26 Gill Blood Group System

26.1 Introduction

GIL, the only antigen of the Gill system, is an antigen of very high frequency located on the water and glycerol channel aquaporin-3 (AQP3). The GIL– phenotype results from homozygosity for a splice site mutation in *AQP3*.

26.2 GIL (GIL1) and anti-GIL

Five examples of anti-GIL have been identified, all in white women who had been pregnant at least twice [1]. No GIL – individual was found by screening 23 251 white Americans or 2841 African Americans with anti-GIL. Red cells of two of the babies of mothers with anti-GIL gave a positive DAT, but there were no clinical symptoms of HDFN. Anti-GIL may have been responsible for an HTR and results of monocyte monolayer assays with two anti-GIL suggested a potential to cause accelerated destruction of transfused GIL+ red cells.

26.3 Aquaporin-3 and GIL

Aquaporin-3 (AQP3) is a member of the aquaporin family of water channels described in Chapter 15 (for reviews see Chapter 15 and [2]). Aquaporins, including AQP3, have the characteristic 'hourglass' structure, spanning the membrane six times, shown in Figure 15.1.

AQP3 cDNA was isolated from a rat kidney cDNA library by screening with a PCR product with a sequence similar to that of other aquaporins [3]. Rat *AQP3* cDNA was used to screen a human kidney cDNA library [4] and the isolated human *AQP3* cDNA used to screen a human placental genomic library [5]. *AQP3* comprises six exons that encode the following amino acid residues: exon 1, 1–36; exon 2, 37–78; exon 3, 79–125; exon 4, 126–165; exon 5, 166–237; exon 6, 238–292. The 5′-flanking region has a TATA box, two Sp1 sequences, and some consensus sequences including AP2 sites [5]. *AQP3* was shown, by fluorescence *in situ* hybridisation, to be located on chromosome 9q13 (erratum to [4]). The predicted protein consists of 292 amino acids, with the typical aquaporin six membrane-spanning topology, *N*-glycosylated at Asn141 on loop C (Figure 15.1). Unlike AQP1, which forms tetramers in the membrane, AQP3 appears to exist in red cell membranes in multiple oligomeric forms (dimers, trimers, tetramers) composed of weakly associated monomers [6].

In 1998, Roudier *et al.* [7] showed that AQP3 is present in red cells and then, in 2002, that AQP3 is the GIL blood group antigen [8]. They found by immunoblotting with anti-rat AQP3, which cross-reacts with human AQP3, that red cells of two individuals with the GIL– phenotype were deficient in AQP3. Both GIL– individuals, one from the USA and one from France, were homozygous for G>A in the invariant 5′ donor splice site of intron 5 (IVS5+1g>a), resulting in a transcript lacking exon 5 and introducing a reading frameshift and premature termination of translation, predicting a truncated protein lacking amino acids 165–237. The sister and 10 children of one of the propositi were heterozygous for the mutation and expressed approximately a half-dose of AQP3 on their red cells. COS-7 cells became GIL+ following transfection with *AQP3* cDNA.

Human Blood Groups, Third Edition. Geoff Daniels.

26.4 Functional aspects

Based on their permeability characteristics, there are two types of aquaporins: those permeated only by water, which includes AQP1 (Chapter 15), and the aquaglyceroporins, which are permeated by water and by small solutes, especially glycerol, and includes AQP3. AQP3 is permeable to glycerol and water, plus urea and hydrogen peroxide [2,9].

In addition to red cells, AQP3 is present in a variety of tissues, including kidney, skin, lung, eye, and colon, where it is located in the basolateral plasma membrane. GIL–, AQP3-deficient individuals are apparently healthy, possibly because the absence of AQP3 can be compensated by other aquaporins [1,8]. *AQP3* knockout mice showed a urinary concentrating defect, manifesting as nephrogenic diabetes insipidus, and skin defect arising from failure to maintain skin hydration [2]. Mice do not have AQP3 on their red cells [6]. The function of AQP3 in red cells is not known, although it could make them less susceptible to osmotic stress during exposure to high glycerol concentration [7]. GIL– red cells exhibited a drastic reduction of glycerol permeability, but water and urea transports were normal [8].

References

1 Daniels GL, DeLong EN, Hare V, *et al.* GIL: a red cell antigen of very high frequency. *Immunohematology* 1998;14:49–52.

2 Hara-Chikuma M, Verkman AS. Physiological roles of glycerol-transporting aquaporins: the aquaglyceroporins. *Cell Mol Life Sci* 2006;63:1386–1392.

3 Ishibashi K, Sasaki S, Fushimi K, *et al.* Molecular cloning and expression of a member of the aquaporin family with permeability to glycerol and urea in addition to water expressed at the basolateral membrane of kidney collecting ducts. *Proc Natl Acad Sci USA* 1994;91:6269–6273.

4 Ishibashi K, Sasaki S, Saito F, Ikeuchi T, Marumo F. Structure and chromosomal localization of a human water channel (AQP3) gene. *Genomics* 1995;27:352–354. Erratum *Genomics* 1996;30:633.

5 Ianase N, Fushimi K, Ishibashi K, *et al.* Isolation of human aquaporin 3 gene. *J Biol Chem* 1995;270:17913–17916.

6 Roudier N, Bailly P, Gane P, *et al.* Erythroid expression and oligomeric state of the AQP3 protein. *J Biol Chem* 2002;277:7664–7669.

7 Roudier N, Verbavatz J-M, Maurel C, Ripoche P, Tacnet F. Evidence for the presence of aquaporin-3 in human red blood cells. *J Biol Chem* 1998;273:8407–8412.

8 Roudier N, Ripoche P, Gane P, *et al.* AQP3 deficiency in humans and the molecular basis of a novel blood group system, GIL. *J Biol Chem* 2002;277:45854–45859.

9 Miller EW, Dickinson BC, Chang CJ. Aquaporin-3 mediates hydrogen peroxide uptake to regulate downstream intracellular signaling. *Proc Natl Acad Sci USA* 2010;107:15681–15686.