14 Dombrock Blood Group System

14.1 Introduction

Prior to 1992, Dombrock remained a simple, polymorphic blood group system with two antigens, Do^a (DO1) and Do^b (DO2), the products of alleles. The discovery by Banks *et al.* [1] that red cells of the rare phenotype Gy(a–) Hy– Jo(a–) were also Do(a–b–) led to Gy^a, Hy, and Jo^a joining the Dombrock system; three antigens of high frequency, DOYA, DOMR, and DOLG joined later (Table 14.1). Table 14.2 shows Dombrock phenotypes and genotypes. Antigens of the Dombrock system are located on a GPI-linked glycoprotein, a member of the ADP-ribosyltransferase family (ART4, CD297). Asn265Asp represents the Do^a/Do^b polymorphism.

DO (*ART4*) is located on chromosome 12p13.2-12.1.

14.2 The Dombrock glycoprotein, ART4, and the gene that encodes it

Dombrock system antigens are on a glycoprotein that is anchored to the red cell membrane through glycosylphosphatidylinositol (GPI) (see Chapter 19). PNHIII red cells, the complement-sensitive population of red cells from patients with paroxysmal nocturnal haemoglobinuria (PNH), lack GPI-linked proteins and are deficient in Dombrock system antigens [2–4]. Immunochemical analyses revealed that Do^a, Gy^a, Hy, and Jo^a are on an *N*-glycosylated membrane protein of apparent MW 46 750–57 500 Da, without substantial *O*-glycosylation [1–3]. A putative dimer was also detected by immunoprecipitation [2].

Family analyses with numerous markers, including the gene for von Willebrand factor gene (*VWF*), localised *DO* (*ART4*) to chromosome 12p13.2-12.3 [5,6].

Gubin *et al.* [7] screened a database of about 5000 expressed sequence tags (ESTs) derived from differentiating erythroid cells for genes localised to chromosome 12p and encoding a GPI-anchor motif. *ART4*, a gene encoding a member of a family of mono-ADP-ribosyltransferases, was identified as a candidate for *DO* [8]. Stable transfection of a K562 erythroleukaemic cell line with the candidate open reading frame led to expression of Do^a, Gy^a, Hy, and Jo^a at the cell surface [7]. *ART4* spans 14 kb and contains 3 exons that appear to encode a protein of 314 amino acids with five putative *N*-glycosylation sites and six cysteine residues (including one in the signal peptide). Exon 1 encodes residues 1–45, including a 44 amino acid signal peptide, exon 2 encodes residues 49–285, and exon 3 encodes residues 286–314, including a 17 amino acid GPI-anchor motif, producing a membrane-bound protein of 253 amino acids. Alternative suggestions are that the signal peptide is only 22 amino acids, with Met22 representing the translation-initiation codon, and that the C-terminal 30 amino acids form the GPI-anchor motif. This would give a mature protein of 240 amino acids [9].

Although ART4 belongs to a family of adenosine diphosphate (ADP)-ribosyltransferases that catalyse the transfer of ADP-ribose from nicotinamide adenine dinucleotide (NAD^+) to a protein substrate, no enzyme activity has been demonstrated for ART4 and its biological role remains unknown [10]. The product of *DO*B* contains an Arg-Gly-Asp motif, characteristic of adhesion molecules involved in cellular interaction, but this motif

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Table 14.1 Antigens of the Dombrock system.

Antigen				Molecular basis*		
No.	Name	Frequency	Antithetical antigen	Nucleotides	Exon	Amino acids
DO1	Do^a	66%†	DO2	793A	2	Asn265
DO2	Do^b	82%†	DO1	793G	2	Asp265
DO3	Gy^a	High		Various		Various
DO4	Hy	High		323G (T)	2	Gly108 (Val)
DO5	Jo^a	High		350C (T)	2	Thr117 (Ile)
DO6	DOYA	High		547T (G)	2	Tyr183 (Asp)
DO7	DOMR	High		431C (A), 432C (A)	2	Ala144 (Glu)
DO8	DOLG	High		674T (A)	2	Leu225 (Gln)

*Molecular basis of antigen-negative phenotype in parentheses.
†Northern Europeans; Do^b calculated from gene frequencies.

Table 14.2 Dombrock phenotypes and usual genotypes.

