P1PK Blood Group System

Number of antigens 3

Polymorphic	P1
High prevalence	P^k (albeit weakly expressed on most RBC phenotypes)
Low prevalence	NOR

Terminology

ISBT symbol (number)	P1PK (003)
History	The P1 antigen (originally named P) was discovered by Landsteiner and Levine in 1927. The antigen was named P because this was the first letter after the already assigned M, N, and O. In addition to P1, the P system previously also contained P, P^k, and LKE antigens. However, uncertainty about the genetic loci and biochemical pathways underlying these antigens arose, so in 1994 they were moved to the Globoside Collection. In 2010, the P^k antigen was replaced into the P system, which was renamed the P1PK system. In 2011, the NOR antigen was provisionally assigned to the same system.

Expression

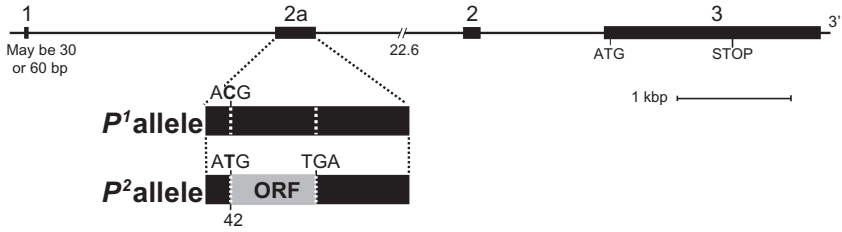
Soluble form	P1: Pigeon egg white, hydatid cyst fluid, *Echinococcus* cyst fluid
Other blood cells	P1/P^k: Weakly on lymphocytes, granulocytes, monocytes, platelets

Gene

Chromosome	22q13.2
Name	*A4GALT*

The Blood Group Antigen (3/e). DOI: http://dx.doi.org/10.1016/B978-0-12-415849-8.00005-3

Organization	Four exons distributed over ~26.6 kbp
Product	4-α-galactosyltransferase



Database accession numbers

GenBank	NG_007495 (gDNA); AJ245581 (cDNA; partial exon 3); GU902278 (cDNA, exon 1 and 2a)
Entrez Gene ID	53947

Molecular bases of the P_1 and P_2 phenotypes due to changes in exon 2a of *A4GALT*[1]

The open reading frame in exon 3 (accession number AJ245581) encodes 4-α-galactosyltransferase, the enzyme that synthesizes P1 and P^k. Changes in exon 2a distinguish P_1 and P_2 phenotypes. Differences from reference allele *A4GALT*P1.01* (accession number GU902278) are given below. A nucleotide change of C>T (ACG>ATG) in exon 2a of *A4GALT* introduces an open reading frame in transcripts that include exons 1 and 2a. This is associated with fewer enzyme-encoding transcripts (comprising exons 1, 2, and 3) in the presence of the P^2 allele, but it is unknown how this transcriptional regulation occurs.

Phenotype	Allele name	Exon	Nucleotide	Amino acid change^	Ethnicity (prevalence)
P_1 phenotype					
P1+P^k+(P_1)	*A4GALT*P1.01*				
P_2 phenotype					
P1–P^k+(P_2)	*A4GALT*P2.01*	2a	42C>T	Start codon introduced	(Common)
P1–P^k+(P_2)	*A4GALT*P2.02*	2a	42C>T; 122T>G	Start codon introduced; Gly28Trp	(Several)

^ = Investigations are in progress to determine if the open reading frame in exon 2a is translated.

Molecular bases of P1+/– P^k+, NOR+, and p ($PP1P^k$–, $P1P^k_{null}$) phenotypes due to changes in exon 3 of *A4GALT*[2,3]

Nucleotide differences from reference allele *A4GALT*01* (Accession number AJ245581), and amino acids affected, are given. This reference allele (comprising the open reading frame in exon 3) encodes 4-α-galactosyltransferase, which adds α-galactose to paragloboside (lacto-*N*-neotetraosylceramide) to form the P1 antigen. It also adds α-galactose to lactosylceramide (CDH) to form the P^k antigen (CTH). As the CTH is the precursor for the P antigen (see **GLOB** System and Section III), changes in *A4GALT* that prevent addition of galactose to CDH (the precursor of P^k antigen) also prevent addition of 3-β-*N*-acetylgalactosamine to form P, and therefore give rise to the p [$P1PP^k$–, previously known as the Tj(a–)] phenotype. An altered form of the transferase can also add α-galactose to globoside (Gb4) to form the NOR antigen, in addition to P1 and P^k.

