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Killer-cell immunoglobulin-like receptor (KIR) nomenclature report, 2002

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During discussion at the World Health Organization (WHO) Nomenclature Committee for Factors of the HLA System meeting in Victoria, Canada in May 2002, it was decided to form a subcommittee to co-ordinate the naming of alleles of the genes encoding the killer-cell immunoglobulin-like receptors (KIR) (1). These genes are encoded on chromosome 19 (19q13.4) and have varying degrees of polymorphism. The receptors encoded by the *KIR* genes are expressed by natural killer (NK) cells and a subset of T cells and some of them have been shown to have specificity for determinants of HLA class I molecules. The extracellular ligand-binding part of KIR consists of two or three immunoglobulin (Ig)-like domains. The discussions which took place in Victoria are further to earlier discussions on KIR nomenclature at the NK Polymorphism meeting (27–29th July 2001) in Cambridge, UK. In addition, a request has been made by the International Union of Immunological Societies (IUIS) to provide a standardized nomenclature for the expressed protein products of the KIR genes.

KIR gene nomenclature

The first KIR to be defined were inhibitory receptors, and when initially coined, the acronym stood for killer-cell inhibitory receptor. With appreciation that this family of molecules included both activating and inhibitory receptors, the KIR acronym was retained and is now accepted as an abbreviation for Killer-cell Immunoglobulin-like Receptor (2). Unlike HLA genes, which for practical and historical reasons are named by the WHO Nomenclature Committee for Factors of the HLA System, the naming of KIR genes is the responsibility of the HUGO Genome Nomenclature Committee (HGNC). Agreement

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was reached with the HGNC for naming the *KIR* genes and a total of 17 genes have been recognized and named (Table 1), the ones most recently assigned being *KIR2DL5A, KIR2DL5B, KIR2DP1, KIR3DL3,* and *KIR3DP1*. The subcommittee will continue to work closely with the HGNC in the future to ensure all newly described genes are assigned appropriate names.

The names given to the *KIR* genes are based on the structures of the molecules they encode. The first digit following the KIR acronym corresponds to the number of Ig-like domains in the molecule and the 'D' denotes 'domain'. The D is followed by either an 'L' indicating a 'Long' cytoplasmic tail, an 'S' indicating a 'Short' cytoplasmic tail or a 'P' for pseudogenes. The final digit indicates the number of the gene

KIR gene names

Gene symbol	Protein symbol	Description	Aliases	Reference or submitting author
KIR2DL1	KIR2DL1	killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 1	cl-42, nkat1, 47.11, p58.1, CD158a	(10,11)
KIR2DL2	KIR2DL2	killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 2	cl-43, nkat6, CD158b1	(10,11)
KIR2DL3	KIR2DL3	killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 3	cl-6, nkat2, nkat2a, nkat2b, p58, CD158b2	(10,11)
KIR2DL4	KIR2DL4	killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 4	103AS, 15.212, CD158d	(12)
KIR2DL5A	KIR2DL5A	killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 5A	KIR2DL5.1, CD158f	(13)
KIR2DL5B	KIR2DL5B	killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 5B	KIR2DL5.2, KIR2DL5.3, KIR2DL5.4	(13)
KIR2DS1	KIR2DS1	killer cell immunoglobulin-like receptor, two domains, short cytoplasmic tail, 1	EB6ActI, EB6ActII, CD158h	(14)
KIR2DS2	KIR2DS2	killer cell immunoglobulin-like receptor, two domains, short cytoplasmic tail, 2	cl-49, nkat5, 183ActI, CD158j	(10,11)
KIR2DS3	KIR2DS3	killer cell immunoglobulin-like receptor, two domains, short cytoplasmic tail, 3	nkat7	(15)
KIR2DS4	KIR2DS4	killer cell immunoglobulin-like receptor, two domains, short cytoplasmic tail, 4	cl-39, KKA3, nkat8, CD158i	(11,15)
KIR2DS5	KIR2DS5	killer cell immunoglobulin-like receptor, two domains, short cytoplasmic tail, 5	nkat9, CD158g	(15)
KIR2DP1	KIR2DP1	killer cell immunoglobulin-like receptor, two domains, pseudogene 1	KIRZ, KIRY, KIR15, KIR2DL6	(13)
KIR3DL1	KIR3DL1	killer cell immunoglobulin-like receptor, three domains, long cytoplasmic tail, 1	cl-2, NKB1, cl-11, nkat3, NKB1B, AMB11, KIR, CD158e1	(10)
KIR3DL2	KIR3DL2	killer cell immunoglobulin-like receptor, three domains, long cytoplasmic tail, 2	cl-5, nkat4, nkat4a, nkat4b, CD158k	(10)
KIR3DL3	KIR3DL3	killer cell immunoglobulin-like receptor, three domains, long cytoplasmic tail, 3	KIRC1, KIR3DL7, KIR44, CD158z	(16)
KIR3DS1	KIR3DS1	killer cell immunoglobulin-like receptor, three domains, short cytoplasmic tail, 1	nkat10, CD158e2	(15)
KIR3DP1	KIR3DP1	killer cell immunoglobulin-like receptor, three domains, pseudogene 1	KIRX, KIR48, KIR2DS6, KIR3DS2P, CD158c	(13)

