calvo B, Vitoria JC, Vazquez F and Castano L. HLA-DRB1 and MICA in autoimmunity: common associated alleles in autoimmune disorders. Ann. N. Y. Acad. Sci. 2003; 1005:314-318.
65. Goto K, Ota M, Ohno S, Mizuki N, Ando H, Katsuyama Y, Maksymowych WP, Kimura M, Bahram S and Inoko H. MICA gene and ankylosing spondylitis: linkage analysis via a transmembrane-encoded triplet repeat polymorphism. Tissue Antigens 1997; 49:503-507.
66. Tsuchiya N, Shiota M, Moriyama S, Ogawa A, Komatsu-Wakui M, Mitsui H, Geraghty DE and Tokunaga K. MICA allele typing of HLA-B27 positive Japanese patients with seronegative spondylarthropathies and healthy individuals: differential linkage disequilibrium with HLA-B27 subtypes. Arthritis Rheum. 1998; 41:68-73.
67. Yabuki K, Ota M, Goto K, Kimura T, Nomura E, Ohno S, Mizuki N, Katsuyama Y, Makysymowych WP, Bahram S, Kimura M and Inoko H. Triplet repeat polymorphism in the MICA gene in HLA-B27 positive and negative caucasian patients with ankylosing spondylitis. Hum. Immunol. 1999; 60:83-86.
68. Martinez-Borra J, Gonzalez S, Lopez-Vazquez A, Gelaz MA, Armas JB, Kanga U, Mehra NK and Lopez-Larrea C. HLA-B27 alone rather than B27-related class I haplotypes contributes to ankylosing spondylitis susceptibility. Hum. Immunol. 2000; 61:131-139.
69. Ricci-Vitiani L, Vacca A, Potolicchio I, Scarpa R, Bitti P, Sebastiani G, Passiu G, Mathieu A and Sorrentino R. MICA gene triplet repeat polymorphism in patients

with HLA-B27 positive and negative ankylosing spondylitis from Sardinia. J. Rheumatol. 2000; 27:2193-2197.
70. Gambelunghe G, Gerli R, Bocci EB, Del Sindaco P, Ghaderi M, Sanjeevi CB, Bistoni O, Bini V and Falorni A. Contribution of MHC class I chain-related A (MICA) gene polymorphism to genetic susceptibility for systemic lupus erythematosus. Rheumatology (Oxford) 2005; 44:287-292.
71. Lopez-Vazquez A, Rodrigo L, Fuentes D, Riestra S, Bousono C, Garcia-Fernandez S, Martinez-Borra J, Gonzalez S and Lopez-Larrea C. MICA-A5.1 allele is associated with atypical forms of celiac disease in HLA-DQ2-negative patients. Immunogenetics 2002; 53:989-991.
72. Lopez-Vazquez A, Rodrigo L, Fuentes D, Riestra S, Bousono C, Garcia-Fernandez S, Martinez-Borra J, Gonzalez S and Lopez-Larrea C. MHC class I chain related gene A (MICA) modulates the development of coeliac disease in patients with the high risk heterodimer DQA1*0501/DQB1*0201. Gut 2002; 50:336-340.
73. Lopez-Vazquez A, Fuentes D, Rodrigo L, Gonzalez S, Moreno M, Fernandez E, Martinez-Borra J and Lopez-Larrea C. MHC class I region plays a role in the development of diverse clinical forms of celiac disease in a Saharawi population. Am. J. Gastroenterol. 2004; 99:662-667.
74. Bolognesi E, Karell K, Percopo S, Coto I, Greco L, Mantovani V, Suoraniemi E, Partanen J, Mustalahti K, Maki M and Momigliano-Richiardi P. Additional factor in some HLA DR3/DQ2 haplotypes confers a fourfold increased genetic risk of celiac disease. Tissue Antigens 2003; 61:308-316.
