

## Gene Section

### Review

# KLRK1 (killer cell lectin-like receptor subfamily K, member 1)

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## Abstract

KLRK1 encodes a type II transmembrane-anchored glycoprotein that is expressed as a disulfide-linked homodimer on the surface of Natural Killer (NK) cells, gamma/delta TcR+ T cells, CD8+ T cells, and a minor subset of CD4+ T cells. It associates non-covalently with the DAP10 signaling protein and provides activating or costimulatory signals to NK cells and T cells. NKG2D binds to a family of glycoproteins, in humans the MICA, MICB, and ULBP1-6 membrane proteins, which are frequently expressed on cells that have become infected with pathogens or undergone transformation.

### Keywords

KLRK1, C-type lectin-like receptor

## Identity

**Other names:** D12S2489E, CD314, KLR, NKG2-D, NKG2D

**HGNC (Hugo):** KLRK1

**Location:** 12p13.2

## DNA/RNA

### Note

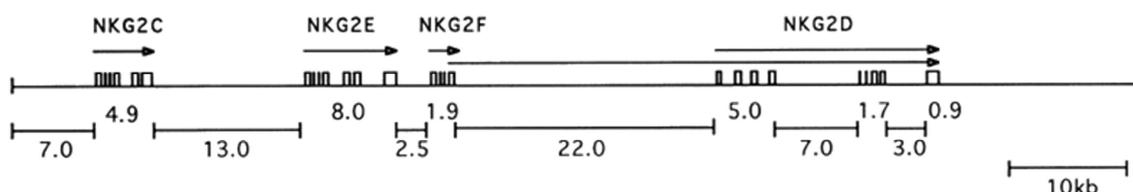
KLRK1 is present on chromosome 12 within a cluster of genes referred to as the "NK complex" (NKC) because several genes that are preferentially expressed by Natural Killer (NK) cells are located in this region, including on the centromeric side KLRD1 (CD94) and on the telomeric side KLRC4 (NKG2F), KLRC3 (NKG2E), KLRC2 (NKG2C), and KLRC1 (NKG2A) (Houchins et al., 1991).

### Description

The KLRK1 gene is 17702 bases located on the negative strand of chromosome 12 spanning bases 10372353 to 103900054 with a predicted 7 exons.

### Transcription

There is evidence for alternative splicing of KLRK1, but only one isoform encoding a functional protein has been described in humans. In one of the KLRK1 splice variants the fourth exon of KLRC4 is spliced to the 5-prime end of KLRK1.



Schematic representation of the KLRC2 (NKG2C), KLRC3 (NKG2E), KLRC4 (NKG2F), and KLRK1 genes on human chromosome 12p13.2 (taken from Glienke et al., 1998, figure 4).

MGWIRGRRSRHSWEMSEFHNYNLDLKKSDFSTRWQKQRCPPVVKSKCRENASPFFFCFIAVAMGIRFIIMVTIWSAVFL  
 NSLNFQEVQIPLTESYCGPCPKNWICYKNNCYQFFDESKNWYESQASCMSQNASLLKVYSKEDQDLLKLVKSYHWMGLV  
 HIPTNGSWQWEDGSILSPNLLTIIEMQKGDICALYASSFKGYIENCSTPNTYICMORTV

Amino acid sequence of KLRK1 is shown, with the predicted transmembrane domain underlined. The R residue in the transmembrane is required for association of KLRK1 with the DAP10 signaling protein to form the mature receptor complex. Three potential sites for N-linked glycosylation are in bold.

KLRK1 is transcribed by NK cells, gamma/delta-TcR+ T cells, CD8+ T cells and some CD4+ T cells (Bauer et al., 1999). Transcription of KLRK1 is enhanced by stimulation of NK cells with IL-2 or IL-15 and decreased by culture with TGF-beta.

### Pseudogene

No known pseudogenes.