Table 1

encoding a protein with this structure. Thus *KIR2DL1*, *KIR2DL2* and *KIR2DL3* all encode receptors having two extracellular Ig-like domains and a long cytoplasmic tail (3). Where two or more genes have very similar structures and have very similar sequences, they may be given the same number but distinguished by a final letter, for example the *KIR2DL5*A and *KIR2DL5B* genes (4). The similarity of these two genes suggests they are related by a recent gene duplication event.

Certain KIR genes have arisen through recombination between two other KIR genes and are effectively functional hybrids of the parent genes. The question for gene nomenclature is whether the recombinant gene should have a new unique name or be given a name that in some way represents its evolutionary ontogeny. If we consider a hypothetical recombination between *3DL1* and *3DL2*, we could name the new product according to these parent genes, either by concatenating their names (i.e., *3DL13DL2*) or by arbitrarily choosing to name the gene after the parent which has contributed the 5′ end of its sequence (i.e., *3DL1* if the recombination was 5′ *3DL1* × *3DL2* 3′ or *3DL2* if the recombination was 5′*3DL2* × *3DL1* 3′). This system of naming derived from the parent gene makes many assumptions about the nature of the recombination and the function of the new gene and presumes that there have been no further modifications to the gene that would merit providing a new name. The alternative of assigning a new name to the recombinant gene using the same criteria that have been applied in naming all other new *KIR* genes (based on domain structure, cytoplasmic tail length and sequence similarity) avoids the ambiguities of these assumptions. In this case, the new gene could be assigned *3DL*'*n*' where 'n' represents the next number in the series.

Perhaps the simplest solution to naming alleles of a recombinant gene is to assign the allele with the gene name of the gene contributing the immunoglobulin-like domains, providing sufficient homology is maintained. In such situations where the 3′ region of the recombinant allele is inconsistent with the L/S designation of the gene, a suffix would be added to the allele name to indicate the aberrant nature of the allele. Using this nomenclature, it would be possible to rename the alleles of the *3DS1* gene, which behave as alleles of the *3DL1* gene, in the *3DL1* series with an 'S' suffix to indicate their short tail.

KIR protein nomenclature

Consistent with standard genetic nomenclature, the names of genes and alleles are given in italic typeface. The names for the KIR proteins are the same as those used for the *KIR* genes, however, they will be presented as normal typeface, see Table 1.

Like other cell surface molecules of the immune system, the KIR molecules have also been given a CD designation and are recognized as members of the CD158 series (see the list of aliases and previous designations given in (Table 1) (5–7).