Phenotype	Allele name	Exon	Nucleotide	Amino acid	Ethnicity (prevalence)
P1+/– P^k+	*A4GALT*01*^	3			(Common)
P1+/– P^k+	*A4GALT*02*^	3	109A>G	Met37Val	(Common)
NOR+, P1+, P^k+	*A4GALT*04*#	3	631G>C	Gln211Glu	(Rare)
Null phenotypes					
p	*A4GALT*01N.01.01*	3	241_243delTTC	Phe81del	Japanese, English (Few)
p	*A4GALT*01N.01.02*	3	241_243delTTC (with 903G>C)	Phe81del	Italian (Rare)
p	*A4GALT*01N.02*	3	287G>A	Cys96Tyr	Italian (Rare)
p	*A4GALT*01N.03.01*	3	299C>T	Ser100Leu	Amish (Several)
p	*A4GALT*01N.03.02*	3	299C>T (with 903G>C)	Ser100Leu	Pakistani (Rare)
p	*A4GALT*01N.04*	3	301delG	Ala101fs 113Stop	Chinese (Rare)
p	*A4GALT*01N.05*	3	418_428delins	Gln140fs 218Stop	Asian (Rare)
p	*A4GALT*01N.06*	3	470_496delins	Asp157fs 276Stop	English (Rare)
p	*A4GALT*01N.07*	3	473G>A	Trp158Stop	Brazilian (Rare)

(*Continued*)

(Continued)

Phenotype	Allele name	Exon	Nucleotide	Amino acid	Ethnicity (prevalence)
p	*A4GALT*01N.08*	3	502_504insC (with 914C>T)	Tyr169fs282 Stop	Maghreb (Few)
p	*A4GALT*01N.09.01*	3	548T > A	Met183Lys	Swedish (Several)
p	*A4GALT*01N.09.02*	3	548T > A (with 987G > A)	Met183Lys	Swedish (Rare)
p	*A4GALT*01N.10*	3	559G > C	Gly187Arg	Thai (Rare)
p	*A4GALT*01N.11*	3	560G > A	Gly187Asp	Swedish (Rare)
p	*A4GALT*01N.12*	3	656C > T	Ala219Val	French (Rare)
p	*A4GALT*01N.13*	3	657delG	Ala219fs349 Stop	Israel (Few)
p	*A4GALT*01N.14*	3	731_732insG	Ile245fs281 Stop	Norwegian (Rare)
p	*A4GALT*01N.15*	3	751C > T	Pro251Ser	(Rare)
p	*A4GALT*01N.16*	3	752C > T	Pro251Leu	Japanese (Rare)
p	*A4GALT*01N.17*	3	769delG	Val257fs349 Stop	Polish (Rare)
p	*A4GALT*01N.18*	3	783G > A	Trp261Stop	Japanese (Rare)
p	*A4GALT*01N.19*	3	972_997del	Thr324fs436 Stop	USA (Rare)
p	*A4GALT*01N.20*	3	1026_1029 insC	Thr344fs446 Stop	Japanese (Few)
p	*A4GALT*01N.21*	3	196_201insC	Thr68fs282 Stop	Thai (Rare)
p	*A4GALT*02N.01*	3	68_69insT	Leu23fs53Stop	Israel (Rare)
p	*A4GALT*02N.02*	3	290C > T	Ser97Leu	Polish (Rare)
p	*A4GALT*02N.03*	3	752C > T	Pro251Leu	Japanese (Rare)
p	*A4GALT*02N.04*	3	902delC	Pro301fs349 Stop	(Rare)
p	*A4GALT*02N.05*	3	972_997del	Thr324fs436 Stop	French (Rare)

For changes in *B3GALNT1* giving rise to P_1^k and P_2^k phenotypes, see **GLOB** System.
^Can be *in cis* to P^1 or P^2 polymorphism in exon 2a, i.e., can travel with either P_1 or P_2 phenotype.
‡*In cis* to P^1 allele, i.e., travels with the P_1 phenotype.

