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Review

ABO blood group antigens and differential glycan expression: Perspective on the evolution of common human enzyme deficiencies

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SUMMARY

Enzymes catalyze biochemical reactions and play critical roles in human health and disease. Enzyme variants and deficiencies can lead to variable expression of glycans, which can affect physiology, influence predilection for disease, and/or directly contribute to disease pathogenesis. Although certain well-characterized enzyme deficiencies result in overt disease, some of the most common enzyme deficiencies in humans form the basis of blood groups. These carbohydrate blood groups impact fundamental areas of clinical medicine, including the risk of infection and severity of infectious disease, bleeding risk, transfusion medicine, and tissue/organ transplantation. In this review, we examine the enzymes responsible for carbohydrate-based blood group antigen biosynthesis and their expression within the human population. We also consider the evolutionary selective pressures, e.g. malaria, that may account for the variation in carbohydrate structures and the implications of this biology for human disease.

INTRODUCTION

Glycans are monosaccharide polymers that play an important role in human physiology and pathophysiology (Cummings, 2009). Glycans are synthesized by enzymes that add distinct glycan moieties to protein or lipid substrates (Varki, 2017). As such, the variations in glycans adorning glycoproteins or glycolipids are not entirely related to the sequence of the protein or lipid. For example, *O*-linked glycosylation (o = oxygen) can occur at serine (Ser) and Threonine (Thr) amino acids, whereas Asn (asparagine) in the sequon Asn-X-Ser/Thr (in which X is any amino acid except proline) is often a site of *N*-linked glycosylation (n = nitrogen). Glycosylation depends on the cell's repertoire of glycosyltransferases, their localization in the cell, nucleotide sugar donor's requisite to their synthesis, the final destination of the glycoprotein or lipid, as well as the actions of degradative glycosidases that trim glycans (Varki, 2017). Glycan modifications can be dynamically regulated and serve as fundamental mechanisms for modulating cell behavior, including affinity of a glycoprotein or glycolipid to a host of carbohydrate binding proteins (Arthur et al., 2015a; Bochner and Zimmermann, 2015; Johannes et al., 2018; Rabinovich et al., 2012). Genetic variants and defects in the enzymes responsible for the biosynthesis of glycans or their monosaccharide precursors can lead to reduced or complete absence of particular glycans.

The ABO(H) blood groups are carbohydrate based, and each individual has a specific blood type, e.g, A, B, AB, or O. The ABO(H) antigens may be the best-known carbohydrate antigens, given their importance for blood transfusion and transplantation, but there are many other clinically significant carbohydrate antigens. In this review, we will explore the biosynthesis of carbohydrate blood group antigens, the characteristics and clinical consequences of anti-carbohydrate antibodies, the prevalence of blood types, their genetic basis, and their evolution and health implications. In doing so, we will review seven of the carbohydrate-based blood group systems previously described (Reid and Olsson, 2012) in addition to the relatively new SID blood group system that was more recently created by the International Society of Blood Transfusion (ISBT, 2022a; ISBT, 2022b) (Table 1).

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Table 1. Examples of blood group systems based on carbohydrate antigens

Blood Group System Name	Gene(s)	Chromosome	Enzyme(s)
H	*FUT1* *FUT2* (*Se*)	19q13.33	Fucosyltransferase 1 Fucosyltransferase 2
ABO	*ABO*	9q34.2	A antigen: α(1,3)-*N*-acetylgalactosaminyltransferase B antigen: α(1,3)-galactosyltransferase
Lewis	*FUT3* (*Le*)	19p13.3	Fucosyltransferase 3
I	*GCNT2*	6p24.3-p24.2	Glucosaminyl (*N*-acetyl) transferase 2
Globoside	*GLOB* (*B3GALNT1*)	3q26.1	β(1,3)-*N*-acetylgalactosaminyltransferase 1
P1PK	*A4GALT*	22q13.2	α(1,4)-galactosyltransferase
FORS	*GBGT1*	9q34.2	Globoside α(1,3)-*N*-acetylgalactosaminyltransferase 1
SID	*B4GALNT2*	17q21.32	β(1,4)-*N*-acetylgalactosaminyltransferase 2

To provide context to carbohydrate-based blood group antigen structures, it is helpful to briefly review glycan structures and nomenclature (Figure 1). In solution, monosaccharides exist as an equilibrium mixture of acyclic and cyclic forms. In the acyclic form, the anomeric carbon is the carbonyl carbon of an aldehyde or ketone functional group. In the cyclic form, the anomeric carbon is attached to an oxygen in the ring and to a hydroxyl group. Aldehyde monosaccharides are called aldoses, and in these molecules the aldehyde carbon is numbered as C-1. In ketoses (ketone monosaccharides, such as sialic acid), the carbonyl carbon is numbered C-2. Alpha and beta are used to refer to the configuration at the anomeric carbon. The alpha anomer refers to the configuration where the hydroxyl attached to the anomeric carbon is on the opposite face of the ring compared with the substituent on the other carbon flanking the ring oxygen. In contrast, if these two substituents are on opposite faces of the ring, this is called the beta anomer. Analogous terminology is used to refer to alpha and beta glycosidic linkages between two monosaccharides. For example, an α(1,2) linkage indicates that the anomeric carbon is linked to the second carbon in another monosaccharide, in an α orientation. Sometimes, the 1 is left out of the linkage name, so it is described simply as α2. For sialic acids, as the anomeric carbon is 2, it is understood that the linkage may be α(2,3), α(2,6), or α(2,8) or simply α3, α6, or α8.

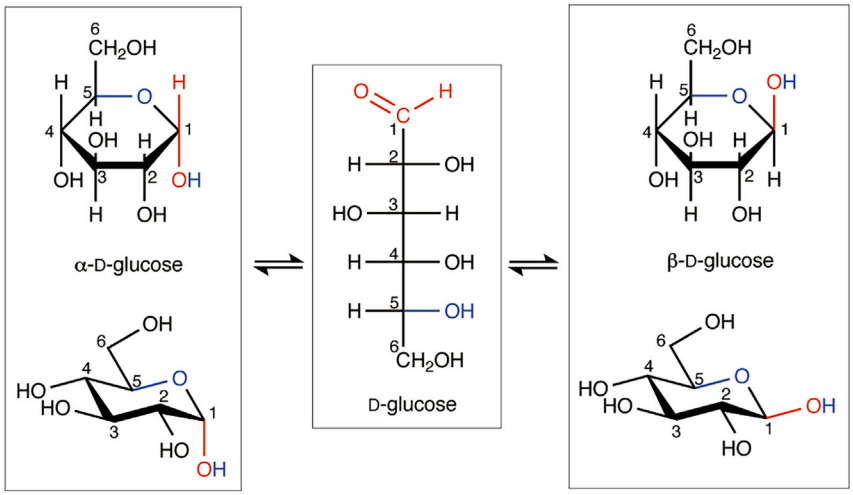

Figure 1. Glycosidic bond nomenclature

The anomeric carbon is defined as the carbonyl carbon in the acyclic form of a monosaccharide. This is often the first carbon, although in monosacchrides such as sialic acid, the second carbon serves as the anomeric carbon. If the hydroxyl group on the anomeric carbon is downward in the cyclic form, it can create an α glycosidic linkage with another monosaccharide. If the hydroxyl group is upward, it can form a β glycosidic linkage.

This manuscript will use the term *deficiency* to indicate a clinically meaningful reduction in enzyme activity. Certain blood types (e.g. blood group O) result from enzyme deficiencies, which can lead to health advantages and disadvantages. Importantly, these enzyme deficiencies do not always lead to disease. However, others can lead to severe disease. For example, type I (severe) fucosidosis, which will be discussed later in the text, is a deficiency of α-L-fucosidase 1, caused by mutations in the *FUCA1* gene, which results in severe disease and is often fatal in childhood. We will not review all types of enzyme deficiencies that can lead to changes in glycan structure, as these have been excellently reviewed elsewhere (Ng and Freeze, 2018). Instead, we will focus on those enzyme deficiencies that contribute to blood group antigen formation. In doing so, we will also describe enzyme deficiencies that lead to distinct blood group structures in the context of other common enzyme deficiencies often described in medicine in general.

When describing blood group antigen distribution by race, we recognize that race itself can be a social, as opposed to a biological, construct (Smedley and Smedley, 2005). As such, the distribution patterns outlined likely reflect ancestry and other selection patterns that correlate, but may not be attributed to, a given race as defined in each reported study. However, as studies have used these identifiers, to accurately reflect what was reported we have attempted to use similar identifiers as employed in the cited studies while recognizing that the field will be benefited by employing more accurate and biologically appropriate approaches to describing blood group antigens among populations in the future. Achieving such a consensus will require agreement across the entire field of transfusion medicine and is unfortunately beyond the scope of this review.

ABO BLOOD GROUP SYSTEM

Genetics and synthesis of H antigens

The H antigen and ABO blood group systems are closely related (Cohn et al., 2020). The term blood group O is used, but the antigen of that blood group is termed the H antigen. Although the genetic, and even structural, basis for the H, A, and B antigens was not defined until many years after their discovery, (Yamamoto et al., 1990) many studies have provided the structural and enzymatic basis for these antigens and related structures (Clausen and Hakomori, 1989; Clausen et al., 1986; Dabelsteen et al., 1991). The O blood group, which is sometimes indicated as O(H), contains only the H antigen (ISBT, 2021). The H antigen is a precursor to create A and/or B antigens, which will be discussed later.

Type 1, 2, 3, or 4 glycan chains are biosynthetic precursors to the H antigen (Varki et al., 2022). Type 1 chains are Galβ(1,3)GlcNAcβ(1,3)-R, whereas type 2 are Galβ(1,4)GlcNAcβ(1,3)-R (Figure 2). The terminal Gal-GlcNAc disaccharide found in these structures is referred to as lactosamine. Most H antigens synthesized during erythropoiesis are on type 2 chains. The *FUT1* gene encodes a fucosyltransferase 1 enzyme (FUT1) that adds fucose (Fuc) in an α(1,2) linkage to the terminal Gal to make type 2 H antigen on RBCs. In contrast, type 1 H antigens are soluble molecules in secretions (e.g. saliva, plasma, etc.) that may be adsorbed onto the surface of RBCs. FUT2, which is encoded by the *FUT2* (*Se*) gene, can catalyze the addition of Fuc in an α(1,2) configuration to terminal Gal of either type 1 or 2 H, but soluble H antigen consists solely of type 1 H (Dean, 2005; Reid and Olsson, 2012). Individuals expressing FUT2 are known as "secretors" (*SeSe or Sese*), and their type 1 H found in saliva is typically found in mucins and in human milk on free oligosaccharides, whereas in plasma it is typically found on glycosphingolipids that can be carried by circulating lipoproteins; the latter can passively, and reversibly, transfer between these lipoproteins and RBC membranes. The *FUT2*01N.02* allele, caused by NM_000511.6(FUT2):c.461G>A (p.Trp154Ter), also known as rs601338 or W154X, is the most common reason for non-secretor status and is mostly found in Europeans, Africans, and Iranians (Reid and Olsson, 2012) (NCBI, 2008). (Note: The term rsID stands for reference single nucleotide polymorphism cluster IDs, which is a nomenclature for describing genetic variants. A summary of relevant rsIDs is found in Table 2 and Table 3). Type 1 and 2 H antigens are both found on glycolipids, whereas type 1 H is common on *O*-glycans and type 2 H is prevalent on *N*-glycans (Varki et al., 2022). (*O*-glycans are oligosaccharides that are attached to the oxygen in Ser or Thr residues, whereas *N*-glycans are attached to the nitrogen in the amide of Asn). Type 3 chains are Galβ(1,3)GalNAcα(1,3)-R, and type 4 chains are Galβ(1,3)GalNAcβ(1,3)-R. Type 3 and 4 H are both on mucin *O*-glycans, whereas type 4 H is on glycolipids.