KIR allele nomenclature

Following the success of the nomenclature used for HLA alleles, it was decided to name *KIR* allele sequences in an analogous fashion. After the gene name, an asterisk will be used as a separator before a numerical allele designation. The first three digits of the numerical designation will be used to indicate alleles that differ in the sequences of their encoded proteins. The next two digits will be used to distinguish alleles that only differ by synonymous (non-coding) differences within the coding sequence. The final two digits will be used to distinguish alleles that only differ by substitutions in an intron, promoter, or other non-coding region of the sequence. A complete listing of all *KIR* allele sequences assigned official names can be found in Table 2.

Evidence exists indicating that the *3DS1* and *3DL1* genes behave as alleles of the same gene. It is likely that at some time in the future the alleles of these genes will be combined under one gene name. To avoid confusion, it has been decided to name the alleles of both genes in a single numerical series, thus *3DL1*001–3DL1*009* are followed by *3DS1*010–3DS1*014*. Likewise the alleles of the *2DL5A* and *2DL5B* genes have also been named in a single series, because of the similarity of these sequences.

Naming KIR haplotypes

The *KIR* gene family forms part of the leukocyte receptor complex (LRC), which includes several related gene families that encode cell-surface receptors of the immune system and have extracellular regions made up of Ig-like domains. Within the LRC, the *KIR* genes appear the most variable. In addition to allelic polymorphism, there is haplotypic variability due to the different number and kind of *KIR* genes. This situation is analogous to that of the HLA-DRB genes, but contrasts with that of the HLA class I gene organization which is relatively fixed. Because haplotypic diversity is a major contributor to the population diversity of KIR and of NK cell repertoires, there was agreement amongst the committee that it would be useful to devise a robust and versatile nomenclature system that could be used to describe the gene content of different KIR haplotypes. With this in mind it was suggested that each KIR Haplotype be designated 'KH'

KIR allele names

Allele name	Previous name	Cell ID	Accession Number	Reference or submitting author
*2DL1*001*	NKAT1	?	L41267	(10)
*2DL1*002*	cl-42	?	U24076	(11)
*2DL1*00301*	cl-47.11	NK-lib	U24078	(11)
*2DL1*00302*	2DL1M, 2DL1v2	MU	AF285431	(17)
*2DL1*004*	2DL1v	NV	AF022045	(18)
*2DL1*005*	2DL1W102, 2DL1v3	WC	AF285432	(17)
*2DL2*001*	cl-43	?	U24075	(11)
*2DL2*002*	NKAT6	?	L76669	(15)
*2DL2*003*	2DL2v2, 2DL2M	MU	AF285434	(17)
*2DL2*004*	2DL2v1	WC	AF285433	(17)
*2DL3*001*	NKAT2, cl-6	?, NK3.3	L41268, U24074	(10,11)
*2DL3*002*	NKAT2a	?	L76662	(15)
*2DL3*003*	NKAT2b	?	L76663	(15)
*2DL3*004*	KIR-023GB	?	U73395	(19)
*2DL3*005*	2DL3v	PP	AF022048	(18)
*2DL3*006*	2DL3W308	WC	AF285435	(17)
*2DL4*00101*	NK3.3#27	NK3.3	X99480	(20)
*2DL4*00102*	2DL4v1	PP, NV	AF034771	(18)
*2DL4*00201*	15.212	?	X97229	(20)
*2DL4*00202*	2DL4v2	PP, NV	AF034772	(18)
*2DL4*003*	KIR103AS	YT, NK92	U71199	(12)
*2DL4*004*	KIR103LP	?	AF002979	(21)
*2DL4*005*	2DL4v3	NV	AF034773	(18)
*2DL4*006*	2DL4v4	RR	AF285436	(17)
*2DL4*007*	–	LP	AF276292	A Selvakumar, New York, USA
*2DL5A*001*	2DL5.1	NV, XX-1060P11	AF204903, AF217485, AL133414	(13,22,23)
*2DL5B*002*	2DL5.2	NV	AF217486	(22)
*2DL5B*003*	2DL5.3	WCS	AF217487	(22)
*2DL5B*004*	2DL5.4	CC	AF260138, AF260139, AF260140, AF260141	(22)
*2DS1*001*	Eb6ActI	PA	X89892	(14)
*2DS1*002*	2DS1v	NV	AF022046	(18)
*2DS1*003*	Eb6ActII	GT	X98858	(24)
*2DS1*004*	2DS1v1	WC	AF285437	(17)
*2DS2*001*	NKAT5, cl-49	?,?	L41347, U24079	(10,11)
*2DS2*002*	183ActI	23D	X89893	(14)
*2DS2*003*	TG14#35	TG14	AJ002103	R Biassoni, Genova, Italy
*2DS2*004*	2DS2v1	WC	AF285438	(17)
*2DS2*005*	2DS2v2	FC	AF285439	(17)
*2DS3*00101*	NKAT7	?	L76670	(15)

