Colton Blood Group System

Number of antigens 4

Polymorphic	Co[b]
High prevalence	Co[a], Co3, Co4

Terminology

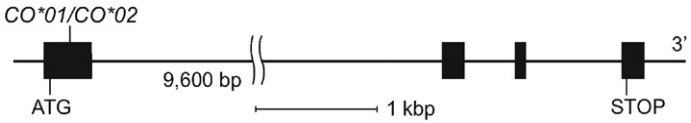
ISBT symbol (number)	CO (015)
History	Named in 1967 for the first of the three original producers of anti-Co[a]. Should have been named Calton, but the handwriting on the tube was misread.

Expression

Tissues	Kidney (apical surface of proximal tubules, basolateral membranes, subpopulation of collecting ducts in cortex, descending tubules in medulla), liver bile ducts, gall bladder, eye (epithelium, cornea, lens, choroid plexus), hepatobilliary epithelia, capillary endothelium[1]

Gene

Chromosome	7p14.3
Name	*CO* [*AQP1* (*Aquaporin-1*)]
Organization	4 exons distributed over 11.6 kbp of gDNA
Product	Channel-forming integral protein (CHIP); Aquaporin 1 (AQP1); CHIP-1; CHIP28[1]



The Blood Group Antigen (3/e). DOI: http://dx.doi.org/10.1016/B978-0-12-415849-8.00017-X

Database accession numbers

GenBank	AY953319 (gene), M77829 (mRNA)
Entrez Gene ID	358

Molecular bases of Colton phenotypes

Reference allele, *CO*01* (M77829) encodes Co[a] (CO1), CO3, CO4. Differences from this allele are given.

Allele encodes	Allele name	Exon	Nucleotide	Restriction Enzyme	Amino acid	Ethnicity (prevalence)
Co(a–b+) or CO:–1,2	*CO*02.01 or CO*B*	1	134C>T	*PflMI*+	Ala45Val	(Many)
Co(a–b+) or CO:–1,2	*CO*02.02*	1	133G>A		Ala45Thr[2]	(Rare)
^Co(a–b–) CO:3,–4 or CO:–1,–2, 3,–4	*CO*01. −04*	1	140A>G		Gln47Arg	Caucasians, Turkish (Rare)

^ = When *in trans* to *CO*02*, expression of Co[b] on RBCs is weakened.

Molecular bases of silencing of *CO*

Homozygosity or compound heterozygosity leads to Co_{null} [Co(a–b–) Co3–, CO:–3,–4] phenotype. Differences from *CO*01* reference allele (M77829) are given.

Allele name	Exon	Nucleotide	Amino acid	Ethnicity (prevalence)
*CO*01N.01*	1	del all or part exon 1	No protein	Northern European (Rare)
*CO*01N.02*	1	307insT	Gly104 fs →Stop	French (Rare)
*CO*01N.03*	3	576C>A	Asn192Lys	Portuguese (Rare)
*CO*01N.04*	1	232delG	Ala78 fs→119Stop	Indian (Rare)
*CO*01N.05*	1	113C>T	Pro38Ser[3]	Polish (Rare)
*CO*01N.06*	3	601delG	fs Val201Stop	Caucasian (Rare)

Molecular bases of weak expression of Co antigens

KLF1 encodes erythroid Krüppel-like factor (EKLF). Several nucleotide changes in this gene are responsible for *In(Lu)* (see Lutheran). *KLF1* has 3 exons; the initiation codon is in exon 1, and the stop codon is in exon 3. GenBank accession numbers are U37106 (gene) and NM_006563 (mRNA). Differences from *CO*01* reference allele (M77829) or *KLF1*01* reference allele (Accession number NM_006563) are given.

Allele name	Exon	Nucleotide change	Amino acid change	Ethnicity (prevalence)
*CO*01M.01*^	1	112C>T	Pro38Leu	Northern European (Rare)
*KLF1*BGM10*	3	973G>A^^	Glu325Lys	(Rare)

^ = When *in trans* to *CO*02*, expression of Co^b on RBCs is weakened.
^^ = Heterozygosity for this nucleotide change in a patient with dyserythropoietic anemia caused suppression of antigens in CO, IN, and LW blood group systems[4,5].

