REVIEW

Immunogenetics in stem cell donor registry work: The DKMS example (Part 2)

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Abstract

DKMS is a leading stem cell donor registry with more than 9 million donors. Donor registry activities share many touch points with topics from immunogenetics or population genetics. In this two-part review article, we deal with these aspects of donor registry work by using the example of DKMS. In the second part of the review, we focus on donor typing of non-HLA genes, the impact of donor age, gender and CMV serostatus on donation probabilities, the identification of novel HLA, KIR and MIC alleles by high-throughput donor typing, the activities of the Collaborative Biobank and pharmacogenetics in the donor registry context.

KEYWORDS

CMV, DKMS, donor registry, HLA, KIR, MICA/MICB, unrelated hematopoietic stem cell transplantation

1 | INTRODUCTION

This article is the second part of a two-part review on topics from immunogenetics and population genetics that are related to the work of DKMS, a leading stem cell donor registry with more than 9.6 million donors in six countries. Part 1 of the review (Schmidt et al., 2020) covered typical donor registry activities closely related to the human leukocyte antigen (HLA) system, namely high-throughput

HLA typing of potential stem cell donors, HLA haplotype frequencies and resulting matching probabilities, and donor file optimization with regard to HLA diversity. In this second part of the review, we deal with non-HLA donor parameters and DKMS activities beyond standard donor registry work: donor typing beyond the classical HLA loci, impact of non-HLA parameters on donation probabilities, identification of novel HLA, killer cell immunoglobulin-like receptor (KIR), and major histocompatibility complex (MHC) class I

polypeptide-related sequence A/B (MICA/MICB) alleles, the setup and activities of the Collaborative Biobank coordinated by DKMS and pharmacogenetics in the donor registry context. We conclude the review with a brief outlook.

2 | DONOR TYPING: BEYOND THE CLASSICAL HLA LOCI

Massive cost reductions resulting from next-generation sequencing (NGS)-based HLA typing (Schmidt et al., 2020) enabled a substantial extension of the DKMS standard typing profile of new donors beyond HLA. This standard typing profile currently includes the following parameters beyond the six "classical" HLA loci (A, B, C, DRB1, DQB1, DPB1):

- ABO and Rh blood groups (Lang et al., 2016),
- Cytomegalovirus (CMV) Immunoglobulin G (IgG) serostatus (Behrens et al., 2019; full publication submitted),
- 16 KIR genes (Schmidt, Lange, Hofmann, Schetelig, & Pingel, 2019; Wagner et al., 2018),
- MICA/MICB (publication submitted),
- HLA-E (Hofmann et al., 2017; full publication in preparation),
- HLA-DRB3/4/5, HLA-DQA1, and HLA-DPA1 (since October 2019)
- and the C-C motif chemokine receptor 5 Delta32 (CCR5Δ32) deletion (Solloch et al., 2017).

Apart from the CMV IgG serostatus, all parameters are analysed by applying NGS methods. Figure 1 shows the cumulative and monthly numbers of samples from DKMS donors genotyped at DKMS Life Science Lab (LSL) for the various parameters. Based on the numbers given in Figure 5 of Part 1 of this review (Schmidt et al., 2020), we invest 25% of the cost savings due to the switch from Sanger sequencing-based to NGS-based HLA typing into typing profile extensions beyond the classical HLA loci. Reasons for including the various parameters in the standard donor typing profile can be divided in three groups:

The first group comprises donor blood groups (ABO, Rh) and CMV IgG serostatus. These donor parameters are required for every transplantation. We think such parameters should be made available as early as possible to reduce the risk of unnecessary delays of the donor search process. To waive any blood drawing in the donor recruitment process, we developed, validated and implemented a high-throughput method for determination of the CMV IgG serostatus from buccal swabs (Behrens et al., 2019; full publication submitted). To prevent false-negative calls due to empty swabs, the assay includes total protein quantification. About 5% of the samples collected contain insufficient material. In addition, about 10% of the samples yield inconclusive results. Therefore, CMV results may be reported for about 85% of the samples. Compared to the very high accuracy of genetic testing, accuracy of the CMV assay is lower (97%) due to its quantitative nature but nevertheless sufficiently

good for the purpose of upfront testing of newly registered stem cell donors. Availability of the CMV IgG serostatus strongly influences the probability to be requested as stem cell donor (see paragraph *Donation probabilities*).

KIR, MICA/MICB, HLA-E, HLA-DRB3/4/5, HLA-DQA1 and HLA-DPA1 constitute the second group. For these parameters, there is published evidence available indicating that respective donor characteristics or donor-patient matching may affect stem cell transplant outcome. Examples for such results include Cooley et al. (2010), Venstrom et al. (2012) and Boudreau et al. (2017) for KIR; Kitcharoen, Witt, Romphruk, Christiansen, and Leelayuwat (2006), Askar et al. (2014), Carapito et al. (2016) and Fuerst et al. (2016) for MICA (and partly also MICB); Ludajic et al. (2009), Tsamadou et al. (2017) and Tsamadou et al. (2019) for HLA-E; and Fernández-Viña et al. (2013) for HLA-DRB3/4/5, HLA-DQA1, and HLA-DPA1. Due to these and other published results, these parameters beyond the classical HLA genes are candidates for consideration during the donor search process.

