15 Colton Blood Group System

15.1 Introduction

The Colton system contains a single polymorphism, with relatively high and low incidence alleles represented by Co^a and Co^b antigens, respectively. A third antigen, Co3, is present on all cells save those of the null phenotype, Co(a–b–). Absence of Co4 is associated with a Co(a–b–) Co:3 phenotype (Table 15.1).

The *CO* locus is on chromosome 7p and the Co(a–b–) phenotype is sometimes associated with acquired chromosome 7 monosomy. The Colton antigens are located on aquaporin-1 (AQP1), a water channel-forming protein.

15.2 The Colton glycoprotein, aquaporin-1, and the gene that encodes it

Thirteen members of the aquaporin family of water channels are found in humans; 2 of these, AQP1, the Colton glycoprotein, and AQP3, the Gill glycoprotein (Chapter 26), are present in human red cells (reviews in [1,2]). The MW of AQP1 is 28 kDa in its unglycosylated form and 40–60 kDa in its glycosylated form. There are between 120 000 and 160 000 molecules per red cell, arranged as tetramers, with each tetramer containing one glycosylated molecule [3]. PCR amplification of a human fetal liver cDNA template with degenerate oligonucleotide primers representing the amino acid sequence of the N-terminal region of AQP1 provided a probe for isolation. The sequence of the 807 bp open reading frame of *AQP1* cDNA from a human bone marrow cDNA library predicted a 269 amino acid polypeptide, which spans the membrane six times and has cytoplasmic N- and C-termini [4] (Figure 15.1). The two halves of AQP1 are sequence-related: each has three membrane-spanning domains and each has a loop, one extracellular (E in Figure 15.1) and one cytoplasmic (B), containing the Asn-Pro-Ala (NPA) motif characteristic of the aquaporin family. In accordance with several structural models these two NPA motifs may interact within the membrane to form a single aqueous channel spanning the bilayer [5–7]. The first extracellular loop may be *N*-glycosylated, the oligosaccharide resembling the *N*-glycan of band 3 and expressing ABH activity [8].

The 17 kb *AQP1* gene consists of 4 exons encoding amino acids 1–128, 129–183, 184–210, and 211–269, and has been localised, by *in situ* hybridisation, to chromosome 7p14 [9]. The *AQP1* promoter contains TATA and CCAAT boxes, Sp1, AP1, AP2, and E-box elements, and erythroid-specific CACCC and Krüppel-like (CACCCA) elements [10].

Localisation of *AQP1* to the same region of chromosome 7 as the Colton blood group gene led to the discovery that the Colton antigens are on AQP1 [11]. Smith *et al.* [8] found that AQP1 could be selectively precipitated with anti-Co^a and -Co^b from red cells of the appropriate Colton phenotypes. Anti-Co3 precipitated AQP1 from Co(a+b–) and Co(a–b+) cells.

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Table 15.1 Antigens of the Colton system.

Antigen				Molecular basis*		
No.	Name	Frequency	Antithetical antigen	Nucleotides	Exon	Amino acids
CO1	Co^a	High	CO2	134C	1	Ala45
CO2	Co^b	8.5%†	CO1	134T	1	Val45
CO3	Co3	High		Various		Various
CO4	Co4	High		140A (G)	1	Gln47 (Arg)

*Molecular basis of antigen-negative phenotype in parentheses.
†Northern Europeans.

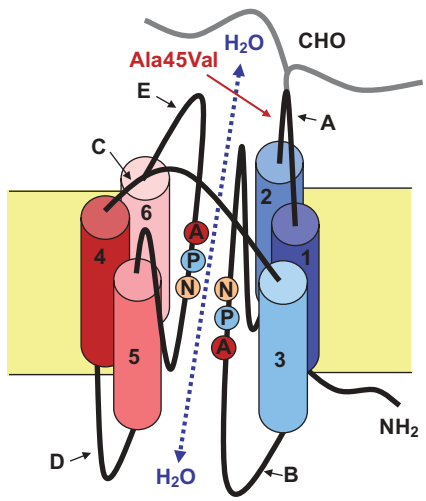

Figure 15.1 Three-dimensional model for AQP1 in the plasma membrane [5–7]. The six membrane-spanning domains are shown as cylinders and numbered from the N-terminus. A, C, and E represent the three extracellular loops; B and D, two cytoplasmic loops. B and E are extended loops that pass into the membrane to form a pore through which water molecules pass. NPA represents the Asn-Pro-Ala motifs in loops E and B. CHO, *N*-glycan at Asn42; Ala45Val, site of Colton polymorphism.

