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ORIGINAL ARTICLE

A case report of a rare p phenotype individual and a review of molecular biological analysis of p phenotype in the Chinese population

Xiaoxiang Wei[1,2] | Dong Xiang[1] | Liangfeng Fan[1] | Zhonghui Guo[1] | Dong Ran[3] | Shengdi Bu[2] | Xiaojie Tan[2] | Qin Li[1]

[1]Blood Group Reference Laboratory, Shanghai Blood Center, Shanghai, PR China

[2]Department of Blood Transfusion, The First People's Hospital of Nanning, Nanning, PR China

[3]Department of Medicine Laboratory, The Eighth People's Hospital of Nanning, Nanning, PR China

Correspondence
Qin Li, Blood Group Reference Laboratory, Shanghai Blood Center, No.1191, Hongqiao Rd. Shanghai 200051, PR China.
Email: liqin@sbc.org.cn

Abstract

Objectives: To explore the serological characteristics and molecular mechanisms of an individual with the p phenotype in the Chinese population by analysing the serological and genetic background.

Background: The p phenotype, which lacks all antigens in the P1PK blood group system, is extremely rare in the Chinese population. Individuals with the p phenotype typically produce anti-PP1P^k antibodies. The P1, P^k antigens belong to the P1PK blood group system, while the P antigen is part of the GLOB blood group system. The antigens in the P1PK system are synthesised by α1,4-galactosyltransferase (α4Gal-T), while the antigens in the GLOB system are produced by 3-β-N-acetylgalactosaminyl-transferase (β3GalNAc-T1). These glycosyltransferases are encoded by the *A4GALT* and *B3GALNT1* genes.

Materials and Methods: Serological techniques were employed to determine the blood types and antibodies of an individual with the p phenotype. Additionally, first- and third-generation sequencing methods were used to analyse the *A4GALT* and *B3GALNT1* genes in the sample.

Results: The serum from the tested individual showed positive reactions with all red blood cells (RBCs) from two sets of panel RBC reagents, while it reacted negatively with a confirmed p phenotype red blood cell. The antibodies in the serum exhibited IgM + IgG properties, with IgG being the predominant type. The antibody titers at room temperature, 37°C, and 4°C were 128, 64, and 256, respectively. Sequencing analysis revealed a homozygous mutation in the *A4GALT* gene at rs5751348: G > T; c.343A > T; c.903C > G, while no mutation was detected in the *B3GALNT*1 gene.

Conclusions: The tested individual exhibited the p phenotype and likely produces anti-PP1P^k antibodies. The allele carrying rs5751348: G > T; c.343A > T; c.903C > G in the *A4GALT* gene has been provisionally designated *A4GALT*02 N.28* (pending official recognition by ISBT).

KEYWORDS

A4GALT, anti-PP1P^k, Chinese population, p phenotype

1 | INTRODUCTION

The polymorphism of the P blood group system was first discovered in 1927.[1] In the 1950s, the blood group system was expanded, with the observation of two rare phenotypes, Tj(a−) (now obsolete) and P^k.[2] The GLOB system was established in 2002.[3] Subsequently, antigens originally belonging to the P blood group system were reclassified and divided into two distinct blood group systems by the International Society of Blood Transfusion (ISBT).[3,4]

The P1PK blood group system (ISBT 003) includes P1, P^k, and NOR antigens, all of which are synthesised by α1,4-galactosyltransferase (α4Gal-T).[4] The GLOB blood group system (ISBT 028) includes P, PX2, and ExtB antigens, which are synthesised by 3-β-N-acetylgalactosaminyl-transferase (β3GalNAc-T1).[3] The P1 antigen is synthesised from its substrate paragloboside (Lc4) through the action of α4Gal-T, while the P^k antigen is produced from lactosylceramide (LacCer) via the same enzyme. The substrate for NOR antigen is currently believed to be the P antigen, which is modified by α4Gal-T to form NOR. The P antigen is derived from its precursor P^k antigen through the enzymatic activity of β3GalNAc-T1. Similarly, the PX2 antigen may be synthesised from paragloboside (Lc4) under the catalysis of β3GalNAc-T1.[5] Additionally, the B antigen from ABO blood group system can be elongated by β3GalNAc-T1 to form the ExtB antigen.[6] In addtion, the single-nucleotide polymorphisms (SNPs) in intron 1 of *A4GALT*, particularly rs5751348, correlate with P1 (P1-positive) or P2 (P1-negative) phenotypes, respectively.[7]

