Names for CTL2 (ISBT 039) Blood Group Alleles

Intro

General description: The CTL2 blood group system consists of three high-prevalence antigens, VER, RIF and BROS, and the antithetical Cs^a and Cs^b antigens, which share the same polymorphism with the neutrophil antigens HNA-3a and 3b[PMID: 20037594]. All antigens are carried on the Choline like transporter 2 (CTL2) protein, also known as SLC44A2 (solute carrier family 44 member 2). This multi-pass protein consists of either 704 (isoform 2), or 706 amino acids (isoform 1), with predicted 10 transmembrane domains and 5 extracellular loops. The protein is encoded by *SLC44A2,* 42,103 bases, chromosome *19p13.2* (*chr19:10,602,455-10,644,557*) (GRCh38/hg38). The rare VER– null phenotype is associated with hearing impairment in the upper frequency range.

The *CTL2* gene (*SLC44A2*) codes for a variety of alternatively spliced mRNAs, producing different proteins, including variants "P1" and "P2", which differ by two different exons 1a and 1b, resulting in protein lengths of 704 and 706 amino acids, respectively[PMID: 20665236]. The 704-amino-acid CTL2 protein P1, also known as "isoform 2", is expressed in red blood cells (RBC) and neutrophils [PMID: 36695047]. All CTL2 blood group polymorphisms are associated with the 704-amino-acid variant. Accordingly, SNV rs2288904, discriminating Cs^a from Cs^b in red blood cells and HNA-3a from 3b on neutrophils at the same time, is located at c.455C>A (c.461 on the 706 aa protein coding mRNA), leading to the p.Arg152Gln (p.154 on the 706 aa protein) amino acid exchange in the CTL2 isoform 2 expressed in RBCs and neutrophils.

GenBank accessions in the CTL2 blood group allele table reference the genomic sequence NC_000019.10 (chr19:10,602,455 to 10,644,557, GRCh38/hg38), including exons 1a and 1b, representing the 704 and 706 amino acid CTL2 variants. Transcript NM_001145056.2 and protein sequence NP_001138528.1 are specific to the 704-amino-acid CTL2 isoform 2. However, NC_000019.10, NM_001145056.2 and NP_001138528.1 are all representatives of minor allele of CTL2, with c.455A of SNV rs2288904 (allele Cs^b/HNA-3b), encoding p.152Gln. GenBank accession KM024996.1 on the other hand, though lacking parts of intronic sequences, represents the 704 amino acid CTL2 isoform 2 with the major allele c.455C, p.152Arg, encoding Cs^a/HNA-3a. Besides this important polymorphism, the two mRNAs extracted from the two genomic references KM024996.1 and NC_000019.10 are identical except for a silent mutation at c.198T>C (p.66Asp).

Gene name:	*CTL2, SLC44A2*
Number of exons:	22
Initiation codon:	Within exon 1
Stop codon:	Within exon 22
Entrez Gene ID:	57153
LRG:	no record
Sequence:	KM024996.1 (genomic) With incomplete intronic sequences. Representative of the c.455C/p.152Arg allele of SNV rs2288904, encoding the Cs^a/HNA-3a phenotypes. NC_000019.10 (genomic) Chr19:10,602,455-10,644,557, GRCh38/hg38. Representative of the c.455A/p.152Gln allele of SNV rs2288904, encoding the Cs^b/HNA-3b phenotypes. NM_001145056.2 (transcript) NP_001138528.1 (protein)
Reference allele:	*CTL2*01* (shaded)
Reference allele *CTL2*01* encodes:	CTL2.1 (VER), CTL2.2 (RIF), CTL2.3(Cs^a), CTL2.5(BROS)
Antithetical antigens:	[CTL2.3(Cs^a) CTL2.4(Cs^b)]

Phenotype	Allele name	Nucleotide change [1)]	Exon Intron	Predicted amino acid change [2)]	(Reference No.) PMID	Accession number	rs number
CTL2:1 or VER+, or CTL2.1, also positive for Cs[a] or HNA-3a	***CTL2*01***				PMID: 36695047		
CTL2:–2 or RIF–, or CTL2.2-	***CTL2*01.-02***	c.1192C>A (c.1198C>A)	14	p.Pro398Thr (p.Pro400Thr)	(1), Abstract PMID: 36695047		rs1401833882
CTL2:–3,4 or Cs[b], or CTL2.4, or HNA-3b	***CTL2*01.04***	c.455G>A (c.461G>A)	7	p.Arg152Gln (p.154ArgGln)	(2), Abstract		rs2288904
CTL2:–5 or BROS-, or CTL2.5-	***CTL2*01.-05***	c.451C>T (c.457C>T)	7	p.Leu151Phe (p.Leu153Phe)	(3), Abstract	NM_001145056.2	rs147820753
Null Phenotypes							
CTL2:–1 or VER–	***CTL2*01N.01***	Deletion of exons 1 to 14 (37 kbp). Break-points with coordinates from chromosome 19:10,598,733-10,636,021		no protein product	(1), Abstract PMID: 36695047		

VER: name suggested after the name of the city of origin of the null proband, Verona in Italy

VER–: deletion of 37 kbp (exons 1 to 14 along with the 5' UTR region of *SLC44A2*)

RIF: name suggested after the name of the North Mediterranean coast of Morocco from where all the reported RIF– people originate to date.

BROS: stands for the laboratories that were involved in the description of the antigen BROS: Bristol, Rotterdam and Sanquin.

