Names for KN (ISBT 022) Blood Group Alleles

Intro

General Description	The Knops blood group system consists of 9 antigens carried on a glycoprotein of **2039** amino acids and called the Complement Receptor I (CR1). It has a leader sequence of 41 to 46 amino acids, depending on translation initiation site, which is cleaved from the membrane protein. The coding sequence starts at nucleotide 28. The Helg**e**son phenotype, initially thought to be a KN serologic null, may be more likely the result of lower-level CR1 density and may also involve lack of a high-prevalence KN antigen [Pham Transfusion 2010 50(7):1435-43].
General Description (from GeneCards)	*CR1* (Complement C3b/C4b Receptor 1 (Knops Blood Group)) is a **p**rotein **c**oding gene **that is a member of the receptors of complement activiation (RCA) family and is located in the "cluster RCA" region of chromosome 1.** Diseases associated with *CR1* include **m**alaria and Plasmodium **f**alciparum **m**alaria. Among its related pathways are **immune response, lectin-induced complement pathway and innate immune system**. Gene Ontology (GO) annotations related to this gene include complement component C3b binding and complement component C4b receptor activity. An important paralog of this gene is *CR1L* .
Gene name:	*CR1* (aliases CD35, KN, C3BR, C4BR)
RefGene Name	LRG_814
Number of exons:	39
Initiation codon:	beginning of exon 1
Stop codon:	end of exon 38
Entrez Gene ID:	1378
LRG sequence:	NG_007481.1 (genomic) NM_000573.3 (transcript)
Reference allele *KN*01* encodes:	KN1, KN3, KN4, KN8, KN9, KN11 Acceptable: *KN*A* , or Kn^a if inferred by haemagglutination
Antithetical antigens:	[KN1 KN2]; [KN3 KN6]; [KN4 KN7]; [KN9 KN10]; [KN11 KN12]
Comment:	The antithetical KN antigens KN9/KN10 (KCAM/KDAS) and KN 11/12 (DACY/YCAD) are adding additional polymorphism to almost all *KN** alleles known so far and listed in the Allele Table. A **proposal** for extended *KN** terminology, also considering KCAM/KDAS and DACY/YCAD polymorphism is given at the end of this file. This proposal is currently unratified by the ISBT WP RCI & BGT.

Phenotype	Allele name	Nucleotide change	Exon Intron	Predicted amino acid change	(Reference No.) PMID	Accession number	rs number
KN:1 or Kn(a+) KN:3 or McC(a+) KN:4 or Sl1+ KN:8 or Sl3+ KN:9 or KCAM+ KN:11 or DACY+	***KN*01* or *KN*A***	c.4681G c.4768A c.4801A c.4828T c.4843A c.3623A	29 29 29 29 29 22	p.Val1561 p.Lys1590 p.Arg1601 p.Ser1610 p.Ile1615 p.His1208		n.a.	n.a.
KN:2 or Kn(b+) KN:10 or KDAS+	***KN*02* or *KN*B***	c.4681A>G c.4843A>G	29 29	p.Val1561Met p.Ile1615Val	PMID: 14962306 PMID: 32870515	n.a.	rs41274768 rs6691117
KN:–5 or Yk(a–)	***KN*01.-05***	c.4223C>T	26	p.Thr1408Met	PMID: 21214579	n.a.	rs3737002
KN:6 or McC(b+) KN:7 or Vil+ KN:10 or KDAS+	***KN*01.06***	c.4768A>G c.4801A>G c.4843A>G	29 29 29	p.Lys1590Glu p.Arg1601Gly p.Ile1615Val	PMID: 11313284 PMID: 32870515	n.a.	rs17047660 rs17047661 rs6691117
KN:7 or Vil+	***KN*01.07***	c.4801A>G	29	p.Arg1601Gly	(1), Abstract PMID: 6865671	n.a.	rs17047661
KN:–8 or Sl3–	***KN*01.-08***	c.4828T>A	29	p.Ser1610Thr	PMID: 11896343	n.a.	rs4844609
KN:10 or KDAS+	***KN*01.10***	c.4843A>G	29	p.Ile1615Val	(2), Abstract PMID: 32589271	n.a.	rs6691117
KN:12 or YCAD+	***KN*01.12***	c.3623A>G	22	p.His1208Arg	PMID: 32870515	n.a.	rs2274567

Note: Nucleotides are numbered from the initiation codon, so numbering will differ from publications prior to 2012 by –27 nucleotides.

‡ KN:4 was listed in older literature with the alias Sl^a or S1 and KN:7 with the alias Sl2.

