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Mini–review to analyse the phenotype, genotype, and alloantibody titre against Diego antigens in the Chinese population

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ABSTRACT

Diego blood antigens are important antigens in Mongoloid people and native South Americans owing to the Dia positivity rate found in these populations. However, the prevalence of Di^{a+} is different among native populations of America and China. Our study reviewed the genotype, phenotype, and alloantibody titre of Diego blood group antigens to explain the existence of the dosage effect for Diego antigens. The prevalence of Di^{a+} varied from 2.26% to 10.43% in the Chinese population was lower than that observed in Native Americans living in USA, Brazil, and Venezuela. The Di(a+b–)/Di(a+b+) ratio in the Chinese was 0.0044~0.0268, which was also lower than that observed in native Americans at 0.0203~0.1628, indicating that the major allele was Di(a+b+) in Di^{a+} Chinese or Asians. We also collected Di(a+b–), Di(a+b+), and Di(a–b+) samples from Chinese samples to examine the agglutinin titres with anti–Di^a and anti–Di^b and the results supported the existence of the dosage effect for Diego antigens. The agglutinin titres of anti–Di^a in Di(a+b+) specimens were lower than those in Di(a+b–) specimens, and agglutinin titres of anti–Di^b in Di(a+b+) specimens were lower than those in Di(a–b+) specimens. Alloantibodies against Di^a and Di^b antigen are majorly responsible for haemolytic disease of the new–born and anti–Di^a reactions resulting in stillborn foetus and transfusion reactions, such as fever and rash, were also reported in the Chinese population.

Keywords: Diego antigens, phenotype, genotype, alloantibody

BACKGROUND

In 1956, the first case of haemolytic disease of new–born (HDN) induced by anti–Di^a was reported in Venezuela and HDN caused by anti–Di^b was reported in 1967[1,2]. The Diego group has been ranked 10th among erythrocytic groups by the International Society of Blood Transfusion (ISBT). The Diego group comprises of 22 antigens located at Band 3, which are encoded by the *SLC4A1* gene located at 17q12–q21. These 22 antigens grouped to Diego result from single nucleotide polymorphisms (SNPs) at the *SLC4A1* gene. The Di^a/Di^b result from an SNP at nt.2561 of the *SLC4A1* gene, meaning that the nucleotide was

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2561C for the Di^b antigen and 2561T for the Di^a antigen[3−5]. Di^a and Di^b are the most important antigens in the Diego group that cause problems during clinical blood transfusions[6]. The frequency of the Di^b antigen is very high and is found in individuals of all ethnicities, while Di^a occurs almost exclusively among native South Americans and Mongoloid people and is very rare in people of European origin.

Since the 22 antigens of the Diego group result from SNPs, molecular genotyping is a useful method to examine the SNPs and identify the Diego antigens. Although monoclonal antibodies against Di^a and Di^b antigens are available in commercial kits, these kits were unpopular since the Di^a antigen is only distributed among specific races and Di^b occurs in all ethnic populations[7,8]. Therefore, there are few studies that discuss the dosage effect of Diego antigens. Since the Di^a antigen is a necessary antigen in screening or panel cells, and the Di(a−b−) phenotype has not been published, we investigated the agglutinin titre in individuals with the genotypes, Di(a−b+), Di(a+b+), and Di(a+b−) (a very rare combination of alleles) and calculated the frequency of Di(a−b+), Di(a+b+) and Di(a+b−) in the Chinese population from the Di^{a+} rate by using monoclonal anti−Di^a[9].

Previous reports found that alloantibodies against Di^a induced HDN and delayed haemolytic transfusion reaction, while anti−Di^b caused delayed haemolytic transfusion reaction[10,11]. Our study reviewed an original case report from China to discuss clinical problems caused by alloantibodies against Di^a and Di^b.

The aim of this study was to review the phenotype and genotype of Diego antigens and the alloantibody response against Diego antigens in the Chinese population. We also compared the present study with European or American and discussed the existence of dosage effect for Diego antigens.

PHENOTYPE

Although monoclonal antibody anti−Di^a and anti−Di^b are commercially available, various distribution of Diego antigens in different area and ethnics were limited the mAb widely used in clinics. Di^a antigen distribution is limited to Native Americans and the Mongoloid people, and other ethnic were very low frequency, while the Di^b antigen shows a very high prevalence in people of all ethnicities. This irregular distribution results in difficulties in the availability of the appropriate commercial kit. Recent studies investigated the frequency of Diego antigens using monoclonal anti−Di^a and screened rare banks for Jk(a−b−) using monoclonal anti−Di^b. One such study published the positive rates of Di(a−b+) from blood donors and consequently inferred the frequencies of phenotype.

