Human Immunology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Human Immunology

journal homepage: www.elsevier.com/locate/humimm

Short population report

Estimation of optimal donor number in Bone Marrow Donor Registry: Hong Kong's experience

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ARTICLE INFO

Keywords:
Alleles
Frequency haplotypes
HLA antigens
Hong Kong
Chinese
Matching probability

ABSTRACT

Better outcome for hematopoietic stem cell transplantation (HSCT) requires optimal matching between donor and recipient at the HLA-A, -B, -C, and -DRB1 loci. This study estimates the likelihood of identifying HLA matched donors in Hong Kong.

7595 volunteer unrelated Chinese donors at the Hong Kong Bone Marrow Donor Registry were typed with HLA-A, -B, -C and -DRB1 genotypes. The matching probabilities for 8/8 and 7/8 HLA match via the matching models were determined.

Based on current 100,000 donors in the HKBMDR, the matching probabilities are 45% at 8/8 HLA match and 65% at 7/8 match. By increasing the registry to 200,000, the likelihoods of match become 54% and 73% at 8/8 and 7/8 match stringencies respectively.

Our findings may be helpful in planning future donor recruitment and HLA typing. A cost-effective Bone Marrow Donor Registry with a larger pool of donors could increase chance of matching and the success of HSCT.

1. Introduction

Hong Kong Bone Marrow Donor Registry (HKBMDR) manages volunteer unrelated donor database to facilitate the unrelated hematopoietic stem cell transplantation as the curative treatment for patients with haematological malignancies or many other disorders in Hong Kong. Better outcome in haematopoietic stem cells transplantation (HSCT) requires optimal matching between donor and recipient at the HLA-A, HLA-B, HLA-C, and HLA-DRB1 loci (i.e. an 8/8 high resolution HLA match). Since the level of polymorphism of HLA genes is extremely high, and allelic variation is population-specific, optimally HLA-matched unrelated donors and cord-blood units are not always available for patients, even within large registries [1,2]. Therefore, mismatch may be considered acceptable in many clinical situations when non-transplantation therapy offers little chance of cure. However, mismatching at only one of these loci (7/8 HLA match) was found to have an 8% reduction in the 5-year overall survival rate [3].

At present, there are close to 29 million potential stem cell donors in the Bone Marrow Donors Worldwide registry [4]. Though the number of donors continues to grow worldwide, there are significant resource implications in donor recruitment and HLA typing. Therefore, the challenge of thoughtful donor recruitment strategy becomes increasingly relevant. These include recruitment efforts focused on young male donors [5] or on relatives of registered donors with rare human leukocyte antigen (HLA) phenotypes [6], minority donor recruitment programs [7–10], and regional priority setting of recruitment activities based on HLA frequency differences [11–14].

The decisive question of "What is the likelihood of finding a suitable matched adult donor in their registry?" definitely warrants registries strategy planning. Recently, Schmidt et al. [15] reported that population-specific matching probabilities (MP) are a key parameter to assess the benefits of unrelated stem cell donor registries and the need for further donor recruitment efforts. The authors described a general framework for MP estimations of specific and mixed patient populations under consideration of international stem cell donor exchange. Calculations were based on HLA-A, -B, -C, -DRB1 loci high-resolution haplotype frequencies (HF) of up to 21 populations. Based on the existing donor numbers, the largest MP increases in addition of 500,000

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http://dx.doi.org/10.1016/j.humimm.2017.08.007
Received 24 December 2016; Received in revised form 18 July 2017; Accepted 29 August 2017

same-population donors were observed for patients from Greece (+0.21) while only small MP increases occurred for European Americans (+0.004) and Germans (+0.01). Due to the large Chinese population, the optimal distribution of 5,000,000 new donors worldwide included 3.9 million Chinese donors [15]. Nevertheless, the authors observed the need for same-population donor recruitment in order to increase population-specific MP efficiently. National strategies that neglect domestic donor recruitment should therefore be critically reassessed, especially if only few donors have been recruited so far.

HF is calculated from DNA-typed registry donors with Markov Chain Monte Carlo (MCMC) algorithm *PHASE* [16]. Four-locus high-resolution HF (HLA-A, HLA-B, HLA-C, and HLA-DRB1) were used for adult donors. The HF and effective adult-donor registry size for each group were then put into a matching model that assumes genotypes are in HWE [17,18]. The strategy involved modeling the likelihood that an 8/8 or 7/8 HLA-matched adult donor exists in the registry. For better analysis, information of adult-donor availability including donor refusal, discrepant donor typing and loss of contact would be desirable.

According to the calculations, the study by NMDP found that the likelihood of finding an available 8/8 HLA matched donor is 75% for white patients of European descent but only 46% for White patients of Middle Eastern or North African descent [19]. Similarly, the chance of finding an 8/8 HLA-matched donor for other groups is lower and varies with racial and ethnic background. For Black Americans of all ethnic backgrounds, the probabilities are 16 to 19%; for Asians, Pacific Islanders, and Native Americans, they range between 27% and 52%.