† Arg1601 and Ser1610 are required for KN:8 (Sl3) expression

All *KN*01.06* alleles known so far are KDAS (KN10) positive and KCAM (KN9) negative and express almost exclusively DACY (KN11). PMID: 32870515

Almost all *KN*01.05* alleles known so far are KCAM positive (KN9) and KDAS (KN10) negative and express almost exclusively DACY (KN11). PMID: 32870515

The *KN*01.07* known so far usually express KDAS (KN10) and are DACY (KN11) positive. PMID: 32870515

The *KN*01.10* known so far usually express KDAS (KN10) and are YCAD (KN12) positive. PMID: 32870515

References

PMID	14962306	Moulds JM, Thomas BJ, Doumbo O, Diallo DA, Lyke KE, Plowe CV, Rowe JA and DJ Birmingham. Identification of the Kna/Knb polymorphism and a method for Knops genotyping.Transfusion. 2004 May;44(5):799-800
PMID	21214579	Veldhuisen B, Ligthart PC, Vidarsson G, Roels I, Folman CC, van der Schoot CE, M de Haas. Molecular analysis of the York antigen of the Knops blood group system.Transfusion. 2011 Jul;51(7):1389-96.
PMID	11313284	Moulds JM, Zimmerman PA, Doumbo OK, Kassambara L, Sagara I, Diallo DA, Atkinson JP, Krych-Goldberg M, Hauhart RE, Hourcade DE, McNamara DT, Birmingham DJ, Rowe RA and JJ Moulds. Molecular identification of Knops blood group polymorphisms found in long homologous region D of complement receptor 1. Blood. 2001 May 1;97(9):2879-85.
Abstract	(1)	Lacey P, Laird-Fryer B, Block U, Lar J, Guilbeau L and JJ Moulds. A New High Incidence Blood Group Factor, Sla and its hyothetical allele. Transfusion 1980 20(5):632.
PMID	6865671	Molthan L. The status of the Mccoy/Knops antigens. Med Lab Sci. 1983 Jan;40(1):59-63.
PMID	11896343	Moulds JM, Zimmerman PA, Doumbo OK, Diallo DA, Atkinson JP, Krych-Goldberg M, Hourcade DE and JJ Moulds. Expansion of the Knops blood group system and subdivision of Sl(a).Transfusion. 2002 Feb;42(2):251-6.
Abstract	(2)	Moulds JM, Pierce S, Peck KB, Tulley ML, Doumbo O, JJ Moulds. KAM: A New Allele in the Knops Blood Group System. Transfusion 2005 45(S3): 27A.
PMID	32589271	Scharberg EA, Rink G, Schulz D, Rothenberger S, Sturtzel A, Gillhuber N, SeybothS and P Bugert. KDAS, a new blood group antigen in the Knops blood group system antithetical to KCAM. Transfusion 2020 60(8):E25-E27.
PMID	32870515	Grueger D, Zeretzke A, Habicht CP, Skaik Y, Wagner FF, Scharberg EA, Costelloe A, Martens J, Veboom M, Bugert P and C Schneeweiss. Two novel antithetical KN blood group antigens may contribute to more than a quarter of all KN antisera in Europe. Transfusion 2020 60(10): 2408-2418.

Track of changes

			from	to
1	**Version**		**v3.0 160903**	**v4.0 31-MAR-2022**
2	Author	created	Joanne Moulds, 2016	Margaret Keller, March 2022
3	Review	reviewed	n.a.	Christoph Gassner, March 2022
4	General	Formatting		Updated to newest project-2-excel format with addition of columns for rs number, PMID. Added tab with reference details.
5	Allele Table	Allele removed		In the allele table, entries KN:–9 or KCAM–, *KN*01.–09* will become obsolete and be replaced by KN:10, KDAS, *KN*01.10* , defined by the SNV c.4843A>G (rs 6691117). KDAS (=KCAM-) is antithetical to KCAM.
6	Allele Table	Allele		Allele KN:10 and KDAS added as antithetical to KCAM based on PMID 32589271.
7	Allele Table	Allele		Allele KN:12 and DACY/YCAD added as antithetical pair, based on PMID 32870515.
8	Allele Table	negative signs		Continued use of negative signs according to genomics meetings and reviewer Christoph Gassner
9	References	numbering changed		References numbering changed and additional references (PMID 32589271 and 32870515) added
10	Tab sheet	Tab sheet added		Tab sheet 'Proposal & AG per Allele' added.
11	**End Version**		**v3.0 160903**	**v4.0 31-MAR-2022**

This proposal-page will be discussed in the next WP-meeting

This is a **proposal** for extended *KN** terminology, also considering KCAM/KDAS and DACY/YCAD polymorphism. Alleles shown are expected to exist according to PMID: 32870515, Table 2.