The two glycosyltransferases are encoded by the *A4GALT* and *B3GALNT1* genes. The *A4GALT* gene, located on chromosome 22q13.2, comprises three exons, with its entire coding region contained within exon 3.[8] Similarly, the *B3GALNT1* gene on chromosome 3q26.1 spans five exons but retains all coding sequences in exon 5.[9] These two genes encode 353-amino-acid and 331-amino-acid proteins, respectively, both functioning as type II glycosyltransferases.[10,11]

The absence of all antigens in the P1PK blood group system results in the rare p phenotype.[4] Individuals with the p phenotype typically produce anti-PP1P^k antibodies, which are clinically important.[5] These antibodies can agglutinate all RBC phenotypes, except for the p phenotype, bind to complement and cause hemolysis, leading to severe transfusion reactions. Additionally, they can result in early miscarriage in pregnant women and hemolytic disease of the fetus and newborn.

The p phenotype is exceptionally rare. The frequency of the p phenotype in the European population is approximately 5.8 per million.[12] In contrast, the frequency of the p phenotype in the Chinese population is lower than that in the European population. No p phenotype case was screened in more than 1 million Chinese population in Hong Kong,[13] and about 20 cases are reported in the Chinese population.[14–31]

This study identified a patient who appeared to have the p phenotype and produce anti-PP1P^k antibodies. The study aimed to clarify the serological characteristics of the phenotype and antibodies and determine the genetic background responsible for this rare phenotype.

2 | MATERIALS AND METHODS

2.1 | Blood sample

A 56-year-old Han nationality female, diagnosed with renal malignancy, had no history of blood transfusion. She had three pregnancies, two healthy children, and one previous miscarriage. During her preoperative blood preparation, mismatched results were found in the forward and reverse typing of her ABO blood group. Her blood samples, with or without ethylenediaminetetraacetic acid (EDTA), were sent to the Shanghai Blood Center for further blood type determination.

2.2 | ABO blood type determination

The forward and reverse typing were performed using the conventional tube technique, following standard guidelines.[32]

2.3 | Antibody identification and titre determination

Antibody identification was conducted using the microcolumn gel card method. To detect IgM antibodies, the serum of the patient and panel RBCs were added to the gel card (104 230 601, JiangSu ZoJiWat Bio-pharmaceutical Co Ltd), and the results were observed after centrifugation. For the identification of IgG antibodies, the serum of the patient and 2-Mercaptoethanol (2-Me) were mixed at a volume ratio of 1:1, reacted at 37°C for 30 min, and then the treated serum and panel RBCs were added to the anti-human globulin gel card (848 189 333, BIO-RAD). The mixture was incubated at 37°C for 10 min, and the results were observed after centrifugation. Two sets of panel RBC reagents were used for detection: one from Shanghai Hemo-Pharmaceutical & Biological Inc. (Shenxing, Lot No 20240516) and the other from Immucor, Inc. (Lot No 20927). Additionally, a p phenotype RBC, frozen at −80°C, was thawed and incubated with the patient's serum to observe the results.

Monoclonal anti-P1 (Shenxing, 20 230 612, Shanghai Hemo-Pharmaceutical & Biological Inc.) was used to screen P1-positive RBCs from O-type RBCs. Isotonic saline was used to dilute the serum of the patient treated with or without 2-Me in multiple ratio. The diluted serum was then reacted with the screened group O, P1 positive RBCs, and the results were observed using the microcolumn gel card method.