Do^a	Do^b	Gy^a	Hy	Jo^a	Genotype
+	–	+	+	+	*DO*A/A*
+	+	+	+	+	*DO*A/B*
–	+	+	+	+	*DO*B/B*
–	–	–	–	–	*DO*GY/GY*
–	w	w	–	–*	*DO*HY/HY*
w	–	+	w	–	*DO*JO/JO*
w	w	w	w	–*	*DO*HY/JO*
–	–	w	w	w	*DO*DOYA/DOYA*
–	+	–	w	w	*DO*DOMR/DOMR*
+	–	w	+	+	*DO*DOLG/DOLG*

w, weakened expression of antigen.
*Very weak Jo^a may be detected by adsorption and elution.

is disrupted in the product of *DO*A*, where it becomes Arg-Gly-Asn, suggesting that it is of little importance [7].

14.3 Dombrock antigens

14.3.1 Do^a and Do^b (DO1 and DO2)

In 1965, Swanson *et al.* [11] identified an antibody in the serum of Mrs Dombrock that defined a new antigen (Do^a) on the red cells of 64% of Europeans. Not until 1973 was the antithetical antibody, anti-Do^b, identified by Molthan *et al.* [12].

The Do polymorphism results from a SNP in the Dombrock gene: *DO*A* encodes Asn265; *DO*B* encodes Asp265 (Table 14.1) [7,13]. *DO*B* has a *BseRI* restriction site that is not present in *DO*A* [14]. There are two synonymous SNPs, 378C/T (Tyr126) and 624T/C (Leu208). *DO*A* is usually associated with 378C, 624T and *DO*B* with 378T, 624C, but *DO*A* with 378T (*DO*A-HA*), *DO*A* with 624C (*DO*A-SH*), and *DO*B* with 378C (*DO*B-SH*) have been found [15,16].

Molecular genotyping for purposes of predicting Dombrock phenotype is very valuable because Dombrock reagents are often unavailable and serological Dombrock typing is difficult and unreliable. In one set of genotyping tests, eight donors who had been serologically typed as Do(b–) were found to be *DO*A/B* heterozygotes and subsequently shown to have a weak Do^b antigen [13]. Consequently, despite the pitfalls of predicting phenotype from SNP testing, such as the presence of null allele, testing for the 793A/G *DO* SNP would generally be considered a more reliable method of determining Dombrock phenotype than serological typing.

There are only limited antigen frequency studies concerning Dombrock. Almost all data have been derived from investigations with anti-Do^a alone. Most of the information is summarised in Table 14.3. From the Northern European gene frequencies [17] the following genotype frequencies have been calculated: *DO*A/A* 0.1764, *DO*A/B* 0.4872, *DO*B/B* 0.3364 (assuming *DO*B* is the only allele of *DO*A*). The frequency of Do^a is somewhat lower in black people and substantially

Table 14.3 Incidence of Do[a] and calculated frequencies of *DO*A* and *DO*B* genes in various populations.

Population	Total tested	No. Do(a+)	Do[a] frequency	Gene frequencies		References
				*DO*A*	*DO*B*	
Northern Europeans	755	501	0.6636	0.4200	0.5800	[11,17]
White North Americans	1091	696	0.6379	0.3983	0.6017	[18,19]
African Americans	161	89	0.5528	0.3313	0.6687	[19]
African Americans	76	34	0.4474	0.2566	0.7434	[17]
Japanese	760	179	0.2355	0.1257	0.8743	[20,21]
Thais	423	57	0.1348	0.0698	0.9302	[22]

*DO*B* gene frequency assumes that *DO*B* is the only allele of *DO*A*.

Table 14.4 *DO*A/B* genotype frequencies on four populations of American blood donors, obtained by testing on the BeadChip array [23].

Ethnic group	No. tested	Genotypes		
		*DO*A/A*	*DO*A/B*	*DO*B/B*
Caucasians	1243	0.13	0.51	0.36
African Americans	690	0.09	0.41	0.50
Hispanic	119	0.13	0.53	0.34
Asian	51	0.06	0.31	0.63

Table 14.5 Some Dombrock alleles, the associated nucleotide changes encoding amino acid substitutions, and gene frequencies on four populations of American blood donors, obtained by testing on the BeadChip array [23].