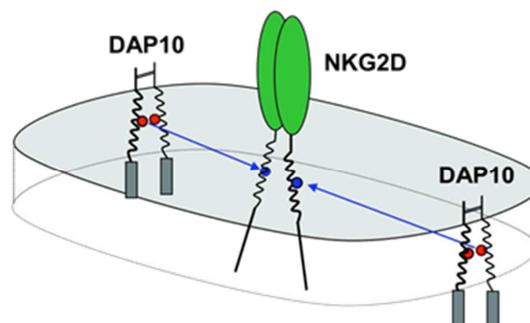
## Protein

### Note

KLRK1 is a type II transmembrane-anchored membrane glycoprotein expressed as a disulfide-bonded homodimer on the cell surface. Expression of KLRK1 on the cell surface requires its association with DAP10, which is a type I adapter protein expressed as a disulfide-bonded homodimer (Wu et al., 1999). On the cell surface, the receptor complex is a hexamer; two disulfide-bonded KLRK1 homodimers each paired with two DAP10 disulfide-bonded homodimers (Garrity et al., 2005). A charged amino acid residue (aspartic acid) centrally located within the transmembrane region of DAP10 forms a salt bridge with a charged amino acid residue (arginine) in the transmembrane region of KLRK1 to stabilize the receptor complex (Wu et al., 1999).

### Description

KLRK1 is a type II membrane protein comprising 216 amino acids with a predicted molecular weight of 25,143 kDa. The protein has an N-terminal intracellular region, a transmembrane domain, a membrane-proximal stalk region, and an extracellular region with a single C-type lectin-like domain. KLRK1 is expressed on the cell surface as a disulfide-bonded homodimer with a molecular weight of approximately 42 kDa when analyzed under reducing conditions and approximately 80 kDa under non-reducing conditions. A cysteine residue just outside the transmembrane region forms the disulfide bond joining the two subunits of the homodimer. There are three potential sites for N-linked glycosylation in the extracellular region of KLRK1. Treatment of the KLRK1 glycoprotein with N-glycanase reduces the molecular weight to approximately the size of the core polypeptide.



Schematic representation of the KLRK1 (NKG2D) - DAP10 receptor complex (taken from Garrity et al., 2005, figure 7).

### Expression

KLRK1 protein is expressed on the cell surface of NK cells, gamma/delta-TcR+ T cells, CD8+ T cells, and some CD4+ T cells (Bauer et al., 1999).

### Localisation

KLRK1 is expressed as a type II integral membrane glycoprotein on the cell surface of NK cells, gamma/delta-TcR+ T cells, CD8+ T cells, and some CD4+ T cells (Bauer et al., 1999).

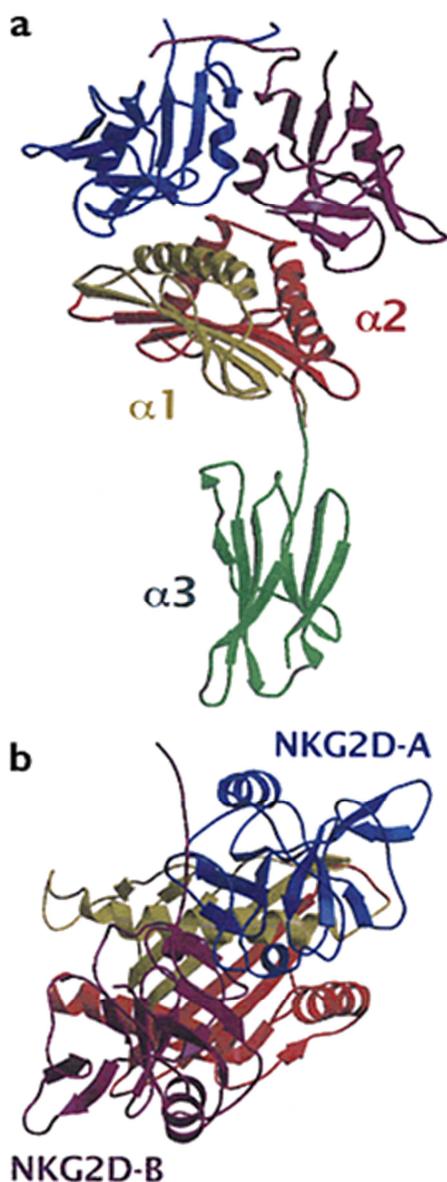
In the absence of DAP10, KLRK1 protein is retained in the cytoplasm and degraded (Wu et al., 1999).