75. Rueda B, Pascual M, Lopez-Nevot MA, Koeleman BP, Ortega E, Maldonado J, Lopez M and Martin J. Association of MICA-A5.1 allele with susceptibility to celiac disease in a family study. Am. J. Gastroenterol. 2003; 98:359-362.
76. Fernandez L, Fernandez-Arquero M, Gual L, Lazaro F, Maluenda C, Polanco I, Figueredo MA and Gomez de la Concha E. Triplet repeat polymorphism in the transmembrane region of the MICA gene in celiac disease. Tissue Antigens 2002; 59:219-222.
77. Woolley N, Mustalahti K, Maki M and Partanen J. Cytokine gene polymorphisms and genetic association with coeliac disease in the Finnish population. Scand. J. Immunol. 2005; 61:51-56.
78. Ban G, Chu J, Mao C, Yang Z, Xu S, Chu Z, Huang X and Zhang S. A study of the relationship between MICA gene and systemic lupus erythematosus. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2002; 19:298-301.
79. Sugimura K, Ota M, Matsuzawa J, Katsuyama Y, Ishizuka K, Mochizuki T, Mizuki N, Seki SS, Honma T, Inoko H and Asakura H. A close relationship of triplet repeat polymorphism in MHC class I chain-related gene A (MICA) to the disease susceptibility and behavior in ulcerative colitis. Tissue Antigens 2001; 57:9-14.
80. Seki SS, Sugimura K, Ota M, Matsuzawa J, Katsuyama Y, Ishizuka K, Mochizuki T, Suzuki K, Yoneyama O, Mizuki N, Honma T, Inoko H and Asakura H. Stratification analysis of MICA triplet repeat polymorphisms and HLA antigens associated with ulcerative colitis in Japanese. Tissue Antigens 2001; 58:71-76.
81. Glas J, Martin K, Brunnler G, Kopp R, Folwaczny C, Weiss EH and Albert ED. MICA, MICB and C1_4_1 polymorphism in Crohn's disease and ulcerative colitis. Tissue Antigens 2001; 58:243-249.

82. Fdez-Morera JL, Rodrigo L, Lopez-Vazquez A, Rodero SR, Martinez-Borra J, Nino P, Gonzalez S and Lopez-Larrea C. MHC class I chain-related gene A transmembrane polymorphism modulates the extension of ulcerative colitis. Hum. Immunol. 2003; 64:816-822.
83. Liu CJ, Lee YJ, Chang KW, Shih YN, Liu HF and Dang CW. Polymorphism of the MICA gene and risk for oral submucous fibrosis. J. Oral Pathol. Med. 2004; 33:1-6.
84. Lo FS, Lee YJ, Huang CY, Lin CH, Chang SC, Dang CW and Liu HF. Polymorphism in the transmembrane region of the major histocompatibility complex class I chain-related gene A: association of five GCT repetitions with Graves' disease in children. Thyroid 2003; 13:839-843.
85. Wiencke K, Spurkland A, Schrumpf E and Boberg KM. Primary sclerosing cholangitis is associated to an extended B8-DR3 haplotype including particular MICA and MICB alleles. Hepatology 2001; 34:625-630.
86. Norris S, Kondeatis E, Collins R, Satsangi J, Clare M, Chapman R, Stephens H, Harrison P, Vaughan R and Donaldson P. Mapping MHC-encoded susceptibility and resistance in primary sclerosing cholangitis: the role of MICA polymorphism. Gastroenterology 2001; 120:1475-1482.
87. Touitou I, Picot MC, Domingo C, Notarnicola C, Cattan D, Demaille J and Kone-Paut I. The MICA region determines the first modifier locus in familial Mediterranean fever. Arthritis Rheum. 2001; 44:163-169.
88. Medlej-Hashim M, Delague V, Chouery E, Salem N, Rawashdeh M, Lefranc G, Loiselet J and Mégarbané A. Amyloidosis in familial Mediterranean fever patients: correlation with MEFV genotype and SAA1 and MICA polymorphisms effects. BMC Med. Genet. 2004; 5:4.
