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The HLA Epitope Donor Database for Platelet Matching

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ABSTRACT: This study aims to create a platelet donor database with detailed HLA epitope typing in the Jining area and to serve as a solid foundation for treating refractory thrombocytopenia patients who require platelet transfusions. HLA-A, -B epitope phenotype data were collected from a total of 565 unrelated healthy populations in the Jining area. According to the data, a platelet donor database was created and established with known HLA epitope phenotypes. The database donors' HLA-A, -B epitopes were tested separately by sequence-specific primer (PCR-SSP). According to the distribution frequency of HLA-A, -B epitope phenotypes (n = 565), the following results were obtained: 73 HLA-A, -B phenotypes, including 55 with a frequency > 0.003. The sum of frequencies was 96.81%. With a database size of 565 donors, an approximate 84.20% patient HLA-A, -B cross-reactive group (CREG) match coverage was achieved. When it was necessary for identical ABO-type platelet transfusion, the corresponding database modifications were made according to the distribution frequency of the ABO blood group of the population.This study provides the concept for a platelet epitope matching database. It establishes a donor database of known platelet HLA epitopes in the Jining population, which lays a solid foundation for the safe treatment of platelet transfusion in this area.

Keywords: HLA-alloimmunization; Epitope; Polymorphism; Human leukocyte antigen (HLA); Platelet transfusion refractoriness (PTR); Platelet donor database

1. Introduction

Platelet transfusion is primarily used to prevent or treat bleeding due to platelet factors in patients with thrombocytopenia or dysfunction [1,2]. However, there is a possibility that some patients will show signs of platelet transfusion refractoriness (PTR) or failure [3]. The key to successful platelet transfusion lies in preventing and managing PTR.

Numerous clinical investigations have shown that transfusion of HLA antigen-matched platelets can reduce the formation of HLA antibodies, hence minimising unsuccessful transfusions. However, due to the high polymorphism of HLA antigens, it is generally necessary to find matching donors in thousands to tens of thousands of cases. This method is time-consuming and expensive and does not necessarily find a matching donor [4–8]. Therefore, finding an alternative to HLA antigen matching has become a research focus in recent years.

Matching at the epitope level, based on the characterization of short sequences of amino acids from linear or discontinuous regions of HLA molecules, may be more relevant for assessing HLA compatibility between patients and donors and the effect of donor-specific HLA antibodies. Additional advantages to this epitope matching approach may extend to more efficient matching for highly sensitized patients and avoiding certain challenges associated with standard matching, such as the need to maintain a large panel of HLA-typed apheresis donors [7,9–13]. In 2020, Karren et al. analyzed 37 cases of HLA antigen-matched platelet transfusion after 24 h in aplastic anemia, finding that the platelet count increments (PCI) with HLA epitope-matched transfusion were equivalent to those with HLA antigen-matched

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transfusion. This indicates that HLA epitope-matched platelets could be used as an alternative method for HLA antigen matching [14]. In a prospective, randomized, non-inferiority trial, Marsh et al. found that HLA epitope-matched platelets were not inferior to HLA antigen-matched platelets, providing direct evidence that HLA epitope matching could be a substitute for HLA antigen matching [15]. The principle of HLA epitope matching can also be applied to select HLA-matched donors for organ transplantation [16,17]. There are few reports about the platelet HLA epitope donor database in China.

In this study, we used HLA epitope typing technology to directly detect 7 cross-reactive group (CREG) public epitopes on the HLA-A and HLA-B loci of donors through 13 PCR reactions and constructed a CREG public epitope donor database consisting of 565 individuals. This database aims to provide data support for research on the HLA epitope-matched platelet transfusion strategy and to explore a more convenient approach for identifying suitable HLA-matched platelet donors.

2. Materials and Methods

2.1. Subjects

Five hundred and sixty-five (565) platelet donors were randomly selected in Jining from January 2021 to October 2023 and confirmed by ID card and inquiry. Five (5) mL venous blood were collected from each person using Ethylene Diamine Tetraacetic Acid (EDTA) and stored at 4 ℃ for testing. All blood samples were tested within two weeks of collection. All blood samples were tested within two weeks after sampling. All donors met the following criteria: 18 years ≤ age ≤ 45 years, blood donating ≥ 1 time per year, and platelets donating ≥ 2 times yearly.

