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A comprehensive human leukocyte antigen analysis of 36 782 cord blood units stored in the Australian Public Cord Blood Banking Network

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ABSTRACT

Background and aims: The network of public cord blood banks (CBBs) in Australia, known as AusCord, comprises CBBs located in Brisbane, Sydney and Melbourne. A novel comprehensive analysis has been performed to determine whether the cryopreserved, searchable cord blood unit (CBU) inventory of approximately 36 000 units share similar tissue types or haplotypes.
Methods: Human leukocyte antigen (HLA) data was analysed using Microsoft Excel following standardisation of typing data.
Results: The analysis has found that the majority of stored, searched and released CBU exhibit a tissue type that is unique within and between the CBBs. Therefore, each collection performed by the CBBs is likely to comprise a tissue type that is not already stored among the total AusCord inventory. HLA alleles (HLA-A*34, HLA-B*56, HLA-DRB1*08:03), which are uncommon in European populations, were associated with Pacific Islander and/or Indigenous Australian populations and confirmed to be more frequent among donors who, when screened, self-identified as these ethnicities.
Conclusions: These data indicate that (i) continued addition of CBU to existing inventories is likely to further increase the HLA diversity and (ii) screening donors for ethnicity or strategically locating collection sites where ethnic minorities reside can successfully result in collection of rare HLA associated with ethnic minority groups for whom finding donors might otherwise be more difficult.

Introduction

Cord blood (CB) is an off-the-shelf, readily available source of hematopoietic progenitor cells (HPCs) that is used to treat many diseases, including hematologic malignancies, metabolic diseases, and bone marrow failure syndromes. CB is more permissive of human leukocyte antigen (HLA) mismatches compared with adult donor sources, presumably due to the naivety of T cells, as evidenced by reports of reduced rates of graft-versus-host disease [1]. However, adult sources of HPC allografts tend to be preferred by transplant centers (TCs) due to superior total nucleated cell counts, CD34+ cell counts, faster time to neutrophil and platelet engraftment or an unfamiliarity with selection and use of CB.

The Australian network of public cord blood banks (CBBs), known as AusCord, have released 1233 cord blood units (CBUs) (as of December 2017) from its cryopreserved inventory of more than 36 000 stored between the Sydney Cord Blood Bank (SCBB) in Sydney, New South Wales, the BMDI Cord Blood Bank in Melbourne, Victoria, and the Queensland Cord Blood Bank at the Mater (QCBB) in Brisbane, Queensland. The AusCord inventory accounts for approximately 4.5% (36 000/794 124 as of June 21, 2020) of the global CBU inventory listed on the World Marrow Donor Association Search and Match database. A statistical analysis of the HLA diversity within the Australian inventory of publicly available CBUs has not previously been performed. CB donations are known to extend the access to HPC transplant (HPCT) for non-European patients, ethnic minorities, and rare HLA types that arise from ethnic mixing [2,3]. This is especially

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relevant to the multicultural Australian population, where overseas born citizens account for 29.1% of the population [4]. Furthermore, patients of Aboriginal and Torres Strait Islander descent are more reliant on the Australian CBU inventory and adult donor programs due to their unique HLA.

The HLA complex is highly polymorphic and plays a fundamental role in the mediation of the human immune system. The tissue typing of patients and donors is typically restricted to six pairs of loci for major histocompatibility complex class I HLA-A, HLA-B, HLA-C, and major histocompatibility complex class II HLA-DRB1, HLA-DP1, and HLA-DQ1 genes. Matching patient and donor at varying levels across these loci has shown to be a key determinant in graft-versus-tumor effect and graft-versus-host disease, and in the case of postconditioning recipient immunity, graft rejection [5–7].

The number of HLA genes being considered in graft selection algorithms is increasing. This is driven primarily by advances in genetic sequencing capability and demonstrated improved clinical outcomes associated with an expanded HLA-matching approach [8]. However, HLA-A, B and DRB1 were traditionally considered the minimum assessment criteria. The historical limitations in testing methodology and resultant legacy of this approach have resulted in a significant proportions of the global inventory having HLA tissue typing limited to these baseline alleles. This limits the scope of analysis of cryopreserved CB inventories.

AusCord aim to collect, store and release CBUs with HLA types that represent the diverse and ever-changing HLA demographic of the Australia population. Achieving this aim will increase access to HPCT options for Australian patients and reduce the transplant costs associated with acquisition of HPCT options from overseas CBBs. This study aimed to analyze the HLA types of all CBU in the three AusCord CBBs to determine the interbank and intrabank commonality of HLA alleles and tissue types of searchable (i.e., listed on donor registries) and searched inventory, as well as CBU released for transplantation. Given the regional significance of the HLA of donors who self-identified as Indigenous Australian, Polynesian, or Maori, these have been analyzed as ethnic minority subsets. Further, the analysis was performed to better understand the AusCord inventory, guide decisions regarding continuance of the CB collection program, and formulate strategies to meet underrepresented ethnic groups.

Methods

Datasets

This retrospective analysis compared the frequency of specific HLA allele subtypes, HLA tissue types and HLA haplotypes of CBU cryopreserved at the three AusCord CBBs. CBUs were collected from consenting donors at collection sites managed by the QCBB, SCBB and BMDI CBB programs. A total of 36 782 CBU banked between 1996 and 2019 were included across the various analyses. The sample size for individual subset analysis was dependent on the subject/focus (e.g., searchable versus shipped inventory), HLA loci included in the analysis (HLA-C was found to be less commonly typed compared with HLA-A, B, DRB1) and data available from the CBB (see results for dataset sizes).