Individuals with the so-called "Bombay" phenotype lack functional FUT1 and FUT2 enzymes and, therefore, lack both type 1 and type 2 H antigen (Aust et al., 1962; Bhende et al., 1952; Dean, 2005; Levine et al., 1955; Reid and Olsson, 2012). As the H antigen is required for synthesizing A and B antigens, individuals with Bombay phenotype also do not generate A or B structures. The "Para-Bombay" phenotype arises if an

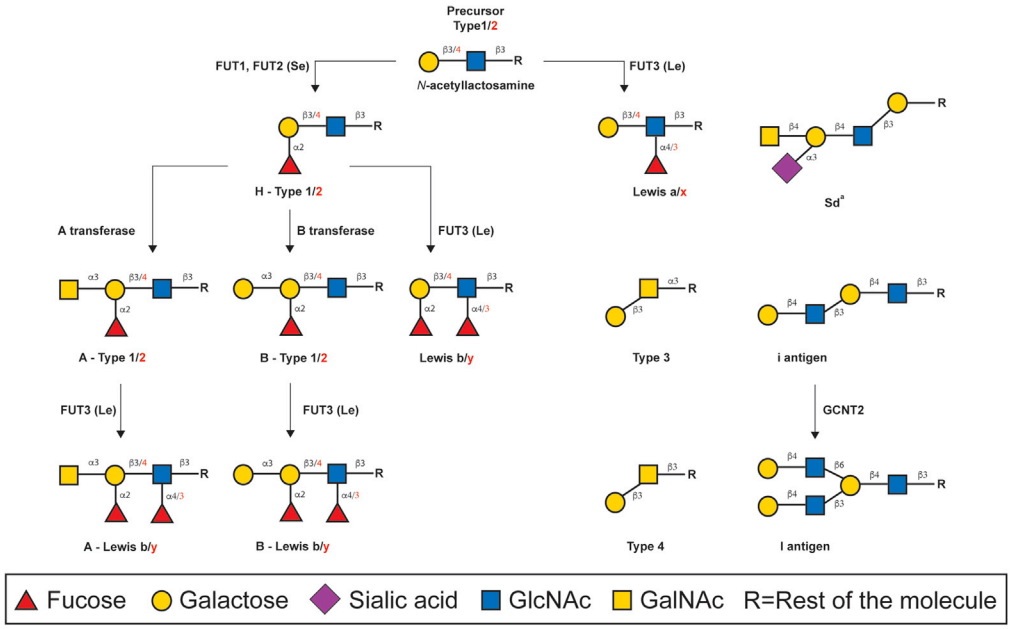

Figure 2. Overview of ABO(H) and Lewis blood group antigen biosynthesis

ABO(H) and blood group antigen biosynthesis occurs in a stepwise fashion. Inheritence of enzymes capable of creating distinct modifications results in positivity for the respective blood group antigen. Many of these modifications can be found on glycolipids or glycoproteins. The i antigen is a precursor to the I antigen. Symbol nomenclature for each monosacchride is shown. Black text corresponds with black linkage, and red text corresponds with red linkage. GlcNAc = *N*-acetylglucosamine, GalNAc = *N*-acetylgalactosamine.

individual does not express FUT1 but does express FUT2; the type 1 H antigen (and, possibly, the corresponding A and/or B antigens) may or may not be detectable in their secretions but will passively adsorb onto the RBCs (Reid and Olsson, 2012).

In summary, the RBCs of non-secretors express type 2 H, which is synthesized during erythropoiesis. The RBCs of secretors express endogenously synthesized type 2 H antigen and passively adsorbed type 1 H antigen. Bombay phenotype RBCs contain neither type 1 nor type 2 H antigens, and para-Bombay phenotype RBCs contain only passively adsorbed type 1 H antigen.

Genetics and synthesis of A and B antigens

The ABO blood group system contains the A, A_1, B, and A,B antigens, whereas the H blood group system contains the H antigen, which is the precursor for the others (ISBT, 2021). A and B structures are added to type 1 and 2 H chains. Blood group O individuals cannot synthesize A or B antigens, and so they only express the H antigen. The A antigen on RBCs is synthesized by the A glycosyltransferase (α1,3-*N*-acetylgalactosaminyltransferase) adding GalNAc in an α(1,3)-linkage to Gal within the H antigen (Dean, 2005; Reid and Olsson, 2012). The most common subgroup of A is known as A_1, whereas the A_2 subgroup is less common. The A_2 subgroup expresses 4- to 5-fold less A antigen than A_1 and has fewer A antigens on type 3 and type 4 H (Svensson et al., 2009). There are additional A subgroups that are beyond the scope of this review. The B antigen arises when the B glycosyltransferase (α1,3-galactosyltransferase) adds Gal in an α(1,3)-linkage to the H antigen terminal Gal (Dean, 2005). Interestingly, the A and B glycosyltransferases differ in sequence by only 4 amino acids (Yamamoto et al., 1990). Thus, it is not surprising that some variant enzymes can simultaneously create both A and B antigens (e.g. B(A) and cisAB phenotypes) (Reid and Olsson, 2012; Storry and Olsson, 2009). However, typically blood group AB individuals express both A and B enzymes and carry both antigens on their RBCs. Because the A and B glycosyltransferases are not 100% efficient, blood group A, B, and AB individuals also express some H antigen (Curtis et al., 2000; O'Donnell et al., 2002). The relative amounts of H antigen are found in the following sequence of phenotypes: O > A_2 > B > A_2B > A_1 > A_1B > Para-Bombay > Bombay (Reid and Olsson, 2012).

Table 2. Selected rsIDs (from the International Society of Blood Transfusion and the ClinVar database) for carbohydrate-based blood group systems

Gene	Phenotype	Reference allele	Variant allele (example)	rsID(s)
FUT1	H+ (RBCs)	*FUT1*01*		Not listed
	H− (RBCs)		*FUT1*01N.01*	rs749165173
FUT2	H+ (secretions)	*FUT2*01*		Not listed
	H− (secretions)		*FUT2*01N.01*	rs112722916 rs1047781
ABO	A1	*ABO*A1.01*		Not listed
	A1		*ABO*A1.02*	rs1053878
	A2		*ABO*A2.01*	rs56392308 rs1053878
	B	*ABO*B.01*		rs8176747 rs8176749 rs8176746 rs8176741 rs7853989 rs8176720 rs8176743
	B		*ABO*B.02*	Not listed
	O	Not listed		Not listed
	O		*ABO*O.01.01*	rs1556058284
FUT3		Not finalized	Not finalized	rs3745635
GCNT2	I+	*GCNT2*01*		Not listed
	I−		*GCNT2*01N.01*	rs56141211
GLOB (*B3GALNT1*)	P+	*GLOB*01*		Not listed
	P−		*GLOB*01N.01*	rs200235398
A4GALT	P1+ P^k+	*A4GALT*01*		Not listed
	P		*A4GALT*0XN.01.01*	rs387906279
GBGT1	FORS1−	*GBGT1*01N.01*		Not listed
	FORS1+		*GBGT1.01.01*	rs375748588
B4GALNT2	Sd(a+)	*SID*01*		Not listed
	Sd(a−)		*SID*01N.01*	rs7224888

Although only one variant allele is shown, there can be many more, with their own rsIDs

Newborns may express only 50% of adult levels of ABO(H) antigens on RBCs (Grundbacher, 1980; Yamamoto, 2004), but by 2–4 years of age, ABO(H) antigen expression reaches adult levels. The A,B antigen is present in individuals who express A or B antigens. Although this antigen is not a single molecular structure, it is defined serologically as a common epitope shared by the distinct A and B antigens and therefore reflects antibody reactivity that binds shared features of these structures that permits reactivity with both A and B antigens (Korchagina et al., 2005). The Band 3 protein on the RBC is thought to be a key site of ABO(H) antigens on proteins. These antigens can also be found on soluble molecules, platelets, some leukocytes, endothelium, and many different types of epithelial cells (Curtis et al., 2000; Liu and Wang, 2022; O'Donnell et al., 2002; Reid and Olsson, 2012). The term histo-blood group is used to describe the widespread tissue distribution of antigens in the body.

Interestingly, human blood group *O* alleles mostly arose from mutations in *A* alleles, leading to the inevitable expression of H antigen as the individuals inherit an inactive A enzyme. Blood group O individuals most commonly possess the *ABO*O.01.01* allele, which is identical to the most common *A1* allele (*ABO*A1.01*) for the first 261 nucleotides (Cserti and Dzik, 2007; Franchini and Bonfanti, 2015; Storry and

Table 3. Selected rsIDs (from OMIM.org) for medical conditions (not including pseudogenes) described in the text

Medical condition	Variant allele (example)	rsID
Caspase 12 (functional)	*Csp12L*	rs497116
CYP3A5 deficiency	*CYP3A5*3*	rs776746
Lactase persistence	*MCM6*, IVS13, C/T	rs4988235
NAT2 deficiency	*NAT2*5B*	rs1801280
ALDH2 deficiency	*ALDH2*2*	rs671
G6PD deficiency	*G6PD* A-	rs1050828

Olsson, 2009). However, the NM_020469.2 (ABO):c.261delG (p.Thr88Profs) frameshift mutation (rs155 6058284) results in a premature stop codon, rendering a product that is inactive for both A and B glycosyltransferase activity (Cserti and Dzik, 2007; NCBI, 2022d). The next most common blood group O allele has the same position 261 deletion, as do nearly all other blood group *O* alleles (Cserti and Dzik, 2007). It is also worth noting that a variant *B* allele associated with a lack of B antigen expression (i.e., blood group-O RBCs) has been described (Bugert et al., 2008).

Anti-blood group antibodies

Prior to the identification of ABO(H) antigens, transfusion outcomes were highly variable and difficult to predict (Landsteiner, 1900; Schwarz and Dorner, 2003). Karl Landsteiner, who discovered the ABO(H) blood group antigens, predicted that incompatibility between the naturally occurring, i.e. existing prior to any transfusion or transplant, anti-A and anti-B antibodies in the plasma of the recipient and the A and B antigens on the transfused donor RBCs may be responsible for the negative outcomes previously observed following transfusion. Later, it was discovered that individuals primarily make IgM antibodies against the A and B antigens not expressed on their own cells (e.g. blood group A individual makes anti-B antibodies), known as Landsteiner's Law (Branch, 2015). Of note, individuals can also make anti-ABO antibodies of the immunoglobulin G (IgG) and IgA isotypes (Branch, 2015). Blood group O individuals tend to make higher titers of anti-A and anti-B IgG antibodies compared with non-O individuals (Ukita et al., 1989). Anti-ABO(H) antibodies can cause acute hemolytic transfusion reactions (HTRs) following ABO(H) incompatible RBC, which can be fatal. To prevent this, ABO(H) antigen testing of donors and recipients and then a crossmatch is performed prior to transfusion (Balbuena-Merle et al., 2019; Harris et al., 2007; Josephson et al., 2010). Either a serologic crossmatch of donor RBCs with recipient plasma or an electronic crossmatch (checking for ABO(H) incompatibility) must be performed.

Maternal anti-A and B IgG antibodies can cross the placenta and cause hemolytic disease of the fetus and newborn (HDFN). Individuals with the Bombay phenotype make naturally occurring anti-H antibodies, which are often IgM and IgG (Bullock et al., 2018). These antibodies can cause severe HTRs (Reid and Olsson, 2012; Storry and Olsson, 2009), whereas those with the Para-Bombay phenotype make lower titer anti-H, which is less clinically significant. ABO(H) antibodies are also important for organ and tissue transplant because they can cause hyperacute graft rejection. Furthermore, an anti-A1 antibody is found in a small percentage of individuals with the A_2 subgroup (Storry and Olsson, 2009). These anti-A1 antibodies can cause ABO(H) typing discrepancies, but rarely cause HTRs, HDFN, or impact organ and hematopoietic stem cell transplants (Saboor et al., 2020; Vinson et al., 2018). Considerations regarding ABO compatibility can contribute to blood shortage challenges, as experienced during the COVID-19 pandemic (Covington et al., 2022; Josephson et al., 2010; Rodriguez et al., 2020; Verkerke et al., 2021, 2022).