Table 2

Continued

Allele name	Previous name	Cell ID	Accession Number	Reference or submitting author
*2DS3*00102*	59C_K3	Pag1	X97231	R Biassoni, Genova, Italy
*2DS3*00103*	2DS3v	NV	AF022047	(18)
*2DS4*00101*	cl-39, cl-17, KKA3_34–52	?,?, 4053, Mal 43–52	U24077, AF002255, AJ417555, X94609	(11,25,26), HW Chan, Pittsburgh, USA
*2DS4*00102*	NKAT8	?	L76671	(15)
*2DS4*002*	2DS4v1	RR	AF285440	(17)
*2DS4 *003*	Deletion V, KIR1D	3321	AJ417554	(26,27)
*2DS5*001*	NKAT9	?	L76672	(15)
*2DS5*002*	–	NV	AF208054	(28)
*2DS5*003*	–	WC	AF272389	(28)
*2DP1*001*	KIR15	NV	AF204906, AF204907, AF204908	(13)
*2DP1*002*	–	CTB-61M7	AC011501	(29)
*3DL1*00101*	NKAT3, cl-11, AMB11.115	?,?, AMB11	L41269, U30274, X94262	(10,30,31)
*3DL1*00102*	Nnkat-3	?	AF262968	(32)
*3DL1*002*	NKB1, cl-2	NKB1,?	U31416, U30273	(30,33)
*3DL1*003*	3DL1v	NV	AF022049	(18)
*3DL1*00401*	W204	WC	AF262970	(32)
*3DL1*00402*	M322	MU	AF262969	(32)
*3DL1*005*	3DL1v2	YW	AF262971	(32)
*3DL1*006*	NJN55	?	AF262972	(32)
*3DL1*007*	r3k10	RR	AF262973	(32)
*3DL1*008*	r3k2	RR	AF262974	(32)
*3DL1*009*	–	3321, 4053	AJ417556, AJ417557	(34)
*3DL2*001*	NKAT4	?	L41270	(10)
*3DL2*002*	cl-5, AMC5	?,?	U30272, X94374	(30,31)
*3DL2*003*	1.1, NKAT4A	?,?	X94373, L76665	(15,31)
*3DL2*004*	17.1C	?	X93595	(31)
*3DL2*005*	NKAT4b	?	L76666	(15)
*3DL2*006*	3DL2Wv2	WC	AF262966	(32)
*3DL2*007*	b3DL2b	BS	AF262965	(32)
*3DL2*008*	r3k17	RR	AF262967	(32)
*3DL2*009*	rrk100	RR	AF263617	(17)
*3DL2*010*	–	?	AY059418	(35)
*3DL2*011*	–	?	AY059419	(35)
*3DL2*012*	–	?	AY059420	(35)
*3DL3*001*	KIRCl	?	AF072407, AF072408, AF072409, AF072410	(16)