The total dataset includes all searchable CBU (n = 36 782; during the 1996-2019 calendar years) and all released CBU (n = 1233; 1996-2017) with the haplotype analyses excluding CBU where maternal haplotype could not be confirmed.

The term Pacific Islander has been used to describe a cohort that included Polynesian and Maori donors. Self-identification of other Pacific Islanders (e.g., Melanesian, Micronesian) was omitted due to the small sample sizes that did not permit statistically relevant comparison of cohorts.

HLA analysis

The analysis included HLA-A, HLA-B, HLA-DRB1, and where available, HLA-C. To obtain HLA-C typing, CBU must have had molecular typing performed. Therefore, the number of CBU with HLA-C data available represent the number of CBUs with molecular tissue typing. All CBUs currently banked at the CBB undergo next-generation sequencing to obtain molecular HLA typing, including HLA-C. Low-resolution results (serologic typing) were used for the analysis. Where high-resolution results were available, only the low-resolution equivalent typing was used (i.e., two-digit typing) to standardize the dataset. The number of alleles and extent of typing was dependent on the CBB and when the testing was performed. All typing was performed in contracted, Therapeutic Goods Administration–licensed and appropriately accredited (e.g., American Society for Histocompatibility and Immunogenetics) tissue typing laboratories. HLA data were provided directly by the CBB or the Australian Bone Marrow Donor Registry, who receive the data directly from the tissue typing laboratories.

To perform comparison of HLA within and between each bank, the data were converted to a single string. For example, *HLA-A*01,02, HLA-B*07,44, HLA-DRB1*04,15* was converted to *12744415*. If a string was found more than once in a bank, it was only included once in the analysis. All HLA types were listed with the smaller number first to ensure accuracy of results. Independent comparisons were performed with and without HLA-C data. Standard Microsoft Excel formulas (e.g., “match,” “vlookup,” “IF,” “>”) were used to organize, validate and analyze comparable datasets. This novel method of analyzing HLA was performed as a nonbias analytical approach that can be readily adopted by other centers.

To perform haplotype analysis, only CBUs with maternal typing results were included. Maternal typing was used to confirm haplotypes. Maternal typing is mainly performed before the shipment of a CBU to a TC, but may have been available for CBU listed on donor registries. CBUs were excluded where haplotypes could not be confirmed (e.g., where both loci at an HLA gene matched between mother and CBU).

Comparisons between tissue types and haplotypes are presented in Venn diagrams. Datasets in Venn diagrams do not include replicate tissue types (e.g., *HLA-A*01,01, HLA-B*08,08, HLA-DRB1*03,03* is represented once in each Venn diagram). HLA-C was not included in the haplotype analysis. The publicly available National Marrow Donor Program (NMDP) HaploStats website was used to check frequencies of the most common AusCord haplotypes within the global inventories (www.haplostats.org). HaploStats automatically predicted the high-resolution typing for the haplotype data.

Broad versus split allele reporting

Most alleles were consistently reported as either their broad or split alleles; however, there were three alleles (B14, B15 and B40) that were reported as either broad or split (Table 1). B15, the broad allele for B62, B63, B75, B76, B77, was among the five most commonly reported alleles at SCBB and BMDI CBB (Figure 1). B40, the broad allele for B60 and B61, was among the most five commonly reported alleles at QCBB (Figure 1). This is an important consideration when reviewing the common allele results. A check for data skewing was performed by analyzing data with and without the broad alleles. The analysis found that there was similar genetic diversity within the AusCord CBU inventory when broad alleles (B14, B15, B40) were excluded compared with when they were included (Table 2). Therefore, it was deemed suitable to present all data in this study as inclusive of broad and split alleles.

Table 1
Proportion of broad alleles in the total dataset.

Broad antigen	Split alleles	Percent broad in total dataset	Broad antigen	Split alleles	Percent broad in total dataset
A2	A203, A210	0	B21	B49, B50, B4005	0
A9	A23, A24, A2403	0	B22	B54, B55, B56	0.12
A10	A25, A26, A34, A66	0.07	B27	B2708	0
A19	A29, A30, A31, A32, A33, A74	0.03	B39	B3901, B3902	NA
A24	A2403	0	B40	B60, B61	89.2
A28	A68, A69	4.5	B51	B5102, B5103	0
B5	B51, B52, B5102, B5103	0.02	B70	B71, B72	0
B7	B703	0	DR1	DR103	0
B12	B44, B45	0	DR2	DR15, DR16	0
B14	B64, B65	87.3	DR3	DR17, DR18	0
B15	B62, B63, B75, B76, B77	88.3	DR5	DR11, DR12	0
B16	B38, B39, B3901, B3902	0	DR6	DR13, DR14, DR1403, DR1404	0
B17	B57, B58	0.03	DR14	DR1403, DR1404	0

Data obtained from http://hla.alleles.org/antigens/broads_splits.html on May 13, 2021.
NA, not available.