15.3 Co^a and Co^b (CO1 and CO2)

In 1967, Heistö *et al.* [12] gave the name anti-Co^a to three antibodies defining a new inherited public antigen. Three years later, Giles *et al.* [13] identified the antithetical anti-body, anti-Co^b, and a new blood group polymorphism was born.

From seven separate studies with anti-Co^a on a total of 13 460 white donors from Northern Europe and North America, 27 were Co(a–), giving a frequency for Co^a of 99.8% [12–17]. From five series of tests with anti-Co^b on 5186 white donors from England, Canada, Australia, and New Zealand, 443 or 8.5% were Co(b+) [13,17–19]. Gene and genotype frequencies calculated from these data (assuming that *CO*A* and *CO*B* are the only alleles present) are shown in Table 15.2; those calculated from the results of tests with anti-Co^a correlate remarkably well with those derived from tests with anti-Co^b. Of 1706 African Americans, all were Co(a+) [15]. The following Co^b frequencies were obtained: 4.6% in Miami Hispanics (799 tested) [20]; 2% in Cree Indians (100 tested) [21]; 0.58% in Japanese (2244 tested) [22].

The Colton polymorphism is associated with a 134C>T change in exon 1, the *CO*A* allele encoding alanine at position 45 and the *CO*B* allele encoding valine on the first extracellular loop of AQP1 (loop A), close to the site of *N*-glycosylation (Asn42) [8] (Figure 15.1). Altered glycosylation may prevent expression of Colton antigens; *Xenopus* oocytes expressing human AQP1 do not bind anti-Co^a [8]. A *Pfi*MI restriction site is created by the *CO*B* allele.

Co^a and Co^b are resistant to denaturation by the proteases papain, trypsin, chymotrypsin, and pronase, by sialidase, and by the disulphide bond reducing agent AET.

Co^a was not detected by flow cytometry on lymphocytes, monocytes, or granulocytes [23].

Table 15.2 Antigen, gene, and genotype frequencies in white people, determined from tests with anti-Co^a [12–17] and -Co^b [13,17–19].

		With anti-Co^a	With anti-Co^b
Antigens	Co^a	0.998	
	Co^b		0.085
Genes	*Co^a*	0.955	0.956
	Co^b	0.045	0.044
Genotypes	*CO*A/A*	0.912	0.914
	*CO*A/B*	0.086	0.084
	*CO*B/B*	0.002	0.002

15.4 Co3 and the Co$_{null}$ and Co$_{mod}$ phenotypes

In 1974 the awaited Co$_{null}$ phenotype, Co(a–b–), was identified in a French-Canadian woman and two of her four siblings [24]. Her parents and other two siblings were Co(a+b–). The serum of the propositus contained an antibody, anti-Co3, which reacted with all cells except those of the Co(a–b–) phenotype and could not be separated into anti-Co^a and anti-Co^b components. Subsequently other Co$_{null}$ individuals have been ascertained through the presence of anti-Co3, all of European extraction [25–31], with the exception of one Indian woman [32]. No negative was found as a result of testing 40 000 donors (29 000 North Americans, 9000 Australians, 2000 Finns) with anti-Co3 [28].

Molecular genetical analyses have been performed on Co(a–b–) Co:–3 propositi revealed the following mutations in *AQP1*.

1 Homozygosity for a deletion encompassing most or all of exon 1 [33] (*CO*N.01*). No AQP1 was detected by immunoblotting. Red cells had normal morphology, haematocrit, and haemoglobin levels, but a slightly reduced lifespan *in vivo* [34].

2 Homozygosity for a single base insertion at nucleotide 307 (exon 1), initiating a reading frameshift after Gly104, in the third membrane-spanning domain [33] (*CO*N.02*). No AQP1 was detected by immunoblotting.

3 Homozygosity for 576C>A in exon 3 of *CO*A*, encoding Asn192Lys [29] (*CO*01N.03*). This substitution converts the Asn-Pro-Ala motif in the third extracellular loop (E in Figure 15.1) to Lys-Pro-Ala. It is predicted that such a change in this important motif would result in failure of the protein to reach the membrane.

4 Homozygosity for a deletion of G232 in exon 1 of *CO*A*, introducing a reading frameshift after the codon for Ala78 (*CO*01N.04*), in an Indian woman from a small ethnic group and whose parents were first cousins [32].