However, most transplant physicians do not routinely use these parameters for unrelated stem cell donor selection at present. Reasons may include small effect sizes, existence of competing models for the same parameter, contradictory results, or lack of confirmation of positive results by independent cohorts. Therefore, one may argue that the inclusion of these parameters in the standard typing profile has been premature.

On the other hand, even transplant physicians who want to use genetic donor data beyond the classical HLA genes in the donor selection process face practical or organizational difficulties that may prevent the use of such data. Upfront typing of additional parameters can improve the situation in these cases. For example, a study on the feasibility of KIR-based donor selection concluded that presearch KIR genotyping, that is KIR genotyping at donor recruitment as done by DKMS, would accelerate the search process and make it more effective (Weisdorf et al., 2019). Outside the setting of studies, additional parameters such as KIR, MICA or HLA-E, that are not provided upfront, will not be considered in stem cell donor searches. This is simply because there are no standard processes for requesting these data. Thereby, donor registries and not transplant physicians or immunogeneticists define the parameters that can be used for donor selection. In practice, it may even be difficult for transplant physicians or search coordinators to access information on non-HLA typing results from donor upfront typing, depending on the specific parameters and national registries involved. Ideally, information on those additional parameters would be provided to transplant physicians and search coordinators via the standard processes that are also used for the classical HLA genes. Upon request, we provide information on accessing such data of DKMS donors (registryservices@dkms.de).

The third group contains only the CCR5Δ32 deletion. For this parameter, there is evidence of patient benefit, but only for patients with human immunodeficiency virus (HIV) infection in combination with an additional disease that is an indication for allogeneic stem cell transplantation. Furthermore, these patients should have

FIGURE 1 Cumulated and monthly numbers of samples from newly recruited DKMS donors genotyped at DKMS LSL. Coloured lines show gene-specific cumulative numbers, grey columns indicate monthly throughput. Black horizontal bars show yearly mean throughput. The *y*-axis is square root scaled. KIR_PA: KIR presence/absence of genes; KIR_AL: KIR allele level. The figure is a slightly modified update from Figure 1 in Schöfl et al. (2017)
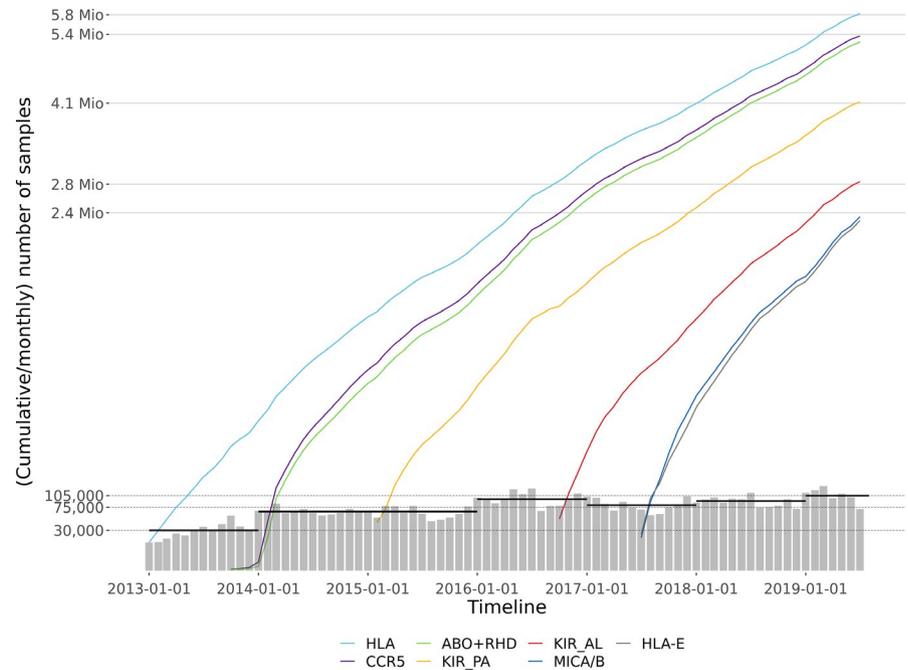
a common HLA genotype to have a realistic chance to find an HLA-matched CCR5Δ32-homozygous donor (about 1% of the European population (Solloch et al., 2017)). Typing of the CCR5 gene in all new donors has been inspired by the "Berlin patient" Timothy Brown who is regarded to be the first patient ever cured from an HIV infection (Hütter et al., 2009). This patient also suffered from acute myeloid leukaemia (AML) and was transplanted from a DKMS donor with homozygous CCR5Δ32 deletion. At least 10 HIV patients have received CCR5Δ32-homozygous stem cell transplants so far, thereof 6, including the Berlin patient, from unrelated donors (Hütter, 2018). Among these six cases, two patients from London and Düsseldorf have shown no viral rebound 19 and 3 months after HIV treatment interruption, respectively (Gupta et al., 2019; Jensen et al., 2019). In four of the six unrelated donor cases, the stem cell product was provided by a DKMS donor.