Forty-four (44) PTR patients who underwent platelet transfusions at the Jining First People's Hospital and the Affiliated Hospital of Jining Medical University were recruited from June 2022 to November 2023. Five (5) mL of venous blood by adding EDTA and 5 mL of self-coagulated venous blood were collected per person for HLA epitope testing and platelet cross-matching.

This study was approved by the medical ethics committee of Jining Blood Center.

2.2. HLA CREG Public Epitope Detection

All donors and patients were tested using the "Platelet HLA and HPA Gene Matching Kits" from Jiangsu Zojiwat Biopharmaceutical Co., Ltd., Wuxi, China (Batch No. 2203001). Thirteen PCRs were performed on each sample, reacting with a separate PCR amplification primer mix (Mix EP1-EP13). The experiments were conducted strictly in accordance with the instructions provided by the reagent manufacturer. The PCR primer mix, DNA samples, and Taq polymerase were sequentially added to the wells of the PCR plate and placed into the PCR amplification instrument for reaction. The PCR amplification products were subjected to gel electrophoresis. The electrophoretogram was recorded using the gel imaging system and then analyzed to determine the HLA epitope. The method was subjected to a Laboratory Developed Test (LDT).

2.3. Information of the Platelet Donor Database

Blood donor information, such as blood donation code, name, gender, nationality, ID number, date of birth, address, telephone number, ABO blood type, HLA-A, -B epitopes, was entered into the apheresis platelet donor data query system.

2.4. Validation of the HLA Epitope Donor Database

HLA epitope matching for medical evidence-based data study on platelet transfusion is still in its early stages, hence no platelet HLA matching categorization criteria has been established. Only the selections of A and B loci epitopes that are completely identical, A locus epitopes that are identical with homozygous B locus epitopes, or B locus epitopes that are identical with homozygous A locus epitopes, were prioritized. When patient X has a positive epitope, a donor with a positive or negative epitope can be selected. When patient X has a negative epitope, only a negative donor can be selected, regardless of half-matching or partial-matching.

2.5. Application of Platelet Donor Database

For patients with ineffective platelet transfusion, according to the HLA epitope typing of the patient, searching for a platelet donor with a complete epitope match or an epitope-negative donor in the HLA epitope donor database was

conducted. Platelet cross-matching tests were performed by solid phase agglutination method using the platelet antibody detection kit (Sanquin Reagents B.V, Holland, Lot No. 8000456807 and 8000458834). Then, platelets with negative results were selected for transfusion to the patient.

2.6. The Probability of Having at Least One HLA-Epitope-Matched Donor in the Platelet Donor Database

In a platelet donor database composed of n donors, if the frequency of a specific phenotype is F, the probability of finding at least one donor who is fully compatible with the phenotype is P, then $P = 1 - (1 - F)^n$ [18]. Using Fi as the frequency of the phenotype, the probability that a patient can find ≥1 phenotype perfectly matched donor is $P = \sum Fi \times [1 - (1 - Fi)^n]$ (i represents all possible phenotypes) [19]. If ABO isotype platelet transfusion is considered, the probability of finding at least one HLA fully matched and ABO isotype donor is calculated according to the ABO blood group distribution frequency of the population. The bank capacity can be expanded according to the distribution of A, B, O and AB types.

2.7. Statistical Analysis

The data tables were established using Excel, and all data were analyzed using the online analysis platform SPSSAU. HLA-A, -B epitope frequencies were estimated using the maximum mathematical expected value algorithm (Expectation-Maximization, EM) [20].

3. Results

3.1. Distribution Frequency of HLA-A, -B Epitopes in the Jining Population

In this study, 565 samples were detected. Among the 7 epitopes at HLA-A, -B sites, A2C frequency was the highest (0.78418), followed by B5C (0.71664), while B8C frequency was the lowest (0.16639) (Table 1).

