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

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During discussion at the 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) (Marsh et al. 2002). 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 (27–29 July 2001) in Cambridge, UK. In addition a request has been made by the International Union of Immunological Societies (IUIS) to provide a standardised nomenclature for the expressed protein products of the KIR genes.

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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 (Long et al. 1996). 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 was reached with the HGNC for naming the *KIR* genes and a total of 17 genes have been recognised 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

Table 1 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	(Colonna and Samaridis 1995; Wagtmann et al. 1995a)
KIR2DL2	KIR2DL2	Killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 2	cl-43, nkat6, CD158b1	(Colonna and Samaridis 1995; Wagtmann et al. 1995a)
KIR2DL3	KIR2DL3	Killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 3	cl-6, nkat2, nkat2a, nkat2b, p58, CD158b2	(Colonna and Samaridis 1995; Wagtmann et al. 1995a)
KIR2DL4	KIR2DL4	Killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 4	103AS, 15.212, CD158d	(Selvakumar et al. 1996)
KIR2DL5A	KIR2DL5A	Killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 5A	KIR2DL5.1, CD158f	(Vilches et al. 2000c)
KIR2DL5B	KIR2DL5B	Killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 5B	KIR2DL5.2, KIR2DL5.3, KIR2DL5.4	(Vilches et al. 2000c)
KIR2DS1	KIR2DS1	Killer cell immunoglobulin-like receptor, two domains, short cytoplasmic tail, 1	EB6ActI, EB6ActII, CD158 h	(Biassoni et al. 1996)
KIR2DS2	KIR2DS2	Killer cell immunoglobulin-like receptor, two domains, short cytoplasmic tail, 2	cl-49, nkat5, 183ActI, CD158j	(Colonna and Samaridis 1995; Wagtmann et al. 1995a)
KIR2DS3	KIR2DS3	Killer cell immunoglobulin-like receptor, two domains, short cytoplasmic tail, 3	nkat7	(Dohring et al. 1996)
KIR2DS4	KIR2DS4	Killer cell immunoglobulin-like receptor, two domains, short cytoplasmic tail, 4	cl-39, KKA3, nkat8, CD158i	(Dohring et al. 1996; Wagtmann et al. 1995a)
KIR2DS5	KIR2DS5	Killer cell immunoglobulin-like receptor, two domains, short cytoplasmic tail, 5	nkat9, CD158 g	(Dohring et al. 1996)
KIR2DP1	KIR2DP1	Killer cell immunoglobulin-like receptor, two domains, pseudogene 1	KIRZ, KIRY, KIR15, KIR2DL6	(Vilches et al. 2000c)
KIR3DL1	KIR3DL1	Killer cell immunoglobulin-like receptor, three domains, long cytoplasmic tail, 1	cl-2, NKB1, cl-11, nkat3, NKB1B, AMB11, KIR, CD158e1	(Colonna and Samaridis 1995)
KIR3DL2	KIR3DL2	Killer cell immunoglobulin-like receptor, three domains, long cytoplasmic tail, 2	cl-5, nkat4, nkat4a, nkat4b, CD158 k	(Colonna and Samaridis 1995)
KIR3DL3	KIR3DL3	Killer cell immunoglobulin-like receptor, three domains, long cytoplasmic tail, 3	KIRC1, KIR3DL7, KIR44, CD158z	(Torkar et al. 1998)
KIR3DS1	KIR3DS1	Killer cell immunoglobulin-like receptor, three domains, short cytoplasmic tail, 1	nkat10, CD158e2	(Dohring et al. 1996)
KIR3DP1	KIR3DP1	Killer cell immunoglobulin-like receptor, three domains, pseudogene 1	KIRX, KIR48, KIR2DS6, KIR3DS2P, CD158c	(Vilches et al. 2000c)

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 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 (Vilches and Parham 2002). 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 *KIR2DL5A* and *KIR2DL5B* genes (Gomez-Lozano et al. 2002). 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 recognised as members of the CD158 series (see the list of aliases and previous designations given in Table 1) (André et al. 2001; Moretta et al. 1997; Pascal et al. 2002).

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 either 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* to *3DL1*009* are followed with *3DS1*010* to *3DS1*014*. Likewise the alleles of the *2DL5A* and *2DL5B* genes have also been named in a single series, due to 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 seen for the HLA-DRB genes, but contrasts with that of the HLA class I gene organisation 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" 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 characterised 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 (Hsu et al. 2002a; Uhrberg et al. 1997; and other references). 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.