Gene names		Nucleotide and amino acid						Gene frequency			
	ISBT	323 108	350 117	431/432 144	547 183	674 225	793 265	Caucasian	African American	Hispanic	Asian
*DO*A*	*DO*01*	G Gly	C Thr	CC Ala	T Tyr	T Leu	A Asn	0.37	0.278	0.36	0.21
*DO*B*	*DO*02*	G Gly	C Thr	CC Ala	T Tyr	T Leu	G Asp	0.63	0.647	0.61	0.79
*DO*HY*	*DO*02.–04*	T Val	C Thr				G Asp	0	0.040	0	0
*DO*JO*	*DO*01.–05*	G Gly	T Ile				A Asn	0	0.035	0.03	0
*DO*DOYA*	*DO*01.–06*	G Gly	C Thr	CC Ala	G Asp	T Leu	A Asn				
*DO*DOMR*	*DO*02.–07*	G Gly	C Thr	AA Glu		T Leu	G Asp				
*DO*DOLG*	*DO*02.–08*	G Gly	C Thr	CC Ala	T Tyr	A Glu	A Asn				

lower in eastern Asians (Table 14.3). These indications are supported by genotyping studies [23] (Tables 14.4 and 14.5). Genotypes obtained by molecular tests on 220 Chinese North Han were *DO*A* 0.1159, *DO*B* 0.8841 [24].

14.3.2 Gy[a] (DO3) and Gy(a–), the Do$_{null}$ phenotype

An American family of Czech origin, in which four of seven children from a second cousin mating lacked a new public antigen Gy[a], was described by Swanson *et al.* [25]

in 1967. The propositus and her sister had anti-Gy^a in their sera; the propositus was in her fifth pregnancy and her sister had two children. A second family, also of Czech descent, contained two Gy(a–) sisters, both of whom had been pregnant and had anti-Gy^a in their sera [26]. Six more Gy(a–) individuals were found in an English family, possibly of Romany stock [27]. The four multiparous sisters had anti-Gy^a, whereas their two Gy(a–) brothers did not. Six Gy(a–) propositi have been found in Japanese; all were female and all were ascertained through the presence of anti-Gy^a [28].

Gy(a–) phenotype, in which the red cells lack all antigens of Dombrock system (Do$_{null}$), results from inactivating mutations in the Dombrock gene.

*DO*01N.01*. An American patient, homozygous for 442C>T in exon 2 of a *DO*A* allele, converting the codon for Gln148 to a stop codon [29].

*DO*01N.02*. A blood donor from Réunion Island, homozygous for an 8 bp deletion (nucleotides 3423–350) in exon 2 of a *DO*A* allele, creating a frameshift, premature stop codon, and loss of the GPI-anchor motif [30].

*DO*02N.01*. The original Gy(a–) propositus and two Gy(a–) sisters from another family, all of Czech origin, were homozygous for a single nucleotide change in the acceptor splice site of intron 1 (IVS1–2a>g) of *DO*B*, which results in splicing out of exon 2, introducing a frameshift and premature stop codon [31].

*DO*02N.02*. A Canadian patient homozygous for a single nucleotide change in the donor splice site of intron 1 (IVS1+2t>c) of *DO*B*, which results in splicing out of exon 2, introducing a frameshift and premature stop codon [29].

*DO*02N.03*. Homozygosity for 185T>C in *DO*A*, encoding Phe62Ser in a highly conserved FDDQY motif near the C-terminus of ART family proteins. Expression analysis confirmed that Ser62 was responsible for the absence of the Dombrock protein and homology modelling suggested that the mutation disrupts important aromatic side chain interactions between Phe62 and His160 [32].

No Gy(a–) individual was found among 9350 Japanese blood donors [28] or 10 145 Americans, including 75 African Americans and 611 native Americans [25]. Gy(a–) has not been found in people of African origin.

14.3.3 Hy (DO4) and Jo^a (DO5)

The first anti-Hy was identified in the serum of an African American woman at the delivery of her third child [33]. Other examples of anti-Hy followed [34–36]; all were made by Hy– black propositi, most of whom had Hy– siblings. Hy– red cells are Do(a–) and have weakened expression of Do^b and Gy^a [1,34].

In 18 individuals, the Gy(a+^{w}) Hy– phenotype was associated with 323G>T, encoding Gly108Val, in exon 2 of *DO*B* that has 378C (*DO*B-SH*), referred to here as *DO*HY* (Table 14.5) [37]. In most of these samples there was also an 898C>G change in exon 3 encoding Leu-300Val, but this probably represents a polymorphism in people of African origin and does not affect Do^b expression [16].

Screening with anti-Gy^a, diluted so that it would not react with Gy(a+^{w}) Hy– cells, revealed no negatives among 4530 white North Americans, 735 Czechs, 683 white South Africans, 846 black North Americans, 1023 black South Africans, 633 South African Asian Indians, or 1679 Pima Native Americans [34]. Two of 597 Apache were Gy(a+^{w}) Hy– [34], the only individuals reported who are not of African origin, although some racial admixture was suspected.