Allele frequencies of non-HLA parameters obtained from high-throughput typing of potential stem cell donors are relevant for assessing chances to find donors with preferred genotypes. Furthermore, they are of potential interest for population genetics in general. We published allele frequencies of several non-HLA parameters from large samples:

- We estimated ABO allele and allele group frequencies from a sample of *n* > 113,000 German individuals (Lang et al., 2016). The most frequent allele groups were ABO*O.01.01 (31.8%), ABO*A1.01.01 (20.3%) and ABO*O.02.01 (18.5%).
- We determined KIR allele frequencies from a sample of >337,000 predominantly European individuals by applying an amplicon-based sequencing approach on Illumina devices (Wagner et al., 2018). Primers were targeted at KIR exons 3, 4, 5, 7, 8 and 9 (with a combined amplicon for exons 8 and 9). Analyses were carried out using the proprietary NEXTYPE software. Due to the large

cohort size, we could report allele frequencies for 69% of the alleles included in Immuno Polymorphism Database (IPD)-KIR version 2.7.1 (Robinson, Mistry, McWilliam, Lopez, & Marsh, 2010). For another 16% of alleles, we could report allele group frequencies. These allele groups could not be further resolved as the differentiating polymorphisms lay outside the sequenced amplicons. Despite our large cohort, 15% of the IPD-KIR 2.7.1 alleles were not detected, probably either because they were not included in our predominantly European cohort or because the original submissions contained sequencing errors. Compared to inhibitory KIR genes, activating KIR genes showed limited allelic diversity: the number of alleles observed was smaller for activating KIR genes, and, with the exception of KIR2DS4, allele frequency distributions of activating KIR genes were each dominated by one abundant allele with frequencies between 60% (KIR2DS1*002) and 97% (KIR2DS5*002). In a subset of >185,000 samples, we identified 5,203 distinct sequences with variations from reported alleles, including more than 2,000 sequences found in at least two individuals. We are validating these sequences using full-gene characterization. Validated new KIR alleles are reported to the IPD-KIR database on an ongoing basis (see paragraph *Identification of novel alleles*).

- Furthermore, we estimated KIR haplotype frequencies at allelic resolution in families of self-assessed German descent from the DKMS donor file (Solloch et al., 2019). Data from *n* = 403 families enabled us to reduce the number of possible KIR haplotypes for each individual. By restricting potential haplotypes to 92 previously described KIR copy number haplotypes, we identified a set of 551 allelic KIR haplotypes and calculated corresponding frequencies for *n* = 790 parents. The 84 most common allelic KIR haplotypes had a cumulative frequency of 50%. A full publication has been submitted.

- We recently analysed MICA and MICB allele frequencies of a large, predominantly European cohort (publication submitted). In the German population, MICA*008 was the most common MICA allele with a frequency of 42.3%, followed by MICA*002 (11.7%). The 15 most common MICA alleles had a cumulative frequency of 99.5%.
- We analysed HLA-E allele and haplotype frequencies for donors of self-assessed German, Turkish, Polish, Russian or Italian descent from DKMS Germany (Sauter, Schefzyk, Hofmann, Lange, & Schmidt, 2018). Sample sizes ranged from n = 2,035 (Italian descent) to n > 325,000 (German descent). HLA-E*01:01g was the most common allele group in all populations considered with frequencies ranging from 53.0% (Italy) to 57.0% (Russia), followed by HLA-E*01:03g with frequencies from 43.0% (Russia) to 46.9% (Italy). A full publication is in preparation.
- We estimated frequencies of the CCR5Δ32 deletion in 87 countries based on >1.33 million potential stem cell donors registered with DKMS in Germany, Poland or the United Kingdom (Solloch et al., 2017). The highest CCR5Δ32 deletion rates could be observed in Northern Europe (16.4% in individuals of Norwegian descent, 15.6% in individuals of Estonian descent), with a gradual decline in the south-east direction.

3 | DONATION PROBABILITIES

We mentioned the well-known positive impact of "complete" HLA typing (i.e. 4–6 classical HLA loci at high resolution) on donation probabilities in the first part of the review (Schmidt et al., 2020, paragraph *HLA typing: Classical HLA loci*). Here, we focus on the impact of donor age and gender and of CMV serotyping on donation probabilities.