Table 1. Frequencies of HLA-A, -B epitopes in the Jining population.

HLA Epitopes	Frequencies (*n* = 565)
A1C	0.66886
A2C	0.78418
A10C	0.25041
B5C	0.71664
B7C	0.39703
B8C	0.16639
B12C	0.60956

3.2. Phenotypic Distribution Frequencies of HLA-A, -B Locus Epitopes

A total of 73 phenotypes were detected in 565 blood donors in this study, with 55 phenotypes having a frequency greater than 0.003. The sum of their frequencies was 96.81% (Table 2).

Table 2. HLA-A, -B epitope phenotypes and their frequencies > 0.003 in the platelet donor database (*n* = 565).

HLA-A, -B Epitope Phenotypes	Frequencies	HLA-A, -B Epitope Phenotypes	Frequencies
A1CA2CB5CB12C	0.116814159	A2CA10CB12C	0.012389381
A1CA2CB5C	0.053097345	A1CA10CB5CB7CB12C	0.010619469
A1CA2CB5CB7C	0.049557522	A1CA2CA10CB5C	0.010619469
A1CA2CB7CB12C	0.040707965	A1CA2CB5CB7CB8C	0.010619469
A1CB5CB12C	0.040707965	A1CB12C	0.010619469
A1CA2CB5CB7CB12C	0.038938053	A2CA10CB5CB8C	0.010619469
A2CB5C	0.038938053	A2CB12C	0.010619469
A2CB5CB12C	0.033628319	A1CA2CA10CB5CB7C	0.008849558
A2CA10CB5CB12C	0.030088496	A1CA10CB8CB12C	0.007079646
A1CA2CB12C	0.028318584	A1CA2CB5CB8CB12C	0.007079646
A1CA2CA10CB5CB12C	0.02300885	A2CA10CB5CB7CB12C	0.007079646
A1CB5CB7C	0.02300885	A2CB8CB12C	0.007079646
A2CB5CB7C	0.02300885	A1CA10CB7CB12C	0.005309735
A2CA10CB5C	0.021238938	A1CA2CA10CB12C	0.005309735
A2CB5CB8C	0.021238938	A1CA2CB5CB7CB8CB12C	0.005309735
A1CA2CB8CB12C	0.019469027	A1CB5CB7CB8C	0.005309735
A1CB7CB12C	0.019469027	A1CB8CB12C	0.005309735
A2CB7CB12C	0.019469027	A2CB5CB7CB8CB12C	0.005309735
A1CA2CB7C	0.017699115	A2CB5CB8CB12C	0.005309735
A1CB5CB7CB12C	0.015929204	A2CB7C	0.005309735
A2CA10CB5CB7C	0.015929204	A10CB5CB12C	0.003539823
A2CA10CB7CB12C	0.015929204	A10CB5CB8C	0.003539823
A2CB5CB7CB12C	0.015929204	A1CA10CB5C	0.003539823
A1CA10CB12C	0.014159292	A1CA10CB5CB7C	0.003539823
A1CB5C	0.014159292	A1CA2CB7CB8CB12C	0.003539823
A1CA10CB5CB12C	0.012389381	A1CB5CB8C	0.003539823
A1CA2CB5CB8C	0.012389381	A1CB7C	0.003539823
A1CA2CB7CB8C	0.012389381	Cumulative frequency	0.96810

96.81% of the total population.

3.3. The Probability of Finding ≥1 HLA-A,-B Epitope Matching the Donor

According to the phenotype distribution frequencies of HLA-A, -B epitopes in the Jining population, the probability (P) of finding at least one HLA-A, -B epitope matching donor in a certain number of donors (N) was calculated. P values were correlated with the number of platelet donors (N) as well as the frequency of the HL A epitope phenotype, with a logarithmic curve between P and N (Figure 1). Four regression equations were derived for HLA epitope phenotype frequency (Fi) as a function of N ($10 \leq N \leq 2000$), which were 0.001, 0.003, 0.006 and 0.007, respectively.