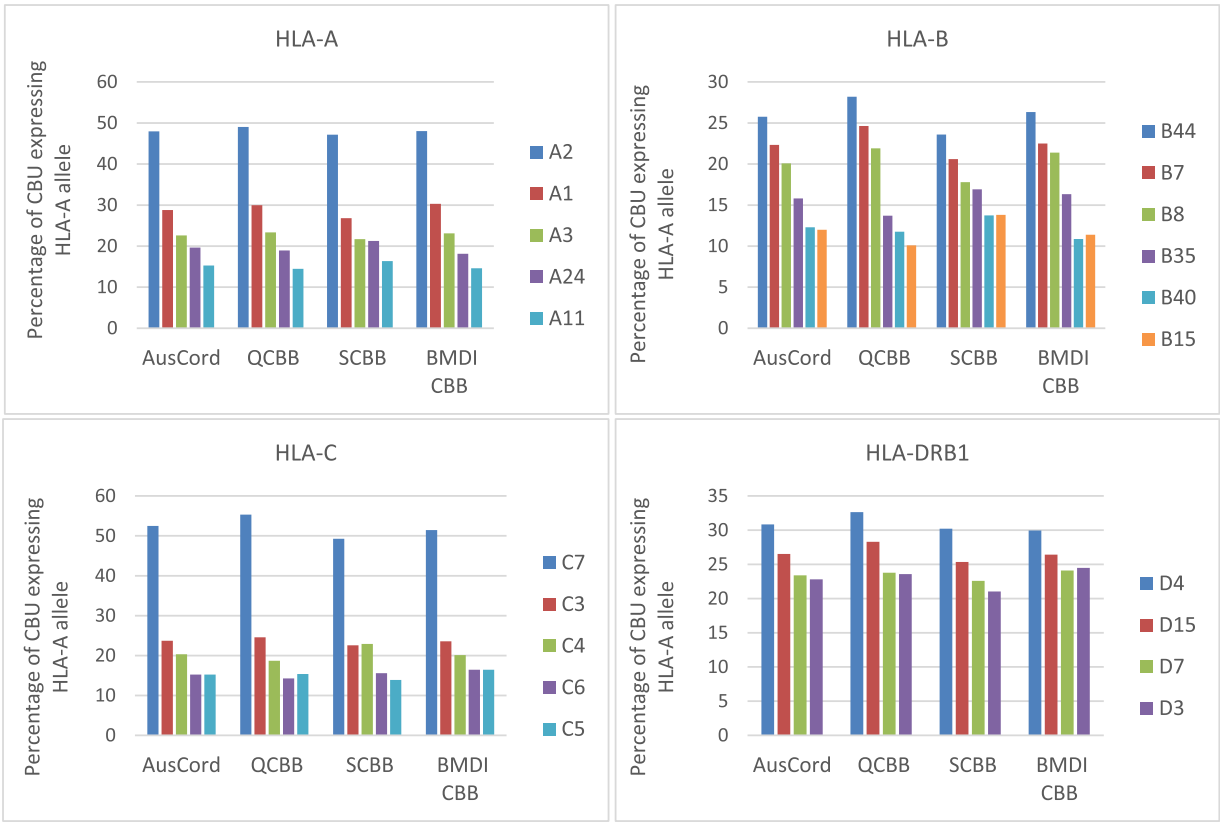

Fig. 1. Most common HLA-A, B, C and DRB1 alleles at each AusCord CBB. Frequency expressed as a total number of CBU exhibiting the allele. Alleles were counted once in the case of homozygosity. B15 and B40 are broad alleles (see Table 1).

Table 2
Analysis of CBU with unique tissue types.

	AusCord				QCBB		SCBB		BMDI CBB	
	All Alleles		Excluding B14, B15, B40							
	Including HLA-C	Excluding HLA-C	Including HLA-C	Excluding HLA-C	Including HLA-C	Excluding HLA-C	Including HLA-C	Excluding HLA-C	Including HLA-C	Excluding HLA-C
Total number of CBU included in analysis	21 815	36 782	15 676	26 272	9453	10604	6385	14 971	5977	11 207
% of CBU with unique HLA	75.5	59.3	64.1	57.7	78.1	70.1	87.1	72.6	85.5	72.0
% of CBU with TT represented twice	10.3	14.5	13.6	14.0	10.3	12.4	6.8	12.5	7.5	12.5
% CBU with TT represented thrice	3.8	6.5	5.5	6.5	2.7	4.9	1.7	4.9	1.9	4.6

Tissue types based on six (HLA-A, HLA-B, HLA-DRB1) or eight (HLA-A, HLA-B, HLA-C, HLA-DRB1) loci. “Unique” indicates tissue type only represented once in the inventory.
TT, tissue type.

Statistical analysis

The χ^2test for independence was used to determine whether there was a significance difference of HLA allele subtype frequencies between populations. Significance was considered if $P < 0.05$.

Results

Specific HLA gene allele frequency within the total searchable inventory

Gene polymorphism and inheritance of ethnic minority HLA genes is often the reason why CBUs are the preferred allograft source for HPCT. Within the Australian context, this is highly relevant to the Indigenous Australian population, who exhibit greater frequencies of the HLA-A*34, HLA-B*13, and HLA-B*56 alleles [9–11], compared with donors of European descent, who represent the majority of adult stem cell donors globally. It is important to note that while HLA-B*13 is not a common allele across most populations, it is commonly found in Indigenous Australian and Pacific Islander haplotypes.

The AusCord inventory was analyzed for specific HLA allele frequency, expressed as a total number, as a surrogate marker for the collection of rare HLA alleles. HLA-A*02, HLA-B*44, HLA-C*07, and HLA-DRB1*04 were the most common alleles at all three banks. Further, the five most common alleles for each HLA gene were similar in rank at each of the banks (Figure 1; full list of ranked HLA shown in supplementary data). Homozygosity was most common among these most common alleles (data not shown). As expected, these most commonly represented alleles within the searchable inventory were also the most commonly represented alleles within the searched and released CBU at each of the banks (data not shown).

