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Pathogenic and likely pathogenic germline variation in patients with myeloid malignancies and their unrelated HLA-matched hematopoietic stem cell donors

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Abstract

Aims: The revised 2022 World Health Organization classification recognizes myeloid neoplasms with associated germline predisposition as a defined subcategory, underscoring the clinical significance of likely pathogenic (LPV) and pathogenic (PV) germline variation in these diseases. To better understand the role of LPV/PV in blood or marrow transplants (BMT), a curative therapy for myeloid neoplasms, we measure their frequency and association with mortality in two cohorts of donor-recipient pairs.

Methods: LPV/PV frequencies in 665 cancer-related genes were measured using exomechip genotyping data in 1990 acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) patients and their unrelated donors, registered with the Center for International Blood and Marrow Transplant Research. Cox proportional hazard models were used to test variant association with recipient mortality one-year post-transplant.

Results: Thirteen autosomal dominant (AD) LPV/PV in eight genes were found in 2.8% of patients and 2.2% of donors; those linked to autosomal recessive conditions appeared in 11.1% of patients and 11% of donors. The most common AD LPV/PV mutations in recipients were found in *DDX41* (*n* = 18). For donors, the most frequent AD PVs occurred in *CHEK2* (*n* = 21) and Fanconi Anemia (FA) genes (*n* = 7). *DDX41* and *CHEK2* variation did not correlate with patient survival, but patients with donors with an LPV/PVs in an FA gene had lower survival (HR = 2.38, 95%CI: 1.06-5.31, *P* = 0.035) than patients whose donors did not have an FA LPV/PV.

Conclusion: We identified LPVs/PVs in cancer genes in donors and recipients and are the first to show an association of donor FA PVs with mortality after BMT.

Keywords: Myeloid malignancies, blood and marrow transplant, hereditary hematologic malignancies, survival analyses, Fanconi Anemia, genetic counseling

INTRODUCTION

Germline studies have demonstrated that inherited variants contribute to familial myeloid leukemia risk in adults, even in the absence of a known family history of the disease[1-3]. With the growing availability of clinical genetic testing, there is an increasing appreciation for several inherited predisposition syndromes and germline causal variants, which may underlie apparent *de novo* presentations of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS)[1]. Large genomic studies of these cancer predisposition genes in leukemia populations have the potential to help inform medical management , donor selection for blood and marrow transplant (BMT), and genetic counseling practice around medical management for patients and their families.

Evaluation for an underlying familial syndrome in a patient with acute leukemia or MDS should involve a medical and family screening history, focused physical examination, and diagnostic genetic testing[4-6]. The World Health Organization (WHO) and National Comprehensive Cancer Network (NCCN) have recently made such recommendations for both AML and MDS[7]. However, there is no consensus on the optimal management of individuals diagnosed with a hereditary hematologic malignancy predisposition syndrome, with or without a personal history of acute leukemia or MDS, so management must be individualized[6]. Genetic counseling of leukemia patients is challenging because of the inability to prevent or even attenuate marrow failure in at-risk individuals, the need for skin punch biopsy (*versus* blood) which leads to delayed test turnaround time, the ill-defined prevention strategies for at-risk relatives, and undefined medical management due to lack of a complete picture of related diseases, disease spectrum, penetrance, and age of onset[8]. Genetic counseling in the context of BMT is especially nuanced, given the role relatives can play in patients' curative therapy as blood or marrow donors, and there is burgeoning evidence that donor genetics may play a role in survival after transplant[9-11]. Additionally, the optimal delivery model including when to perform genetic counseling and germline testing for a patient and donor is not well described.

To identify pathogenic variations in hematologic and solid tumor predisposition genes and determine their impact on survival after transplant, we use exome chip data on two cohorts of almost 2,000 AML and MDS patients and their HLA-matched unrelated healthy donors representing over a decade (2000-2011) of data reported to the Center for International Blood and Marrow Transplant (CIBMTR)[12]. Here, we report the

existence of LPV/PV in AML and MDS patients and donors and that donor variation impacts patient survival after BMT. These data further highlight the need for continued genomic science and genetic counseling research around the characterization of germline variation in susceptibility to hematologic malignancies and to survival after curative therapy for these diseases.