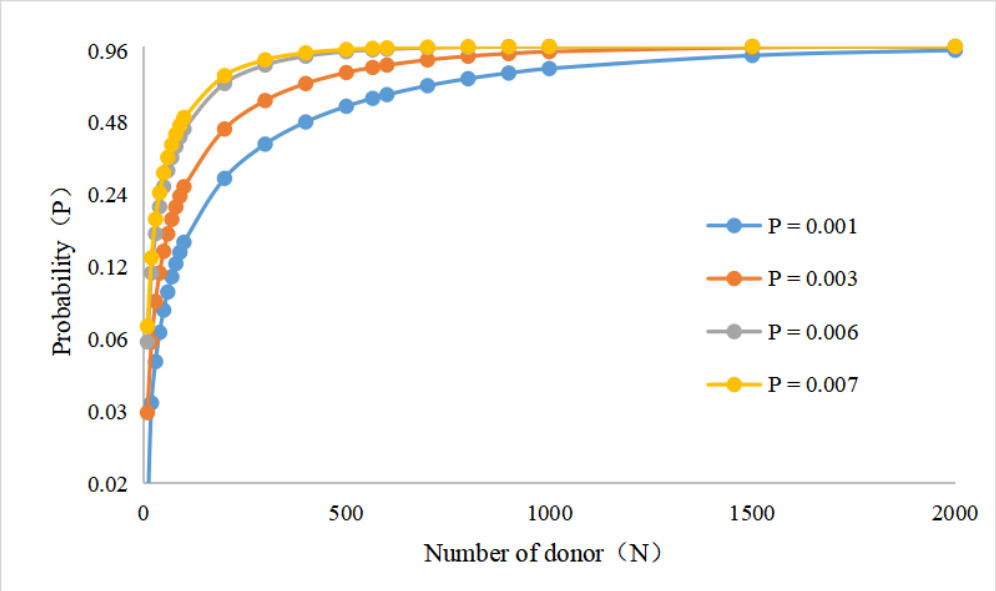

Figure 1. The probability curve of finding one HLA-A, -B fully compatible donor varied with the number of donors.

$$P = 0.2071\ln(N) - 0.6967,\ R2 = 0.9281 \quad (1)$$

$$P = 0.2355\ln(N) - 0.7263,\ R2 = 0.9549 \quad (2)$$

$$P = 0.2309\ln(N) - 0.5799,\ R2 = 0.9537 \quad (3)$$

$$P = 0.2245\ln(N) - 0.5213,\ R2 = 0.9491 \quad (4)$$

The correlation coefficients of curves (1) and (4) were < 95%, suggesting that epitopes with a phenotypic frequency of ≤ 0.001 needed larger sample data, while epitopes with a phenotypic frequency of ≥ 0.007 only required 200–300 sample data to meet the requirement. The correlation coefficients of curves (2) and (3) were > 95%, suggesting that these equations can be used to obtain reliable results for the phenotypic frequencies between 0.003 and 0.006. Assuming that the phenotypic frequency of a patient is 0.00326, which is close to 0.003, the regression equation (2) can be selected. When the number of platelet donors in the platelet bank is 300, the chance of finding a matching donor is P = 0.2355ln(300) − 0.7263 = 62.45%, and the matching probability can reach 84.20% when the number of donors is 565. The results showed that a probability of 84.20% could be obtained with the 565 individuals included in the HLA epitope donor database, and 96.81% of the people in the Jining area could find at least one HLA-matched donor. With a database size of 565 donors, the probability of identifying a match with ABO blood type and HLA-A, -B CREG match coverage was as follows: A 40.25%, B 44.49%, O 43.81%, AB 15.77%.

3.4. Probability of Finding ≥ 1 HLA-A, -B Epitope Matched and ABO Identical Donor

According to the distribution frequencies of HLA epitopes at HLA-A, B loci and ABO blood types in the Jining population, the probability (P) of finding at least 1 donor with complete matching of HLA-A, -B epitope and the same type of A, B, O, and AB with donors (N) is shown in Figure 2.