5 Homozygosity for a deletion of 601G in exon 3 of *CO*A*, resulting in Val201Stop, (CO*01N.06) in two propositi [30,31].

A Co(a–) blood donor with weak Co^b was heterozygous 134C/T (*CO*A/B*), with 112C>T mutation in the *CO*A* allele (*CO*01N.05*). Encoded Pro38Ser was probably responsible for the absence of Co^a antigen expression [35].

Homozygosity for 113C>T in exon 1, encoding Pro-38Leu [33] (*CO*M.01*), resulted in a Co$_{mod}$ phenotype. Trace amounts of apparently normal AQP1 were detected on immunoblots of red cell membranes probed with monoclonal anti-AQP1 and the red cells reacted weakly with an extremely potent anti-Co3 [28]. *Xenopus* oocytes transfected with *AQP1* cDNA containing the Pro38Leu mutation had osmotic water permeabilities higher than those transfected with no *AQP1* cDNA, but substantially lower than those transfected with normal *AQP1* cDNA [33].

Red cells of a child with a unique form of congenital dyserythropoietic anaemia (CDA), but no *AQP1* mutation, had less than 10% of normal AQP1 levels and were Co(a–b–), but reacted with potent anti-Co3, and had very low osmotic water permeability [36,37]. Her red cells were also CD44-deficient, In(a–b–), and AnWj–, had weak LW^{ab}, but expressed normal Lutheran antigens. She, and two other patients with similar symptoms of CDA, were heterozygous for 973G>A in *KLF1*, the gene for the erythroid transcription factor EKLF (see Section 6.8.1) [38,39]. This mutation encodes the substitution of Glu325, which is predicted to contact DNA, by lysine in the second zinc finger domain. Since the disease phenotype occurs in the presence of a non-mutated allele, it is likely that the mutated protein actively interferes with EKLF-dependent processes by destabilising transcription complexes. Transfection experiments in K562 cells demonstrated that EKLF Glu325Lys has reduced ability to activate haemoglobin beta and CD44 gene expression [38].

Like Co^a and Co^b, Co3 is resistant to protease, sialidase, and AET treatment of red cells.

15.5 Co4 and the Co(a–b–) Co:3 phenotype

Anti-Co4, an antibody to a high frequency antigen, was found in a Co(a–b–) Turkish woman with two Co(a+b–)

children. Her phenotype was not Co_{null} as her red cells expressed normal levels of Co3, normal quantities of AQP1, and exhibited normal water permeability. Her antibody did not react with Co(a–b–) cells, but could not be anti-Co3 as it did not react with her own Co:3 red cells [40]. She was homozygous for 140A>G encoding Gln47Arg (*CO*01.–04*). As she was homozygous for *CO*A* (Ala45), it is probable that both Ala45 and Gln47 are required for Co^a expression. Transfection experiments in K562 cells demonstrated that Gln47 is also required for Co^b expression [40]. Two other Co(a–b–) individuals with the Gln47Arg are reported [40,41].

15.6 Colton antigens and monosomy 7

Monosomy 7 of the bone marrow, the loss of one chromosome 7 from haemopoietic stem cells, is a chromosomal abnormality occasionally associated with acute myeloid leukaemia and preleukaemic dysmyelopoietic syndromes. Monosomy 7 is often associated with Co(a–b–) Co:–3 phenotype or with weakening of Co^a and Co3 [42–44]. Of 35 monosomy 7 patients, eight had either Co(a–b–) Co:–3 or Co($a+^wb-$) Co3-weak red cells [44]. None of these eight had been recently transfused, whereas transfused red cells were present in the circulation of 21 of the remaining 27 Co(a+b–) patients. Zelinski *et al.* [45] suggested that absence of Colton antigens in some monosomy 7 patients results from loss of one allele, owing to the monosomy, and altered expression of the product of the other allele, resulting from the concomitant haematological disorder.

15.7 Colton antibodies

15.7.1 Anti-Co^a

Many examples of anti-Co^a have been identified. Like anti-Co^b and -Co3, they are generally IgG and react best by the antiglobulin test, especially if protease-treated cells are used, although an agglutinating IgM anti-Co^a has been reported [46].

Anti-Co^a has caused severe HDFN [47,48] and has been implicated in acute and delayed HTRs [49,50]. *In vivo* survival studies and monocyte monolayer functional assays also predict that anti-Co^a have the potential to cause HTRs [46,51] and Co(a–) red cells should be selected for transfusion to patients with anti-Co^a.