Figure 2a shows stem cell donation probabilities by age and gender based on data from DKMS Germany in 2018. The underlying age and gender distributions for donations and registered donors are displayed in Figure 2b,c, respectively. For these analyses, only donors with typing information for all six classical HLA loci were considered. Unsurprisingly, young male donors have the highest donation probability as it is well-known that they are generally preferred by transplant physicians (Greco-Stewart et al., 2018; Müller, Feldmann, Bochtler, Morsch, & Schmidt, 2012; Schmidt, Biesinger, Baier, Harf, & Rutt, 2008).

The preference for young donors is consistent with recent study results based on CIBMTR data (Kollman et al., 2016; Shaw et al., 2018). The latter study showed a linear effect of donor age on 2-year overall survival (OS): choosing a donor 20 years older was associated with a 7% decrease in 2-year OS. Using the findings by Shaw et al., a rough estimate based on the comparison of age distributions of actual and registered donors (Figure 2b,c, green lines) suggests the preference for young donors will result in at least about 100 additional survivors (based on 2-year OS rates) from the 5,460 donations of DKMS Germany donors in 2018 alone.

Interestingly, this substantial benefit was difficult to identify at all. The landmark study by Kollman et al. (2001) that showed an
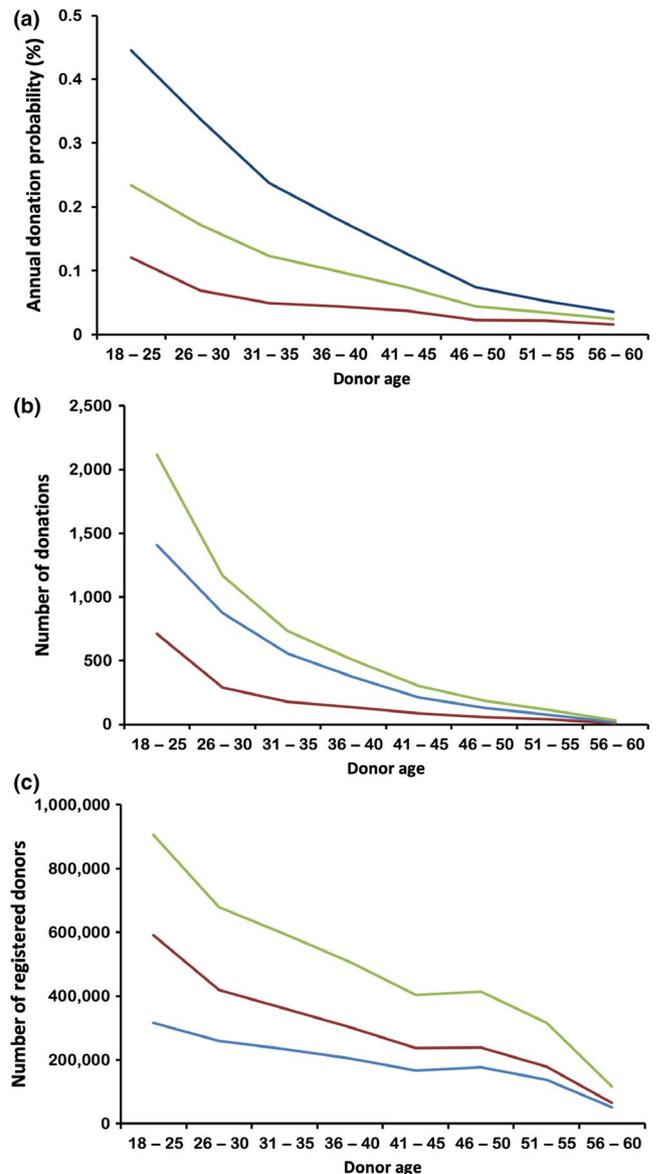

FIGURE 2 Stem cell donation probabilities (a), stem cell donations (b) and registered stem cell donors (c) by donor age and gender. Graphs are based on 2018 data from DKMS Germany. Only donors with typing information for all six classical HLA loci are considered. Red: female; blue: male; green: total

impact of donor age on transplant outcome was based on, from a today's perspective, limited HLA typing (HLA-A, HLA-B and HLA-DRB1 only, class I loci at low resolution). Later studies based on advanced donor-recipient HLA matching showed mixed results: some found an effect of donor age on survival (Ayuk et al., 2013; Jagasia et al., 2012), some did not (Lee et al., 2007; Pidala et al., 2014). It took until the 2016 publication by Kollman et al. that donor age became a unanimously accepted criterion for donor selection.