2.4 | Identification of P1PK and GLOB blood group system antigens

Ten antibodies from different sources were used to determine the patient's antigen expression in the P1PK and GLOB blood group

systems. The first was a commercial monoclonal IgM anti-P1 (Shenxing, 20 230 612). The second was a monoclonal IgM antibody produced using monoclonal antibody technology for human hybridoma in our laboratory. B lymphocytes were derived from an individual with the p phenotype and produced antibodies previously referred to as anti-Tj^a. Through identification, the specificity of the antibody produced in our laboratory was confirmed to be anti-P (data not shown). The remaining eight antibodies are human-derived polyclonal antibodies suspected to be anti-Tj^a, collected from p phenotype patients in over several decades in our laboratory. Due to limitations in experimental conditions at the time, the full specificity of these antibodies could not be identified. Therefore, the abolished term "anti-Tj^a" was used to describe these antibodies. However, these sera contain antibodies such as anti-P1, anti-P, or anti-P^k. The No. 1 and No. 2 human-derived polyclonal antibodies are from AB type and can be directly used as reagent antibodies. Polyclonal antibodies No.3–No.8 are not from AB type individuals. The sera were treated using absorption and elution methods to avoid interference from antibodies of the ABO blood group system. Briefly, monoclonal IgM anti-P1 and No. 1 polyclonal antibodies were used to screen group O, P1 positive and P positive RBCs. The RBCs and No.3–No.8 serum were mixed in a 1:5 volume ratio and incubated at 4°C for 30 min. Subsequently, a 56°C heat elution technique was applied to obtain elution solutions, which were then used as reagent antibodies. The patient's RBC suspension was subsequently tested with the 10 different antibodies, and the results were analysed using the microcolumn gel card method.

2.5 | DNA sequencing

Genomic DNA was extracted using a Tiangen DNA kit (U8618, Tiangen, China) according to the manufacturer's instructions. The PCR primers Pk-(−140) and Pk-1120, along with the PCR amplification procedures for the *A4GALT* gene, were designed by Hellberg et al.[33] The PCR primers P-(−6)-F and P-1015-R, along with the PCR amplification procedures for the *B3GALNT1* gene, were also designed by Hellberg et al.[34] The sequencing results of the first-generation sequencing were aligned with the NCBI data NG_007495.1 (*A4GALT*) and NG_007854.1 (*B3GALNT1*). The analysis of the *A4GALT* and *B3GALNT1* genes was performed by Haorui Gene Technology Co., Ltd. using third-generation sequencing.

3 | RESULTS

3.1 | ABO blood type identification

The results of the forward typing indicated that the sample had blood type AB. In reverse typing, the patient's serum or plasma showed positive reactions with group A, B, and O RBCs (Table 1).

3.2 | Antibody identification and titre determination

The Shenxing panel RBC reagent contained 10 RBCs, while the Immucor panel RBC reagent contained 16 RBCs. The patient's serum tested positive with all 28 RBCs. P and P^k belong to high-frequency antigens; thus, the patient's serum may contain anti-PP1P^k antibodies. An additional RBC with the p phenotype was used for testing with the patient's serum, yielding a negative result. This finding suggested that the antibody specificity in the patient's serum was likely anti-PP1P^k. The antibody was characterised as having IgM + IgG properties, with IgG being the predominant type. The antibody titres at room temperature, 37°C, and 4°C were 128, 64, and 256, respectively.

3.3 | Patient's antigen expression of the P1PK and GLOB blood group systems

Based on serological testing with monoclonal anti-P1 and human-derived anti-P antibodies, the patient's RBCs were confirmed as P1- and P-. Due to the lack of commercially available anti-P^k and anti-PX2 antibodies in our serological testing, the expression status of P^k and PX2 antigens could not be definitively determined by serology alone and required further analysis based on sequencing results. Table 2 shows additional details.

3.4 | Sequencing results

The results of first-generation sequencing showed the sample had c.343A>T and c.903C>G mutations in the coding region of the *A4GALT* gene (Figure 1A,B). In contrast, the third-generation sequencing results showed that the *A4GALT* gene in the sample had

TABLE 1 Results of ABO blood type identification for the patient.