### Function

KLRK1 binds to at least eight distinct ligands: MICA, MICB, ULBP-1, ULBP-2, ULBP-3, ULBP-4, ULBP-5, and ULBP-6 (Bauer et al., 1999; Cosman et al., 2001; Raulet et al., 2013).

These ligands are type I glycoproteins with homology to MHC class I. The KLRK1 ligands frequently are over-expressed on tumor cells, virus-infected cells, and "stressed" cells (Raulet et al., 2013). The crystal structure of KLRK1 bound to MICA has been described (Li et al., 2001). After binding to its ligand, KLRK1 transmits an activating signal via the DAP10 adapter subunit.

DAP10 has a YINM motif in its cytoplasmic domain, which upon tyrosine phosphorylation binds to Vav and the p85 subunit of PI3-kinase (Billadeau et al., 2003; Wu et al., 1999), causing a downstream cascade of signaling in T cells and NK cells, resulting in the killing of ligand-bearing cells and the secretion of cytokines by NK cells and T cells.



Structure of the KLRK1 homodimer (a) and its ligand MICA (b) (taken from Li et al., 2001, figure 1).

### Homology

Pan troglodytes: NP\_001009059  
 Macaca mulatta: NP\_001028061  
 Macaca fascicularis: CAD19993  
 Callithrix jacchus: ABN45890  
 Papio anubis: ABO09749  
 Pongo pygmaeus: Q8MJH1  
 Bos taurus: CAJ27114  
 Sus scrofa: Q9GLF5  
 Mus musculus: NP\_149069  
 Mus musculus: NP\_001076791  
 Rattus norvegicus: NP\_598196  
 Callithrix jacchus: A4GHD0  
 Neovison vison: U6DVF4  
 Microcebus murinus: D1GEY1  
 Varecia variegata: D1GF00  
 Lithobates catesbeiana: C1C4X9

## Mutations

### Note

None identified.

## Implicated in

### Cancer

#### Note

Many types of cancer (carcinomas, sarcomas, lymphomas, and leukemias) over-express the ligands for KLRK1 (Raulet et al., 2013). In some cases, this renders the tumor cells susceptible to killing by activated KLRK1-bearing NK cells. Some tumors shed or secrete soluble ligands that bind to KLRK1, which downregulates expression of KLRK1 on NK cells and T cells (Groh et al., 2002), although the physiological relevance of the shed ligands is controversial. Mice in which the *Klrk1* gene has been disrupted show increased susceptibility to certain cancers caused by transgenic expression of oncogenes (Guerra et al., 2008).

### Viral infection

#### Note

Viral infection of cells can induce transcription and cell surface expression of ligands for KLRK1, rendering these infected cells susceptible to attack by NK cells and T cells (Champsaur and Lanier, 2010; Raulet et al., 2013). Some viruses, for example cytomegalovirus, encode proteins that intercept the ligand proteins intracellularly and prevent their expression on the surface of virus-infected cells.

### Rheumatoid arthritis

#### Note

An expansion of CD4<sup>+</sup>,CD28<sup>-</sup> T cells expressing KLRK1 was observed in the joints of patients with rheumatoid arthritis and KLRK1 ligands were detected on synovial cells in the inflamed tissue (Groh et al., 2003).

### Type I diabetes

#### Note

Peripheral blood NK cells and T cells in patients with type I diabetes demonstrate a slightly decreased amount of expression of KLRK1 on the cell surface, independent disease duration (Rodacki et al., 2007), similar to prior observations in the NOD mouse (Ogasawara et al., 2003).