The example of donor age suggests it may be beneficial for patients when transplant physicians consider parameters in donor selection decisions although no final proof of their relevance for transplant outcome exists. A pre-condition is that there is no serious doubt on the direction of the potential effect as it has been the

FIGURE 3 Stem cell donation probabilities by donor age, gender and CMV IgG serostatus. Graph is based on 2018 data from DKMS Germany. Only donors with typing information for all 6 classical HLA loci are considered. Red: female; blue: male. Solid: CMV+; dashed: CMV-; dotted: CMV IgG serostatus not available
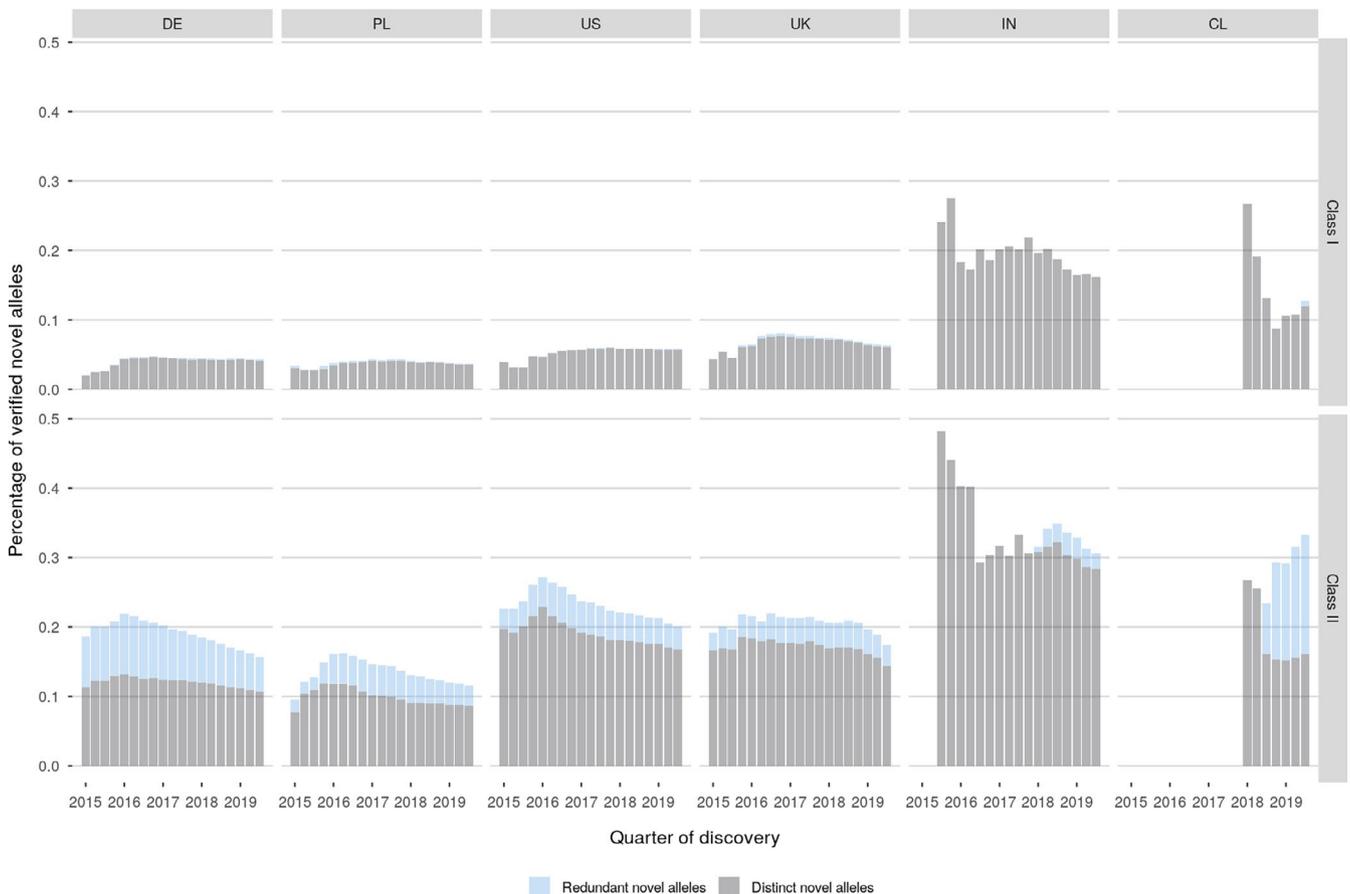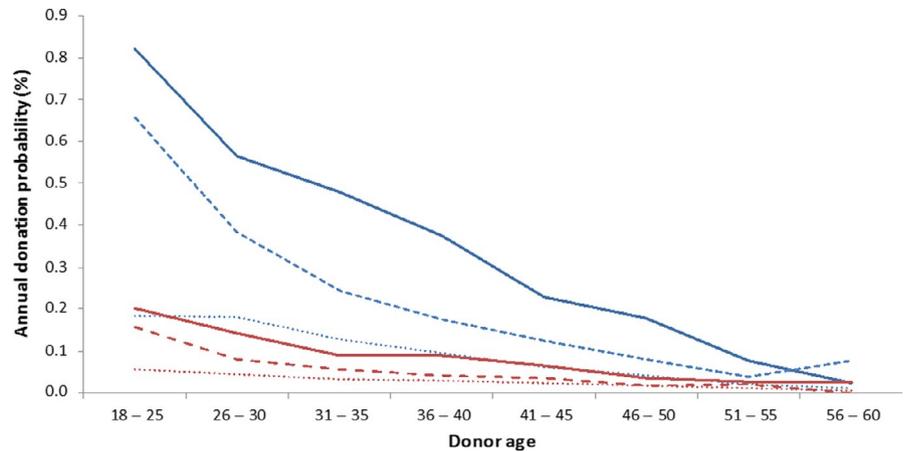

