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The NLR Gene Family: A Standard Nomenclature

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Immune regulatory proteins such as CIITA, NAIP, IPAF, NOD1, NOD2, NALP1, and cryopyrin (also known as NALP3) are members of a family characterized by the presence of a NACHT nucleotide-binding domain (NBD) and leucine-rich repeats (LRRs). Members of this gene family encode a protein structure similar to the NB-LRR subgroup of disease-resistance genes in plants and are involved in the sensing of pathogenic products and the regulation of cell signaling and death. Currently, a variety of different names are used to describe the products encoded by the NBD and LRR containing gene family, its subfamilies, and individual genes, including CATERPILLER (CLR), NOD-LRR, NACHT-LRR, NOD-like receptor, CARD, NALP, NOD, PAN, and PYPAF. This lack of consistency has led to a pressing need to unify the nomenclature for this gene family. Consequently, we propose a standardized nomenclature, NLR, which stands for the nucleotide-binding domain and leucine-rich repeat containing gene family.

The NLR family includes several subfamilies distinguishable by their N-terminal effector domains. There are four recognizable NLR N-terminal domains: acidic transactivation domain, pyrin domain, caspase recruitment domain (CARD), and baculoviral inhibitory repeat (BIR)-like domains (see Table 1 for the human NLR genes). These N-terminal domains have been used by several groups to subdivide the NLR gene family, and there are now multiple names for each subfamily: the largest pyrin-containing subfamily has been named PAN, NALP, and PYPAF; members of the CARD-containing subfamily have been named CARDs or NODs; the BIR-containing subfamily has been named NAIP or BIRC.

In consultation with over 100 scientists, through a stepwise voting process organized by the Human Genome Organisation (HUGO) Gene Nomenclature Committee (HGNC) and conducted via email and updated web pages, a new nomenclature system for human and mouse NLR genes has been agreed upon (see Table S1 available online for human and mouse NLR genes). It was agreed that the family name "nucleotide-binding domain and leucine-rich repeat containing" should be used to highlight these two evolutionarily conserved domains and to reflect the similarity of the NLR family to the plant NB-LRR proteins. Furthermore, the consensus of opinion was that a subfamily-derived nomenclature system based on the N-terminal effector domains should be implemented. Consequently, four subfamily designations have been approved: NLRA, NLR family, acidic domain containing; NLRB, NLR family, BIR domain containing; NLRC, NLR family, CARD domain containing; NLRP, NLR family, pyrin domain containing; NLRX, NLR family with no strong homology to the N-terminal domain of any other NLR subfamily member (Table 1). Each member within a subfamily is given a number, e.g., *NLRP1*. Four members of the NLR family, *CIITA*, *NAIP*, *NOD1*, and *NOD2*, have not been renamed. These four genes are associated with a large volume of literature, and it was agreed that renaming these would cause confusion in the literature. However, each of these genes has been given a subfamily alias to enable electronic data-retrieval systems to link these four genes to the NLR gene family. Clearly related genes, such as *NLRP10* and *Naip3-6*, that do not encode NBD and/or LRR are included for completeness and historic reasons.

