An update on the GLOB blood group system (and former GLOB collection)

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The main change that has occurred in the GLOB blood group system since the GLOB review published in this journal in 2013 is the addition of an antigen. The high-prevalence PX2 antigen, originally recognized as the x_2 glycosphingolipid, is expressed on red blood cells of most individuals and is elevated in the rare PP1P^k-negative p blood group phenotype. P synthase, encoded by *B3GALNT1,* was found to elongate paragloboside to PX2 by adding the terminal β3GalNAc moiety. Hence, PX2 was moved from the GLOB collection to the GLOB system. The presence of naturally-occurring anti-PX2 was noted in P_1^k and P_2^k individuals exhibiting nonfunctional P synthase. Although the clinical significance of this specificity remains unclear, a recommendation to avoid transfusing P^k patients with p phenotype blood has been made. Currently, 13 mutations at the highly conserved *B3GALNT1* locus have been found to abolish P synthase function and are recognized as null alleles by the International Society of Blood Transfusion. A new allele with a missense mutation but resulting in normal expression of P has been assigned *GLOB*02*. Finally, the GLOB collection was made obsolete after the move of LKE antigen to the 901 series. ***Immunohematology* 2018;34:161–163.**

Key Words: GLOB, PX2, *B3GALNT1*

Update on the GLOB System

In a series of experiments, P synthase encoded by *B3GALNT1* was shown to synthesize the PX2 antigen by the addition of GalNAc in β1,3-linkage to the paragloboside precursor (Fig. 1). The presence of naturally occurring anti-PX2 in all tested individuals with the rare P^k phenotype was also noted.[1] Consequently, PX2 was reclassified and moved from the GLOB collection (International Society of Blood Transfusion [ISBT] no. 209), to which it was added as late as 2016, to the GLOB blood group system (ISBT no. 028) and accepted as the second blood group antigen (GLOB2) after P (GLOB1).[2] This change, however, gave rise to some confusion, because P^k, now belonging to the P1PK blood group system (ISBT no. 003), was previously identified as 209.002 (i.e., the second antigen of the GLOB collection). In an attempt to shed light on the already complicated history of P, P1, and P^k, the PX2 antigen was therefore renamed GLOB4 (ISBT no. 028004) by the ISBT Working Party.[3] For clarification, the current terminology of the GLOB blood group system is summarized in Table 1.

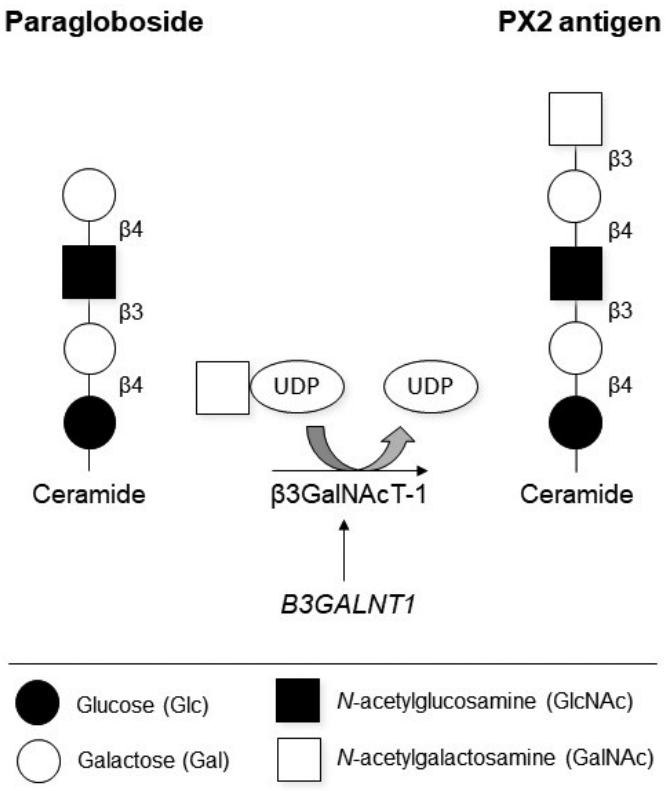

Fig. 1 Schematic summary of PX2 antigen synthesis and its precursor molecule paragloboside. The α- or β-linkages are shown along with the informative numbers in the 1,3 or 1,4 glycosidic bonds.

Another interesting aspect of PX2 concerns host–pathogen interaction. *Clostridium difficile* toxin A is internalized via endocytosis after binding to epithelial cells in the large intestine. This toxin has been shown to bind to the terminal GalNAc of PX2, which is therefore considered the human receptor for the toxin.[4] Interestingly, sialylation of the same epitope inhibits binding and may therefore modulate the toxic effects of *C. difficile*.[5]

Table 1. The GLOB blood group system

Antigen	ISBT system no.	ISBT antigen	ISBT antigen no.
P	GLOB 028	GLOB1	028001
PX2	GLOB 028	GLOB4*	028004

Note that the GLOB system remains but the GLOB collection has been retired and hence 209001, 209002, 209003, and 209004 are obsolete (previously used for P, P^k, LKE, and PX2, respectively).

*Previously known as GLOB2 but after the ISBT congress in Toronto in June 2018, GLOB2 and GLOB3 were made obsolete.[3]

ISBT = International Society of Blood Transfusion; no. = number.

Traditionally, p phenotype blood units (i.e., those lacking P, P1, and P^k antigens) have often been used to manage the transfusion needs of patients with the rare P^k phenotype. The reasoning behind this has simply been a matter of availability. Though the clinical significance of anti-PX2 is not yet fully understood, this may no longer be the most favorable option for P^k patients — because of elevated levels of PX2 on the p phenotype. Thus, a recommendation to avoid transfusing p phenotype units for P^k patients has been made.

Next-generation sequencing data from the 1000 Genomes Project has been extracted for all 36 blood group systems, correlated with known variants and visualized in a custom-designed database, www.erythrogene.com, by Möller et al.[6] Bioinformatic analysis of the *B3GALNT1* locus revealed it to be highly conserved, although an allele with the c.376G>A mutation was found in 5.2 percent of the population worldwide. This allele, shown to be associated with normal expression of P,[7] was named *GLOB*02*. Subsequently, the c.598delT mutation linked to c.376G>A[8] was therefore renamed *GLOB*02N.01* (and *GLOB*01N.10* was retired).

Also, another nonsense mutation at the *B3GALNT1* locus, abolishing P synthase activity, has been identified and added to the 12 alleles already recognized by ISBT. The substitution c.420T>G introduces a premature stop codon, p.Tyr140Ter, and was given the allele name *GLOB*01N.13*.[9] The complete list of GLOB alleles is available at http://www.isbtweb.org/working-parties/red-cell-immunogenetics-and-blood-group-terminology/.

Update on the GLOB Collection

The high-prevalence antigen Luke (LKE) was removed from the GLOB collection (209003) to the 901 series and assigned the ISBT number 901017.3 Hence, the GLOB collection has been rendered obsolete.

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