The total number of alleles reported per HLA loci were HLA-A = 21, 22, 23 for QCBB, SCBB and BMDI CBB, respectively; HLA-B = 44, 41, 46 for QCBB, SCBB and BMDI CBB, respectively; HLA-C = 14, 14, 15 for QCBB, SCBB and BMDI CBB, respectively; and HLA-DRB1 = 13 for all three banks. These data demonstrate that each bank stores a similar range of specific HLA gene alleles, however, this cannot be interpreted as storage of similar tissue types, which include sequences of multiple genes and loci.

HLA analysis of the AusCord searchable, searched and released CBU

An analysis of the AusCord searchable inventory was performed to compare the HLA tissue types of CBU within each bank (intrabank) and between the banks (interbank). The assessment included searchable CBU (n = 36 782), searched CBU (n = 3489) – a subset of the searchable, and released CBU (n = 1233). The analysis included HLA-A, HLA-B and HLA-DRB1, with or without HLA-C (depending on the availability of data). Of the combined AusCord searchable inventory 75% and 59.3% of CBU exhibited a unique tissue type with or without HLA-C included, respectively (Table 2). This observation was replicated in bank-specific analyses of the searchable inventory. Within the searched CBU cohort, 84% of searched CBU were unique within the AusCord inventory (data not shown). Further, there was little overlap in the tissue types of searchable and searched CBUs at each of the banks (Figure 2). Since HLA-C was not routinely typed until a CBU was requested for release, HLA-C was not included in the analysis of searched CBU. HLA-C was included, however, in analyses of released CBU. There were only two identical tissue types that were shipped by all AusCord CBBs when HLA-C was not included, and none when HLA-C was included (Figure 2). Therefore, this analysis indicates that there was little commonality between the tissue types of searchable, searched and released CBU within and between the banks. When the data were analyzed to determine the most common tissue types, these were found to be similar amongst the three banks (Table 3).

Haplotype frequency of the AusCord inventory

The majority of haplotypes identified in the BMDI CBB and SCBB CBUs were unique to their respective inventory (Figure 3). For example, 95.9% of haplotypes identified in the BMDI CBB CBUs were not found in either QCBB or SCBB datasets. The reduced dataset available for QCBB resulted in (i) an increase in the fraction of QCBB haplotypes represented in the other banks, and (ii) a reduced number of haplotypes represented more than once in the QCBB inventory. These data do not detract from the fact that individual banks could store the only CBU for a unique haplotype.

The most common haplotype identified at each CBB was HLA-A*01, HLA-B*08, HLA-DRB1*03 (Table 4), which is a common haplotype found in the global donor inventories according to the NMDP HaploStats database. This, along with other common haplotypes (e.g., HLA-A*02, HLA-B*44, HLA-DRB1*04), was expressed in some of the most common tissue types shown in Table 3. Common haplotypes, with the exception of HLA-A*29, HLA-B*44, HLA-DRB1*07, ranked highly among all ethnicities within the global donor inventories according to NMDP HaploStats (Table 5). Therefore, similar to the aforementioned tissue types, haplotypes identified at each AusCord CBB were relatively unique to the available dataset. Haplotypes that were commonly expressed within the AusCord and global donor inventories are ideal targets for research and development of Advance Therapy Medicinal Products such as gene-modified immune effector cells or inducible pluripotent stem cells, for example, due to the relatively wide scope of their potential clinical utility.

*HLA-A*34, HLA-B*13, HLA-B*56 and HLA-DRB1*08 allele frequency within the Indigenous Australian and Pacific Islander CBUs*

CBUs collected from the child of a mother or father who self-identified as Indigenous Australian or Pacific Islander were analyzed to determine differences in frequencies between populations. A total of 125, 495 and 112 Indigenous Australian CBU were analyzed from the QCBB, SCBB and BMDI CBB, respectively. The 495 Indigenous Australian CBU stored at SCBB were subdivided into (i) 96 collected from four Sydney metropolitan hospitals, and (ii) 399 collected from the Royal Darwin Hospital (RDH), the latter being a collection site established to specifically target the large Indigenous Australian population residing within its catchment area. The Pacific Islander CBU analyzed included 659 Polynesian and 461 Maori donations, which were all stored at the QCBB. The frequency of HLA-A*34, HLA-B*13 and HLA-B*56 expression was significantly greater in Indigenous Australian and Pacific Islander CBU compared with the total (non-Indigenous Australian/Pacific Islander) inventory (Table 6). The frequency of these alleles was greatest in CBU collected from RDH due to the population demographic. HLA-A*34 was the most common HLA-A allele of 16 HLA-A alleles reported for RDH donations, and HLA-B*56 and HLA-B*13 were the second and third most-common HLA-B alleles, respectively, of the 29 HLA-B alleles report for RDH donations. HLA-B*56 was the third most common HLA-B allele reported of the total 34 HLA-B alleles reported for Polynesian CBU. HLA-DRB1*08 was more frequently expressed by Indigenous Australian CBU collected from RDH, compared with the total non-Indigenous Australian SCBB inventory (30.6% versus 5.5%, $P < 0.001$) and the rest of the Indigenous Australian AusCord inventory (30.6% versus 10.5%, $P < 0.001$). Upon further analysis of the high-resolution typing results from these CBU, it was found that the majority (88.5%, n = 108/122) of alleles were HLA-DRB1*08:03, which is most commonly found in northern and central Australia (Figure 4) [9,12]. The remaining alleles were HLA-DRB1*08:01 (n = 8/122) more common to Europe, HLA-DRB1*08:02 (n = 3/122) more common to the Americas and the lesser-known HLA-DRB1*08:06 (n = 1/122) and HLA-DRB1*08:15 (n = 2/122). The frequency of HLA-A*34 (38.1% versus 8.5%, $P < 001$), HLA-B*13 (25.0% versus 3.3%,