Anti-Jo^a (Joseph) was first described when cells and sera of two African American patients with antibodies to high frequency antigens were found to be mutually compatible [38], though subsequent genotyping suggests that the eponymous antibody may actually have been anti-Hy [37]. Another example of anti-Jo^a was found in an African American sickle cell disease patient [39], though he was also subsequently found to have an unexpected genotype, being heterozygous for the *DO*JO* allele and a normal *DO*B* allele [37]. All three antibody makers had been transfused. Many examples of anti-Jo^a have been found since.

Gy(a+^{w}) Hy– red cells are Jo(a–) [40], or at least express very low levels of Jo^a as determined by adsorption and elution tests [41] (Table 14.2). Makers of anti-Jo^a are Gy(a+) Hy+ Jo(a–) [40–43]. There is some degree of weakening of Do^a and Hy antigens on Gy(a+) Hy+ Jo(a–) cells compared with Gy(a+) Hy+ Jo(a+) cells.

Hy+ Jo(a–) phenotype arises from 350C>T in exon 2, encoding Thr117Ile, in *DO*A* with 378T (*DO*A-HA*), referred to here as *DO*JO* (Table 14.5) [37]. It appears that whereas Gly108Val ablates expression of both Hy and Jo^a, and significantly weakens Do^b and Gy^a, Thr117Ile silences Jo^a, but has much less significant effects on Do^a and Hy. The proximity of residues 108 and 117 suggests that they are within range of an antigenic determinant [37]. Hy+ Jo(a–) usually results either from homozygosity for 350C>T (*DO*JO/JO*) or from heterozygosity for 350C>T and 323G>T (*DO*HY/JO*). A phenomenon that is not understood is that some individuals with the

genotypes *DO*B/HY* and *DO*B/JO* have made anti-Hy and -Jo^a, respectively [37,44].

Following tests on 27 226 African Americans, DNA from the 176 (0.28%) donors whose red cells gave weak or negative reactions with anti-Gy^a was analysed for *DO*HY* and *DO*JO*. Of those that had *DO*HY* or *DO*JO*, 8% were *DO*HY/HY*, 75% were *DO*HY/DO* (where *DO*DO* represents the 'wild type'), 7% were *DO*HY/JO*, 8% were *DO*JO/DO*, and 2% were *DO*JO/JO* [44]. In New York *DO*HY* was five times more common than *DO*JO*, whereas a similar study on Afro-Brazilians revealed that *DO*JO* is more than twice as common as *DO*HY* [44]. Table 14.5 shows the results of some frequency studies for Dombrock genes obtained by array technology [23].

14.3.4 DOYA (DO6), DOMR (DO7), and DOLG (DO8)

DOYA, DOMR, and DOLG are antigens of very high frequency absent from Gy(a–) red cells.

Anti-DOYA, which reacted weakly with Hy– and Jo(a–) cells, was found in a Turkish Kurd woman whose red cells were Do(a–b–) and had weak expression of Gy^a, Hy, and Jo^a. She was homozygous for 547T>G in exon 2 of *DO*A*, encoding Tyr183Asp. Her two children were both heterozygous 547T/G. Homology modelling predicted that Asp183 influences the formation or stability of the Cys182–Cys123 disulphide bond [45].

Anti-DOMR, found in a black Brazilian pregnant woman, reacted with Jo(a–) red cells, but did not react or reacted very weakly with Hy– cells. Her red cells were Do(a–b+), weak for Hy and Jo^a, and non-reactive with alloanti-Gy^a, but reactive with monoclonal antibodies to the Dombrock protein. DOMR– results from homozygosity for two nucleotide changes within the same codon, 431C>A and 432C>A, encoding Ala144Glu [46].

Anti-DOLG in the serum of a Sri Lankan woman reacted with Do(a+b–), Jo(a–), and DOYA– red cells, but gave variable reactions with Hy– cells. Her red cells were Do(a+b–) Hy+ Jo(a+) Gy(a+), but with Gy^a marginally reduced in strength. DOLG– results from homozygosity for 674T>A in exon 2, encoding Leu225Glu [47].

14.3.5 Development and distribution of Dombrock antigens

Do^a, Do^b, and Jo^a are fully expressed on cord red cells [11,12,38,40]. In contrast, it is reported that Gy^a and Hy are expressed only weakly on cord cells [27,34]. Rodent monoclonal antibodies to ART4 reacted strongly with red cells, weakly with peripheral blood monocytes and macrophages, and did not react with B- or T-lymphocytes [48]. *DO* mRNA was detected in spleen, lymph node, bone marrow, and fetal liver, but not in thymus or peripheral blood leucocytes [7].