We reviewed recent studies on Di^a frequency and calculated the frequency of Di(a+b−), Di(a+b+), and Di(a−b+) (***Table 1***). In China, the Han population in north China showed the highest frequency of Di^{a+}, 11.03%, followed by 8.04% in blood donors from Shanghai, 5.03% in the Zang minority, 4.36% in the Zhuang minority in southeast China, 4.02% in Koreans in north China, 3.33% in the Manchu minority, 2.53% in the Han population in Taiwan, 2.26% in the Dong minority in southeast China, and 1.43% in the Taiwanese minority (***Table 1***). In Asia, the Dia positivity rate was 10.05% among the Japanese, followed by 6.14% in Koreans living in Korea, and 4.00% in Indians living in India. Native Americans from Brazil and Venezuela showed the highest positivity rates for Di^a, showing: 75.71% in the Parakanã, 54.16% in the Kaingang, 35.54% in the Carib, 10.81% in the Chippewa, 8.03% in the Penobscot, and 5.26% in the Arawak populations. The Mexicans and Inuits also showed a higher positivity rate for Di^a, the rate was 10.21% in Mexicans and 20.93% for Inuits. From the Di^a positivity rate, the frequency of Di(a+b−) and Di(a+b+) were inferred; the Di(a+b−)/Di(a+b+) ratio was 0.004−0.0268 in Asia while in the Native Americans, the ratio was 0.0135−0.1628.

We also observed that the Di(a+b−)/Di(a+b+) ratio followed the prevalence of Di^a positivity (***Fig. 1***). The Di(a+b−)/Di(a+b+) ratio was 0.16 when the Di^a positivity rate was 75.7% and 0.004 when the positivity rate was 2.26%. These results suggest a lower prevalence of Di^a in specific populations, making it difficult to collect Di(a+b−) samples in contrast to populations that have a higher prevalence of Di^a. The agglutinin titres of Di^a using monoclonal anti−Di^a were low in populations with lower prevalence of Di^a compared to those in higher prevalence populations (***Fig. 1***).

GENOTYPE

Because Di^a and Di^b antigens were identified at nt.2561 in the exon of *SLC4A1* gene, molecular analysis techniques were used to screen for the Diego genotype.

The Korean minority from Jilin showed the highest frequency of Di(a+b+) with 11.20%, followed by 9.49% in the Uygur minority from Xinjiang, 8.00% in blood donors from Guangzhou, and 5.59% in blood donors from Shenzhen (***Table 2***). In contrast, the frequency of the rare blood type, Di(a+b−), was 0.45% in Jilin and was the highest frequency although the sample size was 200.

Table 1 **Frequencies of Di(a+b−), Di(a+b+), and Di(a−b+) determined from Di^a positivity rate in Asia and USA**

Ethnic groups	Area	Di^a (%)	Estimated frequency(%)			Di(a+b−)/
			Di(a−b+)	Di(a+b+)	Di(a+b−)	Di(a+b+)
Han[12]	North China	11.03	88.96	10.75	0.29	0.0268
Dong minority[13]	Southeast China	2.26	97.74	2.25	0.01	0.0044
Zhuang minority[14]	Southeast China	4.36	95.64	4.31	0.05	0.0116
Korean minority[14]	North China	4.02	95.98	3.98	0.04	0.0101
Han[15]	Taiwan, China	2.53	97.47	2.52	0.01	0.0040
Taiwanese minority[16]	Taiwan, China	1.43	98.57	1.43	0.01	0.0035
Japanese[7]	Japanese	10.05	89.84	9.91	0.25	0.0252
Korean[17]	Korea	6.14	93.86	6.05	0.09	0.0149
Indian[18]	North India	4.00	96.00	3.96	0.04	0.0101
Zang minority[19]	North China	5.03	95.97	4.97	0.06	0.0125
Manchu minority[19]	North China	3.33	96.66	3.29	0.03	0.0091
Blood donor[20]*	East China (Shanghai)	8.04	91.96	7.88	0.16	0.0203
Carib native Americans[10]	Venezuela	35.54	64.45	32.85	2.70	0.0822
Arawak native Americans[10]	Venezuela	5.26	94.74	5.19	0.07	0.0135
Kaingang native Americans[10]	Brazil	54.16	45.84	48.32	5.84	0.1209
Parakanã native Americans[21]	Brazil	75.71	24.29	65.11	10.60	0.1628
Chippewa native Americans[22]	USA	10.81	89.18	10.54	0.28	0.0266
Penobscot native Americans[23]	USA	8.03	91.96	7.88	0.16	0.0203
Mexicans[24]	USA	10.21	89.79	9.96	0.25	0.0251
African Americans[18]	USA	0.12	99.88	0.12	0.00	0.0000
Poles[25]	Poland	0.47	99.53	0.47	0.00	0.0000
Inuits[18,26]	Siberia	20.93	79.08	19.93	0.99	0.0497
Inuits[18]	Alaska, Canada	0.14	99.86	0.14	0.00	0.0000