METHODS

Study design and population

Data in our study are derived from the Determining the Influence of Susceptibility-COnveying Variants Related to 1-Year Mortality after Blood and Marrow Transplant (DISCOVeRY-BMT) cohorts designed to find common and rare germline genetic variation associated with survival after an unrelated donor BMT. DISCOVeRY-BMT consists of two cohorts (termed cohorts 1 and 2) of acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and myelodysplastic syndrome (MDS) patients and their human leukocyte antigen (HLA)-matched unrelated healthy donors reported to the CIBMTR from 2000-2008 (Cohort 1) and 2009-2011 (Cohort 2)[10-12]. Criteria for unrelated donors include at least 18 years of age and passing a medical examination, including family history, to determine if the donor is healthy. We selected AML and MDS patients and used all available unrelated donors for both Cohort 1 and Cohort 2 for analyses. Study design is shown in Figure 1.

Genotyping and quality control

Genotyping on all samples was performed using the Illumina Infinium HumanExome Beadchip v1.1 (Exome chip) and quality control has been described in detail elsewhere[10]. Frequency analyses were carried out on all donors and recipients. Due to the small number of patients and donors with African ancestry and Hispanic ethnicity (< 2%), association and survival analyses were performed in individuals of European continental ancestry. After sample-level quality control, Cohorts 1/2 have 1,196/327 AML and 332/135 MDS patients, and 1,774/472 donors (controls), respectively, yielding 1,528 donor-recipient pairs in Cohort 1 and 462 donor-recipient pairs in Cohort 2. Cohorts 1 and 2 contain 245 and 10 donor genomes, respectively for which recipient DNA was unavailable; however complete clinical data on the recipients were available and therefore, the donor exome chip data were not removed from further analysis. Following variant quality control, 240,653 and 240,603 patient variants in Cohorts 1 and 2, respectively, and 240,640 and 240,573 donor variants in Cohorts 1 and 2, respectively, were available for analysis. Cluster plots for all variants reported herein were manually inspected for quality.

Selection of genes and pathogenic and likely pathogenic variants for frequency analysis

To identify genes for inclusion in analyses, a detailed literature review was conducted using PubMed, the Online Mendelian Inheritance of Man (OMIM)[3]. Genes were OMIM cancer, OMIM myeloid malignancy, and a PubMed article multiple MESH term search was used: "(myeloid malignancy OR myeloid malignancies OR hematologic malignancies OR hematologic malignancy OR leukemia OR leukemias) AND genetic AND (germline OR somatic)" from 2010 onward in the human species written in English language journals. Following the identification of genes implicated in cancer, either germline or somatic cancer, variants for frequency calculations were selected using the "ClinicalSignificance" column from the variant summary file downloadable from ClinVar (accessed 1/2022). Variants were selected from the following classifications: "Likely pathogenic", "Pathogenic", "Pathogenic/Likely pathogenic", "Pathogenic/Likely pathogenic, risk factor", "Pathogenic, risk factor" and "Likely Pathogenic, risk factor". These variants were further manually reviewed for the accuracy of reporting.

Statistical analysis

Frequency of likely pathogenic and pathogenic variants in DISCOVeRY-BMT

Allele frequencies were calculated within and across cohorts for donors, patients, and disease groups (AML

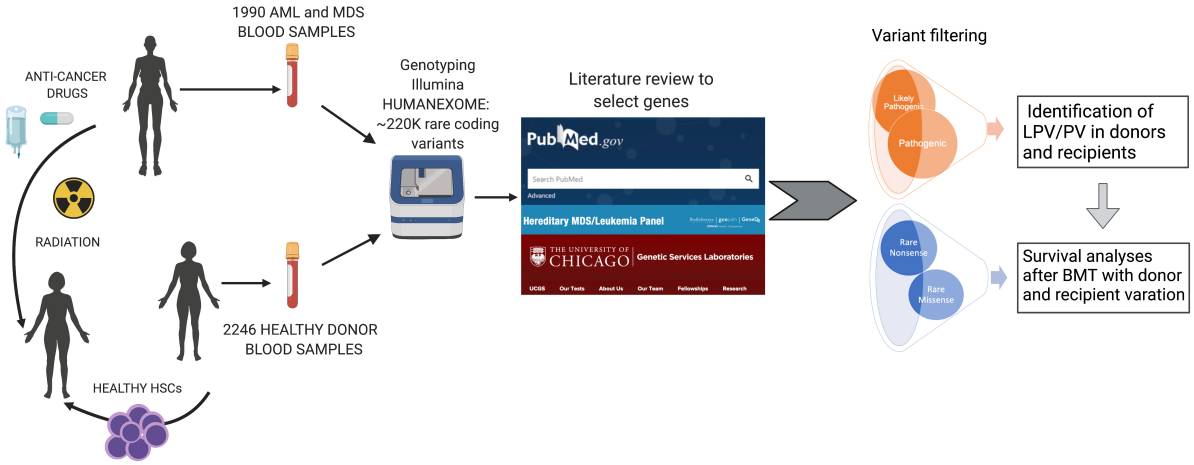

Figure 1. Study schema for frequency and survival analysis of LPV/PV in DISCOVeRY-BMT.

and MDS). Clinical information for all variant carriers was extracted and reviewed; summary statistics on sex, age, disease, or other features were generated. All analyses were performed in R version 4.0.3.