ABO(H) typing and crossmatching has significantly reduced adverse transfusion and transplantation outcomes. However, when these procedures fail, or when clinical situations require ABO(H) barriers to be crossed, anti-ABO(H) antibody levels can influence clinical outcomes (Irving et al., 2012; Janatpour et al., 2008; Josephson et al., 2004, 2010; Shirey et al., 2010; Tyden et al., 2012; Urschel et al., 2013). For example, higher titer anti-ABO(H) antibodies in blood donors can be a barrier to whole blood, platelet, and plasma transfusions. This is because the antibodies in the donor blood product can bind to the cells of the recipient, with possible injury through a variety of mechanisms (McRae et al., 2021). To address this issue, a minor crossmatch can be performed, in which donor plasma is mixed with recipient RBCs. Although conflicting data and practices exist (Fung et al., 2007; Lozano and Cid, 2003), detection of high anti-ABO(H) antibody

levels in whole blood, platelet, and plasma donor units may reduce ABO(H)-related complications (Dunbar et al., 2015; Harm and Dunbar, 2019; Josephson et al., 2004, 2010; Simmons and Savage, 2015; Strandenes et al., 2014). Alternatively, some studies suggest that washing blood products prior to ABO(H) discrepant transfusions can improve outcomes (Blumberg et al., 2018; Refaai et al., 2018; Sahai et al., 2017).

When a routine transfusion is requested, ABO(H) compatible plasma transfusion is typically provided. However, in emergencies, low-titer group A plasma can be administered as a "universal" plasma to recipients of any blood type (Agaronov et al., 2016). ABO(H) incompatible platelet transfusion (e.g. blood group A platelets for a blood group B recipient) may especially contribute to morbidity and mortality in pediatric patients (Balbuena-Merle et al., 2019; Harris et al., 2007; Josephson et al., 2010). Although anti-human leukocyte antigen (HLA) and platelet-specific alloimmune responses can accelerate platelet clearance following transfusion (Arthur et al., 2016; Hod and Schwartz, 2008), ABO(H) antigens on platelets can also affect transfused platelet survival in incompatible transfusion settings (Cooling, 2007). As noted earlier, ABO incompatibility may drive additional underrecognized complications (Blumberg et al., 2018; McRae et al., 2021; Refaai et al., 2018; Sahai et al., 2017). Although ABO(H) barriers can now be crossed for solid organ transplantation (which has greatly increased donor availability) (Irving et al., 2012; Tyden et al., 2012; Urschel et al., 2013), pre-existing anti-ABO(H) antibody titers largely dictate whether successful transplantation occurs (Dean et al., 2018; Janatpour et al., 2008; Lee-Sundlov et al., 2020; Shirey et al., 2010; Urschel and West, 2016). Similarly, persistent naturally occurring anti-ABO(H) antibodies likely contribute to the delayed engraftment that can be observed following ABO(H) incompatible hematopoietic stem cell transplantation (Kimura et al., 2008; Shokrgozar and Tamaddon, 2018; Tomonari et al., 2007).

Removal of anti-ABO(H) antibodies via apheresis to reduce the anti-A and anti-B antibody titers before and after transplantation can reduce complications of ABO(H) incompatibility. Some transplant centers desire a pre-transplant anti-ABO(H) titer of 1:8 or less to initiate an ABO(H) incompatible renal transplant (Dean et al., 2018; Kozaki et al., 2005; Padmanabhan et al., 2009; Rivera et al., 2021; Wilpert et al., 2007). This means that a 1:8 dilution of patient serum is the greatest dilution that still leads to 1 + agglutination (tiny clumps barely visible with the naked eye). In the setting of transplantation, it remains to be determined whether the same A or B structures on RBCs, which are used for compatibility testing, are likewise the most dominant A or B antigenic structures on the endothelial cell surfaces of transplanted organs (Jeyakanthan et al., 2016). In addition, B cell and plasma cell immunity may be reduced in these settings with drugs such as rituximab, everolimus, bortezomib, and antimetabolites (Garcia de Mattos Barbosa et al., 2018; Shokrgozar and Tamaddon, 2018). Eventually, "accommodation" may occur, in which the graft can resist immune-mediated injury and maintain long-term function; nonetheless, a full mechanistic understanding of this phenomenon is not yet available (Garcia de Mattos Barbosa et al., 2018). Recent studies have sought to develop methods of removing A or B antigens from RBCs or donor organs. These may hold promise in further facilitating the ability to cross ABO(H) barriers (Liu et al., 2007; Wang et al., 2022), even when high anti-ABO(H) titers are present in a recipient.

Not all patients who receive an ABO incompatible transfusion experience an HTR (Bacon and Young, 1989; Janatpour et al., 2008), suggesting that qualitative and quantitative differences in anti-ABO(H) antibodies may be responsible for different clinical outcomes when ABO(H) incompatibility occurs. Anti-ABO(H) antibody titers likely contribute to these outcomes (Josephson et al., 2004, 2010); however, antibody levels alone may not be entirely responsible for adverse outcomes (Karafin et al., 2012). Anti-ABO(H) specificity for the types of ABO(H) antigens that reside on RBCs, density of the target antigen, complement levels, and complement regulatory proteins (ex CD55, CD59, etc.) may dictate their hemolytic activity (Arthur et al., 2019, 2021a, 2019; Stowell et al., 2013b). Antibody binding to RBCs can also result in various outcomes, ranging from direct removal of the target antigen in the absence of detectable RBC clearance (e.g. antigen modulation) to rapid intravascular hemolysis (Hod et al., 2008; Liepkalns et al., 2012, 2013; Schirmer et al., 2007; Zimring et al., 2007). Inhibition of antibody effector systems, such as complement, may be useful when treating hemolytic complications of transfusion (Chonat et al., 2019, 2020; Dumas et al., 2016). However, the factors dictating the clinical sequalae of an incompatible RBC transfusion often remain largely unknown, in part due to challenges related to studying these reactions in human patients, given their rarity. *In vitro* assays are being developed to define the activity of anti-A and anti-B antibodies to determine whether such measurements may more accurately predict ABO(H) incompatible transfusion or transplantation outcomes (Cunnion et al., 2017; Stowell, 2017).

Defining key features responsible for the development of clinically relevant anti-ABO(H) antibody formation is critical. As a result, examining factors that drive clinically relevant anti-ABO(H) antibodies, as opposed to naturally occurring antibodies in general, is necessary to address the clinical impact of these antibodies. Despite the frequency with which ABO(H) antigens and corresponding anti-ABO(H) antibodies are tested clinically (Storry and Olsson, 2009; Watkins, 2001), surprisingly little is known regarding the factors that drive their development. Unlike alloantibody formation that occurs following RBC-induced alloantigen exposure (Arthur et al., 2017, 2022a, 2022a; Arthur, 2023; Mener et al., 2018b; Patel et al., 2018b; Stowell et al., 2013a; Zerra et al., 2021), anti-ABO(H) antibodies form spontaneously within the first few months of life. Anti-A and anti-B antibodies are typically detectable at 4–6 months of age, peaking between 5 and 10 years of age (Hillyer et al., 2009). There is uncertainty as to the origin of so called "natural antibodies." Conflicting data exist regarding the potential role of plant materials, microbes, genetic elements, and even transient blood group A and B expression, in the development of naturally occurring antibody formation, in general, and formation of anti-ABO(H) antibodies, in particular (Bernstein, F., 1925, F S, 1934; Furuhata, 1969; Hayakawa et al., 1999; New et al., 2020; Springer, 1956; Springer et al., 1961; Storry and Olsson, 2009; Wagner, 1955; Watkins, 2001). Innate immune factors appear to specifically target microbes decorated in blood group carbohydrate antigens (Arthur et al., 2015b; Blenda et al., 2022; Ho et al., 2022; Stowell et al., 2010, 2014, 2014; Wu et al., 2021b, 2022, 2022), suggesting that a unique interplay may exist between blood group positive microbes, innate immunity, and the development of naturally occurring anti-blood group antibodies. However, studies using germ-free mice suggest that exogenous antigen stimulation is not required for naturally occurring antibody formation (Bos et al., 1989; Bunker et al., 2017; Haury et al., 1997; Hooijkaas et al., 1984, 1985). Consistent with this, naturally occurring antibodies were shown to readily form in the absence of antigen exposure, be polyreactive, and be likely of low affinity (Bos et al., 1989; Bunker et al., 2017; Haury et al., 1997; Hooijkaas et al., 1984, 1985), suggesting that anti-ABO(H) antibodies formation is not influenced by microbial stimulation. Whether anti-ABO(H) antibodies capable of causing a hemolytic transfusion reaction are classic "naturally occurring" antibodies or fall into another antibody category with respect to their stimulation remains to be determined. As mice, which are the most common mammalian models used to study immunity in general, express an AB-cis transferase capable of generating both the A and B antigen (Yamamoto et al., 2001), partial tolerance to this antigen may be responsible for the reduced level of spontaneous anti-A and anti-B antibody formation in this model. This limitation has made it difficult to leverage common immunological approaches to study factors that drive naturally occurring anti-AB antibodies as have been used to define immune players and pathways involved in RBC-induced alloimmunization (Escamilla-Rivera et al., 2021; Jash et al., 2021; Maier et al., 2018; Mener et al., 2018a, 2019, 2019; Patel et al., 2018a).

Prevalence

A 2021 review described the prevalence of blood groups A, B, and O throughout the world (Goel et al., 2021). Blood group O ranged from as low as 29% in India to as high as 80% in parts of Central and South America (Goel et al., 2021). Blood group A ranged from a low of 10% in parts of Central and South America to as high as 40% or more in several countries. Blood group B ranged from 0%–30% depending on the location. Blood group AB was not studied, likely because it is much less common than blood groups A, B, and O. Globally, blood group O is thought to be the most prevalent ABO blood type (Dean, 2005; Storry and Olsson, 2009). Para-Bombay phenotype (non-functional FUT1 but active FUT2) has an estimated global prevalence of less than 1:1000 (Dean, 2005; Lei et al., 2021; Reid and Olsson, 2012). Bombay phenotype (non-functional FUT1 and FUT2) affects approximately 1:10,000 individuals in India and 1:100,000 in Europe (Talukder et al., 2014). The American Red Cross considers individuals with a phenotype prevalence of 1:1,000 to be "rare blood donors," so, it is especially difficult to find compatible blood for these two phenotypes (ARC, 2022). About 20% of the world's population are non-secretors, and up to 25% are weak or non-secretors (Giampaoli et al., 2020; Soejima and Koda, 2021). The ratio of secretors to non-secretors (*sese*) is fairly similar among different populations (Ferrer-Admetlla et al., 2009).

Evolution and health

Because most *O* alleles are derived from mutated *A* alleles, it is believed that most *A* and *B* alleles predominated in early human evolution (Roubinet et al., 2004). Blood group O is thought to have evolved from blood group A to resist severe malaria caused by *Plasmodium falciparum (Pf)* parasites (Cserti and Dzik, 2007). *Plasmodia* invade RBCs and then express their own molecules on the RBC surface (e.g. *Pf* erythrocyte membrane protein 1 or PfEMP1), which leads to microvascular obstruction and impaired oxygen delivery to tissues (Jensen et al., 2020). It is estimated that malaria killed more than 600,000 individuals (mostly

children) in the year 2020 (World Health Organization, 2021). Malaria "hot-zones" in Africa correlate with a high prevalence of blood group O (Cserti and Dzik, 2007). In addition, individuals with blood group O have better malaria outcomes, likely due to decreased RBC rosetting (binding of parasitized RBCs to healthy RBCs) (Afoakwah et al., 2016; Panda et al., 2011; Rowe et al., 2007).