Amino acid sequence[1]

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MASEFKKKLF  WRAVVAEFLA  TTLFVFISIG  SALGFKYPVG  NNQTAVQDNV   50
KVSLAFGLSI  ATLAQSVGHI  SGAHLNPAVT  LGLLLSCQIS  IFRALMYIIA  100
QCVGAIVATA  ILSGITSSLT  GNSLGRNDLA  DGVNSGQGLG  IEIIGTLQLV  150
LCVLATTDRR  RRDLGGSAPL  AIGLSVALGH  LLAIDYTGCG  INPARSFGSA  200
VITHNFSNHW  IFWVGPFIGG  ALAVLIYDFI  LAPRSSDLTD  RVKVWTSGQV  250
EEYDLDADDI  NSRVEMKPK                                      269
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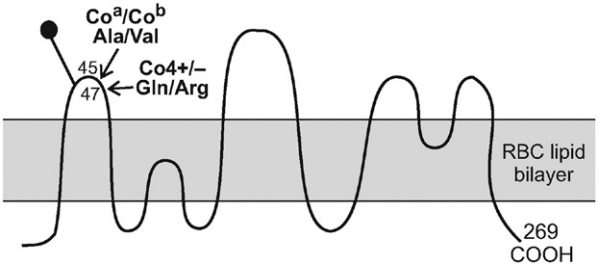
Carrier molecule[1]

A multipass membrane glycoprotein.



M_r (SDS-PAGE)	28,000 unglycosylated form 40,000–60,000 glycosylated form
CHO: N-glycan	Polylactosaminoglycan that carries ABH determinants at residue 42

Cysteine residues	4
Copies per RBC	120,000–160,000 molecules arranged in tetramers

Function

Water transport. AQP1 accounts for 80% of water reabsorption in kidneys, and is a determinant of vascular permeability in the lung[6]. The ^{76}Asn-Pro-Ala^{78} (NPA) motif is essential for this function[6,7].

Disease association

Co^{a} is expressed weakly in Monosomy 7 due to certain chromosome 7 rearrangements that also cause acute leukemia.
One patient with dyserythropoietic anemia had suppression of CO, IN, and LW antigens[4,8]. Other examples have been found.

Phenotypes (% occurrence)

Phenotypes	Most populations
Co(a+b–)	90
Co(a–b+)	0.5
Co(a+b+)	9.5
Co(a–b–)	<0.01
Null: Co(a–b–)	
Unusual: Co(a–b+^{W}); Co(a–b–) CO:3,–4	

Comments

In RBCs, AQP1 exists in the membrane as a dimer, and accounts for 2.4% of the total membrane protein[7,9].

References

[1] Preston, G.M., Agre, P., 1991. Isolation of the cDNA for erythrocyte integral membrane protein of 28 kilodaltons: Member of an ancient channel family. Proc Natl Acad Sci USA 88, 11110–11114.
[2] Arnaud, L., et al., 2010. A functional *AQP1* allele producing a Co(a–b–) phenotype revises and extends the Colton blood group system. Transfusion 50, 2106–2116.
[3] Karpasitou, K., et al., 2010. A silenced allele in the Colton blood group system. Vox Sang 99, 158–162.

[4] Parsons, S.F., et al., 1994. A novel form of congenital dyserythropoietic anemia associated with deficiency of erythroid CD44 and a unique blood group phenotype [In(a−b−), Co(a−b−)]. Blood 83, 860–868.
[5] Singleton, B.K., et al., 2009b. A novel GATA-1 mutation (Ter414Arg) in a family with the rare X-linked blood group Lu(a–b–) phenotype [abstract]. Blood 114, 783.
[6] King, L.S., et al., 2002. Decreased pulmonary vascular permeability in aquaporin-1-null humans. Proc Natl Acad Sci USA 99, 1059–1063.
[7] Kozono, D., et al., 2002. Aquaporin water channels: Atomic structure and molecular dynamics meet clinical medicine. J Clin Invest 109, 1395–1399.
[8] Singleton, B.K., et al., 2009a. A novel EKLF mutation in a patient with dyserythropoietic anemia: The first association of EKLF with disease in man [abstract]. Blood 114, 72.
[9] Agre, P., et al., 2002. Aquaporin water channels – from atomic structure to clinical medicine. J Physiol London 542, 3–16.