Variant-based testing of association with survival

Cox proportional hazard models were used to analyze variant association with 1-year survival following transplant using the genotypes of either the patients or the corresponding donors while controlling for additional patient covariates, including: age at BMT, disease diagnosis (AML or MDS), disease status at BMT, cell source (peripheral blood, marrow), year of BMT, and principal components from EIGENSTRAT[13]. Survival analyses were performed using the survival package in R version 4.0.3 and Kaplan-Meier curves were used to visual associations. Only the most frequent LPV/PV identified in donors and recipients were analyzed.

RESULTS

Following quality control, exome, clinical and demographic data were available on 1,990 donor-recipient pairs with an additional 256 donor genomes available with corresponding clinical and demographic data on the matched recipient but no recipient exome data [Table 1]. Most of the 1,523 AML cases were *de novo* and approximately 9% of patients had therapy-related AML (t-AML). The most frequently reported previous cancers in patients with t-AML were breast, non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma (HL). Therapy-related MDS (t-MDS) comprised 18% of the 467 MDS patients and the most frequently reported antecedent cancers in MDS patients were NHL, breast, ALL, HL, and AML [Table 1].

The literature review and MESH search yielded 122 articles; after removing clinical reviews or uninformative articles for building a gene list, 32 articles were identified. When combined with information from OMIM, this resulted in 667 genes, including genes in commercially available clinical genetic tests for hereditary hematologic malignancies. Gene information from ClinVar on pathogenicity is provided in Supplementary Table 1. For frequency analyses, we first identified variants and genes in ClinVar that were available on the HumanExome and then determined the frequency in DISCOVeRY-BMT. For survival analyses, we analyzed the most frequent LPV/PV in donors and patients to determine if the identified susceptibility variants correlated with survival.

Table 1. DISCOVeRY-BMT acute myeloid leukemia and myeloid dysplastic syndrome patient and 8/8 HLA matched unrelated donor characteristics

Patient and donor characteristics	Cases Cohort 1/Cohort 2 *n* = 1,528 (%)/462 (%)	Controls Cohort 1/Cohort 2 *n* = 1,774 (%)/472 (%)
Age, years		
Mean (range)	46 (< 1-74)/47 (< 1-78)	34 (18-61)/31 (18-60)
Sex		
Female (%)	703 (46)/213 (46)	567 (32)/113 (24)
Male (%)	825 (54)/249 (54)	1,206 (68)/359 (76)
Disease[1]		
AML, all cases*	1,196 (78)/327 (71)	-
de novo AML	976 (81)/285 (87)	-
de novo AML w/ normal cytogenetics	287 (24)/82 (25)	-
de novo AML w/ cytogenetic abnormalities	466 (39)/114 (35)	-
Cytogenetic subtype[2]:		
Core binding factor	47 (10)/32 (14)	-
MLL	56 (12)/23 (20)	-
Any translocation	70 (15)/17 (15)	-
Del5/del7	113 (21)/55 (23)	-
Any trisomy	149 (33)/43 (38)	-
Any monosomy	121 (26)/24 (21)	-
> 3 cytogenetic abnormalities	127 (37)/42 (37)	-
Therapy-related AML	92 (8)/20 (6)	-
Prior diagnosis[2]:		
Breast cancer	31 (34)/7 (35)	-
Non-Hodgkin lymphoma	17 (18)/3 (15)	-
Hodgkin lymphoma	11 (12)/1 (5)	-
Sarcoma	8 (9)/2 (10)	-
Gynecologic cancer	6 (7)/2 (10)	-
Testicular cancer	3 (3)/2 (10)	-
Acute lymphocytic leukemia	3 (3)/1 (5)	-
MDS, all cases	332 (22)/135 (29)	-
de novo MDS	279 (84)/103 (76)	-
Sub disease[2]:		
MDS-unclassified	46 (14)/19 (18)	-
Refractory anemia	62 (19)/10 (10)	-
RAEB 1 and 2[4]	123 (37)/47 (46)	-
RCMD, RCMD-RS	0 (0)/13 (13)	-
RARS	11 (3)/9 (5)	-
Therapy-related MDS	45 (14)/29 (21)	-
By prior diagnosis[2]:		
Non-Hodgkin lymphoma	9 (20)/7 (24)	-
Breast cancer	8 (18)/4 (14)	-
Acute lymphocytic leukemia	4 (9)/2 (7)	-
Hodgkin lymphoma	6 (13)/2 (7)	-