Table 1. New Approved Designations for the Human NLR Family Members

NLR Family	HGNC-Approved Symbol	Approved Name	Other Names and Aliases	Domain Organization	**Protein Sequence**
NLRA	*CIITA*	class II, major histocompatibility complex, transactivator	*NLRA*; *MHC2TA*; *C2TA*	(CARD)-AD-NACHT-NAD-LRR	NP_000237
NLRB	*NAIP*	NLR family, apoptosis inhibitory protein	*NLRB1*; *BIRC1*; *CLR5.1*	BIR3x-NACHT-LRR	NP_004527
NLRC	*NOD1*	nucleotide-binding oligomerization domain containing 1	*NLRC1*; *CARD4*; *CLR7.1*	CARD-NACHT-NAD-LRR	NP_006083
NLRC	*NOD2*	nucleotide-binding oligomerization domain containing 2	*NLRC2*; *CARD15*; *CD*; *BLAU*; *IBD1*; *PSORAS1*; *CLR16.3*	CARD2x-NACHT-NAD-LRR	NP_071445
NLRC	*NLRC3*	NLR family, CARD domain containing 3	*NOD3*; *CLR16.2*	CARD-NACHT-NAD-LRR	NP_849172
NLRC	*NLRC4*	NLR family, CARD domain containing 4	*CARD12*; *CLAN*; *CLR2.1*; *IPAF*	CARD-NACHT-NAD-LRR	NP_067032
NLRC	*NLRC5*	NLR family, CARD domain containing 5	*NOD27*; *CLR16.1*	CARD-NACHT-NAD-LRR	NP_115582
NLRP	*NLRP1*	NLR family, pyrin domain containing 1	*NALP1*; *DEFCAP*; *NAC*; *CARD7*; *CLR17.1*	PYD-NACHT-NAD-LRR-FIIND-CARD	NP_127497
NLRP	*NLRP2*	NLR family, pyrin domain containing 2	*NALP2*; *PYPAF2*; *NBS1*; *PAN1*; *CLR19.9*	PYD-NACHT-NAD-LRR	NP_060322
NLRP	*NLRP3*	NLR family, pyrin domain containing 3	*CIAS1*; *PYPAF1*; *Cryopyrin*; *CLR1.1*; *NALP3*	PYD-NACHT-NAD-LRR	NP_004886
NLRP	*NLRP4*	NLR family, pyrin domain containing 4	*NALP4*; *PYPAF4*; *PAN2*; *RNH2*; *CLR19.5*	PYD-NACHT-NAD-LRR	NP_604393
NLRP	*NLRP5*	NLR family, pyrin domain containing 5	*NALP5*; *PYPAF8*; *MATER*; *PAN11*; *CLR19.8*	PYD-NACHT-NAD-LRR	NP_703148
NLRP	*NLRP6*	NLR family, pyrin domain containing 6	*NALP6*; *PYPAF5*; *PAN3*; *CLR11.4*	PYD-NACHT-NAD-LRR	NP_612202
NLRP	*NLRP7*	NLR family, pyrin domain containing 7	*NALP7*; *PYPAF3*; *NOD12*; *PAN7*; *CLR19.4*	PYD-NACHT-NAD-LRR	NP_996611
NLRP	*NLRP8*	NLR family, pyrin domain containing 8	*NALP8*; *PAN4*; *NOD16*; *CLR19.2*	PYD-NACHT-NAD-LRR	NP_789781
NLRP	*NLRP9*	NLR family, pyrin domain containing 9	*NALP9*; *NOD6*; *PAN12*; *CLR19.1*	PYD-NACHT-NAD-LRR	NP_789790
NLRP	*NLRP10*	NLR family, pyrin domain containing 10	*NALP10*; *PAN5*; *NOD8*; *PYNOD*; *CLR11.1*	PYD-NACHT-NAD	NP_789791
NLRP	*NLRP11*	NLR family, pyrin domain containing 11	*NALP11*; *PYPAF6*; *NOD17*; *PAN10*; *CLR19.6*	PYD-NACHT-NAD-LRR	NP_659444
NLRP	*NLRP12*	NLR family, pyrin domain containing 12	*NALP12*; *PYPAF7*; *Monarch1*; *RNO2*; *PAN6*; *CLR19.3*	PYD-NACHT-NAD-LRR	NP_653288
NLRP	*NLRP13*	NLR family, pyrin domain containing 13	*NALP13*; *NOD14*; *PAN13*; *CLR19.7*	PYD-NACHT-NAD-LRR	NP_789780
NLRP	*NLRP14*	NLR family, pyrin domain containing 14	*NALP14*; *NOD5*; *PAN8*; *CLR11.2*	PYD-NACHT-NAD-LRR	NP_789792
NLRX	*NLRX1*	NLR family member X1	*NOD9*; *CLR11.3*	X-NACHT-NAD-LRR	NP_078894

The following abbreviations are used: AD, acidic activation domain CARD, caspase activating and recruitment domain; LRR, leucine-rich repeat; NACHT, domain present in *NAIP*, *CIITA*, *HET-E*, and *TP-1*; BIR, baculovirus inhibitor of apoptosis repeat; PYD, pyrin domain; and NAD, NACHT-associated domain.

To distinguish between human and mouse NLR genes, the human genes are written in upper case, whereas murine orthologs are distinguished from the human genes by the use of uppercase for the first letter only, followed by lowercase (Table S1). Although several human NLR genes have multiple murine paralogs, some human NLR genes do not appear to have any murine counterparts, reflecting the dynamic evolutionary contraction and expansion of this family.

The nomenclature described in this paper has been approved by the HGNC and the Mouse Genomic Nomenclature Committee. Concerted use of this unified nomenclature will reduce confusion and disparity and promote the transparency of this important field. We urge all investigators to adopt the approved nomenclature in future publications and presentations.

SUPPLEMENTAL DATA

A table of human and mouse NLR genes is available at http://www.immunity.com/cgi/content/full/28/3/285/DC1/.

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