ABO forward typing			ABO reverse typing					
Test condition	Anti-A	Anti-B		Test condition	A1 RBC	B RBC	O RBC	Autologous RBC
IS	4+	4+	Plasma	IS	2+	2+	2+	–
				37°C 10 min	+–	+–	+–	–
			Serum	IS	2+	2+	2+	–
				37°C 10 min	PH	PH	PH	–

Abbreviations: IS, immediate spin; PH, partial hemolysis.

TABLE 2 Results of patient's antigen expression in P1PK and GOLB blood group systems.

	Monoclonal antibodies		Human-derived polyclonal antibodies[a]											Patient serum	
Reagent	Anti-P1	Anti-P	1		2		3	4	5	6	7	8			
Reaction conditions	IS	IS	IS	IAT	IS	IAT	IAT	IAT	IAT	IAT	IAT	IS	IAT	IS	IAT
Patient's RBCs	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Oc	3+	2+	2+	4+	3+	3+	3+	3+	3+	3+	3+	3+	3+	3+	3+

Abbreviations: IS, immediate spin; IAT, indirect anti-globulin test.

[a]No.1–No.7 human-derived polyclonal antibodies were previously labelled as anti-Tj[a] through serological experiments. Sample 8 was sequenced and found to have the c.656 C>T; 903 C>G mutations in the *A4GALT* gene (Table 3, No 16 sample), which indicates a p phenotype, and the humanised antibody is anti-PP1P^k.