## References

Houchins JP, Yabe T, McSherry C, Bach FH. DNA sequence analysis of NKG2, a family of related cDNA clones encoding type II integral membrane proteins on human natural killer cells. *J Exp Med.* 1991 Apr 1;173(4):1017-20

- Glienke J, Sobanov Y, Brostjan C, Steffens C, Nguyen C, Lehrach H, Hofer E, Francis F. The genomic organization of NKG2C, E, F, and D receptor genes in the human natural killer gene complex. *Immunogenetics*. 1998 Aug;48(3):163-73
- Bauer S, Groh V, Wu J, Steinle A, Phillips JH, Lanier LL, Spies T. Activation of NK cells and T cells by NKG2D, a receptor for stress-inducible MICA. *Science*. 1999 Jul 30;285(5428):727-9
- Wu J, Song Y, Bakker AB, Bauer S, Spies T, Lanier LL, Phillips JH. An activating immunoreceptor complex formed by NKG2D and DAP10. *Science*. 1999 Jul 30;285(5428):730-2
- Cosman D, Müllberg J, Sutherland CL, Chin W, Armitage R, Fanslow W, Kubin M, Chalupny NJ. ULBPs, novel MHC class I-related molecules, bind to CMV glycoprotein UL16 and stimulate NK cytotoxicity through the NKG2D receptor. *Immunity*. 2001 Feb;14(2):123-33
- Li P, Morris DL, Willcox BE, Steinle A, Spies T, Strong RK. Complex structure of the activating immunoreceptor NKG2D and its MHC class I-like ligand MICA. *Nat Immunol*. 2001 May;2(5):443-51
- Groh V, Wu J, Yee C, Spies T. Tumour-derived soluble MIC ligands impair expression of NKG2D and T-cell activation. *Nature*. 2002 Oct 17;419(6908):734-8
- Billadeau DD, Upshaw JL, Schoon RA, Dick CJ, Leibson PJ. NKG2D-DAP10 triggers human NK cell-mediated killing via a Syk-independent regulatory pathway. *Nat Immunol*. 2003 Jun;4(6):557-64
- Groh V, Bruhl A, El-Gabalawy H, Nelson JL, Spies T. Stimulation of T cell autoreactivity by anomalous expression of NKG2D and its MIC ligands in rheumatoid arthritis. *Proc Natl Acad Sci U S A*. 2003 Aug 5;100(16):9452-7
- Ogasawara K, Hamerman JA, Hsin H, Chikuma S, Bour-Jordan H, Chen T, Pertel T, Carnaud C, Bluestone JA, Lanier LL. Impairment of NK cell function by NKG2D modulation in NOD mice. *Immunity*. 2003 Jan;18(1):41-51
- Garrity D, Call ME, Feng J, Wucherpfennig KW. The activating NKG2D receptor assembles in the membrane with two signaling dimers into a hexameric structure. *Proc Natl Acad Sci U S A*. 2005 May 24;102(21):7641-6
- Rodacki M, Svoren B, Butty V, Besse W, Laffel L, Benoist C, Mathis D. Altered natural killer cells in type 1 diabetic patients. *Diabetes*. 2007 Jan;56(1):177-85
- Guerra N, Tan YX, Joncker NT, Choy A, Gallardo F, Xiong N, Knoblaugh S, Cado D, Greenberg NM, Raulet DH. NKG2D-deficient mice are defective in tumor surveillance in models of spontaneous malignancy. *Immunity*. 2008 Apr;28(4):571-80
- Champsaur M, Lanier LL. Effect of NKG2D ligand expression on host immune responses. *Immunol Rev*. 2010 May;235(1):267-85
- Raulet DH, Gasser S, Gowen BG, Deng W, Jung H. Regulation of ligands for the NKG2D activating receptor. *Annu Rev Immunol*. 2013;31:413-41
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