Amino acid sequence of α4GalT (protein accession #AAH55286)

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MSKPPDLLLR  LLRGAPRQRV  CTLFIIGFKF  TFFVSIVIYW  HVVGEPKEKG  50
QLYNLPAEIP  CPTLTPPTPP  SHGPTPGNIF  FLETSDRTNP  NFLFMCSVES  100
AARTHPESHV  LVLMKGLPGG  NASLPRHLGI  SLLSCFPNVQ  MLPLDLRELF  150
RDTPLADWYA  AVQGRWEPYL  LPVLSDASRI  ALMWKFGGIY  LDTDFIVLKN  200
LRNLTNVLGT  QSRYVLNGAF  LAFERRHEFM  ALCMRDFVDH  YNGWIWGHQG  250
PQLLTRVFKK  WCSIRSLAES  RACRGVTTLP  PEAFYPIPWQ  DWKKYFEDIN  300
PEELPRLLSA  TYAVHVWNKK  SQGTRFEATS  RALLAQLHAR  YCPTTHEAMK  350
MYL                                                       353
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Carrier molecule[4,5]

The P1, P^k, and NOR antigens are not primary gene products; they are located on glycolipids. The terminal linkage of each antigen is synthesized by the primary gene product (4-α-galactosyltransferase).

All antigens in the P1PK system are based on lactosylceramide, which is also the immediate precursor for P^k antigen. Paragloboside is the precursor for P1 antigen, and globoside (P antigen) is the precursor for NOR antigen (see "Antigens with lactosylceramide as the precursor" and "Biosynthetic Pathways" in Section III).

Copies per RBC	Highly variable and depending on the P_1/P_2 phenotype, *P1* allele zygosity, and status of the *B3GALNT1* gene (see **GLOB** System)

Function

The enzyme transfers Gal to the terminal sugar of paragloboside (for P1) or lactosylceramide (for P^k). It is unclear how acceptor preference is determined, but the higher levels of *A4GALT* transcripts in the P_1 phenotype indicate that it may be at least partially a quantitative question.

Disease association

See individual antigens under Comments.

Phenotypes (% occurrence)

Phenotype	Caucasians	Blacks	Cambodians & Vietnamese
P_1	79	94	20
P_2	21	6	80
Null: p (very rare)			

See GLOB System (**028**).

Comments

RBCs with either the P_1 or the P_2 phenotype express P^k (weakly), P, and LKE antigens, whilst RBCs with the p phenotype lack all these antigens and P1.

References

[1] Thuresson, B., et al., 2011. Identification of a novel *A4GALT* exon reveals the genetic basis of the P_1/P_2 histo-blood groups. Blood 117, 678–687.

[2] Steffensen, R., et al., 2000. Cloning and expression of the histo-blood group Pk UDP-galactose: Gal-beta1-4Glc-beta1-Cer alpha1,4-galactosyltransferase. Molecular genetic basis of the p phenotype. J Biol Chem 275, 16723–16729.

[3] Furukawa, K., et al., 2000. Molecular basis for the p phenotype. Identification of distinct and multiple mutations in the alpha1,4-galactosyltransferase gene in Swedish and Japanese individuals. J Biol Chem 275, 37752–37756.

[4] Bailly, P., Bouhours, J.F., 1995. P blood group and related antigens. In: Cartron, J.-P., Rouger, P. (Eds.), Molecular Basis of Human Blood Group Antigens. Plenum Press, New York, NY, pp. 300–329.

[5] Spitalnik, P.F., Spitalnik, S.L., 1995. The P blood group system: biochemical, serological, and clinical aspects. Transfusion Med Rev 9, 110–122.

P1 Antigen

Terminology

ISBT symbol (number)	P1PK1 (003001 or 3.1)
Obsolete names	P; P_1
History	Discovered in 1927; named P antigen because the letters M, N, and O had been used; renamed P_1 and then P1.

Occurrence

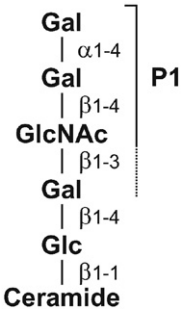
Caucasians	79%
Blacks	94%
Cambodian/Vietnamese	20%

Expression

Cord RBCs	Weaker than on RBCs from adults
Altered	There is considerable variation in the strength of P1 expression on RBCs. This variation is inherited, and at least partially dependent on the zygosity of P^1 alleles[1]. P1 expression is also weakened in the In(Lu) phenotype.

Molecular basis associated with P1 antigen[2,3]

P1 antigen is derived by the addition of an α-galactosyl residue to paragloboside.