Table 2

Continued

Allele name	Previous name	Cell ID	Accession Number	Reference or submitting author
*3DL3*00201*	KIR44a	NV, UV5HL9–5B	AF204909, AF204910, AF204911, AC006293	(13, 29)
*3DL3*00202*	KIR44b	NV	AF204912, AF204913, AF204914	(13)
*3DL3*003*	KIRC1	XX-1060P11	AL133414	(23)
*3DL3*004*	3DL7	?	AF352324	(36)
*3DS1*010*	NKAT10, 3DS1*001	?	L76661	(15)
*3DS1*011*	C97.12#5, 3DS1*002	?	X97233	R Biassoni, Genova, Italy
*3DS1*012*	KIR-123FM, 3DS1*003	?	U73396	(19)
*3DS1*013*	3DS1v, 3DS1*004	NV	AF022044	(18)
*3DS1*014*	3DS1*005	4373	AJ417558	(34)
*3DP1*001*	KIR48a	NV	AF204915, AF204916, AF204917	(13)
*3DP1*002*	KIRX	XX-1060P11	AL133414	(23)
*3DP1*00301*	KIR48b	NV	AF204918, AF204919, AF204920	(13)
*3DP1*00302*	2DS6	CTB-61M7	AC011501	(29)

Table 2

followed by a hyphen and then a unique three digit number, assigned sequentially indicating the different haplotypes. This system would allow 999 *KIR* haplotypes to be named.

Two kinds of *KIR* haplotype have been described based upon gene content, and are designated A and B. No single specific criterion distinguishes all A and B haplotypes, a current working definition being as follows. Group B haplotypes are characterized by one or more of the following genes: *KIR2DL5*, *KIR2DS1*, *KIR2DS2*, *KIR2DS3*, *KIR2DS5* and *KIR3DS1*. Conversely, group A haplotypes are characterized by the absence of all these genes. As a consequence of these differences the B haplotypes have more genes encoding activating *KIR* than A haplotypes. Different investigators have used different criteria to distinguish A and B haplotypes and certain haplotypes are assigned differently when using these different criteria ((8, 9) and other refs). The committee felt that the distinction between A and B haplotypes is a useful one, having potential biological and medical significance, and that efforts should be made to develop a consistent and logical set of criteria for distinguishing them. It was proposed that as part of the haplotype nomenclature, the letters A or B would follow the three digit number. So a haplotype may, for example, be named KH-001A or KH-022B.

To supplement the haplotype name and provide further information, it was suggested that following the haplotype designation, a 17 digit binary code would indicate the presence or absence of the genes on the haplotype. Each digit in the code would represent a distinct gene: a '1' indicating presence of the gene, a '0' its absence. Thus a full haplotype name could be given as KH−001A−11100010011011011. This system can readily accommodate the discovery of additional *KIR* genes by simple introduction of another digit. Wherever possible the order of the genes in the full haplotype designation will reflect their order in the genome. However when digits are added to represent newly discovered genes they will be placed at the end of the code, in the order of their discovery.

To refine haplotype definition, a further series of digits could be used to indicate which allele for each KIR gene is present on a haplotype. It is suggested that such an addition would only be made to the nomenclature once it had become common practice to type *KIR* genes at the allele level.

Naming KIR genotypes

As well as assigning unique designations to KIR haplotypes it was also thought useful to provide a nomenclature system to describe KIR genotypes. It was suggested that each genotype would be indicated by the prefix 'KG' followed by a hyphen, in turn followed by a unique four digit number. This would then be followed with an optional hyphen and 17 digit binary code. As in the naming of haplotypes, the binary code would indicate the presence (a 1) or absence (a 0) of KIR genes in the genotype. So

a KIR genotype may be written KG-0202-11101011011011101. The order of genes would be as used for the haplotype code.

Further refinements of this system to indicate the presence of null alleles or to demonstrate homozygosity of alleles have been suggested. However, in the short term it has been recommended that the community gains familiarity with the system as proposed before implementing any additional complexity.

KIR Sequence Database

In collaboration with the European Bioinformatics Institute, the KIR-DB, a database of the nucleotide and protein sequence alignments for all of the officially recognized *KIR* alleles, has been established. Together with the sequences, information is given on the nomenclature assigned to the different *KIR* alleles. In the near future further tools for the submission and analysis of KIR sequences will be made available from the website. The KIR-DB may be accessed via the World Wide Web from www.ebi.ac.uk/ipd/kir

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