FIGURE 4 Rate of novel HLA alleles by donor country and quarter. Percentages shown are defined per HLA class. Example: In the period from 2016 to 2019, about 0.04% of new DKMS donors from Germany had at least one novel HLA class I allele

case with donor age: Though it was unclear for many years if donor age had an effect on survival after stem cell transplantation or not, it seemed highly improbable that older donors might be preferable over younger donors. Of course, this argument does not imply it is dispensable to strive for the best possible evidence.

Figure 2a also shows a very strong effect of donor gender on donation probabilities. In the age group from 18 to 25 years, for example, the donation probability was 3.7 times higher for male than for female donors. The effect of donor gender on survival after HSCT is still under debate (Nakasone et al., 2015; Shaw et al., 2018).

CMV IgG serostatus information also affects donation probabilities strongly (Figure 3). For male donors aged 18–25, availability of the CMV IgG serostatus increased donation probabilities by a factor of 4.5 (3.6) when the serostatus was positive (negative). The corresponding factors for female donors were 3.7 and 2.9, respectively. The higher donation probabilities of CMV + donors are probably partly related to the fact that positive results have a higher informative value as a negative serostatus may convert. Based on these data, we strongly recommend inclusion of the CMV IgG serostatus into standard donor typing profiles at recruitment.

4 | IDENTIFICATION OF NOVEL ALLELES

A welcome side effect of high-throughput donor registry HLA typing at high resolution lies in the identification of novel alleles. In several publications, we described 3,048 novel HLA alleles (699 HLA-A, 887 HLA-B, 879 HLA-C, 283 HLA-DRB1, 178 HLA-DQB1 and 122 HLA-DPB1 alleles) identified among DKMS donors from Germany, Poland and the United States at the Histogenetics laboratory (Ossining, United States; Hernández-Frederick, Cereb, et al., 2014b; Hernández-Frederick et al., 2016; Hernández-Frederick, Giani, et al., 2014a). The identification and description of novel alleles is of practical use for stem cell donor searches. This is demonstrated by the fact that we found 675 (22.1%) of the abovementioned 3,048 newly described alleles in at least two, 49 (1.6%) even in at least 10 individuals.

Today, DKMS LSL is performing all genotyping for new DKMS donors and therefore is also entrusted with the detection and characterization of novel alleles. Overall, we detect close to 2000 novel HLA alleles each year. Each potential novel allele is verified in a second typing based on an independent PCR. The rate of novel alleles detected differs from country to country, with India showing by far the highest rate (Figure 4). Across countries, we identify about twice as many novel alleles in HLA class II compared to HLA class I. Process optimizations are the underlying reasons for increases before 2016. Since 2016, a slight decrease of the novel allele rate has been observed, most prominently in novel class II alleles of the large DKMS registries with mainly European donors (Germany, Poland, United States and United Kingdom).

An overview of HLA, MIC and KIR alleles submitted to the IPD-international ImMunoGeneTics information system (IMGT)/HLA (Robinson et al., 2015) and IPD-KIR databases is given in Table 1. Apart from novel alleles, the table also includes confirmatory submissions and sequence extensions to complement partially known alleles. Nearly all submitted HLA alleles (2,234 of 2,251 novel alleles, all 1,317 confirmatory alleles and sequence extensions) are already included in the latest IPD-IMGT/HLA database release (3.37.0), while submissions regarding MIC and KIR are still in processing and will be included soon. Overall, release 3.37.0 contains 22,679 classical HLA alleles, thereof 5,656 (24.9%) with whole-gene sequence information. In 2,327 cases (41.4% of all alleles with available whole-gene sequences), these sequences were provided by DKMS LSL.