*The frequency of Di(a+b−), Di(a+b+), and Di(a−b+) were inferred from the positivity rate of anti−Di^b.

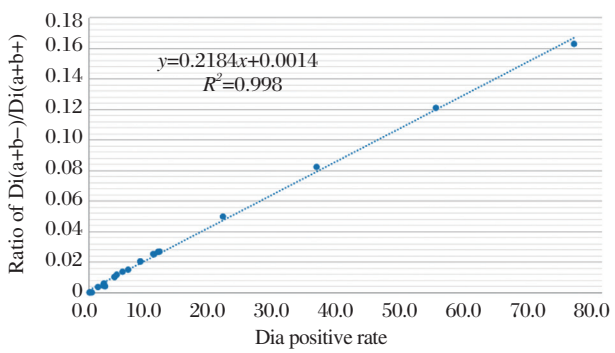

Fig. 1 The Di(a+b−)/Di(a+b+) ratio follows the prevalence of Di^a positivity rate

ALLOANTIBODIES AGAINST Di^a AND Di^b ANTIGENS

Anti−Di^a and anti−Di^b are often encountered in HDN, with anti−Di^a being more common than anti−Di^b due to the deficiency of Di^b antigen being very rare in all ethnic populations. Both anti−Di^a and anti−Di^b are responsible for fatal haemolytic disease. Anti−Di^a production is mainly stimulated by pregnancy and delayed haemolytic transfusion reactions; however, naturally occurring anti−Di^a has also been reported[10, 38−42]. We reviewed case reports from China and found that anti−Di^a reaction leads to rash, delayed haemolytic disease and natural occurring also being reported (***Table 3***). One example of anti−Di^a reaction was notable in that it resulted in a stillborn foetus. Anti−Di^b has also been found responsible for a delayed hemolytic transfusion reactions (HTR) and death[2, 43, 44]. In China, two case reports demonstrated that anti−Di^a induced serve anaemia and fever transfusion reaction (***Table 3***).

DOSAGE EFFECT

Few studies have observed the dosage effect of Diego blood group. In this study we used monoclonal anti−Di^a(IMMUCOR GAMMA, Texas, USA) and human−sourced anti−Di^b from two Di(a+b−) immunized patients to examine the agglutinin titres for the genotypes Di(a−b+), Di(a+b+), and Di(a+b−).

The titres of anti−Di^a were negative and anti−Di^b were 3+ and 2+ in five samples of the Di(a−b+) genotype, followed by anti−Di^a titres of 1+ and anti−Di^b titres of 2+ and 1+ in three samples of the Di(a+b+) genotype, while the anti−Di^a titres were 3+ and anti−Di^b were negative in three samples of the Di(a+b−) genotype(***Table 4***).

These results may reveal the dosage effect of Di^a and Di^b antigens. Di(a+b−) is a very rare blood type in China and this served as the main limitation in the examination of the agglutinin titres to Diego blood group antigens.

Table 2 **Frequencies of Di(a+b−), Di(a+b+), and Di(a−b+) determined from Di^a positivity rate in Asia and USA**

Ethnic groups	Area	Di(a−b+)/*n*(%)	Di(a+b+)/*n*(%)	Di(a+b−)/*n*(%)
Blood donor	East China (Hefei) [27]	254 (98.45)	4 (1.55)	0 (0.00)
Blood donor	Southeast China (Shenzhen) [28]	2821 (94.35)	167 (5.59)	2 (0.07)
Blood donor	Southeast China (Jiangxi) [29]	196 (98.00)	4 (2.00)	0 (0.00)
Blood donor	Southeast China (Guangzhou) [30]	184 (92.00)	16 (8.00)	0 (0.00)
Yi minority	Southwest China (Sichuan) [31]	116 (96.67)	4 (3.33)	0 (0.00)
Blood donor	North China (Liaoning) [32]	1529 (96.96)	47 (2.98)	1 (0.06)
Korean minority	North China (Jilin) [33]	888 (88.8)	112 (11.20)	0 (0.00)
Blood donor (Han)	North China (Xian) [34]	210 (95.45)	4 (4.09)	1 (0.45)
Blood donor (Han)	East China (Nanjing) [35]	1913 (94.94)	100 (4.96)	2 (0.10)
Blood donor	East China (Shanghai) [36]	366 (96.32)	14 (3.68)	0 (0.00)
Uygur minority	West China (Xinjiang) [37]	143 (90.51)	15 (9.49)	0 (0.00)