Co^a Antigen

Terminology

ISBT symbol (number)	CO1 (015001 or 15.1)
Obsolete name	Colton
History	Named in 1967, after the first antibody producer. Should have been named Ca^a from Calton, but the handwriting on the tube was misread.

Occurrence

All populations	99.5%

Antithetical antigen

Co^b (**CO2**)

Expression

Cord RBCs	Expressed

Molecular basis associated with Co^a antigen[1]

Amino acid	Ala45
Nucleotide	C at bp 134 (and G at bp 133) in exon 1 The nucleotide at bp 133 was shown by transfectant studies to be important for expression of Co^a antigen

A change of Gln47 to Arg (in the Co4– phenotype) inhibits expression of Co^a but not Co3.

Effect of enzymes and chemicals on Co^a antigen on intact RBCs

Ficin/Papain	Resistant
Trypsin	Resistant
α-Chymotrypsin	Resistant
DTT 200 mM	Resistant
Acid	Resistant

In vitro characteristics of alloanti-Co^a

Immunoglobulin class	IgG (Rare IgM reported)[2]
Optimal technique	IAT
Complement binding	Some

Clinical significance of alloanti-Co^a

Transfusion reaction	No to moderate/delayed; immediate/hemolytic[3]
HDFN	Mild to severe[4] (rare)

Autoanti-Co^a

One example.

Comments

Siblings of patients with anti-Co^a should be tested for compatibility, and the patient urged to donate blood for cryogenic storage when his/her clinical state permits.

References

[1] Smith, B.L., et al., 1994. Human red cell aquaporin CHIP. I. Molecular characterization of ABH and Colton blood group antigens. J Clin Invest 94, 1043–1049.

[2] Kurtz, S.R., et al., 1982. Survival of homozygous Co^a (Colton) red cells in a patient with anti-Co^a. Vox Sang 43, 28–30.

[3] Covin, R.B., et al., 2001. Acute hemolytic transfusion reaction caused by anti-Co^a. Immunohematology 17, 45–49.

[4] Simpson, W.K.H., et al., 1973. Anti-Co^a and severe haemolytic disease of the newborn. S Afr Med J 47, 1302–1304.

Co^b Antigen

Terminology

ISBT symbol (number)	CO2 (015002 or 15.2)
History	Named in 1970 when it was shown to be antithetical to Co^a.

Occurrence

All populations	10%

Antithetical antigen

Co^a (**CO1**)

Expression

Cord RBCs	Expressed
Altered	Co(a–) RBCs with weak expression of Co^b exist. See System pages

Molecular basis associated with Co^b antigen[1]

Amino acid	Val45 or Thr45
Nucleotide	T at bp 134 or A at bp 133 in exon 1 The nucleotide at bp 133, with 134T, was shown by transfectant studies to be important for expression of Co^b antigen

Effect of enzymes and chemicals on Co^b antigen on intact RBCs

Ficin/Papain	Resistant
Trypsin	Resistant
α-Chymotrypsin	Resistant
DTT 200 mM	Resistant
Acid	Resistant

In vitro characteristics of alloanti-Co^b

Immunoglobulin class	IgG
Optimal technique	IAT
Complement binding	Rare

Clinical significance of alloanti-Co^b

Transfusion reaction	No to moderate/delayed/hemolytic
HDFN	Mild

Comments

Co^b is a poor immunogen, and anti-Co^b is rarely found as a single specificity.

Reference

[1] Smith, B.L., et al., 1994. Human red cell aquaporin CHIP. I. Molecular characterization of ABH and Colton blood group antigens. J Clin Invest 94, 1043–1049.

Co3 Antigen

Terminology

ISBT symbol (number)	CO3 (015003 or 15.3)
Obsolete names	Co^{ab}
History	Reported in 1974, when an antibody to a common antigen (then called anti-Co^aCo^b) was found in a patient whose RBCs typed Co(a–b–).