Effect of enzymes and chemicals on P1 antigen on intact RBCs

Ficin/Papain	Resistant (markedly enhanced)
Trypsin	Resistant (markedly enhanced)
α-Chymotrypsin	Resistant (markedly enhanced)
Pronase	Resistant (markedly enhanced)
Sialidase	Resistant
DTT 200 mM	Resistant
Acid	Resistant

In vitro characteristics of alloanti-P1

Immunoglobulin class	IgM (IgG rare)
Optimal technique	RT (or lower)
Neutralization	Hydatid cyst fluid, pigeon egg white, *Echinococcus* cyst fluid
Complement binding	Rare

Clinical significance of alloanti-P1

Transfusion reaction	No to moderate/delayed (rare)
HDFN	No

Comments

The P1 determinant is widely distributed throughout nature. It has been detected in, for example, liver flukes and pigeon egg white. The determinant is a receptor for a variety of microorganisms, including P-fimbriated strains of *E. coli* with the PapG adhesion, and *Streptococcus suis*[4].

Anti-P1 is a naturally-occurring antibody in many P1– individuals. Anti-P1 is frequently present in serum from patients with hydatid disease, liver fluke disease, and acute hepatic fascioliasis.

References

[1] Thuresson, B., et al., 2011. Identification of a novel *A4GALT* exon reveals the genetic basis of the P_1/P_2 histo-blood groups. Blood 117, 678–687.

[2] Bailly, P., Bouhours, J.F., 1995. P blood group and related antigens. In: Cartron, J.-P., Rouger, P. (Eds.), Molecular Basis of Human Blood Group Antigens. Plenum Press, New York, N.Y., pp. 300–329.

[3] Spitalnik, P.F., Spitalnik, S.L., 1995. The P blood group system: biochemical, serological, and clinical aspects. Transfusion Med Rev 9, 110–122.

[4] Moulds, J.M., et al., 1996. Human blood groups: Incidental receptors for viruses and bacteria. Transfusion 36, 362–374.

P^k Antigen

Terminology

ISBT symbol (number)	P1PK3 (003003 or 3.3)
Obsolete names	Trihexosylceramide; Ceramide trihexose (CTH); Globotriaosylceramide (Gb_3Cer); Gb3
CD number	CD77
History	Named in 1959 when the relationship to P was recognized; the "k" comes from the last name of the first proband to produce anti-P^k.

Occurrence

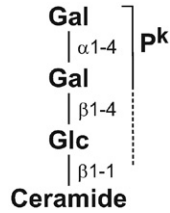
Strongly expressed on RBCs from <0.01% of the population, i.e., individuals with the P_1^k and P_2^k phenotypes. RBCs from all other individuals, except those with the p phenotype, have varying and often small amounts of P^k depending on the genotype ($P^1/P^1 > P^1/P^2 > P^2/P^2$).

Expression

Cord RBCs	Expressed

Molecular basis associated with P^k antigen[1,2]

P^k antigen is derived by the addition of an α-galactosyl residue to lactosylceramide.



Effect of enzymes and chemicals on P^k antigen on intact RBCs

Ficin/Papain	Resistant (markedly enhanced)
Trypsin	Resistant (markedly enhanced)
α-Chymotrypsin	Resistant (markedly enhanced)
Pronase	Resistant (markedly enhanced)
Sialidase	Resistant (markedly enhanced)
DTT 200 mM	Resistant
Acid	Resistant

In vitro characteristics of alloanti-PP1P^k

Immunoglobulin class	IgM; IgG
Optimal technique	RT; 37°C; IAT
Neutralization	Hydatid cyst fluid, *Echinococcus* cyst fluid or pigeon egg white
Complement binding	Yes; some hemolytic

Clinical significance of alloanti-PP1P^k

Transfusion reaction	No to severe (rare) because anti-PP1P^k is rare (cross-match would be incompatible)
HDFN	No to severe
Spontaneous abortions	Cytotoxic IgM and IgG3 antibodies directed against P and/or P^k antigens are associated with a higher than normal rate of spontaneous abortion in women with the rare p [Tj(a–)], P_1^k, and P_2^k phenotypes

Autoanti-P^k

Yes

Comments

P^k was thought to be expressed only by P_1^k/P_2^k phenotype RBCs until it was realized that most RBCs express P^k antigen, albeit weakly. P^k antigen is more strongly expressed on LKE– RBCs than on LKE+ RBCs (see **GLOB Collection**).

Neuraminidase treatment of RBCs exposes neutral glycosphingolipids (e.g., P^k and P antigens) and gangliosides. Anti-P^k can be separated from some anti-PP1P^k by absorption with P1 RBCs.

Siblings of patients with anti-PP1P^k should be tested for compatibility, and the patient urged to donate blood for cryogenic storage when his/her clinical state permits.