Table 3 **Alloantibodies against Di^a and Di^b antigens in Chinese**

Alloantibody	Area	Age(y)	Gender	Transfusion History	Pregnancy History	Clinical Outcome	Major Immuni−zation
Anti−Di^b	Liaoling[45]	54	F	Yes	Yes	Serve anaemia	Pregnancy
Anti−Di^b	Yunnan[46]	55	F	Yes	Yes	Transfusion reaction (fever)	Transfusion
Anti−Di^b	Beijing[47]	60	F	Yes	Yes	Pre−surgery routine test	Unclear
Anti−Di^b	Anhui[48]	25(mother)	F	unknown	Yes	Newborn haemolytic disease	Pregnancy
Anti−Di^a	Gansu[49]	unknown	F	No	Yes	Newborn haemolytic disease	Pregnancy
Anti−Di^a	Shangdong[50]	28(mother)	F	Yes	Yes	Newborn haemolytic disease	Pregnancy
Anti−Di^a	Hubei[51]	unknown	F	Unknown	Yes	Newborn haemolytic disease	Pregnancy
Anti−Di^a	Jiangsu[52]	33(mother)	F	No	Yes	Stillborn foetus	Pregnancy
Anti−Di^a, anti−E	Beijing[53]	65	M	Yes	–	Pre−surgery routine test	Transfusion
Anti−Di^a	Jiangsu[54]	25	F	No	Yes	Pre−caesarean test	Pregnancy
Anti−Di^a, anti−D	Beijing[55]	76	F	No	Yes	Pre−transfusion	Transfusion
Anti−Di^a	Shangdong[56]	28	M	Yes	–	Rash	Transfusion
Anti−Di^a, anti−E	Gansu[57]	67	M	Yes	–	Delayed transfusion reaction	Transfusion
Anti−Di^a	Hubei[58]	55	M	Yes	–	Pre−surgery routine test	Transfusion
Anti−Di^a, anti−E	Shanghai[59]	65	M	No	–	Routine transfusion test	Natural immune

Table 4 **The agglutinin titres of Di(a−b+), Di(a+b+) and Di(a+b−) by anti−Di^a and anti−Di^b**

Genotype	Monoclonal anti−Di^a	Human resourced anti−Di^b−1	Human resourced anti−Di^b−2
Di(a−b+)			
Sample1	neg	3+	2+
Sample2	neg	3+	2+
Sample3	neg	3+	2+
Sample4	neg	3+	2+
Sample5	neg	3+	2+
Di(a+b+)			
Sample1	1+	2+	1+
Sample2	1+	1+	1+
Sample3	1+	2+	1+
Di(a+b−)			
Sample1	3+	neg	neg
Sample2	3+	neg	neg
Sample3	3+	neg	neg

FUTURE PERSPECTIVES

Although the application of genotyping to the Diego blood group was a useful tool to investigate the frequency and estimate the agglutinin titres of anti−Di^a and anti−Di^b to Di^a and Di^b antigens, respectively, a discussion on the existence of the dosage effect in the Diego blood group is necessary. Our study offered evidence to confirm the dosage effects in the Diego blood group. Further studies, however, especially on Native Americans living in Brazil, are needed to in−vestigate the dosage effect.

Since the alloantibodies against Di^a and Di^b anti−gens are majorly stimulated by pregnancy and often cause HDN and the association between alloantibodies and HDN associated with HLA−DRB1 and DQB1 al−leles has also previously been reported. Anti−Di^a and anti−Di^b reactions causing adverse clinical outcomes may be observed at immunity−associated genes by methods, such as HLA or KIR typing[60−63].

CONCLUSIONS

The Di^a antigen is an important antigen in the Chinese population and the Di(a+b+) is the major genotype in Di^{a+} Chinese. Our study noted that Di^{a+} Chinese is more likely to show a lower agglutinin titre than Di^{a+} foreigners, such as Native Americans

from Brazil. Anti−Di^a and anti−Di^b were majorly responsible for HDN while a stillborn foetus resulted from an anti−Di^a reaction; transfusion reactions such as fever and rash were also reported in the Chinese population.

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