Table 2 KIR allele names

Allele Name	Previous name	Cell ID	Accession Number	Reference or submitting author
*2DL1*001*	NKAT1	?	L41267	(Colonna and Samaridis 1995)
*2DL1*002*	cl-42	?	U24076	(Wagtmann et al. 1995a)
*2DL1*00301*	cl-47.11	NK-lib	U24078	(Wagtmann et al. 1995a)
*2DL1*00302*	2DL1 M, 2DL1v2	MU	AF285431	(Rajalingam et al. 2001)
*2DL1*004*	2DL1v	NV	AF022045	(Valiante et al. 1997)
*2DL1*005*	2DL1W102, 2DL1v3	WC	AF285432	(Rajalingam et al. 2001)
*2DL2*001*	cl-43	?	U24075	(Wagtmann et al. 1995a)
*2DL2*002*	NKAT6	?	L76669	(Dohring et al. 1996)
*2DL2*003*	2DL2v2, 2DL2 M	MU	AF285434	(Rajalingam et al. 2001)
*2DL2*004*	2DL2v1	WC	AF285433	(Rajalingam et al. 2001)
*2DL3*001*	NKAT2, cl-6	?, NK3.3	L41268, U24074	(Colonna and Samaridis 1995; Wagtmann et al. 1995a)
*2DL3*002*	NKAT2a	?	L76662	(Dohring et al. 1996)
*2DL3*003*	NKAT2b	?	L76663	(Dohring et al. 1996)
*2DL3*004*	KIR-023 GB	?	U73395	(Selvakumar et al. 1997a)
*2DL3*005*	2DL3v	PP	AF022048	(Valiante et al. 1997)
*2DL3*006*	2DL3W308	WC	AF285435	(Rajalingam et al. 2001)
*2DL4*00101*	NK3.3#27	NK3.3	X99480	(Cantoni et al. 1998)
*2DL4*00102*	2DL4v1	PP, NV	AF034771	(Valiante et al. 1997)
*2DL4*00201*	15.212	?	X97229	(Cantoni et al. 1998)
*2DL4*00202*	2DL4v2	PP, NV	AF034772	(Valiante et al. 1997)
*2DL4*003*	KIR103AS	YT, NK92	U71199	(Selvakumar et al. 1996)
*2DL4*004*	KIR103LP	?	AF002979	(Selvakumar et al. 1997b)
*2DL4*005*	2DL4v3	NV	AF034773	(Valiante et al. 1997)
*2DL4*006*	2DL4v4	RR	AF285436	(Rajalingam et al. 2001)
*2DL4*007*	–	LP	AF276292	A. Selvakumar, New York, USA
*2DL5A*001*	2DL5.1	NV, XX-1060P11	AF204903, AF217485, AL133414	(Vilches et al. 2000a, 2000c; Wilson et al. 2000)
*2DL5B*002*	2DL5.2	NV	AF217486	(Vilches et al. 2000a)
*2DL5B*003*	2DL5.3	WCS	AF217487	(Vilches et al. 2000a)
*2DL5B*004*	2DL5.4	CC	AF260138, AF260139, AF260140, AF260141	(Vilches et al. 2000a)
*2DS1*001*	Eb6ActI	PA	X89892	(Biassoni et al. 1996)
*2DS1*002*	2DS1v	NV	AF022046	(Valiante et al. 1997)
*2DS1*003*	Eb6ActII	GT	X98858	(Biassoni et al. 1997)
*2DS1*004*	2DS1v1	WC	AF285437	(Rajalingam et al. 2001)
*2DS2*001*	NKAT5, cl-49	?, ?	L41347, U24079	(Colonna and Samaridis 1995; Wagtmann et al. 1995a)
*2DS2*002*	183ActI	23D	X89893	(Biassoni et al. 1996)
*2DS2*003*	TG14#35	TG14	AJ002103	R. Biassoni, Genova, Italy
*2DS2*004*	2DS2v1	WC	AF285438	(Rajalingam et al. 2001)
*2DS2*005*	2DS2v2	FC	AF285439	(Rajalingam et al. 2001)
*2DS3*00101*	NKAT7	?	L76670	(Dohring et al. 1996)
*2DS3*00102*	59C_K3	Pag1	X97231	R. Biassoni, Genova, Italy
*2DS3*00103*	2DS3v	NV	AF022047	(Valiante et al. 1997)
*2DS4*00101*	cl-39, cl-17, KKA3_34–52	?, ?, 4053, Mal 43–52	U24077, AF002255, AJ417555, X94609	(Bottino et al. 1996; Maxwell et al. 2002; Wagtmann et al. 1995a), H.W. Chan, Pittsburgh, USA
*2DS4*00102*	NKAT8	?	L76671	(Dohring et al. 1996)
*2DS4*002*	2DS4v1	RR	AF285440	(Rajalingam et al. 2001)
*2DS4 *003*	Deletion V, KIR1D	3321	AJ417554	(Hsu et al. 2002b; Maxwell et al. 2002)
*2DS5*001*	NKAT9	?	L76672	(Dohring et al. 1996)
*2DS5*002*	–	NV	AF208054	(Vilches et al. 2000b)
*2DS5*003*	–	WC	AF272389	(Vilches et al. 2000b)
*2DP1*001*	KIR15	NV	AF204906, AF204907, AF204908	(Vilches et al. 2000c)
*2DP1*002*	–	CTB–61M7	AC011501	(Martin et al. 2000)
*3DL1*00101*	NKAT3, cl-11, AMB11.115	?, ?, AMB11	L41269, U30274, X94262	(Colonna and Samaridis 1995; Pende et al. 1996; Wagtmann et al. 1995b)
*3DL1*00102*	Nnkat-3	?	AF262968	(Gardiner et al. 2001)
*3DL1*002*	NKB1, cl-2	NKB1, ?	U31416, U30273	(D'Andrea et al. 1995; Wagtmann et al. 1995b)