	Kn(a+) KN001	Kn(b+) KN002	McC(a+) KN003	McC(b+) KN006	Sl1+ KN004	Vil+("Sl2+") KN007	Sl3+ KN008	Yk(a+) KN005	KCAM KN009	KDAS KN010	DACY KN011	YCAD KN012
rs:id	rs41274768	rs41274768	rs17047660	rs17047660	rs17047661	rs17047661	rs4844609	rs3737002	rs6691117	rs6691117	rs2274567	rs2274567
nt. position NM_000573.4	c.4681		c.4768		c.4801		c.4828		c.4843		c.3623	
nucleotide	G	A	A	G	A	G	T>A	C>T	A	G	A	G
p. position NP_000564.2	p.1561		p.1590		p.1601		p.1610	p.1408	p.1615		p.1208	
amino acid	Val	Met	Lys	Glu	Arg	Gly	Ser/Thr	Thr/Met	Ile	Val	His	Arg
p. position NP_000642.3	p.2011		p.2040		p.2051		p.2060	p.1858	p.2065		p.1658	

total	AFR	AMR	EAS	EUR	SAS													
25.70	8.20	25.70	34.50	46.80	19.00	*KN*01 or KN*A*	pos	neg	pos	neg	pos	neg	pos	pos	pos	neg	pos	neg
1.30	0.20	3.60	0.20	3.40	0.30	*KN*02 or KN*B*	neg	pos	pos	neg	pos	neg	pos	pos	neg	pos	pos	neg
22.90	4.40	34.20	31.20	25.70	29.00	*KN*01.-05.01*	pos	neg	pos	neg	pos	neg	pos	neg	pos	neg	pos	neg
1.30	0.10	2.00	0.00	2.90	1.90	*KN*01.-05.01.02*	pos	neg	pos	neg	pos	neg	pos	neg (p.1408Val	pos	neg	pos	neg
0.10	0.00	0.00	0.10	0.00	0.30	*KN*01.-05.02*	pos	neg	pos	neg	pos	neg	pos	neg	pos	neg	neg	pos
0.60	0.00	1.70	1.40	0.20	0.00	*KN*01.-05.03*	pos	neg	pos	neg	pos	neg	pos	neg	neg	pos	pos	neg
7.50	27.00	2.40	0.00	0.30	0.00	*KN*01.06.03*	pos	neg	neg	pos	neg	pos	neg	pos	neg	pos	pos	neg
0.00	0.10	0.00	0.00	0.00	0.00	*KN*01.06.04*	pos	neg	neg	pos	neg	pos	neg	pos	neg	pos	neg	pos
0.10	0.20	0.00	0.00	0.10	0.00	*KN*01.07.02*	pos	neg	pos	neg	neg	pos	neg	pos	pos	neg	neg	pos
10.30	37.50	2.50	0.00	0.50	0.00	*KN*01.07.03*	pos	neg	pos	neg	neg	pos	neg	pos	neg	pos	pos	neg
1.70	6.40	0.30	0.00	0.00	0.00	*KN*01.07.04*	pos	neg	pos	neg	neg	pos	neg	pos	neg	pos	neg	pos
0.50	0.00	0.60	0.00	2.00	0.10	*KN*01.-08*	pos	neg	pos	neg	pos	neg	neg	pos	pos	neg	pos	neg
0.30	0.80	0.30	0.10	0.10	0.20	*KN*01.10.03*	pos	neg	pos	neg	pos	neg	pos	pos	neg	pos	pos	neg
27.50	15.20	26.80	32.70	18.00	48.90	*KN*01.10.04*	pos	neg	pos	neg	pos	neg	pos	pos	neg	pos	neg	pos
0.10	0.10	0.00	0.00	0.10	0.20	*KN*01.12*	pos	neg	pos	neg	pos	neg	pos	pos	pos	neg	neg	pos
99.90	100.20	100.10	100.20	100.10	99.90	total												
50.70	13.00	62.50	65.80	77.60	50.50	sum KCAM	"wildtype"											
49.20	87.20	37.60	34.40	22.50	49.40	sum KDAS	"minor antigen"											
70.40	78.20	73.00	67.40	81.90	50.50	sum DACY	"wildtype"											
29.50	22.00	27.10	32.80	18.20	49.40	sum YCAD	"minor antigen"											

Numerical codes **proposed** for KCAM/KDAS and DACY/YCAD polymorphism:

	KCAM	KDAS	DACY	YCAD
*KN*xx.xx.01*	pos	neg	pos	neg
*KN*xx.xx.02*	pos	neg	neg	pos
*KN*xx.xx.03*	neg	pos	pos	neg
*KN*xx.xx.04*	neg	pos	neg	pos