It was reported that adult-donor availability and match probabilities may differ according to racial and ethnic background [19]. However, relevant data is lacking in Hong Kong. In this study, we designed to estimate the donor pool and matching probability based on our previous published gene and haplotype frequencies in Hong Kong population [20].

2. Materials and methods

2.1. Sample collection and genotyping

The allele and haplotype frequencies as reported previously were used in the analysis [20]. In brief, the group name was designated based on the lowest allele number or the most frequently seen allele in the population. SSP or SBT was also used to resolve some assignments with several alternative allele combinations and some specific alleles.

2.2. Statistics analysis

The frequencies of HLA-A, -B, -C and -DRB1 alleles were calculated from the number of observed genotype. Hardy-Weinberg equilibrium for each loci was assessed by PyPop using MCMC simulation from Guo and Thompson [21], and genotype frequency deviance within each loci was detected by PyPop invoking Arlequin [22]. P value of <0.01 was considered as statistical significant.

By using the formulae described by Schmidt et al. [15] with modification, the probability $p(n)$ for a random patient from a given population to find at least one matching donor in a registry including n individuals of a donor population is given with $p(n) = \Sigma_i f_i[1-(1-f_i)^n]$ is the matching probability in "n" sample size, fi being the frequencies of the i-th genotype and i-th is any genotype from the rank of genotypes in the order of the highest to the lowest frequencies in a donor population. Genotype frequencies can be derived from the estimated HF under the assumption of Hardy-Weinberg equilibrium (HWE).

3. Results and discussion

The HLA genotypes and haplotypes frequency mentioned in the following section have been recently published [20]. Summary statistics for Hong Kong haplotypes is shown in Table 1. We compared the top 100 haplotypes of HKBMDR & HKCBB by haplotype frequencies with the two publications [23,24]; we noted that 88 are in common, the rank correlation is 0.909 for HLA-A-B-DRB1 haplotype. There appears to be no excessive immigration from other places to Hong Kong. We also compared the China population paper which had provided the detailed top haplotypes for 4 loci, we found that 43 are common in HLA-A-C-B-DRB1 haplotype and the correlation is low with only 0.477 [25].

Table 1
Summary statistics for Hong Kong Haplotypes.

HLA loci available		A-C-B-DRB1
Sample size (N)		7595
Sample size (2N)		15,190
Number of haplotypes (>0.006%)		2146
Sum (%) of haplotype frequencies within the top	10	19.6
	25	27.6
	50	35.5
	100	45.1
	250	59.3
	500	71.4
	1000	83.8
Number of haplotypes with frequency	≥0.01	9
	≥0.005	21
	≥0.001	157
	≥0.0005	345
	≥0.0001	1532

With the use of MCMC algorithm to estimate HLA haplotype frequencies [14], it was found that the number of haplotypes increases with number of donor samples studies as summarized in Table 2. Originally we tested the HLA haplotype frequencies in 2500 samples and noted a bigger number of haplotypes as compared with other papers. Then we increased the sample size to 5000 and 7500 and noted that the increase was quite significant in our population with many more haplotypes. This pattern was unique in the Hong Kong population and different from that in other ethnic groups, e.g. Caucasians and European populations whereby a plateau of number of haplotypes was seen with increase in sample size [23]. It was reported by Mori et al. in 1997 of occurrence of common haplotypes (0.01%) in Caucasian Americans was 184 as compared with 210 of Asian Americans in the NMDP database suggesting that the former had smaller degree of genetic diversity than the later [26]. In 2013, a large sample database was reported by Gragert et al., the occurrence of common haplotyptes was 325 for Caucasians and 503 for API [23].

As of December 2015, there were only around 100,000 donors in the HKBMDR. Applying the similar methodology in calculating the likelihood of finding a "matched" donor in US [19], likelihood of finding an 8/8 HLA match or >7/8 HLA Match by different donor registry size in the HKBMDR was shown in Fig. 1. The likelihood of finding an available 8/8 HLA matched donor is 45% while increases to 65% for finding 7/8 HLA matched donor. It is similar to the finding of other studies conducted among Asians, Pacific Islanders, and Native Americans which reported a likelihood ranging between 27% and 52% [19].

The chance of successful engraftment and disease free survival are associated with the HLA compatibility between the recipient and the prospective donor. The diversity of the HLA genes at the allelic level and the heterogeneity of HLA data of the registered donors have a significant bearing on the probability of finding a volunteer unrelated HSC donor for patients from a particular population. This can be seen in

Table 2
Estimated number of haplotypes increases (frequencies > 0.006%) with donor sample size.

Donor Sample Size	2500	5000	7500
Number of Haplotypes	1673	1955	2135