Occurrence

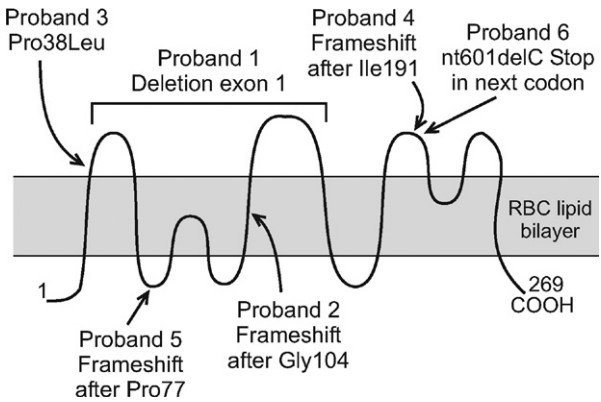
All populations	Greater than 99.9%

Expression

Cord RBCs	Expressed

Molecular basis associated with lack of Co3 antigen

Refer to System pages.



Effect of enzymes and chemicals on Co3 antigen on intact RBCs

Ficin/Papain	Resistant
Trypsin	Resistant
α-Chymotrypsin	Resistant
DTT 200 mM	Resistant
Acid	Resistant

In vitro characteristics of alloanti-Co3

Immunoglobulin class	IgG
Optimal technique	IAT
Complement binding	Yes

Clinical significance of alloanti-Co3

Transfusion reaction	Mild hemolytic
HDFN	Severe

Autoanti-Co3

One example described as mimicking anti-Co3 made by a patient with non-Hodgkins lymphoma.

Comments

RBCs from a baby with congenital dyserythropoietic anemia (CDA) were Co(a–b–), In(a–b–), AnWj–, and had a weak expression of LW[1,2]. More cases have been reported.
Siblings of patients with anti-Co3 should be tested for compatibility, and the patient urged to donate blood for cryogenic storage when his/her clinical state permits.

References

[1] Agre, P., et al., 1994. Human red cell Aquaporin CHIP. II. Expression during normal fetal development and in a novel form of congenital dyserythropoietic anemia. J Clin Invest 94, 1050–1058.

[2] Parsons, S.F., et al., 1994. A novel form of congenital dyserythropoietic anemia associated with deficiency of erythroid CD44 and a unique blood group phenotype [In(a−b−), Co(a−b−)]. Blood 83, 860–868.

Co4 Antigen

Terminology

ISBT symbol (number)	CO4 (015004 or 15.4)
History	First identified in 2002, and named with next available number in the Colton system in 2010 after a second Co4– proband (Turkish) was found with functional AQP1. Both cases had anti-Co4 in their plasma.

Occurrence

All populations	Only three Co4– probands have been reported

Expression

Cord RBCs	Presumed expressed

Molecular basis associated with Co4 antigen[1,2]

Amino acid	Gln47
Nucleotide	A at bp 140 in exon 1
CO:–4	Arg47 and G at bp 140

Effect of enzymes and chemicals on Co4 antigen on intact RBCs

Ficin/Papain	Resistant
Trypsin	Resistant
α-Chymotrypsin	Presumed resistant
DTT 200 mM	Presumed resistant

In vitro characteristics of alloanti-Co4

Immunoglobulin class	IgG
Optimal technique	IAT

Clinical significance of alloanti-Co4

No data because the antibody is rare.

Comments

Anti-Co4 is reactive with Co(a+b–) and Co(a–b+), but not Co(a–b–) RBCs; CO:–4 RBCs type Co(a–b–) but Co3+ and have functional AQP1[1].
Siblings of patients with anti-Co4 should be tested for compatibility and the patient urged to donate blood for cryogenic storage when his/her clinical state permits.

References

[1] Arnaud, L., et al., 2010. A functional *AQP1* allele producing a Co(a–b–) phenotype revises and extends the Colton blood group system. Transfusion 50, 2106–2116.
[2] Wagner, F.F., Flegel, W.A., 2002. A clinically relevant Co(a)-like allele encoded by *AQP1* (Q47R) [abstract]. Transfusion 42 (Suppl.), 24S–25S.