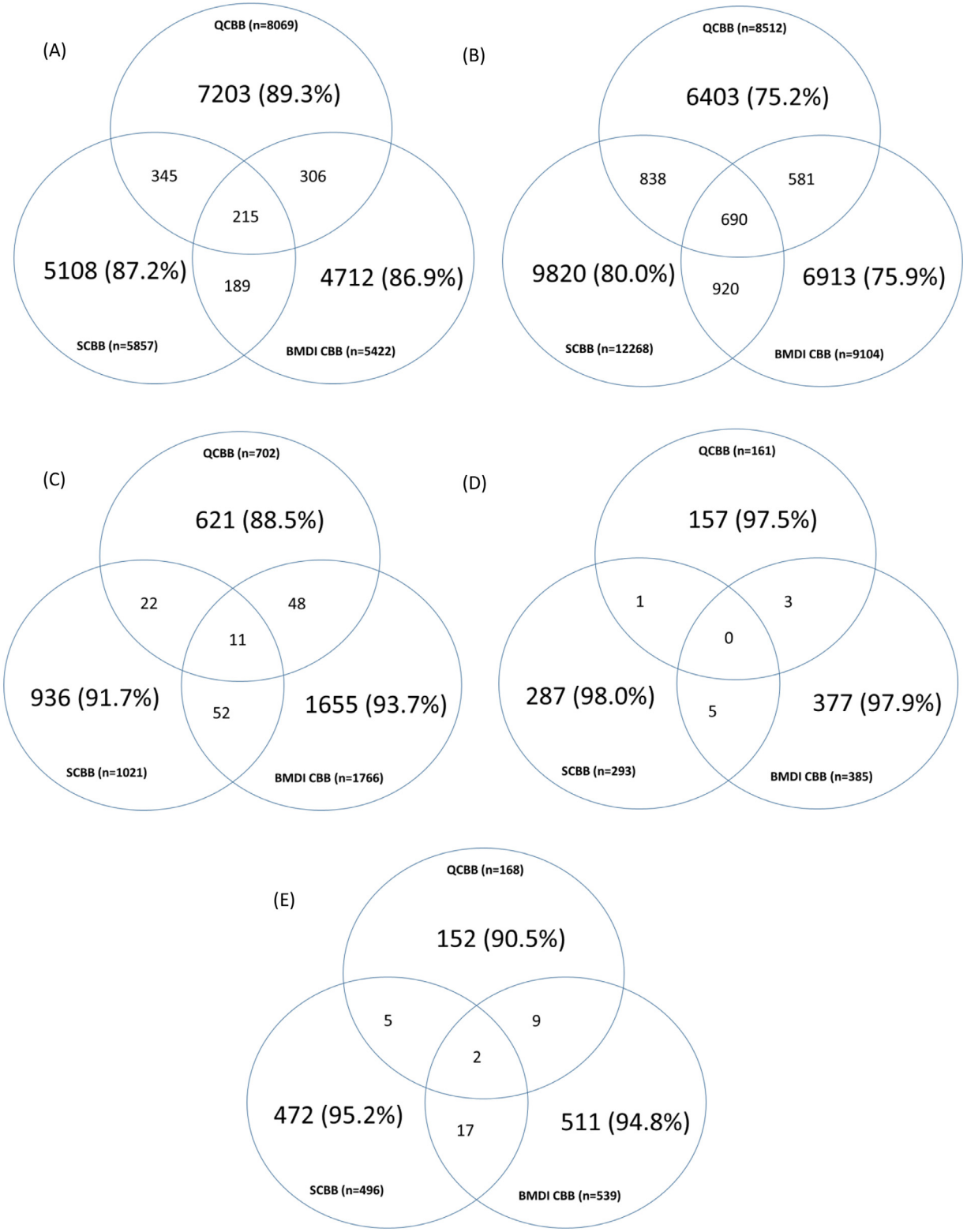

Fig. 2. Commonality of searchable, searched and released CBU between the AusCord CBBs. (A) Searchable inventory: HLA-A, HLA-B, HLA-C, HLA-DRB1. (B) Searchable inventory: HLA-A, HLA-B, HLA-DRB1. (C) Searched CBU; HLA-A, HLA-B, HLA-DRB1. (D) Released CBU: HLA-A, HLA-B, HLA-C, HLA-DRB1, (E) Released CBU: HLA-A, HLA-B, HLA-DRB1. Example of calculation from (A): % of unique HLA strings in QCBB inventory = (7203/8069)*100 = 89.3%.

$P < 0.001$), and HLA-B*56 (26.1% versus 6.5%, $P < 0.001$) was also greater in RDH collections compared with all other Indigenous Australian CBU from the AusCord inventory.

These data indicate that self-identification of Indigenous Australian ethnicity by parents of CBU donors, and situating a collection site within Indigenous Australian and Pacific Islander communities, are successful strategies for capturing the rare alleles associated with Indigenous Australian and/or Pacific Islander populations. This strategy can be adopted in other geographic regions to capture relevant ethnic minority tissue types.

Table 3
Total number of most common tissue types in the AusCord CBB inventories.