[1)] Nucleotide change, counting for CTL2 with 704 amino acids (Nucleotide change, counting for CTL2 with 706 amino acids)

[2)] Predicted amino acid change on CTL2 protein with 704 amino acids (Predicted amino acid change on CTL2 protein with 706 amino acids)

References

PMID: 20037594 Greinacher A, Wesche J, Hammer E, Furll B, Volker U, Reil A, Bux J. Characterization of the human neutrophil alloantigen-3a. Nat Med. 2010;16:45–48.

PMID: 20665236 Kommareddi PK, Nair TS, Thang LV, Galano MM, Babu E, Ganapathy V, Kanazawa T, McHugh JB, Carey TE. Isoforms, expression, glycosylation, and tissue distribution of CTL2/SLC44A2. Protein J. 2010 Aug;29(6):417-26. doi: 10.1007/s10930-010-9268-y.

PMID: 36695047 Koehl B, Vrignaud C, Mikdar M, Nair TS, Yang L, Landry S, Laiguillon G, Giroux-Lathuile C, Anselme-Martin S, El Kenz H, Hermine O, Mohandas N, Cartron JP, Colin Y, Detante O, Marlu R, Le Van Kim C, Carey TE, Azouzi S, Peyrard T. Lack of the human choline transporter-like protein SLC44A2 causes hearing impairment and a rare red blood phenotype. EMBO Mol Med. 2023 Mar 8;15(3):e16320. doi: 10.15252/emmm.202216320.

Abstract (1) Vrignaud C., Mikdar M., Koehl B., Nair T.S., Yang L., Laiguillon G., El Kenz H., Cartron J.P., Colin Y., Detante O., Le Van Kim C., Carey T.E., Azouzi S., Peyrard T. (2019) Alloantibodies directed to the SLC44A2/CTL2 transporter define two new red cell antigens and a novel human blood group system. *Transfusion,* 59 (Suppl. S3), 18A[abstract].

Abstract (2) De Oliveira Rios J, Soudry A, Duval R, Raneri A., Poyot T., Babinet J., Montalembert .M., Bonini Domingos C.R., Le Van Kim C., Romana M., Peyrard T., Azouzi S. The Csa and Csb red cell antigens of the Cost blood group collection correspond to the HNA3a and HNA3b neutrophil antigens: Unexpected twins with implications for sickle cell anemia. Blood 2023 ; 142 : 69898 [abstract].

Abstract (3) Mankelow TJ, Green F, Tilley L, Karamatic Crew V, Jones B, Borowski A, Jackson R, Weerkamp F, Folman CC, Ligthart PC, Thornton N. A Leu151Phe substitution in Choline transporter like protein 2 (CTL2), adjacent to Arg152Gln, encoding Csa/Csb antigens, encodes a novel high prevalence red cell antigen. Vox Sang. Vol. 119 Suppl. 1, June 2024. PA26-L04. DOI:10.1111/vox.13650

Track of changes

			from	to
1			**v2.0 30-SEP-2024**	**v2.1 17-OCT-2024**
2	Author	created by	Thierry Peyrard, September 2024	Thierry Peyrard, October 2024
3	Reviewer	reviewed by	Christoph Gassner, August 2024	Christoph Gassner, October 2024
4	Allele	corrected	*CTL2*01.04* c.455C>A (c.461C>A).	*CTL2*01.04* corrected to c.455G>A (c.461G>A).
5	**End Version**		**v2.0 30-SEP-2024**	**v2.1 17-OCT-2024**

Track of changes

			from	to
1			**v1.2 31-DEC-2023**	**v2.0 30-SEP-2024**
2	Author	created by	Thierry Peyrard, December 2023	Thierry Peyrard, September 2024
3	Reviewer	reviewed by	Slim Azouzi, Christof Weinstock, December 2023	Christoph Gassner, August 2024
4	Intro	extended		Christoph Gassner, August 2024. The new antigens were added to the Intro. The facts of the two CTL2 protein variants with lengths of 704 and 706 amino acids each were detailed and a new accession number was defined as a genomic reference sequence for a CTL2 704 amino acid protein of the Csa/HNA-3a phenotype (KM024996.1).
5	Coding of reference allele	supplemented		The coding of the reference allele for the new antigens Cs^a /HNA-3a and BROS has been added.
6	Antithetical antigens	added		Antigens Cs^a and Cs^b, respectively HNA-3a and 3b were identified as antithetic antigens.
7	Header of allele table	changed		The content of the header has been changed
8	Content of allele table	phenotypes added		Description of phenotypes was supplemented
9	Content of allele table	new antigens and alleles added		2 new alleles were added: *CTL2*01.04* , coding for Cs^b (HNA-3b) and *CTL2*01.-05* , coding for BROS negativity.
10	Content of allele table	positions of mutants supplemented		The nucleotide and amino acid exchanges for the two CTL2 protein variants with lengths of 704 and 706 amino acids are now displayed for all variants.

Track of changes

			from	to
1			**v1.2 31-DEC-2023**	**v2.0 30-SEP-2024**
11	References	supplemented		Three references were added in the intro of the table. The core reference for the discovery of the the CTL2 blood group system was added (PMID: 36695047). References for the new antigens and alleles were added.
12	**End Version**		**v1.2 31-DEC-2023**	**v2.0 30-SEP-2024**

Track of changes

			from	to
1			**v1.1 31-MAR-2022**	**v1.2 31-DEC-2023**
2	Author	created by	Thierry Peyrard, April 2022	Thierry Peyrard, December 2023
3	Reviewer	reviewed by	Jill Storry Dec. 2021, Christof Weinstock, April 2024	Slim Azouzi, Christof Weinstock, December 2023
4	References	Reference added		Abstract (2)
5	Intro	Antigens added		Cs^{a} and Cs^{b}
6	**End Version**		**v1.1 31-MAR-2022**	**v1.2 31-DEC-2023**