Another possible advantage of blood group O is that the presence of naturally occurring anti-A and B antibodies, which can protect against ABO(H)-incompatible enveloped viruses (e.g. SARS-Cov-2) (Boukhari et al., 2021; Cooling, 2015; Preece et al., 2002). One recent meta-analysis found that blood group O had a reduced risk of COVID-19 infection. A meta-analysis also found that blood group A was a slight risk factor for COVID-19 infection, whereas group O was associated with a mildly lower risk of infection (Gutiérrez-Valencia et al., 2022).

A GWAS study of more than 2,200 controls and 1,600 patients with severe COVID-19 disease found a protective effect (odd ratio 0.65, p value = 1.06×10^{-5}) of blood group O (compared with non-O) (Ellinghaus et al., 2020). However, a GWAS meta-analysis of more than 50,000 individuals with COVID-19 and 700,000 with no record of SARS-CoV-2 infection found that the *ABO* gene was not associated with COVID-19 severity (Horowitz et al., 2022). Another meta-analysis of more than 125,000 COVID-19 cases and 2.5 million controls found a statistically significant association after correction for multiple testing between the *ABO* locus and COVID-19 (Pathak et al., 2022); this study determined the phenotypic impact related to infection susceptibility. Although several of these studies have suggested that blood group O may be associated with decreased severity of COVID-19, despite several hypotheses, a definitive determination of the effect of ABO blood type on COVID-19 disease severity has not yet been made (Goel et al., 2021; Gutiérrez-Valencia et al., 2022; Hoiland et al., 2020; Wu et al., 2021a).

Conversely, individuals with blood group O have an increased likelihood of severe cholera, which is caused by a toxin from *Vibrio cholerae* bacteria (Harris and LaRocque, 2016; Kuhlmann et al., 2016). Thus, individuals in the cholera-endemic Ganges Delta region (bordered by India and Bangladesh) have a low prevalence of blood group O and a high prevalence of blood group B (Dewan, 2015; Glass et al., 1985). Studies of intestinal enteroids expressing blood group O showed increased cyclic adenosine monophosphate (cAMP) production compared with blood group A (Kuhlmann et al., 2016; Stowell and Stowell, 2019a), possibly due to a direct impact of host cell glycosylation independent of GM1 on cholera toxin engagement (Wands et al., 2015). The cAMP is stimulated by the cholera toxin and leads to the CFTR protein releasing chloride ions into the gastrointestinal lumen, which is followed by sodium ions and water, causing diarrhea. A meta-analysis also found a 16.3% increased risk of developing a *Helicobacter pylori* infection among blood group O individuals (Chakrani et al., 2018). This may be due to the fact that *H. pylori* express blood group antigen binding adhesion (BabA), which can bind to type 1 H that is expressed on gastric mucosa (Lee et al., 2006; Yang et al., 2022). Individuals with blood group O are also less likely to develop gastric and pancreatic cancer, compared with blood group A (Edgren et al., 2010; Liumbruno and Franchini, 2013; Wolpin et al., 2009).

Individuals with blood group O have 20%–30% lower von Willebrand Factor (vWF) and factor VIII (FVIII) levels compared with individuals with non-O blood groups (Franchini et al., 2007; Ward et al., 2020; Mehic et al., 2020; Stowell and Stowell, 2019b). A, B, and H antigens can be found on vWF and may affect the circulating half-life of vWF (O'Donnell et al., 2002; Sarode et al., 2000). As VWF is associated with the coagulation factor VIII (FVIII), it is thought that vWF can extend the half-life of FVIII, or perhaps altered glycosylation of FVIII itself can alter its half-life or interaction with the immune system in general (Arthur et al., 2021b; Pipe et al., 2016; Zerra et al., 2020). In this regard, blood group O individuals have ~25% less vWF and FVIII, which may explain their decreased thrombotic and cardiovascular risk compared with those with blood group A (Groot et al., 2020; Liu et al., 2017; O'Donnell and Laffan, 2001). In addition, studies have shown increased bleeding severity in blood group O individuals. ABO(H) antigens are also expressed on platelet glycoproteins and may also contribute to the differences in bleeding and thrombotic tendency in individuals of different blood groups (Hollenhorst et al., 2022; Mehic et al., 2020).

Because of the limited supply of RBC units for transfusion and incompatibility caused by naturally occurring anti-ABO(H) antibodies, development of a "universal" RBC product would be valuable. Toward this goal, researchers are trying to enzymatically convert blood group A RBCs (which is the second most common ABO blood type) to blood group O RBCs (Rahfeld and Withers, 2020). One approach uses two enzymatic

steps, in which the first uses a GalNAc deacetylase to convert the GalNAc to galactosamine. Interestingly, bacterial enzymes in the body can cause acquired B antigen in this manner (Campbell and Palmer, 1980). Although the antigen is not truly B, it could cross-react with some anti-B blood typing reagents. In the second enzymatic step, a galactosaminidase is used to remove the galactosamine to create the H antigen. These RBCs are known as enzyme-converted O RBCs or ECO-RBCs. Development of this strategy for clinical use has been hampered by incomplete and inefficient enzymatic reactions, agglutination that interferes with serologic crossmatching, and cost.

ABO(H) antigens have also been linked to health factors in genome-wide association studies (GWAS). In patients with acute coronary syndrome (ACS), *O* and *A2* alleles, which lead to high levels of H antigen, were associated with higher levels of interlukein-10, which is linked to poor outcomes in ACS (Johansson et al., 2015). In a different GWAS study, blood group O individuals with coronary artery disease were less likely to have myocardial infarction (Reilly et al., 2011). This finding may relate to decreased vWF and FVIII levels associated with this blood type. A GWAS by the CARDIoGRAMplusC4D Consortium examined more than 180,000 cases of coronary artery disease among more than 1.1 million participants. They found that rs651007, closest to the *ABO* gene, was 1 of 241 associations linked to coronary artery disease (Aragam et al., 2021). A GWAS meta-analysis was conducted of more than 27,000 cases of venous thromboembolism (VTE) and 1 million controls (Wolford et al., 2022). Although an SNP at the *ABO* locus was one of the 38 significant loci identified, its statistical association was not significant after Bonferroni correction for multiple testing. GWAS studies have also found significant findings relating to the ABO gene locus, including an association with heparin-induced thrombocytopenia (HIT) (Karnes et al., 2022).

Secretor status likewise correlates with infectious disease risk (Mottram et al., 2017) (NCBI, 2008). Non-secretors have resistance to norovirus, rotavirus, and *H. pylori*, which may explain why it was selected during human evolution (Azad et al., 2018). The association of non-secretors and rotavirus was evaluated in a case-control observational study at 6 pediatric medical centers in the United States from 2011 to 2013 (Payne et al., 2015). The study enrolled more than 1,500 children younger than 5 years who had diarrhea and/or vomiting. It found that 1 (0.5%) of 189 of patients with severe rotavirus gastroenteritis was a non-secretor, whereas the others were secretors. In contrast, 23% of healthy controls were non-secretors. Ultimately, non-secretors had 98% of protection against severe rotavirus gastroenteritis, which was better than that provided by full vaccination. The mechanism may relate to the rotavirus spike protein VP4 binding to blood group antigens (MacDonald et al., 2020). In contrast, non-secretors have increased susceptibility to *Candida*, *Hemophilus influenza*, *Neisseria meningitis*, *Streptococcus pneumoniae,* and mumps. In addition, non-secretors are more likely to develop type 1 diabetes, inflammatory bowel disease, and kidney disease (Azad et al., 2018).

There are several GWAS studies of FUT2 and gastrointestinal illnesses. One study in the US found a link between non-secretor status and Crohn disease, which is a type of inflammatory bowel disease (McGovern et al., 2010). A different study in Korea reported a similar association (Ye et al., 2020). Another GWAS found a link between rs601338 (the most common inactivating *FUT2* mutation in whites and Blacks, causing W154X), with celiac and inflammatory bowel disease (Parmar et al., 2012). A separate GWAS study showed that children who were non-secretors, with rs601338, had a decreased risk of diarrheal disease in the first few years of life (Bustamante et al., 2016). One GWAS study found that secretors are more likely to have reduced vitamin B_{12} absorption (Hazra et al., 2008). The authors proposed that individuals with *H. pylori* gastritis, which is associated with secretor phenotype, have reduced gastric secretion of intrinsic factor (which is needed for vitamin B_{12} absorption).

LEWIS BLOOD GROUP SYSTEM

Genetics and synthesis

The Lewis blood group system is closely related to H and ABO blood groups. Lewis blood group antigens are found most characteristically on type 1 lactosamine termini, which are soluble molecules. They are predominantly synthesized by an α(1,3/4)-fucosyltransferase known as FUT3, which is encoded by the *FUT3* (*Le*) gene. This enzyme adds Fuc in an α(1,4) configuration to GlcNAc within type 1 lactosamine termini to make the Le^a antigen (Dean, 2005; Mondal et al., 2018; Reid and Olsson, 2012). Once FUT3 creates the Le^a antigen, neither FUT2 nor the A or B glycosyltransferases can act upon it. In secretors, FUT3 may add an additional Fuc in an α(1,4) configuration to GlcNAc within type 1 H units to make the di-fucosylated Le^b antigen (Dean, 2005; Mondal et al., 2018; Reid and Olsson, 2012). The FUT2 enzyme is located in the proximal Golgi and acts on type 1 lactosamine termini prior to FUT3, which can be predominant in the distal Golgi. Individuals expressing both

FUT2 and FUT3 have RBCs that type as Le (a-b+) and express very low levels of Le^a. A and/or B glycosyltransferases add the A or B antigen, respectively, to most type 1 H chains before FUT3 acts. These individuals can express ALe^b and/or BLe^b antigens on their RBCs. Ultimately, RBCs adsorb Lewis antigens on glycolipids form the plasma (Henry et al., 1995). Lewis antigens are also found on lipoproteins, lymphocytes, platelets, gastrointestinal tissues, kidneys, adrenal glands, skeletal muscle, and elsewhere.

Some individuals express a less enzymatically active, "weak," FUT2 enzyme (*Se^wSe^w or Se^wse*) (Combs, 2009, 2019). Weak secretors that have functional FUT3 will type as Le (a+b+). Because FUT3 becomes active before FUT2, some children will type Le (a+b−), then Le (a+b+), and finally Le (a−b+) as they age (Combs, 2009). Several conditions can lead to a loss of Lewis antigens (Reid and Olsson, 2012). During pregnancy, the RBCs of women can become Le (a−b−), likely because of their increased plasma volume and increased quantity of lipoproteins (Combs, 2009, 2019; Marchese, 2017; Reid and Olsson, 2012). Finally, when Lewis antigens adsorb onto RBCs, additional antigens can be created; for example, Le^{bH} is found on RBCs with high H expression (blood group O or A_2 RBCs) that also have Le^b. In addition, Le^{ab} is found on adult RBCs displaying either Le^a or Le^b or both. Thus, the Lewis blood group system consists of six antigens: Le^a, Le^b, Le^{ab}, Le^{bH}, ALe^b, and BLe^b (ISBT, 2021).

Anti-blood group antibodies

Antibodies against Lewis antigens are usually naturally occurring IgM, which do not typically react at physiologic temperature or cause HTRs or HDFN (Cohn et al., 2020; Combs, 2009; Reid and Olsson, 2012). Anti-Lewis antibodies usually occur in individuals who do not express a functional FUT3 enzyme. Of note, Le(a-b+) individuals do not make anti-Le^a, presumably because of very small amounts of Le^a on RBCs and in body fluids. For transfusion, some blood banks provide Lewis-antigen negative units, whereas others provide crossmatch compatible units that may not be antigen negative. Soluble Le antigens in the residual supernatant plasma present in RBC units can also help neutralize anti-Lewis antibodies in recipients. Similar to anti-ABO(H) antibodies, the factors and immune cells responsible for the generation of anti-Lewis antibodies remain incompletely defined.