Table 1 also includes submissions with incomplete sequences (1,220 of 3,568 HLA allele submissions (34.2%)). These submissions were made before 2016. Since then, we have only submitted whole-gene sequences and also plan to do so in the future. To avoid submitting erroneous sequences, we developed a dual redundant reference sequencing strategy (DR2S) that combines Illumina shotgun with Pacific Biosciences single molecule real-time (SMRT) sequencing data (Albrecht et al., 2017; Klasberg et al., 2018). Both sequencing methods have specific weaknesses: possible loss of phasing when two heterozygous positions are separated by more than 500 base pairs for Illumina shotgun sequencing, high error rates especially in homopolymeric and repetitive sequence regions for SMRT

sequencing. By combining both methods, the specific strength of each method (low error rate for Illumina shotgun sequencing, generation of contiguous long reads for SMRT sequencing) can compensate for the weakness of the other. The DR2S strategy was also applied to characterize and submit all major and many common and well-documented (CWD; Eberhard, Schmidt, Mytilineos, Fleischhauer, & Müller, 2018; Hurley et al., 2020; Sanchez-Mazas et al., 2017) HLA-DPB1 alleles in full length, thus considerably enhancing the respective data in the IPD-IMGT/HLA database (Klasberg et al., 2019).

In order to facilitate the submission process for novel alleles, we developed TypeLoader2. This software tool supports the automated bulk submission of whole-gene HLA, MIC and KIR sequences (Schöne et al., 2019; Surendranath et al., 2017). TypeLoader2 runs on Windows and Linux and is freely available at https://github.com/DKMS-LSL/typeloader.

It should be noted that even with NGS technology and software support, the high-throughput submission of new alleles is a resource-intensive effort. This is especially true if—as described here—full-gene sequences, which have been validated by the application of two complementary sequencing methods, are submitted to the databases. At DKMS LSL, two employees are exclusively occupied with the processing of new or confirmatory alleles or sequence extensions. However, we prioritized the full genomic characterization of more frequent alleles and non-HLA gene families over the submission of very rare novel alleles observed only once in several million samples. Therefore, we are submitting only a fraction of the observed novel alleles.

5 | COLLABORATIVE BIOBANK (CoBi)

CoBi is a collaborative research platform initiated and coordinated by DKMS. It has been established in close cooperation with German transplant and collection centres and operates within a framework consented by all cooperation partners. With CoBi, we want to provide a long-term resource for future research projects aimed at advancing prevention, diagnosis and treatment of blood cancer, improving the outcome of hematopoietic stem cell transplantation and optimizing donor selection for allogeneic stem cell transplantation.

At the primary care facilities, 18 ml blood (patients) and 9 ml blood (donors) are collected from individuals who consented in participation. At the biobank, the samples are linked to a registered individual via login into a trusted third party and a new pseudonym is generated for long-term storage. Whole blood or DNA is stored at −20° Celsius. In addition, medical and sample-related data of the participating donors and patients are stored in encrypted form in the core database. Samples can be requested by research groups worldwide. A transparent access policy and review process are in place (https://www.cobi-biobank.com/wp-content/uploads//2017/04/Access_Policy_V4-0.pdf).

As of 30 June 2019, more than 30,000 donor and 3,000 patient samples were stored at CoBi, among them 2,500 paired samples.

TABLE 1 Number of sequences submitted by DKMS LSL to the IPD-IMGT/HLA and IPD-KIR databases (cut-off date: September 13, 2019)

Locus	Novel alleles	Confirmatory alleles and sequence extensions	Total	Whole-gene total n (%)
HLA total	**2,251**	**1,317**	**3,568**	**2,348 (65.8)**
HLA-A	427	201	628	486 (77.4)
HLA-B	640	310	950	485 (51.1)
HLA-C	760	413	1,173	926 (78.9)
HLA-DRB1	61	5	66	0 (0)
HLA-DQB1	97	106	203	101 (49.8)
HLA-DPB1	266	282	548	350 (63.9)
MIC total	**288**	**176**	**464**	**464 (100)**
MICA	103	108	211	211 (100)
MICB	185	68	253	253 (100)
KIR total	**366**	**131**	**497**	**497 (100)**
KIR2DL1	71	17	88	88 (100)
KIR2DL4	38	24	62	62 (100)
KIR2DL5	39	18	57	57 (100)
KIR2DS1	18	4	22	22 (100)
KIR2DS2	43	9	52	52 (100)
KIR3DL3	76	15	91	91 (100)
KIR3DP1	81	44	125	125 (100)

Participation of centres is voluntary. Sample collections from patients and donors increased at an annual rate of about 30% in recent years. The initiation of a new centre is time-consuming as it requires a positive vote of the locally responsible Ethical Committee. While few collection centres carry out stem cell collections for DKMS, many transplant centres are needed in order to collect the same number of patient samples. These facts contribute to the excess of donor samples. Currently, all donor and patient samples stored at CoBi come from German individuals. We plan to expand the CoBi scope to donors and patients from interested European centres. CoBi is also open for donors from other registries than DKMS.