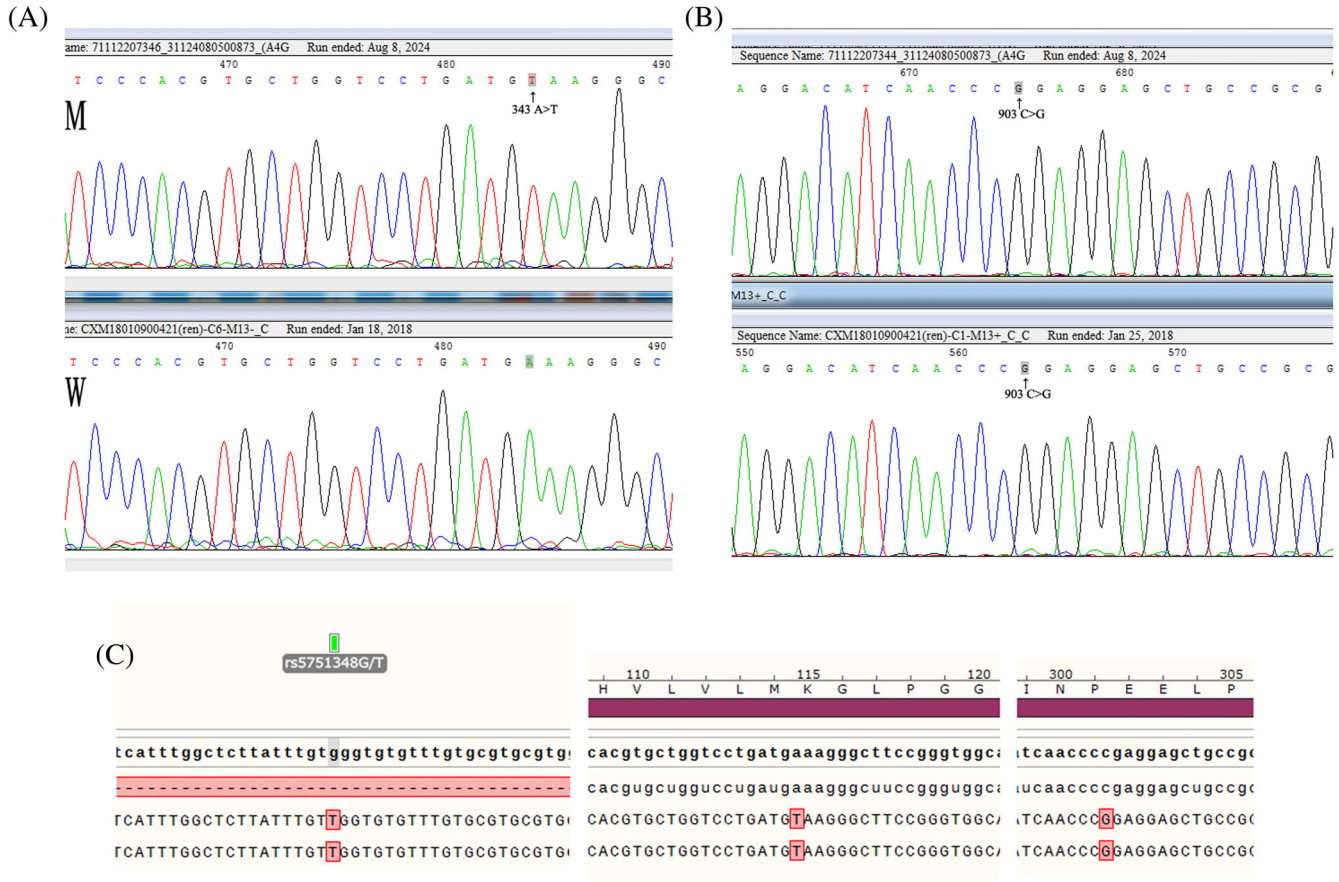

FIGURE 1 Results of the first- and third-generation sequencing to analyse the A4GALT gene. A, B: The first-generation sequencing showed c.343 A>T and c.903 C>G alleles. M means mutation, W means wild type. C: Third-generation sequencing showed rs5751348: G>T; C.343A>T; c.903C>G homozygous mutation. In the sequencing samples, the base at position 903 of the *A4GALT* gene coding region is all G, and no C is found.

rs5751348: G>T; c.343A>T; c.903C>G homozygous mutation (Figure 1C). The c.903C>G was a synonymous mutation, while the c.343A>T might encode a truncated protein sequence of 115 amino acids (p.Lys115Ter). The rs5751348: G>T is associated with the P2 (P1-negative) phenotype. No mutation was detected in the *B3GALNT1* gene through first- or third-generation sequencing.

Based on sequencing results, serological findings, and the biosynthetic pathways of relevant antigens, the patient's RBCs were conclusively identified as P-, P1-, and P^k-.

4 | DISCUSSION

The antigens of the P1PK and GLOB blood group systems are both glycosphingolipid antigens, which have similar biosynthetic mechanisms. The *A4GALT* and *B3GALNT1* genes encode α4Gal-T and β3GalNAc-T1, respectively. Biosynthesis of the antigens in P1PK and GLOB blood group systems occurs through the sequential addition of monosaccharides to a precursor substrate, catalysed by the two aforementioned glycosyltransferases. The synthase of P1, P^k, and NOR

TABLE 3 Alleles found in *A4GALT* gene in the Chinese population.