HLA type				Number and percent[a] of CBU with indicated tissue type			
A*	B*	C*	DRB1*	AusCord	QCBB	SCBB	BMDI CBB
01, 01	08, 08	07, 07	03, 03	98 (0.45%)	57 (0.60%)	18 (0.28%)	23 (0.39%)
01, 03	07, 08	07, 07	03, 15	93 (0.43%)	45 (0.48%)	21 (0.33%)	27 (0.45%)
01, 02	08, 44	05, 07	03, 04	64 (0.29%)	34 (0.36%)	11 (0.17%)	19 (0.32%)
01, 02	07, 08	07, 07	03, 15	50 (0.23%)	28 (0.30%)	12 (0.19%)	10 (0.17%)
02, 03	07, 44	05, 07	04, 15	35 (0.16%)	17 (0.18%)	7 (0.11%)	11 (0.18%)
01, 01	08, 57	06, 07	03, 07	30 (0.14%)	18 (0.19%)	2 (0.03%)	10 (0.17%)
01, 02	08, 15	03, 07	03, 04	28 (0.13%)	13 (0.14%)	9 (0.14%)	6 (0.10%)
01, 03	08, 35	04, 07	01, 03	26 (0.12%)	14 (0.15%)	7 (0.11%)	5 (0.08%)
03, 29	07, 44	07, 16	07, 15	23 (0.11%)	11 (0.12%)	6 (0.09%)	6 (0.10%)
01, 03	07, 08	07, 07	03, 04	22 (0.10%)	8 (0.08%)	11 (0.17%)	3 (0.05%)

[a] Percent of total number of CBU included in analysis (see Table 2).

Discussion

The findings have shown that the AusCord inventory displays a wide range of tissue types and haplotypes, with more than 75% of the 36 000 CBUs banked having a unique tissue type. The relatively unique nature within and between CBB inventories was observed for searchable, searched and released CBU, demonstrating that each CBU collection is likely to be capturing a tissue type that is not common to the total AusCord inventory. Differences in HLA within and between CBB inventories could be due to (i) the high degree of variability due to the number of HLA subtypes, (ii) the genetic diversity of the communities donating to each CBB or (iii) differences in migration patterns to each CBB's dedicated CB collection centre catchment.

Targeting ethnic minorities can successfully result in storage of CBU with rare HLA that are less likely to be found on global donor registries, as evidenced by the HLA of CBU collected from Indigenous Australian and Pacific Islander donors. The significantly increased frequency of alleles expressed by Indigenous Australians who donated to the RDH collection center demonstrates that the location of collection sites has a key role to play in rare HLA acquisition.

There are many clinical trials investigating new roles for CB transplantation and new methodologies that could increase the utility of existing CB inventories. CB has been reported to be a suitable source for manufacture of anti-CD19 chimeric antigen receptor–transduced natural killer cells [13]. Expansion of CB HPC is being examined as a solution to the disadvantage of a limited cell dose, and CB is also being examined as a potential treatment for brain injuries [14–16].

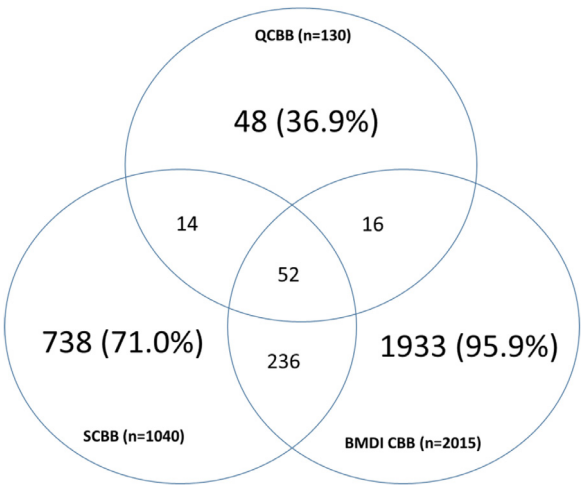

Fig. 3. Commonality of haplotypes at each of the AusCord CBBs.

Therefore, there is potential to use GMP-grade manufacturing methods as well as the existing GMP-grade CBU inventory to support clinical research and clinical trials. This analysis has identified common tissue types and haplotypes that are valuable research resources due to their potential wide scope of utility in the Australian and global population. It has also identified within each bank the CBU with common homozygous haplotypes that may be of benefit for CB-derived induced pluripotent stem cell haplobanking strategies [17]. Future analyses may focus on highlighting differences between the AusCord CBB inventory and the rest of the international inventory.

CB is an important source of HPC that, as a cryopreserved product, is readily available to ship from the CBB directly to a TC. In addition to well-known advantages of CB transplantation, there is another unique advantage to CBU as an off-the-shelf product with known disease risk that can be shipped as freight during global pandemics or other events causing risk to the allograft supply chain. For example, the coronavirus disease 2019 outbreak brought uncertainty as to the coronavirus disease 2019 infection status of adult donors. It also caused international and domestic travel bans that impacted transport of fresh cells and mandatory quarantine requirements for couriers, resulting in many registries around the world advising TCs to consider CB as a first choice or backup treatment option. According to World Marrow Donor Association data, this resulted in an increase in search activity experienced by many CBB around the world. Australian TCs must pay a fee that is in the tens of thousands for CBU that are imported from overseas CBBs. In addition, international shipment of CBUs is associated with an increased risk of shipper mishandling and delays that may lead to loss of product quality. While an internationally acquired CBU may be the best treatment option for a patient, if similar products are available nationally, supply from an Australian CBB imparts significant cost savings and risk mitigation to shipments.