Table 2 (continued)

Allele Name	Previous name	Cell ID	Accession Number	Reference or submitting author
*3DL1*003*	3DL1v	NV	AF022049	(Valiante et al. 1997)
*3DL1*00401*	W204	WC	AF262970	(Gardiner et al. 2001)
*3DL1*00402*	M322	MU	AF262969	(Gardiner et al. 2001)
*3DL1*005*	3DL1v2	YW	AF262971	(Gardiner et al. 2001)
*3DL1*006*	NJN55	?	AF262972	(Gardiner et al. 2001)
*3DL1*007*	r3k10	RR	AF262973	(Gardiner et al. 2001)
*3DL1*008*	r3k2	RR	AF262974	(Gardiner et al. 2001)
*3DL1*009*	–	3321, 4053	AJ417556, AJ417557	(Crum et al. 2000)
*3DL2*001*	NKAT4	?	L41270	(Colonna and Samaridis 1995)
*3DL2*002*	cl-5, AMC5	?, ?	U30272, X94374	(Pende et al. 1996; Wagtmann et al. 1995b)
*3DL2*003*	1.1, NKAT4A	?, ?	X94373, L76665	(Dohring et al. 1996; Pende et al. 1996)
*3DL2*004*	17.1C	?	X93595	(Pende et al. 1996)
*3DL2*005*	NKAT4b	?	L76666	(Dohring et al. 1996)
*3DL2*006*	3DL2Wv2	WC	AF262966	(Gardiner et al. 2001)
*3DL2*007*	b3DL2b	BS	AF262965	(Gardiner et al. 2001)
*3DL2*008*	r3k17	RR	AF262967	(Gardiner et al. 2001)
*3DL2*009*	rrk100	RR	AF263617	(Rajalingam et al. 2001)
*3DL2*010*	–	?	AY059418	(Shilling et al. 2002)
*3DL2*011*	–	?	AY059419	(Shilling et al. 2002)
*3DL2*012*	–	?	AY059420	(Shilling et al. 2002)
*3DL3*001*	KIRCI	?	AF072407, AF072408, AF072409, AF072410	(Torkar et al. 1998)
*3DL3*00201*	KIR44a	NV, UV5HL9–5B	AF204909, AF204910, AF204911, AC006293	(Martin et al. 2000; Vilches et al. 2000c)
*3DL3*00202*	KIR44b	NV	AF204912, AF204913, AF204914	(Vilches et al. 2000c)
*3DL3*003*	KIRC1	XX-1060P11	AL133414	(Wilson et al. 2000)
*3DL3*004*	3DL7	?	AF352324	(Long et al. 2001)
*3DS1*010*	NKAT10, 3DS1*001	?	L76661	(Dohring et al. 1996)
*3DS1*011*	C97.12#5, 3DS1*002	?	X97233	R Biassoni, Genova, Italy
*3DS1*012*	KIR-123FM, 3DS1*003	?	U73396	(Selvakumar et al. 1997a)
*3DS1*013*	3DS1v, 3DS1*004	NV	AF022044	(Valiante et al. 1997)
*3DS1*014*	3DS1*005	4373	AJ417558	(Crum et al. 2000)
*3DP1*001*	KIR48a	NV	AF204915, AF204916, AF204917	(Vilches et al. 2000c)
*3DP1*002*	KIRX	XX-1060P11	AL133414	(Wilson et al. 2000)
*3DP1*00301*	KIR48b	NV	AF204918, AF204919, AF204920	(Vilches et al. 2000c)
*3DP1*00302*	2DS6	CTB-61M7	AC011501	(Martin et al. 2000)

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 (1) or absence (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 recognised 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 the *KIR* sequences will be made available from the web site. The KIR-DB may be accessed via world wide web from www.ebi.ac.uk/ipd/kir/.

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