89. Mehra NK, Jaini R, Balamurugan A, Kanga U, Prabhakaran D, Jain S, Talwar KK and Sharma BK. Immunogenetic analysis of Takayasu arteritis in Indian patients. Int. J. Cardiol. 1998; 66 Suppl 1:S127-132; discussion S133.
90. Kimura A, Kobayashi Y, Takahashi M, Ohbuchi N, Kitamura H, Nakamura T, Satoh M, Sasaoka T, Hiroi S, Arimura T, Akai J, Aerbajinai W, Yasukochi Y and Numano F. MICA gene polymorphism in Takayasu's arteritis and Buerger's disease. Int. J. Cardiol. 1998; 66 Suppl 1:S107-113; discussion S115.
91. Jaini R, Mandal S, Khazanchi RK and Mehra NK. Immunogenetic analysis of Buerger's disease in India. Int. J. Cardiol. 1998; 66 Suppl 1:S283-285.
92. Goto K, Ota M, Ando H, Mizuki N, Nakamura S, Inoue K, Yabuki K, Kotake S, Katsuyama Y, Kimura M, Inoko H and Ohno S. MICA gene polymorphisms and HLA-B27 subtypes in Japanese patients with HLA-B27-associated acute anterior uveitis. Invest. Ophthalmol. Vis. Sci. 1998; 39:634-637.
93. Goto K, Ota M, Maksymowych WP, Mizuki N, Yabuki K, Katsuyama Y, Kimura M, Inoko H and Ohno S. Association between MICA gene A4 allele and acute anterior uveitis in white patients with and without HLA-B27. Am. J. Ophthalmol. 1998; 126:436-441.
94. Sanjeevi CB, Gambelunghe G, Falorni A, Shtauvere-Brameus A and Kanungo A. Genetics of latent autoimmune diabetes in adults. Ann. N. Y. Acad. Sci. 2002; 958:107-111.

95. Berzina L, Shtauvere-Brameus A, Rumba I and Sanjeevi CB. Microsatellite allele A5.1 of MHC class I chain-related gene A is associated with latent autoimmune diabetes in adults in Latvia. Ann. N. Y. Acad. Sci. 2002; 958:353-356.
96. Novota P, Kolesar L, Slavcev A and Cerna M. Fluorescence-based automated fragment analysis of microsatellite polymorphism within the transmembrane region of the MIC-A gene. Folia Biol (Praha) 2004; 50:21-23.
97. Picco P, Porfirio B, Gattorno M, Buoncompagni A, Falcini F, Cusano R, Bordo D, Pistoia V, Ravazzolo R and Seri M. MICA gene polymorphisms in an Italian paediatric series of juvenile Behcet disease. Int. J. Mol. Med. 200; 10:575-578.
98. Hassan AB, Nikitina-Zake L, Padyukov L, Karlsson G, Gupta M, Lundberg IE and Sanjeevi CB. MICA4/HLA-DRB1*04/TNF1 haplotype is associated with mixed connective tissue disease in Swedish patients. Hum. Immunol. 2003; 64:290-296.
99. Chung-Ji L, Yann-Jinn L, Hsin-Fu L, Ching-Wen D, Che-Shoa C, Yi-Shing L and Kuo-Wei C. The increase in the frequency of MICA gene A6 allele in oral squamous cell carcinoma. J. Oral Pathol. Med. 2002; 31:323-328.
100. Karacki PS, Gao X, Thio CL, Thomas DL, Goedert JJ, Vlahov D, Kaslow RA, Strathdee S, Hilgartner MW, O'Brien SJ and Carrington M. MICA and recovery from hepatitis C virus and hepatitis B virus infections. Genes Immun. 2004;5:261-266.
101. Groh V, Bahram S, Bauer S, Herman A, Beauchamp M and Spies T. Cell stress-regulated human major histocompatibility complex class I gene expressed in gastrointestinal epithelium. Proc. Natl Acad. Sci. U S A. 1996; 93:12445-12450.