No	Allele Name	Nucleotide Changes	Amino acid changes	Location	Data sources
1	*A4GALT*02 N.28* (pending official recognition by ISBT)	rs5751348: G>T c.343A>T c.903C>G	p.Lys115Ter	Intron 1 Exon 3	This work
2	Currently unnamed	IVS + 228C>T[a]	p.Pro310=[b]	Intron 1	Reference 23
3	Currently unnamed	c.1-504_1044del1548	Unpredictable	Intron 2 Exon 3	Reference 26
4	Like *A4GALT*02 N.25*	c.100G>A c.418_428delins	P.Val34Ile, p.Gln140Trpfs*73	Exon 3	References 16, 25
5	Currently unnamed	c.109A>G c.987G>A[a,c]	p.Met37Val, p.Gly329Glu	Exon 3	Reference 23
6	Like *A4GALT*01 N.03.02*	c.299C>A	p.Ser100Ter	Exon 3	Reference 30
7	*A4GALT*0XN.04*	c.301delG	p.Ala101Profs*13	Exon 3	Reference 14
8	Currently unnamed	c.304_305ins G	p.Asp101Glyfs*180	Exon 3	Reference 21
	Like *A4GALT*02 N.28*[d]	c.343A>T	p.Lys115Ter	Exon 3	Reference 25
9	Like *A4GALT*02 N.28*[d]	c.343A>T c. 903C>G	p.Lys115Ter	Exon 3	Our lab's data, not previously reported References 17, 27
10	Currently unnamed	c.370_371del	p. Leu124Argfs*9	Exon 3	Reference 31
11	*A4GALT*02 N.25*	c.418_428delins	p.Gln140Trpfs*73	Exon 3	Reference 15
12	Currently unnamed	c.456_457ins ACACCCC	p.Glu152Alafs*131	Exon 3	Reference 23
13	Currently unnamed	c.507C>G	p.His169Asp	Exon 3	Reference 31
14	*A4GALT*01 N.10*	c.559G>C	p.Gly187Arg	Exon 3	References 28, 29
15	Like *A4GALT*01 N.10*	c.559G>C c.903C>G	p.Gly187Arg	Exon 3	Reference 22
16	Like *A4GALT*0XN.12*	c.656C>T c. 903C>G	p.Ala219Val	Exon 3	Our lab's data, not previously reported
17	Currently unnamed	c. 849_851del c. 903C>G	p.Phe283del	Exon 3	Our lab's data, not previously reported
18	Currently unnamed	c. 903C>G	p.Pro310=	Exon 3	Reference 19

[a]This variant was detected in a relative of the proband, who is heterozygous for the *A4GALT* mutation (one mutant and one wild-type allele) and therefore does not display the p phenotype.
[b]It is speculated that this variant may reduce transcriptional efficiency, although experimental validation has not been performed.
[c]c.109A>G mutation is named *A4GALT*01.02*, while c.987G>A mutation is present in the *A4GALT*0XN.09.02* allele.
[d]The nucleotide expression of rs5751348 was not detected.

antigens is α 4Gal-T, which is encoded by the *A4GALT* gene. The mutation of the *A4GALT* gene may lead to the inactivation of α 4Gal-T, resulting in failure to synthesise P1, P^k, and NOR antigens. When the P antigen is synthesised, the substrate is the P^K antigen, and the synthase is β3GalNAc-T1, which is encoded by the *B3GALNT1* gene. If the P^k antigen expression is abnormal or *B3GALNT1* gene mutation occurs, then the P antigen cannot be synthesised normally.

In this study, the patient's had rs5751348: G>T; c.343A>T; c. 903C>G homozygous mutation. According to the ISBT nomenclature guidelines for P1PK blood group system alleles, we have designated this allele as *A4GALT*02 N.28* (pending official recognition by ISBT). The c. 343A>T mutation was first discovered in 2013,[17] which leads to the premature formation of stop codons in the *A4GALT* gene, inactivating α4Gal-T and preventing the synthesis of P1, P^k, and NOR antigens. The c. 903C>G was synonymous mutation and is generally not a key factor leading to the p phenotype.[17] However, in one case of the p phenotype, only c.903C>G mutation was found, and whether other mechanisms lead to the formation of the p phenotype in the sample remains unclear (Table No.3).[19] The single-nucleotide variant rs5751348 was assumed to carry potential transcription factor-binding sites for runt-related transcription factor 1 (RUNX1) and early growth response 1 (EGR1), which may facilitate the formation of antigen polymorphism in the P1PK blood group system.[35,36] No mutation was detected in the *B3GALNT1* gene of the patient. The RBCs of the patient do not express P antigen due to the non-expression of the P^k antigen as the substrate. Based on the sequencing and serological test results, the patient has a p phenotype. Due to the lack of commercially available anti-PX2 antibodies, we were unable to detect the expression of PX2 antigen on the patient's RBCs. However, literature reports indicate that the PX2 antigen is highly expressed on erythrocytes of individuals with the p phenotype.[10] Therefore, we infer that this patient's RBCs likely exhibit elevated PX2 antigen expression.