This study demonstrates that the AusCord inventory is yet to achieve full coverage of tissue types for the Australian population. Moreover, this coverage would be further diminished if CBUs with low total nucleated cell and CD34+ cellularity were removed from the analysis, and, in fact, is diminished each time a CBU is removed from the inventory when released for a transplant. While it would be ideal to know the number of banked CBU required to achieve coverage, it is not something that can be easily determined for heterogenous populations such as Australia, as reported by other publications [18,19]. Tissue types of a population are dynamic, with several unpredictable and influencing forces, such as migration patterns and identification of new alleles. Further, nominating an "ideal" size for an inventory is dependent on the HLA types of the CBUs banked versus the patient's HLA type, neither of which is predictable. There have been attempts in the past to estimate registry or CBB size, but this is usually based on populations with less ethnic diversity. While single loci data can be informative, it does not act as a surrogate for haplotypes, which are more varied. As a philosophy of banking, we believe that increasing recruitment from ethnically blended or diverse ethnic communities

Table 4
Frequency of commonly identified haplotypes at each AusCord CBB.

Haplotype[a]	AusCord (n = 3105) Total number and percent of CBU expressing haplotype	QCBB (n = 130)	SCBB (n = 1040)	BMDI CBB (n = 2015)
HLA-A*01:01 HLA-B*08:01 HLA-DRB1*03:01	181 (5.8%)	6 (4.6%)	51 (4.9%)	124 (6.2%)
HLA-A*02:01 HLA-B*44:02 HLA-DRB1*04:01	75 (2.4%)	6 (4.6%)	19 (1.8%)	50 (2.5%)
HLA-A*03:01 HLA-B*07:02 HLA-DRB1*15:01	73 (2.3%)	3 (2.3%)	25 (2.4%)	45 (2.2%)
HLA-A*29:01 HLA-B*44:03 HLA-DRB1*07:01	51 (1.6%)	3 (2.3%)	12 (1.2%)	36 (1.8%)
HLA-A*02:01 HLA-B*07:02 HLA-DRB1*15:01	46 (1.5%)	1 (0.8%)	12 (1.2%)	33 (1.6%)
HLA-A*01:01 HLA-B*57:01 HLA-DRB1*07:01	37 (1.2%)	1 (0.8%)	9 (0.9%)	27 (1.3%)

[a] Haplotypes of AusCord CBU were determined in low-resolution; however, the table shows high-resolution results based on the most common high-resolution haplotype retrieved from the HaploStats database. Haplotypes only counted once in cases of homozygosity.

Table 5
Commonly identified haplotypes and their ranking on the NMDP HaploStats database.

AusCord (n=3 105)											
% of total	Haplotype	African		Asian or Pacific Islander		Caucasian		Hispanic		Native American	
		Freq	Rank	Freq	Rank	Freq	Rank	Freq	Rank	Freq	Rank
5.8	HLA-A*01:01 HLA-B*08:01 HLA-DRB1*03:01	1.1E-2	2	2.3E-3	35	6.0E-2	1	1.800E-2	2	4.3E-2	1
2.4	HLA-A*02:01 HLA-B*44:02 HLA-DRB1*04:01	4.6E-3	8	3.2E-4	542	1.8E-2	4	3.8E-3	19	1.6E-2	3
2.3	HLA-A*03:01 HLA-B*07:02 HLA-DRB1*15:01	6.0E-3	7	2.0E-3	47	3.0E-2	2	1.2E-2	3	2.3E-2	2
1.6	HLA-A*29:01 HLA-B*44:03 HLA-DRB1*07:01	NR		1.1E-4	1552	1.1E-5	556	3.5E-5	3605	2.2E-5	4117
1.5	HLA-A*02:01 HLA-B*07:02 HLA-DRB1*15:01	3.4E-3	16	5.8E-4	269	1.8E-2	3	1.8E-2	3	1.5E-2	4
1.2	HLA-A*01:01 HLA-B*57:01 HLA-DRB1*07:01	2.2E-3	35	1.5E-2	3	1.1E-2	8	4.5E-3	12	9.9E-3	6

Table 6
Frequency of HLA-A*34, HLA-B*13 and HLA-B*56 in Indigenous Australian and Pacific Islander CBUs.

QCBB Indigenous Australian	QCBB Polynesian	QCBB Maori	SCBB-Sydney Indigenous Australian	SCBB-RDH Indigenous Australian	BMDI CBB Indigenous Australian
HLA-A*34 (% of Indigenous Australian/Pacific Islander vs % of non-Indigenous Australian/Pacific Islander CBU inventory)					
10.4 vs 1.0 $P < 0.001$	10.5 vs 1.0	6.1 vs 1.0	17.7 vs 1.1	38.1 vs 1.1	3.61 vs 0.6
HLA-B*13 (% of Indigenous Australian/Pacific Islander vs % of non-Indigenous Australian/Pacific Islander CBU inventory)					
8.0 vs 4.6 NS	6.5 vs 4.6 $P < 0.05$	5.0 vs 4.6 NS	13.5 vs 6.1 $P < 0.001$	25.0 vs 6.1 $P < 0.001$	6.3 vs 5.3 NS
HLA-B*56 (% of Indigenous Australian/Pacific Islander vs % of non-Indigenous Australian/Pacific Islander CBU inventory)					
6.4 vs 1.5 $P < 0.001$	15.3 vs 1.5 $P < 0.001$	6.3 vs 1.5 $P < 0.001$	17.7 vs 1.5 $P < 0.001$	26.1 vs 1.5 $P < 0.001$	0.9 vs 1.1 NS

Frequency is expressed as a percent of total alleles reported for the population (i.e., Indigenous Australian, Pacific Islander, or total CBUs). Alleles were counted once in the case of homozygosity. Population sizes for Indigenous Australian and Pacific Islander are provided in the text. χ^2 test for association used to determine significance.
NS, not significant.

will result in a more HLA diverse panel of donors but exactly how many would be needed to provide full coverage for future patients is not known. An indirect and unpublished joint report from the Australian Bone Marrow Donor Registry and NMDP found that the current Australian adult donor registry size of 164 234 (which is roughly five times the size of the AusCord inventory) provides coverage for 20% of Indigenous Australian patients and 50% of Northern Caucasian (NCAU) patients at a 10/10 allele match. A significant increase of this inventory size to 2.16 million would result in coverage for 40% of Indigenous Australian patients and 75% of NCAU patients at a 10/10 allele match.