Anti-Co^a in a Co(a+b+) patient, shown to be *CO*A/B* by genomic analysis, was considered either to detect a partial Co^a antigen or to be an autoantibody [52].

15.7.2 Anti-Co^b

Anti-Co^b, a relatively rare antibody, was not detected in sera from 1430 transfused and non-transfused patients, or in sera from seven patients known to have been transfused with Co(a–) blood [12]. Anti-Co^b is often found in sera containing other blood group antibodies.

Anti-Co^b has been responsible for an acute HTR [53] and a mild delayed HTR [54]. *In vivo* survival studies demonstrated accelerated destruction of radiolabelled Co(b+) cells in patients with anti-Co^b [51,55,56]. Red cells compatible by IAT at 37°C should be selected for transfusion to patients with anti-Co^b. There is no report of serious HDFN caused by anti-Co^b.

15.7.3 Anti-Co3

Anti-Co3 has caused severe HDFN requiring neonatal transfusion [27,28]. Transfusion of Co(a+b–) blood to a patient with anti-Co3 resulted in a mild haemolytic reaction [29]. A very high titred anti-Co3 consisted of IgG1, IgG3, and some IgG2, was complement binding, and was haemolytic *in vitro* [28].

A 'mimicking autoanti-Co3' in a non-Hodgkin's lymphoma patient with Co(a–b–) Co:3 red cells directly agglutinated most red cells, but a papain antiglobulin test was required to demonstrate reactivity with the patient's own cells and with Co(a–b–) Co:–3 cells [57].

15.7.4 An antibody reactive only when Co^a and Co^b are both present

An antibody produced by a Co(a+b–) patient reacted by an antiglobulin test with 12 examples of Co(a+b+) red cells, but not with eight examples of Co(a–b+) or many examples of Co(a+b–) cells [58]. It is feasible that binding of this antibody to red cells of *CO*A/B* heterozygotes is dependent on the conformational effects of interactions between valine and alanine at position 45 of different molecules within AQP1 tetramers of the red cell membrane.

15.8 Functional aspects

AQP1 functions to form channels in the plasma membrane that enhance osmotically driven water transport. The extended loops B and E in Figure 15.1 form a channel through the membrane with a pore diameter of about 3 Å,

only slightly larger than the 2.8 Å diameter of a water molecule, so each unit of the AQP1 tetramers forms a separate channel. Interaction with the asparagine residues of the Asn-Pro-Ala motifs enhances transfer of water molecules, whilst preventing H^+ transport [6]. AQP1 may enable red cells to rehydrate rapidly after their shrinkage in the hypertonic environment of the renal medulla [59]. This would act in concert with the urea transporter, which also serves to reduce cell shrinkage in the renal medulla by enhancing the red cell's permeability to urea (Section 9.5).

AQP1 is strongly expressed in the proximal convoluted tubules and descending thin limbs of the kidney and has also been detected in various other epithelia and endothelia. AQP1 plays a role in reabsorption of water from the glomerular filtrate in the proximal tubule and thin descending loop of Henle. AQP1 has been detected in several other organs and tissues: lung, where it may be involved in maintaining water balance; brain, where it could play a part in regulation of cerebral-spinal fluid; and eye, where it might have a role in secretion and uptake of the aqueous humour [1,2].

Three Co_{null} propositi had about an 80% reduction in red cell osmotic water permeabilities and no AQP1 from renal tubules could be detected in their urinary sediment [33]; they were apparently healthy, but were unable to concentrate urine maximally when deprived of water [60]. AQP1 knockout mice are grossly normal, but become severely dehydrated compared with control mice after 36 hours of water deprivation [61]. It is likely, therefore, that AQP1 in the thin descending limb of Henle is required for the production of concentrated urine during times of water shortage [62]. AQP1 function in renal tubules may be shared with other members of the aquaporin family, in particular AQP2; in red cells the function may be shared with AQP3 (see Chapter 26).

Co_{null} red cells have about a 50% reduction in CO_2 membrane permeability compared with cells of normal phenotype [63]. Consequently AQP1 could also provide an important pathway for CO_2 in human red cells, though this has been disputed [64]. Transfection experiments in mammalian endothelial cells have also suggested that AQP1 facilitates transport of O_2 and NO across membranes [65,66].

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