14.3.6 Effects of enzymes and reducing agents

Dombrock system antigens are resistant to papain or ficin treatment of red cells, and an antiglobulin test with papain- or ficin-treated cells is often the optimal method for using Dombrock reagents, especially anti-Do^a and -Do^b. Dombrock system antigens are generally sensitive to trypsin, chymotrypsin, and pronase, which either destroy the antigens or cause a marked reduction in their expression. Sialidase treatment has no effect. The antigens are usually sensitive to the action of the reducing agents AET and DTT [1–3,43,46].

14.4 Dombrock system antibodies

14.4.1 Anti-Do^a and -Do^b

Although not common antibodies, many examples of anti-Do^a and -Do^b are known. They occur in approximately equal numbers suggesting that Do^a and Do^b do not differ markedly in immunogenicity, considering their similar frequencies. Anti-Do^a and -Do^b usually occur in sera containing mixtures of multiple antibodies to red cell antigens, though examples of pure anti-Do^a [49] and -Do^b [50] have been identified. No 'naturally occurring' Dombrock antibodies are reported.

Anti-Do^a and -Do^b generally react by an antiglobulin test, working best with papain-treated cells. They are usually IgG and unable to fix complement [19,51].

Dombrock antibodies have not been implicated in HDFN. Anti-Do^a [52–54] and -Do^b [50,53,55,56] have been responsible for acute and delayed HTRs and antigen-negative red cells should be selected for transfusion. *In vivo* red cell survival studies and *in vitro* monocyte monolayer assays confirm that anti-Do^a and -Do^b can cause accelerated red cell destruction [6,50,57]. Dombrock antibodies are often difficult to detect and are notorious for becoming undetectable. In one patient recurrent acute HTRs were caused by anti-Do^a that was not detectable by crossmatching [54]. In view of the lack of suitable Do^a and Do^b typing reagents, molecular genotyping is the best technology for selecting suitable blood for patients with anti-Do^a or -Do^b, and it has been claimed that provision of Do^a or Do^b compatible red cells selected on the basis of DNA testing has improved red

cell survival in transfusion-dependent patients with the corresponding antibodies [58].

Five monoclonal anti-Do^b were produced as the result of immunising mice with HEK cells transiently transfected with *DO* cDNA [59].

14.4.2 Antibodies to other Dombrock antigens

Gy^a appears to be very immunogenic as virtually all reported Gy(a–) women who have been pregnant have anti-Gy^a in their serum [25–27,34]. An elderly man, who had never been transfused, had transient anti-Gy^a, which disappeared after three months [60]. Unlike most Gy(a–) cells, his red cells could adsorb and elute anti-Hy, leading to the suggestion that this patient may have had an acquired Gy(a–) phenotype [61]. Apart from this one case, there is no reported example of 'naturally occurring' anti-Gy^a, -Hy, or -Jo^a.

Anti-Gy^a, -Hy, and -Jo^a are usually IgG [25,27,34–36,38,39,43,60,62], predominantly IgG1 [57], and react best by an antiglobulin test. One anti-Gy^a also contained some IgA and bound complement as determined by a two-stage antiglobulin test [27]. One anti-Hy, which directly agglutinated Hy+ cells, was IgM plus IgG [62].

Like anti-Do^a and -Do^b, the other Dombrock system antibodies have never been implicated in HDFN, despite numerous opportunities, though the baby of the woman with anti-DOMR had DAT-positive red cells and was jaundiced, but only required phototherapy [46]. One anti-Hy has been responsible for an HTR in a man who received two units of Hy+ blood [35]. A man with anti-Gy^a tolerated 10 units of Gy(a+) blood with no adverse effect [63] and the patient with anti-DOYA was transfused with 3 units of incompatible blood, without evidence of reduced survival [45]. Anti-Hy was responsible for shortened *in vivo* red cell survival [36] and anti-Jo^a in a sickle cell patient caused significant removal of radiolabelled Jo(a+) cells compared with Jo(a–) cells [64]. In monocyte monolayer assays, 4 of 6 anti-Gy^a, 5 of 8 anti-Hy, and 4 of 5 anti-Jo^a gave results suggestive of a likelihood of clinical signs of an HTR following transfusion of incompatible red cells [57].

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