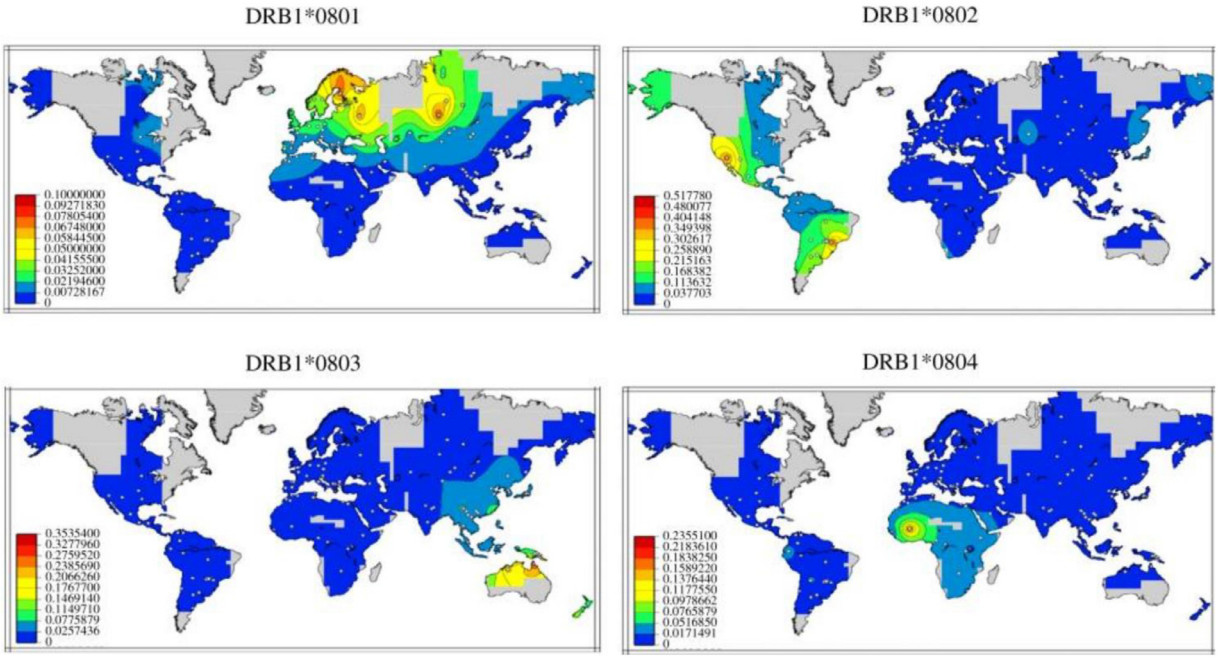

Fig. 4. Global distribution of HLA-DRB1*08 alleles. Adopted from Fernandez Vina *et al.* [12].

The NCAU terminology was used historically (i.e. legacy term), however, it is now bundled into a general and current Caucasion classification along with North West European (current), Southern Caucasian (legacy), Southern European (current), South East European (current). NCAU was used here as it was associated with the data analysis and reported findings. These findings support the conclusion of the AusCord HLA analysis that a significant increase in the CBU inventory size is required to provide drastically improved coverage for Australian patients. Nonetheless, we acknowledge that the inability to calculate current or future coverage of the AusCord CBU inventory for the Australian population is a limitation of the study. A second limitation of the study is that it is restricted to patient data from recipients of AusCord CBUs, which precludes the determination of inventory fulfilment against all Australian transplant patients. A future study will analyze coverage and fulfilment similar to a previously published report for the American inventory [20].

The three CBBs are committed to the continuation of collections for three primary reasons: (i) the addition of high-quality, high cellular CBU that are most likely to be used for transplantation; (ii) growth of inventory to capture tissue types that are not available in the AusCord inventory to service the needs of the future population; and (iii) maintenance of quality assurance systems and regulatory compliance that depend on availability of fresh cord blood. In order to maximize visibility of CBU on global registries that priorities high resolution tissue typing in search algorithms and provide TCs with optimal information to assist with selection of CBUs, the three CBBs are committed to ongoing high resolution typing of historically banked inventory that only have low-resolution typing available. Further, to promote use of the Australian CBUs, the three CBBs have implemented a policy to initiate prerelease testing at the time of CBU reservation (e.g., verification typing, cord blood infectious disease marker testing). While the CBBs cannot determine the level of tissue type “uniqueness” versus “repetition” required to maximize CBU uptake, we believe the philosophy of operations described above will maximize the likelihood of CBU selection

Due to the dynamic multicultural nature of the Australian population and its influence on the HLA genotype and haplotype frequencies of a population, it is imperative to manage adult and infant HPC donor programs to maintain a robust donor pool to support Australian patients of various ethnic backgrounds who are less likely to find suitable matches.

Declaration of Competing Interest

The authors have no commercial, proprietary or financial interest in the products or companies described in this article.

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Author Contributions

Conception and design of the study: GK. Aquisition of data, analysis, and interpretation: GK. Drafting manuscript: GK. Manuscript review, editing, and significant intellectual contribution : JS, AT, KK, PJ, NE.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcyt.2022.06.002.

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