Gb3 (P^k) is the physiologic receptor for shiga toxin from Shigella (Stx) or certain *E. coli* strains (Stx1 and Stx2) on renal epithelium, platelets, and endothelium.

P^k is a receptor for P-fimbriated pyelonephritogenic *E. coli* with the PapG adhesin and *Streptococcus suis*. The p phenotype confers resistance to urinary tract infection with P-fimbriated *E. coli* due to lack of P, P1, and P^k receptors on urothelium. Transcriptional up-regulation of P^k by inflammatory mediators (IFN, IL1) and increased P^k levels contribute to susceptibility to Stx toxicity in renal and vascular tissue in the development of *E. coli*-associated HUS. P^k is involved in signal modulation of α-interferon receptor and CXCR4 (an HIV co-receptor). Some of these effects may be mediated through lipid rafts. P^k may provide protection against HIV-1 infection[3].

References

[1] Bailly, P., Bouhours, J.F., 1995. P blood group and related antigens. In: Cartron, J.-P., Rouger, P. (Eds.), Molecular Basis of Human Blood Group Antigens. Plenum Press, New York, N.Y., pp. 300–329.

[2] Spitalnik, P.F., Spitalnik, S.L., 1995. The P blood group system: biochemical, serological, and clinical aspects. Transfusion Med Rev 9, 110–122.

[3] Lund, N., et al., 2009. The human P(k) histo-blood group antigen provides protection against HIV-1 infection. Blood 113, 4980–4991.

NOR Antigen

Terminology

ISBT symbol (number)	P1PK4 (003.004 or 3.4)
History	Reported in 1982, and named after the city where the original propositus resided (Norton, VA, USA)[1]. Assigned to the P1PK system in 2012.

Occurrence

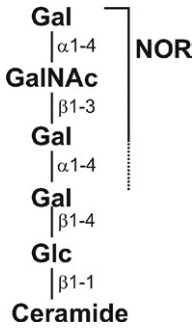
Only found in two families so far, American and Polish.

Expression

Altered	Considerable variation in the strength of NOR expression.

Molecular basis associated with NOR antigen[2–4]

NOR antigen (α-galactosyl-globoside) is derived by the addition of an α-galactosyl residue to globoside as a consequence of a single nucleotide change in *A4GALT*.



Amino acid	Glu211
Nucleotide	G at bp 631 in exon 3 of the *A4GALT*
NOR– (wild type)	Gln211 and C at bp 631

Effect of enzymes and chemicals on NOR antigen on intact RBCs

Ficin/Papain	Resistant (enhanced)
Trypsin	Resistant (enhanced)

In vitro characteristics of alloanti-NOR

Immunoglobulin class	IgM
Optimal technique	RT
Neutralization	Hydatid cyst fluid; avian P1 glycoproteins

Clinical significance of alloanti-NOR

No data because transfusion of NOR+ blood is rare.

Comments

NOR+ RBCs are said to be polyagglutinable because they are agglutinated by most ABO-compatible human sera. It can be distinguished from Cad polyagglutination by its non-reactivity with the lectins *G. soja*, *D. biflorus* or *S. horminum*[1].

The NOR phenotype is characterized by the presence of two unique neutral glycospingolipids (designated NOR1 and NOR2) that react strongly with *Griffonia simplicifolia* IB4 lectin (GSL-IB4)[5]. NOR2 is an extended NOR (NOR1) glycolipid that expresses NOR activity due to the sequential addition of β3GalNAc and α4Gal.

The Gln211Glu change in the 4-α-galactosyltransferase appears to alter its acceptor preferences so that it can add a Gal also to the P antigen, while retaining its capacity to synthesize the P^k and P1 antigens.

References

[1] Harris, P.A., et al., 1982. An inherited RBC characteristic, NOR, resulting in erythrocyte polyagglutination. Vox Sang 42, 134–140.

[2] Duk, M., et al., 2001. Structure of a neutral glycosphingolipid recognized by human antibodies in polyagglutinable erythrocytes from the rare NOR phenotype. J Biol Chem 276, 40574–40582.

[3] Suchanowska, A., et al., 2010. A possible genetic background of NOR polyagglutination [abstract]. Vox Sang 99 (Suppl. 1), 333.

[4] Suchanowska, A., et al., 2011. Genetic background of NOR polyagglutination [abstract]. Vox Sang 101 (Suppl. 1), 20.

[5] Duk, M., et al., 2002. Serologic identification of NOR polyagglutination with *Griffonia simplicifolia* IB4 lectin. Transfusion 42, 806–807.