Prevalence

For whites, 22% are Le(a+b−), 72% are Le(a−b+), very few are Le(a+b+), and 6% are Le(a−b−). For Blacks, 23% are Le(a+b−), 55% are Le(a−b+), very few are Le(a+b+), and 22% are Le(a−b−). For Japanese, 0.2% are Le(a+b−), 73% are Le(a−b+), 16.8% Le(a+b+), and 10% are Le(a−b−) (Reid and Olsson, 2012). The vast majority of Le(a−b−) individuals have a FUT3 enzyme deficiency, but the exact global prevalence has not been estimated. One study estimated that single nucleotide polymorphisms (SNPs) causing a deficiency of FUT3 activity are present in 11.6% of whites and 9.9% of Blacks (Cakir et al., 2002). Interestingly, 10%–40% of some Asian populations express a less enzymatically active, "weak," FUT2 enzyme (*Se^wSe^w or Se^wse*), giving them the Le(a+b+) phenotype (Combs, 2009, 2019) (Reid and Olsson, 2012).

Evolution and health

Lewis antigens are also associated with several diseases. Although rare, the Le (a−b−) Bombay phenotype can occur in leukocyte adhesion deficiency syndrome type II (LAD II). This is caused by defects in the Golgi guanosine diphosphate fucose (GDP-fucose) transporter, which impairs fucosylation (Hellbusch et al., 2007; Tahata et al., 2022). Individuals with a disorder termed "fucosidosis" often type Le (a+b+) (Willems et al., 1991). Fucosidosis is a rare lysosomal storage disease in which there is a severe deficiency of α-L-fucosidase 1 (encoded by the *FUCA1* gene), which removes fucose from glycolipids and glycoproteins (Stepien et al., 2020). The type I form is most severe, with growth retardation, frequent upper respiratory infections, rapid neurodegeneration, and death often occurring before age 10 years (Stepien et al., 2020). *H. pylori* binds Le^b and type 1 H antigens on gastric epithelium and causes gastritis, ulceration, and adenocarcinoma (Cohn et al., 2020; Combs, 2019). Norwalk virus also binds to Le^b and type 1 H antigens to cause gastroenteritis. Le (a−b−) individuals appear to be at an increased risk of cardiovascular disease (CVD) and infection from *Candida* and uropathogenic *Escherichia coli* (Hein et al., 1992; Hilton et al., 1995; Stapleton et al., 1992).

I BLOOD GROUP SYSTEM

Genetics and synthesis

The I blood group system contains only the I antigen (sometimes termed "large I"), which is generated from the i antigen (sometimes termed "small i") (Reid and Olsson, 2012). The i antigen is found in the Ii Blood

Group Collection because its genetics are incompletely understood. The i antigen consists of unbranched repeats (two or more) of *N*-acetyllactosamine units on glycoproteins and glycolipids on RBCs and glycoproteins in plasma. These antigens can be found on unbranched H, A, and B antigens. The I antigen is created when glucosaminyl (*N*-acetyl) transferase 2 (encoded by the *GCNT2* gene, also known as *IGnT*) adds GlcNAc to the i antigen, which is then further elongated. Although RBCs in cord blood mostly express the i antigen, more I antigen is created after birth and reaches adult levels by age 2 years (Cohn et al., 2020). It is rare for adults to express more than trace amounts of i antigen on RBCs. I antigen is expressed on many tissues, leukocytes, and platelets.

Anti-blood group antibodies

Many adults have naturally occurring, cold-temperature reactive anti-I IgM autoantibodies. These autoantibodies do not usually cause HTRs or HDFN and, therefore, are not usually searched for using room temperature or 4°C testing methods (Cohn et al., 2020). Allo-anti-I antibody can, but does not always, occur in individuals with i_{adult} phenotype. The literature on this topic is scarce, but these antibodies can be clinically significant (Chaplin et al., 1986). It would be interesting to determine whether an individual with the i_{adult} phenotype is more prone to make anti-I antibodies and have transfusion reactions; however, this condition is very rare.

Cold agglutinin disease (CAD) is a type of autoimmune hemolytic anemia (AIHA) caused by a bone marrow lymphoproliferative disorder that creates cold agglutinin autoantibodies (Berentsen, 2021; Berentsen et al., 2022; Chonat and Stowell, 2022). CAD is sometimes distinguished from cold agglutinin syndrome (CAS), a similar type of AIHA that can be caused by infections (e.g. *Mycoplasma pneumoniae*, Epstein-Barr virus infection) and malignancies (e.g. B cell lymphoma) (Berentsen et al., 2022). It is most often caused by anti-I IgM antibody and rarely by antibodies with other specificities (Berentsen, 2018). These autoreactive IgM antibodies bind to the patient's RBCs at cold temperatures found in acral body parts (e.g. fingers and toes). This leads to RBC agglutination and binding of C1q complement protein, which leads to C3b binding. When the RBCs return to the warmer body core, the IgM detaches, whereas C3b remains attached. These RBCs may undergo extravascular hemolysis. If C3d is generated from C3b, then these RBCs may be protected from destruction. If the membrane attack complex (MAC) is activated, it can lead to intravascular hemolysis. When CAD patients require transfusion, they should be kept warm and an in-line blood warmer should be used (Berentsen, 2018).

Prevalence

It is estimated that >99% of adults express the I antigen, whereas those who do not express the I antigen have the i_{adult} phenotype. Alleles responsible for weak expression of the I antigen have been described but are rare.

Evolution and health

Alternative splicing of *GCNT2* can lead to 3 different exon 1 sequences, leading to *GCNT2-A*, *GCNT2-B*, and *GCNT2-C* transcripts. The three enzyme isoforms have "similar substrate and branching site" preferences (Fan et al., 2008). The *GCNT2-B* isoform is found in lens epithelium, whereas *GCNT2-C* is found in reticulocytes (Cheong et al., 2017). Mutations in the *GCNT2* gene, especially exons 2 and 3, may lead to congenital cataracts and the i_{adult} phenotype because these exons are shared by the three enzyme isoforms (Pras et al., 2004). Decreased I antigen expression can be seen in a variety of conditions, such as leukemia, thalassemia, stress hematopoiesis, sickle cell disease, and others (Reid and Olsson, 2012).

GLOBOSIDE AND P1PK BLOOD GROUP SYSTEMS

Genetics and synthesis

The Globoside and P1PK blood group systems involve overlapping biosynthetic pathways (Figure 3). The Globoside blood group system includes the P and PX2 antigens, which are on glycolipids and not found on glycoproteins (ISBT, 2021). P antigens can be found on lymphocytes, monocytes, and several different tissues. The P^k antigen is converted into globoside (P antigen) by β(1,3)-*N*-acetylgalactosaminyltransferase 1 (β3GalNAc-T1), which is encoded by the *B3GALNT1* gene, also called *GLOB*. There may be 15 million P antigens per RBC, possibly the highest of any blood group (Hellberg et al., 2013a). β3GalNAc-T1 can also convert paragloboside to PX2 (Westman et al., 2015). It can also synthesize an extended B antigen

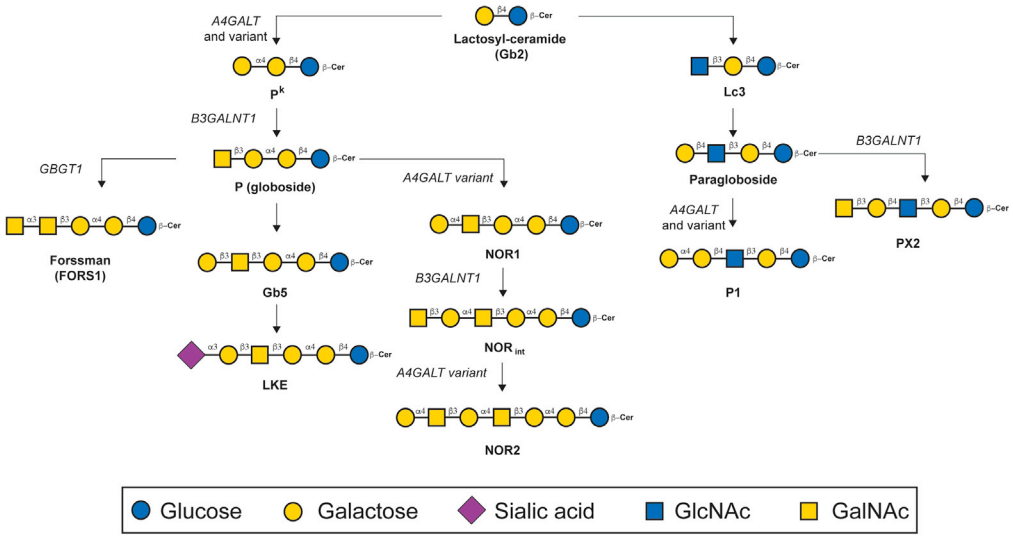

Figure 3. Overview of FORS, P, and NOR blood group antigen biosynthesis

Similar to ABO(H) and blood group antigen biosynthesis, the formation of FORS1, P, NOR, and related antigens occurs in a stepwise fashion. However, these antigens are distinct in that they are exclusively expressed on glycolipids. Inheritence of enzymes capable of creating distinct modifications results in positivity for the respective blood group antigen. Symbol nomenclature for each monosacchride is shown. GlcNAc = *N*-acetylglucosamine, GalNAc = *N*-acetylgalactosamine.

(ExtB), which has an internal B antigen, but is capped with a GalNAc (Clausen and Olsson, 2019). The ExtB structure may be a barrier to creating ECO-RBCs.

The P1PK blood group system includes P1, P^k, and NOR antigens (ISBT, 2021). The $P1P^k$ synthase enzyme (α(1,4)-galactosyltransferase) is encoded by the *A4GALT* gene and acts on paragloboside to synthesize P1 antigen and on lactosylceramide to synthesize P^k antigen (Cohn et al., 2020; Hellberg et al., 2013b; Stenfelt et al., 2020). The P^k antigens are found where P antigens are located, whereas P1 antigens are mostly found on RBCs (Cohn et al., 2020). The RBCs of individuals with the P_1 phenotype express P1, P, and P^k antigens, whereas those with the P_2 phenotype express P and P^k at lower levels than the P_1 phenotype. The P_1 phenotype can occur with the *A4GALT*01* allele, whereas the P_2 phenotype can occur with the *A4GALT*02 allele* (https://www.isbtweb.org/isbt-working-parties/rcibgt/blood-group-allele-tables.html#blood%20group%20allele%20tables).

These two phenotypes occur because of an SNP in a transcription factor binding motif (rs5751348) in intron 1 of the *A4GALT* gene (Cohn et al., 2020; Hellberg et al., 2013b; Stenfelt et al., 2020; Thuresson et al., 2011). These mutations can impact the binding of EGR1, RUNX1, and, perhaps, KLF1 transcription factors (Stenfelt et al., 2020). Consequently, decreased expression of the $P1P^k$ synthase results in reduced amounts of the P^k antigen, and no P1 antigen is synthesized. Our understanding of the genetic mechanisms underlying the $P_1{}^k$ and $P_2{}^k$ phenotypes remains incomplete. Table 4 summarizes these and related phenotypes.

The *A4GALT*01.04* allele is caused by rs397514502, which allows the enzyme to add a galactose to the P antigen, creating the NOR (or NOR1) antigen (Kaczmarek et al., 2016; Kaczmarek et al., 2018; NCBI, 2022c). If NOR1 is acted upon by B3GALNT1 enzyme and then by the *A4GALT*04* enzyme, then NOR2 can be synthesized.