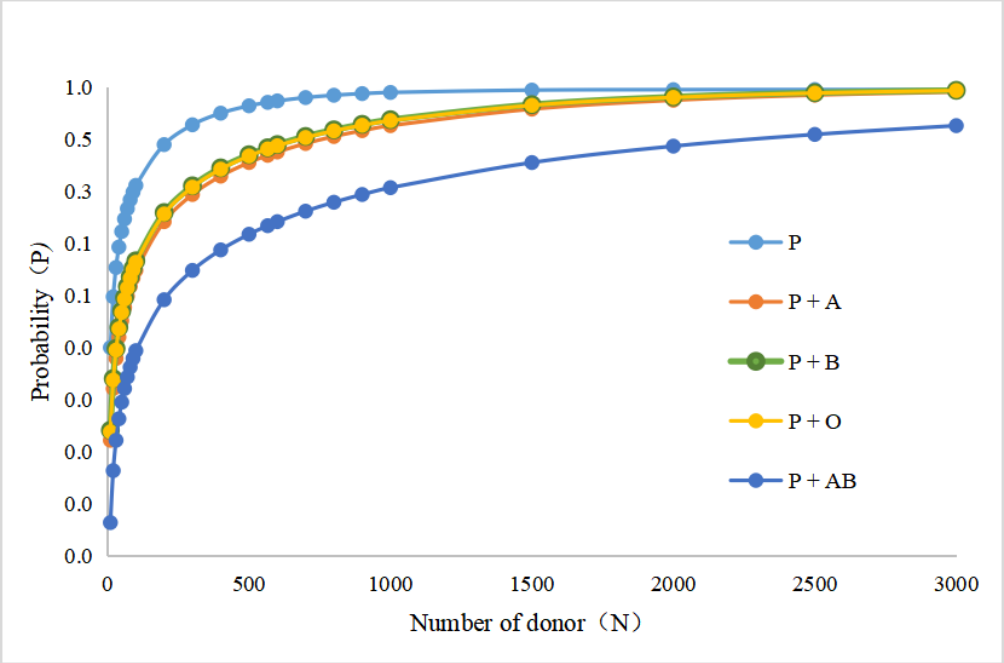

Figure 2. The probability change curve of one HLA epitope full match and one ABO isotype donor.

3.5. Validation of Platelet HLA Epitope Donor Database

Among 44 patients, 39 patients found at least one donor with complete matching of ABO blood type and HLA epitope in 565 donors, with a probability of 39/44 = 88.64%. According to patient epitope typing, only the HLA epitope perfectly matched or compatible donors were selected, and the donors for each patient were grouped. The HLA matching results of four patients are shown in Table 3.

Table 3. Examples of HLA epitope matching in four patients.

HLA Epitope Typing of Patients	ABO Blood Groups	HLA Epitope Typing of Donors	Number of Donors	Compatibility Type	N
A1CA2CB7CB12C	O	A1CA2CB7CB12C	5	CC	24
		A1CB7CB12C/A2CB7CB12C	3/2		
		A1CA2CB12C/A1CA2CB7C	4/2		
		A1CB12C/CA2CB7C/A2CB12C	2/2/4		
A2CA10CB12C	B	A2CA10CB12C	3	CC	4
		A10CB12C	1		
A2CB12C	A	A2CB12C	2	CC	2
A1CA2CB7C	AB	A1CA2CB7C	1	CC	3
		A1CB7C/A2CB7C	1/1		

CC: completely compatible.

3.6. Establishment of Platelet HLA Epitope Donor Database in the Jining Area

The platelet HLA epitope donor database included HLA epitope typing data from 565 platelet donors. The database contained seven HLA-A, -B epitopes, covering all HLA-A, -B antigens. The distribution of ABO blood groups in the platelet donor database was 27.78% (157/565) for type A, 31.86% (180/565) for type B, 30.44% (172/565) for type O, and 9.91% (56/565) for type AB, which was basically consistent with the distribution probability of ABO blood groups in Jining city.