The first research focus by CoBi has been the relevance of the KIR system for transplant outcome. Two retrospective studies in patients with AML or myelodysplastic syndrome (MDS) were conducted so far. The first study was carried out in cooperation with Deutsches Register für Stammzelltransplantationen (DRST) and the German Cooperative Transplant Study Group. Based on more than 2,000 donor-patient pairs, the impact of a combined classifier using information from donor KIR2DS1 and KIR3DL1 genes (Boudreau et al., 2017; Venstrom et al., 2012) could not be replicated (Schetelig et al., 2020). The second study was a cooperation of the European Society for Blood and Marrow Transplantation (EBMT), the Center for International Blood and Marrow Transplant Research (CIBMTR) and CoBi. This cohort comprised data of *n* = 1,704 donor-patient pairs and was independent from the first cohort. Alternative models for grouping KIR genotype information into centromeric and telomeric KIR haplotype motifs (Cooley et al., 2010) were challenged with this study but could not be validated (Schetelig et al., 2019; full publication in preparation).

Further information on CoBi can be found at www.cobi-biobank.de.

6 | PHARMACOGENETICS IN DONOR REGISTRY PRACTICE

HLA typing or donor health evaluation can reveal incidental findings without immediate clinical significance. Nevertheless, knowledge about these findings may be beneficial in some cases. For example, carriers of the HLA-B*58:01 allele have a substantially increased risk for severe cutaneous adverse reactions (SCAR) when exposed to allopurinol, the standard medication against elevated uric acid levels, one of the most often prescribed drugs overall (Aihara, 2011). HLA-B*58:01 allele frequencies are, for example, 0.81% for German (Schmidt et al., 2009), 0.65% for Polish (Schmidt et al., 2011), 1.02% for French (Gourraud et al., 2015), and—depending on region—between 2.5% and 7.5% for Indian individuals (Maiers et al., 2014). If the HLA-B*58:01 allele carrier status is known, allopurinol should not be prescribed unless no therapeutic alternatives exist. However, in many countries including Germany there is no routine testing for HLA-B*58:01 before start of allopurinol medication.

To increase safety of registered stem cell donors entirely outside the context of stem cell donation, DKMS has decided to include a notification about HLA-B*58:01 in the communication with all HLA-B*58:01 carriers in the course of donor request routines. Donors are invited to forward this information to their physicians if they should receive treatment for gout, hyperuricemia or kidney stones. DKMS Germany is currently preparing standards for the information

process for this approach. Based on these pilot experiences, the approach may be extended to other DKMS entities and/or other HLA-associated drug reactions.

7 | CONCLUSION AND OUTLOOK

In this two-part review article, we described, analysed and discussed aspects of donor registry work related to immunogenetics and population genetics by using the example of DKMS. The major development at the intersection of immunogenetics and stem cell donor registries over the last few years has clearly been the use of NGS-based high-throughput HLA typing (Cereb, Kim, Ryu, & Yang, 2015; Lange et al., 2014; Schöfl et al., 2017; Zhou et al., 2015). We showed that this accomplishment had important immediate effects such as higher typing quality (higher resolution, less errors) and dramatic cost savings. These savings enabled donor registries to grow faster than it would have been possible with the costs of Sanger-based HLA typing. For example, the substantial acceleration of DKMS donor file growth since 2014 (Figure 1 of Part 1 of this review; Schmidt et al., 2020) would not have been fundable without NGS-related cost savings.

Beyond that, the long-term impact of NGS-based donor typing on donor-recipient matching currently remains open. So far, the improved sequence information to cost ratio provided by NGS methods has been used to enhance the standard donor typing profile beyond the classical HLA loci (e.g. by DKMS) or to apply whole-gene HLA typing in the donor registry context (e.g. by Anthony Nolan; Mayor et al., 2015). However, so far neither of the two approaches has led to changes of clinical routine at large scale. Possible reasons for this observation have been discussed briefly in this work. Thus, it remains a challenge for immunogeneticists, transplant physicians, outcome registries as CIBMTR and EBMT, biobanks as CoBi, and donor registries to create sound evidence for the relevance of "non-classical" parameters on transplant outcome in order to improve patient benefit. The challenge may even grow in the future, as whole exome or whole genome sequencing of new donors could become an affordable option worth considering for donor registries soon (Singh, 2018).

With respect to the touch points of population genetics and donor registry work, the main challenge for donor registries lies in smart donor file growth, that is growth that specifically addresses the needs of populations that have been underserved so far. This goal was not optimally achieved in the past (van Walraven et al., 2017). As allogeneic transplant activities are growing globally with a focus on developing countries (Aljurf et al., 2019), stem cell donor recruitment from non-Northwestern European populations will be of increasing importance in the future. DKMS has taken account of these developments by starting donor registries in Chile and India (together with Bangalore Medical Services Trust (BMST)). Besides, we plan to start donor recruitment efforts in further countries with predominantly non-European populations soon.

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