Anti-blood group antibodies

Allo-anti-P antibodies are usually naturally occurring IgM and IgG. Anti-P IgG antibodies can attack the placenta and cause spontaneous abortions. They can cause severe HTRs but typically only lead to mild HDFN. Auto-anti-P antibody can appear in young children after a recent viral infection and cause paroxysmal cold hemoglobinuria (PCH). PCH is classically described as a consequence of syphilis, but due to improved treatment this only rarely occurs (Slemp et al., 2014). PCH is caused by a biphasic IgG antibody

Table 4. Summary of the phenotypes in the Globoside and P1PK blood group system

Phenotype	P1 antigen on RBCs?	P antigen on RBCs?	P^k antigen on RBCs?	RBC reactivity with anti-PP1P^k?	Antibodies in plasma?
P_1	Yes	Yes	Sometimes	Yes	None
P_2	No	Yes	Sometimes	Yes	Sometimes anti-P1
P_1^k	Yes	No	Yes	Yes	Anti-P, PX2
P_2^k	No	No	Yes	Yes	Anti-P, P1, PX2
p	No	No	No	No	Anti-PP1P^k

that typically binds P + RBCs at cold temperatures found in the peripheral circulation, which causes C3 to bind. Sometimes these antibodies have specificity for i, I, Pr-like antigen, or others (Bell et al., 1973; Judd et al., 1986; Shirey et al., 1986). When these RBCs return to the central circulation in the core of the body, they are warmed to 37°C and the membrane attack complex is activated and causes hemolysis and hemoglobin in the urine (Berentsen et al., 2019). When a direct antiglobulin test (DAT) is performed, it usually shows bound C3b and/or C3d, but not IgG (Slemp et al., 2014). Antibodies such as anti-P often have a low thermal amplitude, which is the highest temperature at which it will bind to RBCs, whereas complement is most active at physiologic body temperature (Agarwal et al., 1995). The Donath-Landsteiner test is used to confirm the diagnosis. It has been suggested that PCH be renamed as "Donath-Landsteiner test positive hemolytic anemia" because "paroxysms" and "cold" often do not occur now that syphilis is an unlikely cause (NORD,).

Anti-P1 is usually a naturally occurring, room temperature reactive IgM antibody that does not usually cause HTRs or HDFN (Cohn et al., 2020; Reid and Olsson, 2012; Stenfelt et al., 2020). Titers of anti-P1 are increased in individuals with fascioliasis, hydatid cyst disease (caused by *Echinococcus* tapeworms), and in those working closely with birds. Anti-PX2 antibodies may be a mixture of IgG and IgM, but little else is known. Anti-PP1P^k antibodies are naturally occurring anti-P, anti-P1, and anti-P^k antibodies (Cohn et al., 2020; Reid and Olsson, 2012; Stenfelt et al., 2020). Anti-PP1P^k antibodies can cause HTRs and HDFN. These antibodies cause recurrent spontaneous abortion due to high expression of the P and P^k antigens on placental trophoblast and interstitial cells. Anti-NOR antibodies are usually IgM; however, little is known about the clinical significance of anti-NOR and anti-ExtB antibodies.

Prevalence

Approximately 80% and 20% of individuals have the P_1 and P_2 phenotypes, respectively (Reid and Olsson, 2012). Other phenotypes (P_1^k, P_2^k, and p) were found to be rare (<0.01%) in a German study (Pausch et al., 1990). Less than 0.1% of individuals are deficient in B3GALNT1 or A4GALT. The NOR antigen is created by a variant form of A4GALT found in less than 0.1% of individuals (Cohn et al., 2020; Stenfelt et al., 2020).

Evolution and health

The P antigen is a receptor for P-fimbriated *E. coli* strains and Parvovirus B19, which can cause a "slapped cheek" rash known as fifth disease (also called erythema infectiosum). The P1 and P^k antigens can serve as receptors for a variety of pathogens and toxins, including P-fimbriated *E. coli* strains, *Pseudomonas aeruginosa*, and *Streptococcus suis* (Hellberg et al., 2013b). The P^k antigen is also the receptor for Shiga toxin from *Shigella* and *E. coli* strains (Stenfelt et al., 2020).

FORS BLOOD GROUP SYSTEM

Genetics and synthesis

The FORS blood group system was recently described and contains only the FORS1 glycosphingolipid antigen (ISBT, 2021). FORS1 is made when GalNAc is added in α(1-3) configuration to globoside by α(1,3)-*N*-acetylgalactosaminyltransferase 1 (Forssman synthase). Similar to blood group A, FORS1 terminates in an α(1-3)-linked GalNAc. Due to this similarity, some polyclonal anti-A antibody reagents react with FORS1, and for many years, the expression of this antigen was categorized as an A subgroup, called "A_{pae}" (Stamps et al., 1987; Svensson et al., 2013). FORS1 is expressed on gastric, colonic, pulmonary, and renal tissues.

Forssman synthase was considered non-functional until rare individuals with enzyme activity were identified (Hult and Olsson, 2017). Individuals that possess the *GBGT1.01.01* allele caused by NM_021996.5:c.887G>A (p.Arg296Gln), which is also known as rs375748588, are FORS1+ (2022a).

Anti-blood group antibodies

Anti-FORS1 antibodies are usually naturally occurring and mainly IgM (Cohn et al., 2020; Hult and Olsson, 2017). Because these antibodies are rare, their clinical significance is not well known, but they may cause intravascular hemolysis (Hult and Olsson, 2020).

Prevalence

Less than 0.01% of individuals express the FORS1 antigen (Hult and Olsson, 2017).

Evolution and health

P-fimbriated strains of *E. coli* can bind to FORS1, which may increase susceptibility to infection. In contrast, FORS1 expressing cells are less susceptible to Shiga toxin (Cohn et al., 2020; Hult and Olsson, 2017). However, the exact tissue distribution of FORS1 antigen in humans is unknown. Some human cancers express the FORS1 antigen; however, the mechanism of expression is unknown but may be related to mutated A glycosyltransferases (Yamamoto et al., 2019).

SID BLOOD GROUP SYSTEM

Genetics and synthesis

The SID blood group system contains the high-frequency Sd^a antigen. The *B4GALNT2* gene encodes a β(1,4)-N-acetylgalactosaminyltransferase 2 enzyme, which adds a GalNAc in a β(1,4) configuration to Gal within an α(2,3)-sialylated type 2 lactosamine unit: GalNAcβ(1,4)[Neu5Acα(2,3)]Galβ(1,4)GlcNAc-R (Stenfelt et al., 2019). (Note: Neu5Ac is *N*-acetylneuraminic acid, also called sialic acid.) Sd^a expression levels vary considerably by person. Similar to Lewis antigens, Sd^a is thought to be secreted by other tissues and adsorbed onto RBCs (Groux-Degroote et al., 2021; Stenfelt et al., 2019). In addition, RBCs can type Sd(a−) during pregnancy. Sd^a is expressed in normal colonic mucosa, the stomach, the kidneys, urine, milk, saliva, and elsewhere (Groux-Degroote et al., 2021).

Anti-blood group antibodies

Anti-Sd(a) antibodies cause mixed-field agglutination, with unusual orange refractile agglutinates resembling grapes among non-agglutinated RBCs (Lomas-Francis, 2018). They are most often IgM antibodies and typically do not cause HTRs or HDFN (Cohn et al., 2020).

Prevalence

Although approximately 91% of individuals had detectable Sd^a antigen on their RBCs, 96% of individuals had Sd^a in their urine. (Reid and Olsson, 2012). Thus, approximately 4% of individuals are thought to have a deficiency of B4GALNT2 (Stenfelt et al., 2019).

Evolution and health

The Sd^a antigen, which is carried by the Tamm-Horsfall glycoprotein, may reduce the risk of *E. coli* binding to the kidney and large intestine, thereby preventing colonization and infection (Galeev et al., 2021). In addition, Sd^a may inhibit influenza A viral infection and *Plasmodium* invasion of RBCs (Stenfelt et al., 2019). B4GALNT2 deficiency may protect against *Salmonella enterica* invasion in the intestine (Galeev et al., 2021).

COMMON HUMAN ENZYME DEFICIENCIES

There is lack of consensus in the literature about the most common human enzyme deficiency, both in general and with regard to carbohydrate metabolism and glycan biosynthesis. This section reviews common enzyme deficiencies and proposes including enzymes that define human blood groups. The term deficiency is not being used to indicate a disease, but a clinically meaningful reduction in enzyme activity, which can be associated with advantages and/or disadvantages. A summary of common enzyme deficiencies is provided in Table 5.

Table 5. Examples of common human enzyme deficiencies and their impact on health and disease

Enzyme deficiency	% Enzyme activity	Reason for deficiency	Advantages	Disadvantages	Estimated global prevalence
GGTA1 deficiency (α-gal antigen negative)	0%	Pseudogene	↑ resistance to pathogens that bind/express α-gal	↑ susceptibility to red meat & cetuximab allergy	7.9 billion (100%)
CMAH deficiency (Neu5Gc antigen negative)	0%	Pseudogene	↑ resistance to *P. reichenowi* malaria and Neu5Gc+ viruses	↑ susceptibility to *Pf* malaria, etc.	7.9 billion (100%)
Forssman synthase deficiency (FORS1 antigen negative)	0%	Pseudogene, until activating mutations discovered	Possible ↑ resistance to Shiga toxin	Possible ↑ susceptibility to *E. coli*	7.9 billion (99.99%)
Caspase 12 deficiency	0%	Most cases are likely due to nonsense mutations	↑ resistance to severe sepsis	Uncertain	>7.7 billion (>95%)[a]
CYP3A5[b] deficiency (intermediate & poor metabolizers)	Genotype-dependent	*CYP3A5*3* is one of the most common causes	↑ salt & water retention ↓ tacrolimus inactivation	↑ susceptibility to pre-eclampsia/hypertension	>5.9 billion (>75%)
Lactase deficiency (adult-type hypolactasia)	Physiologic decline with age	Possibly due to transcriptional repression by PDX1 or gene methylation	Uncertain	Lactose intolerance	5.1 billion (65%)[c]
NAT2 deficiency (slow acetylators)	Genotype-dependent	*NAT2*5B* and *NAT2*6A* are common causes	↑ resistance to colon cancer, etc.	↑ susceptibility to bladder cancer, isoniazid toxicity, etc.	>4.0 billion (>50%)
Deficiency of A & B glycosyltransferases (blood group O)	0%	The 261delG mutation in an *A* allele is a common cause	↑ resistance to *Pf* malaria, ABO incompatible viruses, etc.	↑ susceptibility to severe cholera & less vWF/FVIII	≥2.4 billion (≥30%)[d]
FUT2 deficiency (non-secretors)	0%	W154X is a common cause	↑ resistance to norovirus, rotavirus, *H. pylori*, etc.	↑ susceptibility to *Candida*, *H. influenza*, etc.	2.0 billion (25%)[e]
ALDH2 deficiency (alcohol flushing syndrome)	*ALDH2*1/*2*: <17-38% *ALDH2*2/*2*: ~0%	*ALDH2*2* allele is caused by E504K mutation	Deterrence of ethanol consumption	↑ risk of cancer, CVD, etc.	0.6 billion (8.0%)
G6PD deficiency	≤60% (genotype-dependent)	More than 200 mutations, mostly point mutations	↓ human malaria morbidity and mortality	↑ susceptibility to hemolytic anemia	0.5 billion (6.3%)

[a]It is uncertain if any form of human caspase 12 possesses enzymatic activity.
[b]Only very prevalent "pharmacogenomic" enzyme deficiencies were included in this table.
[c]The table describes adult-type hypolactasia, but congenital lactase deficiency should also be considered in the estimated global prevalence.
[d]The table describes blood group O, but a subset with Bombay phenotype can have a deficiency of A & B glycosyltransferases.
[e]The table describes non-secretors, but weak secretors were also included in the estimated global prevalence of FUT2 deficiency.