4. Discussion

Platelet transfusion refractoriness is mainly seen in patients with blood diseases or malignant tumors following repeated blood transfusions, at an incidence of 25–70% [21]. Among the causes of PTR, immune factors account for

about 20%, while anti-HLA and anti-HPA are important antibodies leading to immune PTR [22,23]. To ensure successful transfusion therapy for patients with thrombocytopenia due to alloimmunization, comparable antigen-negative matching platelets must be found. Establishing a platelet donor database with known antigens could quickly find antigen-matching platelet donors for all kinds of immune thrombocytopenia patients. However, due to the high polymorphism of HLA antigens, it is often necessary to search through thousands to tens of thousands of cases to find a matched donor. Therefore, the search for alternative methods to HLA antigen matching has gained significant interest among researchers in recent years. Kallon et al. proposed that HLA epitope-matched platelets could be an alternative to HLA antigen matching [14]. A study by Marsh et al. in 2021 provided direct evidence that HLA epitope matching could replace HLA antigen matching [15]. However, the concept and principle of HLA epitope matching were used earlier to select HLA-matched donors for organ transplantation [16,17].

In this study, HLA epitope typing was conducted on 565 blood donors in Jining, resulting in the identification of 73 HLA epitope phenotypes. Among these, 55 phenotypes had frequencies greater than 0.003, representing 96.81% of the total population. Among the 7 epitopes at HLA-A, -B sites, A2C frequency was the highest (0.78418), followed by B5C (0.71664), while B8C frequency was the lowest (0.16639), which was consistent with the HLA-A and -B antigen frequencies in the Chinese population [19,24]. According to the HLA-A, -B epitope phenotype frequency of the population of Jining area, when the platelet donor database had 300 people, the probability of finding at least one HLA-A, -B epitope fully matched donor was 62.45%. When the platelet donor pool had 565 people, the matching probability would reach 84.20%. To conclude, with an HLA epitope donor database of 565 people, there was 84.20% confidence in finding at least one CC donor for 96.81% of people in Jining City.

By analyzing the characteristics of HLA epitope polymorphism in the Jining population and taking into account a specific proportion of clinical patients, a minimum database capacity of 565 HLA epitope platelet donors was established. The validity of HLA epitope data from the platelet donor database was tested in 44 PTR patients, and 39 of 44 patients found at least one ABO and HLA epitope matched donor from 565 donors with a probability of 39/44 = 88.64%. For patients with ineffective platelet transfusion, more than 30 HLA epitope-matched platelets were provided, all verified negative by platelet crossmatch testing. After the transfusion, all patients' platelet counts reached the expected target, and the clinical symptoms were relieved (data to be published). This demonstrated that the platelet donor database generally met the treatment needs of HLA-A and HLA-B alloimmune patients in this region. However, the frequencies of HLA epitopes and the establishment of an appropriate matching level still need to be estimated with larger sample sizes.

This study explored a more convenient approach for identifying suitable HLA-matched platelet donors, which is still an emerging technique. The following problems were encountered. Firstly, the accuracy and stability of the experiments remain to be improved, and some HLA epitopes have not been detected yet, which leads to the elimination of some samples. Secondly, the concept of HLA epitope phenotypes and their classification need further discussion. Thirdly, there are certain deviations in data statistics and analysis methods. Finally, the sample size here was small, and some theoretical phenotypes were not detected, so all HLA phenotypes were not fully covered. Based on these results, we will continue to conduct in-depth research to improve the platelet HLA epitope donor database gradually, provide more empirical medical data for HLA epitope-matched platelet transfusion, and achieve increasingly efficient and scientific matching donor approaches for patients with platelet transfusion refractoriness.

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Author Contributions

Conceptualization, W.G., F.K., and H.G.; Methodology, W.G. and H.C.; Software, W.G.and F.K.;Validation, D.H. and Y.Z.; Formal Analysis, W.G. and H.G.; Investigation, W.G., J.W., and H.G; Resources, N.Z. and H.C.; Data Curation, W.G., H.G., and J.W.; Writing—Original Draft Preparation, W.G.; Writing—Review & Editing, W.G. and F.K.; Visualization, W.G. and H.G.; Supervision, W.G.; Funding Acquisition, W.G.

Ethics Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Medical Ethics Committee of the Jining Blood Center on 15 January 2021.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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