102. Groh V, Rhinehart R, Secrist H, Bauer S, Grabstein KH and Spies T. Broad tumor-associated expression and recognition by tumor-derived gamma delta T cells of MICA. Proc. Natl Acad. Sci. U S A. 1999; 96:6879-6884.
103. Suemizu H, Radosavljevic M, Kimura M, Sadahiro S, Yoshimura S, Bahram S and Inoko H. A basolateral sorting motif in the MICA cytoplasmic tail. Proc. Natl Acad. Sci. U S A. 2002; 99:2971-2976.
104. Groh V, Steinle A, Bauer S and Spies T. Recognition of stress-induced MHC molecules by intestinal epithelial gammadelta T cells. Science 1998; 279:1737-1740.
105. Steinle A, Groh V and Spies T. Diversification, expression, and gamma delta T cell recognition of evolutionarily distant members of the MIC family of major histocompatibility complex class I-related molecules. Proc. Natl Acad. Sci. U S A. 1998; 95:12510-12515.
106. Bauer S, Groh V, Wu J, Steinle A, Phillips JH, Lanier LL and Spies T. Activation of NK cells and T cells by NKG2D, a receptor for stress-inducible MICA. Science 1999; 285:727-729.
107. Li P, Morris DL, Willcox BE, Steinle A, Spies T and Strong RK. Complex structure of the activating immunoreceptor NKG2D and its MHC class I-like ligand MICA. Nat. Immunol. 2001; 2:443-451.
108. Eleme K, Taner SB, Onfelt B, Collinson LM, McCann FE, Chalupny NJ, Cosman D, Hopkins C, Magee AI and Davis DM. Cell surface organization of stress-inducible proteins ULBP and MICA that stimulate human NK cells and T cells via NKG2D. J. Exp. Med. 2004; 199:1005-1010.
109. Yamamoto K, Fujiyama Y, Andoh A, Bamba T and Okabe H. Oxidative stress increases MICA and MICB gene expression in the human colon carcinoma cell line (CaCo-2). Biochim. Biophys. Acta. 2001; 1526:10-12.

110. Groh V, Rhinehart R, Randolph-Habecker J, Topp MS, Riddell SR and Spies T. Costimulation of CD8alphabeta T cells by NKG2D via engagement by MIC induced on virus-infected cells. Nat. Immunol. 2001; 2:255-260.
111. Das H, Groh V, Kuijl C, Sugita M, Morita CT, Spies T and Bukowski JF. MICA engagement by human Vgamma2Vdelta2 T cells enhances their antigen-dependent effectors function. Immunity 2001; 15:83-93.
112. Tieng V, Le Bouguenec C, du Merle L, Bertheau P, Desreumaux P, Janin A, Charron D and Toubert A. Binding of Escherichia coli adhesin AfaE to CD55 triggers cell-surface expression of the MHC class I-related molecule MICA. Proc. Natl Acad. Sci. U S A. 2002; 99:2977-2982.
113. Molinero LL, Fuertes MB, Girart MV, Fainboim L, Rabinovich GA, Costas MA and Zwirner NW. NF-kappa B regulates expression of the MHC class I-related chain A gene in activated T lymphocytes. J. Immunol. 2004; 173:5583-5590.
114. Li P, Willie ST, Bauer S, Morris DL, Spies T and Strong RK. Crystal structure of the MHC class I homolog MIC-A, a gammadelta T cell ligand. Immunity 1999; 10:577-584.
115. Li P, Morris DL, Willcox BE, Steinle A, Spies T and Strong RK. Complex structure of the activating immunoreceptor NKG2D and its MHC class I-like ligand MICA. Nat. Immunol. 2001; 2:443-451.
116. Berman H-M, Westbrook J, Feng Z, Gilliland G, Bhat T-N, Weissig H, Shindyalov I-N and Bourne P-E. The Protein Data Bank. Nucl. Acids Res., 2000; 28: 235-242.