Additionally, as the patient's family members declined to participate in the study, we were unable to perform familial genetic testing to further elucidate the inheritance pattern of the p phenotype in this pedigree. We hope to conduct more in-depth investigations in future studies when opportunities arise.

The p phenotype has been rarely reported in Chinese populations, with approximately 20 documented cases to date.[14–31] Some reports only provided serological findings. Based on both published data and unpublished observations from our laboratory, we have listed 18 *A4GALT* alleles potentially associated with the p phenotype in Table 3. Among the identified alleles, all except IVS + 228C>T and the double mutation c.109A>G, c.987G>A were found to cause the p phenotype. These two mutations, along with the c.456_457insACACCCC allele, were identified in a pedigree comprising 34 members.[23] Both the proband and one of her brother exhibited the p phenotype due to homozygosity for c.456_457insACACCCC. Among the proband's relatives (excluding the 2 p phenotype cases): 6 were c.456_457insACACCCC heterozygotes, 7 carried c.109A>G, c.987G>A, and 3 had IVS + 228C>T. None of the 16 individuals exhibited the p phenotype, consistent with their heterozygous status. An intriguing population-genetic finding emerged from recent study: the p phenotype demonstrates a remarkably high prevalence (>2%) in China's Lahu ethnic group, revealing striking ethnic-specific variation in blood group distribution.[28] Among Chinese individuals with the p phenotype, three *A4GALT* mutations exhibit relatively high frequencies: c.343A>T, c.559G>C, and c.418_428delins. These variants have been identified in distinct pedigrees across different regions of China.[15–17,22,25,27–29]

Anti-PP1P^k antibodies, commonly a mixture of IgG and IgM, are naturally produced in all individuals with the p phenotype.[5] These antibodies can agglutinate all phenotypes of RBCs, except for the p phenotype, causing hemolysis of P1, P positive RBCs in the presence of complement. This phenomenon also exists in cases where hemolysis occurs, in which the serum of the patient and the reagent RBCs react for more than 10 min at 37°C (Table 1). A similar experiment was conducted using EDTA anticoagulant plasma, and the reagent RBCs did not cause hemolysis. EDTA is assumed to chelate Ca2+ ions in plasma, preventing the formation of membrane attack complexes after complement activation, which inhibits hemolysis.

The anti-PP1P^k antibody can lead to habitual miscarriage in early pregnant women.[11,37] A direct relationship may exist between the titre of anti-PP1P^k antibodies and the risk of miscarriage. The fetus is relatively safe when the maternal IgG anti-PP1P^k antibody titre is within 16.[38] Immunoglobulin injection and plasma exchange are effective methods for treating fetal hemolysis caused by anti-PP1P^k.[39]

Although the frequency of the p phenotype in the Chinese population is extremely low, these individuals tend to produce anti-PP1P^k antibodies, which can impact the patients' blood transfusion safety and maternal and infant safety. Based on the results and literature data, in the Chinese population, c.343A>T, c.559G>C, and c.418_428delins in the *A4GALT* gene are alleles with high frequency in individuals with the p phenotype. PCR–SSP technology for these alleles can be designed to conduct large-scale screening in the Chinese population, and additional data on the p phenotype of the Chinese population may be obtained.

AUTHOR CONTRIBUTIONS

Xiaoxiang Wei operated the serological tests and drafted the manuscript. Dong Xiang designed the serological study and analysed the results of serological experiments. Liangfeng Fan, Dong Ran, and Shengdi Bu performed serological tests. Zhonghui Guo analysed the sequencing results. Qin Li designed the study, analysed the sequencing results, and revised the manuscript. All authors reviewed the data, provided comments, and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

PATIENT CONSENT STATEMENT

The patient clearly stated that the relevant research was aimed at identifying blood type and related antibodies, and providing safe blood transfusion services.

ORCID

Qin Li https://orcid.org/0000-0002-9093-5867

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