Glucose-6-phosphate dehydrogenase deficiency

Glucose-6-phosphate dehydrogenase deficiency is one of the most common human enzyme deficiencies, affecting approximately 500 million people worldwide or 6.3% of the estimated 7.9 billion persons alive (Cappellini and Fiorelli, 2008; Frank, 2005; Louicharoen et al., 2009; Luzzatto et al., 2020; Nkhoma et al., 2009; Satyagraha et al., 2021; WHO, 2019). G6PD deficiency, an X-linked recessive condition, makes RBCs more vulnerable to oxidative stress (Cappellini and Fiorelli, 2008; Frank, 2005; Louicharoen et al., 2009; Satyagraha et al., 2021; WHO, 2019). G6PD is the rate-limiting enzyme of the pentose phosphate pathway, which produces NADPH that, in turn, maintains glutathione in a reduced state, thereby protecting cells from reactive oxygen species (Ravikumar and Greenfield, 2020). Unlike other cells, RBCs cannot produce NADPH by an alternative pathway because they lack functional mitochondria (Hwang et al., 2018). Thus, G6PD deficiency primarily manifests as a hemolytic disorder. Although most affected individuals are asymptomatic, they are at risk for hemolysis if they ingest certain foods (e.g. fava beans, termed favism), take certain medications (e.g. quinine, high-dose aspirin, nonsteroidal anti-inflammatory drugs, quinidine, sulfa drugs, quinolones, nitrofurantoin), come in contact with specific chemicals (e.g. naphthalene in mothballs), or become infected (MedlinePlus, 2020). Further, G6PD deficiency affects the accuracy of some laboratory tests, including a common assay used to diagnose and monitor diabetes mellitus: hemoglobin A1c (HbA1c). HbA1c is glycated hemoglobin, which results from nonenzymatic condensation of hemoglobin and glucose. HbA1c provides an estimate of the weighted average of glucose levels during the approximately 3-month lifespan of a red blood cell (Chang et al., 2020). Because G6PD-deficient RBCs can have shorter lifespans than healthy RBCs, HbA1c can be underestimated in G6PD patients (Chang et al., 2020). G6PD variants in persons of African and East Asian ancestry can lower HbA1c levels independently of blood glucose levels (Leong et al., 2020). Alternatives to HbA1c include fructosamine and glycated albumin. G6PD deficiency in blood donors may also impact the survival of their transfused RBCs following refrigerated storage (Francis et al., 2020; Roubinian et al., 2022).

Aldehyde dehydrogenase-2 deficiency

ALDH2 is a mitochondrial enzyme involved in detoxifying acetaldehydes, which are found in ethanol, tobacco smoke, and food, including dietary carbohydrates (Chen et al., 2020). However, in ALDH2-deficient individuals, toxic acetaldehydes accumulate, causing facial flushing after consuming alcoholic beverages (Chen et al., 2014). Approximately 45% of East Asians carry the *ALDH2*2* allele (Chen et al., 2014). This allele is characterized by an NM_000690.4 (ALDH2):c.1510G>A (p.Glu504Lys) variant, also known as E504K (NCBI, 2022b). *ALDH2*1/*2* heterozygotes and *ALDH2*2/*2* homozygotes have 17%–38% and nearly 0% of the wild-type enzyme activity, respectively (Chang et al., 2017). Approximately 8% of the world's population have ALDH2 deficiency, which makes it more prevalent than G6PD deficiency (Chen et al., 2014). ALDH2 deficiency has been linked to increased rates of cancer and CVD, and it may be a risk factor for Alzheimer disease (Zhao and Wang, 2015). Disulfiram (Antabuse), an ALDH2 inhibitor, is approved by Food and Drug Administration (FDA) for alcohol use disorder because it leads to uncomfortable symptoms (e.g. facial flushing) following alcohol ingestion. More recently, ALDH2 deficiency was linked to an increased susceptibility to bone marrow failure. Specifically, the *ALDH2*2* mutation correlates with a worse prognosis in pediatric patients with idiopathic aplastic anemia and a more rapid rate of progression to bone marrow failure in patients with Fanconi anemia (Van Wassenhove et al., 2016).

FUT2 and FUT3 deficiency

Estimates of the global prevalence of FUT3 deficiency are lacking; however, allele frequencies have been studied in many nations and populations (Zhao et al., 2020). Individuals without functional FUT3 are predicted to be Le(a−b−). One source states that 22% of Blacks, 10% of Japanese, and 6% of whites are Le(a−b−) (Reid and Olsson, 2012). Thus, FUT3 deficiency may be more common than G6PD and possibly ALDH2 deficiency. FUT2 deficiency affects 20% of all people, and up to 25% have weak or no FUT2 activity (Soejima and Koda, 2021).

A and B glycosyltransferase deficiency

Blood group O represents a deficiency of A and B glycosyltransferases. It is also worth noting that other individuals, such as a subset of those with Bombay phenotype, can also have a deficiency of A and B glycosyltransferases. However, this cohort is miniscule in comparison to the number with blood group O. Review articles often provide a wide range (29%–80%) for the prevalence of blood group O in different regions of the world (Goel et al., 2021). Studies and analyses from the heavily populated nations of China, India, the United States of

America, Pakistan, and Nigeria found that blood group O was found in 30%, 35%, 47%, 33%, and 53% of individuals, respectively (AABB, 2022; Anifowoshe et al. (2017); Liu et al. (2017); Patidar and Dhiman (2021); Rehman (2020). Thus, blood group O is likely found in ~30% or more of the world's population.

A and B glycosyltransferase deficiency has similarities with G6PD deficiency. Blood group O and G6PD deficiency are thought to have arisen due to offering a survival advantage against human malaria, but both have drawbacks. Blood group O is associated with worse outcomes from cholera and decreased levels of FVIII and vWF, whereas G6PD deficiency is associated with hemolytic anemia under certain types of oxidative stress. Individuals with blood group O cannot enzymatically add monosaccharides to terminal Gal on the H antigen because there is a complete absence of enzyme activity. In contrast, G6PD deficiency usually leads to decreased but not total loss of enzyme activity. Blood group O may have been overlooked as an enzyme deficiency because it is a common blood group worldwide.

Arylamine N-acetyltransferase 2 deficiency

NAT2 is categorized as a drug-metabolizing enzyme, which adds acetyl groups to arylamine carcinogens and medications (Sim et al., 2014). The NAT2 enzyme is mostly expressed in the liver and intestines, whereas the related NAT1 enzyme has a broader tissue distribution. NAT2 polymorphisms were one of the first examples of the importance of pharmacogenomics—how genetics can impact the response to medications. More than 50% of the world's population have *NAT2* genotypes that make them slow acetylators (Sabbagh et al., 2011). These individuals are more susceptible to isoniazid and hydralazine toxicity, prostate, and bladder cancer, among other issues (Magalon et al., 2008). However, they are less likely to develop colon, lung, breast, and laryngeal cancers. The slow-acetylator phenotype is thought to have been selected for due to the rise in agriculture and farming, in which humans were exposed to novel foods and compounds (e.g. heterocyclic amines and polycyclic aromatic hydrocarbons in well-done meat) (Magalon et al., 2008). The slow-acetylator phenotype may have reduced the damaging effects of these carcinogens. A modern study in Central Asia has shown significantly higher percentages of slow acetylators in communities of sedentary agriculturalists in comparison to those of nomadic pastoralists (Magalon et al., 2008). Different studies have found similar results (Patin et al., 2006). This is an example of gene-culture coevolution (Valente et al., 2015).

Lactase deficiency

Lactase is a β-galactosidase digestive enzyme found in the small intestine, which hydrolyses the disaccharide lactose (Galβ(1-4)Glc), the main carbohydrate in a mother's milk, into Gal and Glc. Congenital lactase deficiency is a true enzyme deficiency, but it is very rare (~1 in 60,000 newborns in Finland) (Järvelä et al., 1998). Most often, it is the result of missense mutations or premature stop codons in the *LCT* gene (Diekmann et al., 2015).

Some have suggested that "adult-type hypolactasia (primary lactose malabsorption; lactase non-persistence) is the most common enzyme deficiency present in more than half of the world's human populations" (Järvelä, 2005). Some have estimated that 70% of adults or 65% of the world are affected (Forsgård, 2019; Ingram et al., 2009). However, the decline of lactase enzyme production post-weaning is normal for most adult mammals and, therefore, may not constitute a true genetically based enzyme deficiency in the same sense as the other enzyme deficiencies (Itan et al., 2010). PDX1-mediated transcriptional repression or DNA methylation of the *LCT* lactase gene may cause this physiologic decline (Anguita-Ruiz et al., 2020). Mutations within the *MCM6* gene can impact a regulatory element of the *LCT* gene, causing lactase persistence (Ségurel and Bon, 2017). Evidence suggests that being able to consume milk (a sterile fluid containing protein, fat, sugar, calcium, vitamin D, etc.), without having diarrhea, provided a survival advantage, especially during famines (Wells et al., 2021). Lactase persistence is especially common in Europe, Africa, and Arab populations that domesticated animals. This scenario is another example of gene-culture coevolution. Although Central Asians are unlikely to be lactase persistent, their use of fermented milk (which has less lactose) may have allowed them to benefit from milk without lactase (Segurel et al., 2020).

Cytochrome P450 family 3 subfamily A member 5 deficiency

CYP3A5 is a type of cytochrome P450 enzyme (monooxygenase), which is expressed in hepatic and extrahepatic tissues. This enzyme metabolizes many medications, such as inactivating tacrolimus, which is often prescribed as an immunosuppressant for patients with solid organ transplants (Birdwell et al., 2015). The field of pharmacogenomics determined the genotypes that lead to normal, intermediate, and poor

CYP3A5 metabolizers. For example, having two copies of the *CYP3A5*1* allele corresponds to being a normal metabolizer, whereas having only one copy results in an intermediate metabolizer (Birdwell et al., 2015). Having only the *CYP3A5*3*, *6, *7 alleles results in being a poor metabolizer. Tacrolimus dosing recommendations are based on genotypes (Birdwell et al., 2015). The *CYP3A5*3* allele increases in frequency as the latitude distance from the equator increases (Fuselli, 2019). According to the CYP3A5 frequency tables in the PharmGKB database, less than 23% of sub-Saharan Africans are normal metabolizers (the highest percentage for any group) (PharmGKB,). Thus, it seems reasonable to conservatively estimate that more than 75% of the world's population have a deficiency of this enzyme. CYP3A5 is found in the kidneys and converts cortisol into 6β-hydroxycortisol, which leads to retention of sodium and water (Fuselli, 2019). This led to the sodium retention hypothesis that normal metabolizers near the equator had a survival advantage during droughts. However, this can lead to hypertension and pre-eclampsia.

CYP3A5 is an example of a CYP enzyme deficiency where a very high percentage of the global population is either an intermediate or poor metabolizer. However, there are 57 CYPs in the human genome, and detailing deficiencies for all of them is beyond the scope of this review. For example, approximately 25% of individuals are intermediate or poor metabolizers (having a deficiency of CYP2C9), which leads to warfarin accumulation and possible hemorrhagic complications (Duconge et al., 2009; Klein et al., 2009). CYP2CP alleles account for 15%–20% of the variation in warfarin dosing (Duconge et al., 2009). However, *VKORC1*, encoding vitamin K epoxide reductase complex subunit 1, accounts for 20%–25% of variation in warfarin dosing (Duconge et al., 2009). Estimates for the global prevalence of VKORC1 deficiency are lacking, but some studies have shown that more than 50% of certain populations have a deficiency (González Della Valle et al., 2009; Klein et al., 2009). Commercially available pharmacogenetic testing panels test for are other common human enzyme deficiencies (e.g. enzymes encoded by *MTHFR*, *COMT*, *TMPT* genes, etc.).

Cysteine-dependent aspartate-specific protease 12 deficiency

Caspases cleave proteins after aspartic acid residues and are often involved in programmed cell death. Caspase 12 was thought to modulate inflammation but not have a large impact on apoptosis (Saleh et al., 2004), however its exact purpose is still being determined (Van Opdenbosch and Lamkanfi, 2019). The functional protein leads to hypo-responsiveness to endotoxin (lipopolysaccharide), resulting in increased susceptibility to severe sepsis and mortality (Saleh et al., 2004). Active caspase 12 (caspase 12L) was not identified in whites or Asians but was found in about 20% of some African populations (Saleh et al., 2004; Hervella et al., 2012; Xue et al., 2006; Man and Kanneganti, 2016). The definitively inactive caspase 12S variant is present in 98% of humans (Sanchez-Niño et al., 2010). Thus, >95% of the world's population should be homozygous for this variant and have a deficiency of caspase 12 activity. One source of confusion is that some speculate that caspase 12L is a proteolytically inactive pseudoprotease of unknown function, which means that possibly all humans lack caspase 12 enzyme activity. Instead of being enzymatically active, caspase 12L may regulate other proteases (Green, 2022; Van Opdenbosch and Lamkanfi, 2019).

Forssman synthase deficiency

The *GBGT1* gene was previously thought to be a pseudogene until individuals expressing the functional enzyme were identified (Svensson et al., 2013). Fewer than 0.01% of individuals in the world express a functional Forssman synthase, which creates FORS1 antigen (Reid et al., 2012).

Cytidine monophospho-N-acetylneuraminic acid hydroxylase pseudogene

CMAH is a pseudogene. CMAH enzyme hydroxylates Neu5Ac to synthesize *N*-glycolylneuraminic acid (Neu5Gc), which is a modified sialic acid that is widely expressed in most mammalian cells but not in humans (NCBI, 2022a; Varki et al., 2022; Varki, 2001). Neu5Gc and Neu5Ac define blood groups A and B in cats, respectively, and may be important for dog blood types (Bighignoli et al., 2007; Uno et al., 2019). (The A and B antigens in cats and humans are not the same.) Environmental exposure to Neu5Gc, such as the consumption of red meat, which is rich in Neu5Gc, can result in its incorporation into human glycans (Samraj et al., 2014; Varki, 2001, 2009). Despite this, nearly all humans have anti-Neu5Gc IgM and IgG antibodies that can bind to pig aortic endothelial cells, which is relevant for xenotransplantation (Gao et al., 2017; Senage et al., 2022). If anti-Neu5Gc antibodies bind to human cells, they may lead to inflammation and possibly carcinogenesis and atherogenesis, termed xenosialitis (xeno = foreign, sial = sialic acid, itis = inflammation) (Dhar et al., 2019; Samraj et al., 2014). An advantage of losing CMAH activity is resistance to *P. reichenowi*, a malaria parasite in chimpanzees, *E. coli* K99 (a swine pathogen), and simian virus

40 (SV40), which bind to Neu5Gc on host cells (Altman and Gagneux, 2019). After humans lost CMAH activity, *Pf* evolved from *P. reichenowi*, and the receptor known as erythrocyte binding antigen 175 (EBA-175) mutated from having a specificity for chimpanzee Neu5Gc to a specificity for human Neu5Ac on glycophorins on RBCs (Chattopadhyay et al., 2006; Paul and Padler-Karavani, 2018). Neu5Ac also puts humans at risk of *V. cholerae* toxins, typhoid fever due to *Salmonella typhi*, and many influenza A viruses (Altman and Gagneux, 2019). CMAH loss may also change the nature and overall outcome of sialic acid binding immunoglobulin-like lectins (Siglecs) interactions, thereby impacting immune cell function in ways that may have consequences for human evolution (Okerblom et al., 2017; Varki, 2009, 2010). Specifically, Siglec-13 and -17, which bind to both Neu5Ac and Neu5Gc, became pseudogenes, whereas Siglecs-7, -9, -10, -11, and -16, which preferentially bind to Neu5Ac, emerged in humans (Lin et al., 2021). In addition, soon after the loss of CMAH in the bipedal hominid clade, around 2.1–2.2 million years ago, there were significant increases in brain size in relation to body size (Chou et al., 2002). However, Neu5Gc is rare in vertebrate brains (Davies and Varki, 2015), so the connection between CMAH and brain size is an area of active investigation.

Glycoprotein alpha-galactosyltransferase 1 pseudogene

In humans, glycoprotein alpha-galactosyltransferase 1 is encoded by a complete gene, but only partially transcribed, due to a stop signal in intron 7 (Lantéri et al., 2002). Thus, the enzyme is non-functional in all humans (NCBI, 2022e). Like the B glycosyltransferase, GGTA1 enzyme is an α(1,3)-galactosyltransferase. GGTA1 creates Galα(1-3)Galβ(1-4)GlcNAc-R. Unlike the B glycosyltransferase, however, it does not require the H antigen as a substrate (Lantéri et al., 2002). In humans, anti-α-gal IgM, IgG, and IgA antibodies are naturally occurring and in some individuals represent ∼1% of their immunoglobulins, which means they may be the most abundant antibody in humans (Galili, 2013). These antibodies may protect humans from pathogens that express α-Gal epitopes, including viruses, bacteria, and protozoa (Galili, 2020). However, anti-α-Gal IgE antibodies can cause allergic reactions, such as anaphylaxis, against cetuximab, a therapeutic monoclonal antibody targeting epidermal growth factor receptor (EGFR) (Chung et al., 2008). Anti-α-Gal antibodies can also cause red meat allergy (also called α-Gal syndrome), and these are thought to be formed in response to tick bites. *Amblyomma americanum* (Lone Star tick) is a suspected culprit (Wilson et al., 2019). An observational study of 261 individuals with possible red meat allergy found that symptoms (e.g. urticaria, gastrointestinal symptoms, anaphylaxis) mostly began at least 2 h after eating red meat. Individuals with blood group B (including blood group AB) had significantly lower anti-α-Gal IgG compared with subjects with blood group A or O, likely because blood group B structurally resembles α-Gal. In addition, individuals with blood group B trended toward being underrepresented in the red meat allergy cohort (Wilson et al., 2019).

Anti-α-Gal antibodies can also cause hyperacute rejection of certain xenotransplants, as α-Gal is expressed on common donor animal tissues (Lantéri et al., 2002). To make xenotransplants and xenotransfusions possible (Yamamoto et al., 2021), the α(1,3)-galactosyltransferase gene was knocked out in pigs (Roux et al., 2007). The first successful pig-to-human heart transplant was performed in 2022 using a pig with 10 genetic modifications. Three carbohydrate enzyme genes (*GGTA1*, *CMAH*, and *B4GALNT2*), which create porcine antigens to which humans have naturally occurring antibodies, were knocked out (Griffith et al., 2022; Zhao et al., 2018). (Note: When these three genes are knocked out, the pigs are often referred to as triple knockouts [TKOs] [Ladowski et al., 2021]). Despite the many challenges, the patient's cardiac xenograft functioned normally, until day 49 when it suddenly began to fail. Sixty days after the transplantation, the patient died. The autopsy showed findings that were uncharacteristic of typical rejection (Griffith et al., 2022). Surprisingly, most humans have anti-porcine Sd^a antibodies; ∼96% of humans express Sd^a, and only 1%–2% have naturally occurring anti-human Sd^a antibodies (Cooper et al., 2022). This discrepancy may in part be due to a similar antigen known as Cad, which has been called "super" Sd^a (meaning that it is a strong form of Sd^a). (Cad antigen has no connection with cold agglutinin disease [CAD].) Although Cad and Sd^a have the same trisaccharide terminus, they differ in their sub-terminal structure (Zhao et al., 2018).

A perspective on common human enzyme deficiencies

Claims about the most common enzyme deficiency are somewhat subjective and can be challenging to assess. For example, individuals with blood groups O and B may be considered to have a deficiency of the A glycosyltransferase, while those with blood groups O and A have a deficiency of the B glycosyltransferase. It is possible to consider ∼99.9% of humans as deficient in the *A4GALT*04* variant (which synthesizes NOR antigen), but nearly all express non-variant A4GALT enzyme. It is debatable whether only expressing a functional enzyme variant qualifies as a deficiency of the wild-type enzyme. Some have stated that adult-type hypolactasia is a true enzyme deficiency. Although >95% of humans lack Caspase 12, ∼99.9% lack Forssman synthase,

and 100% lack CMAH and GGTA1, it is not clear whether these should be considered enzyme deficiencies. In these situations, lacking the enzymes seems normal, whereas expressing them seems abnormal.

Ultimately, it can be challenging to define which enzyme deficiency qualifies as the most common in humans. We attempted to identify candidates in the literature; however, we could not evaluate all enzymes. Although allele frequencies are more readily available, we could not always obtain an estimated global prevalence for enzyme deficiency phenotypes. Regardless, patients can have different enzyme deficiencies that can provide substantial health advantages and disadvantages, depending on the situation. Beyond the impact of enzyme deficiencies described above on human health, even when physicians transfuse RBCs to treat *Pf* malaria patients, beyond administering ABO and RhD compatible units, the impact of the blood group on ongoing infection may be an important consideration (Jajosky et al., 2019, 2020).

This review illustrates that cell surface glycans on humans and their ancestors often evolved to avoid binding of pathogens and their toxins and that microbes mutated in response. This "evolutionary arms race" has shaped the human glycome (Paul and Padler-Karavani, 2018). This is exemplified by human evolution to survive malaria. Human ancestors lost the CMAH enzyme, which resulted in a loss of Neu5Gc on cell surfaces and resistance to *P. reichenowi* malaria, which affects chimpanzees. Then, *Pf*, which appears to have mutated from *P. reichenowi*, used EBA-175 to bind to Neu5Ac on glycophorins of human RBCs. Subsequently, evolution selected for a multitude of genetic variants that conferred a survival advantage against *Pf* and other strains of human malaria, including blood group O, G6PD deficiency, Duffy antigen negative RBCs, sickle cell trait, and many others. Consequently, malaria is thought to be one of the most significant recent evolutionary selective pressures on the human genome (Kwiatkowski, 2005). Although the example of human malaria is profound, there are many other drivers of human blood group glycan diversity (Stowell and Stowell, 2019a, 2019b, 2019b). Counterbalancing the selection of blood group O due to *Pf* malaria, cholera causes more severe disease in these individuals. Consequently, a low prevalence of blood group O (and high prevalence of blood group B) is found in the Ganges delta, where cholera has afflicted the region for hundreds to thousands of years (Glass et al., 1985; Harris and LaRocque, 2016).

SUMMARY

Differential expression of glycans, due to carbohydrate-based enzyme variants and deficiencies, is important for human physiology and plays important roles in health and disease. This is clearly illustrated with ABO(H) histo-blood antigens. At least 30% of the world's population are blood group O, caused by a deficiency of both A and B glycosyltransferases, and characterized by the expression of the H antigen on RBCs. Compared with blood group O, blood group A individuals have higher levels of vWF and FVIII and have protection against severe cholera. Most blood group *O* alleles arose from mutations in blood group *A* genes. This may have occurred because blood group O offers protection from severe *Pf* malaria. Individuals with blood group O make naturally occurring anti-A and anti-B antibodies, which may protect against certain infections (e.g. ABO(H)-incompatible enveloped viruses) but also act as a barrier to tissue and organ transplantation. Differential expression of carbohydrate-based enzymes is important in modern medicine (e.g. transfusion, transplantation) and has significant implications for human susceptibility to infection and disease.

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AUTHOR CONTRIBUTIONS

R.J. prepared the initial draft outline of the manuscript, which was additionally commented on and edited by the remaining authors.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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