Acute myeloid leukemia	4 (9)/2 (7)	-
Sarcoma	1 (2)/4 (14)	-
Chronic Lymphocytic Leukemia	2 (4)/3 (10)	-
Other disease	10 (22)/6 (21)	-

RAEB: Refractory anemia excess blasts; RCMD: refractory cytopenia with multilineage dysplasia; RCMD-RS: refractory cytopenia with multilineage dysplasia and ringed sideroblasts; RARS: refractory anemia with ring sideroblasts. [1]subgroup percentages calculated as the percentage of the total number of AML and MDS cases in each cohort; [*]cytogenetics were unavailable on 173 (cohort 1) and 16 patients (cohort 2) and morphology could not be evaluated on 7 (cohort 1) and 3 (cohort 2) patients [2]subgroup percentages calculated as the percentage of the cases of corresponding disease group in each cohort, % sum to greater than 100 due to overlapping groups; [4]5 individuals had RAEB in transformation.

Variant frequency analyses

The ClinVar variants (n = 23,911) meeting LPV/PV criteria described above span 470 of the 665 cancer genes (Clinvar accessed 1/2022). The HumanExome Chip contained 82/470 cancer genes identified in ClinVar and 190 LPV/PVs. We identified 45 LPV/PV across 32 genes in DISCOVeRY-BMT AML or MDS patients and/or donors. Thirteen autosomal dominant (AD) variants in 10 genes were identified in 2.8% of patients (n = 58) and 2.4% of donors (n = 54) donors [Table 2]. The most frequent AD PV in patients, c.3G>A (p.M1I) in *DDX41*, was seen in 11 *de novo* AML, six MDS patients and 0 donors; significantly more patients with this mutation were male than female (15/17, P = 0.002) and had normal cytogenetics (14/17, P = 0.008). We identified a second independent *DDX41* PV at c.490C>T (p.R164W) in one t-AML patient with antecedent sarcoma and one donor [Table 2]. Neither variant has been identified as somatic in COSMIC or TCGA and are acknowledged to be germline in origin. Nineteen donors had the *CHEK2* 470T>C (p.I157T) variant; this was also seen in patients (6 AML, 1 t-AML, and 3 MDS).

Collectively, the second most frequent LPV/PV in AML and MDS transplant donors (n = 7) were those in Fanconi Anemia genes (*FANCM, FANCD2, FANCC,)* which were also detected in three recipients. In *FANCM*, we identified two nonsense variants, rs147021911 (p.Q1701X, c.5101C>T) in three donors and no patients, and rs14467652 (c.5791C>T p.R1931X) in two donors and two patients with AML (one patient with antecedent central nervous system cancer). Both functional variants show reproducible population-level associations with familial breast cancer, early onset breast cancer, and triple-negative breast cancer when heterozygous, and are thus considered breast cancer risk variants, with some evidence for acting as low penetrance pancreatic cancer variants[14-22]. The *FANCD2* pathogenic variant, rs201811817, c.2715+1G>A, seen in one donor and has been associated with breast and testicular carcinoma in the heterozygous state[23,24]; this variant has been seen in the homozygous or compound heterozygous state in multiple Fanconi Anemia cohorts[24]. Lastly one donor had a *FANCC* variant, rs121917783 (c.553C>T, p.R185X), shown to be a breast cancer susceptibility mutation[25]. Additional AD PVs in AML and MDS patients and donors include *APC* (c.3071T>A, p.I1307K), *CHEK2* (c.349A>G, p.R117G), *MITF* (c.1075G>A), and *TSHR* (c.484C>T, c.1349G>A); ATM (c.6095G>A, p.R2032K) was seen in one AML patient [Table 2]. *APC, ATM, CHEK2, and MITF* are established cancer predisposition genes, including cancers of the breast (men and women), prostate, thyroid, colon, kidney, and skin[26], and have recommendations for genetic testing in relatives and medical management. A PV in *LRRK2*, p.G2019S, identified in a donor, is associated with late-onset Parkinson's disease[27]. While not a germline cancer gene, *LRRK2* was selected for evidence of recurrent somatic mutations across cancers and represents a secondary finding[28]. We did not detect any LPV/PV in several genes previously associated with hereditary hematologic malignancies, such as *ANKRD26, CEBPA, ETV6, GATA2, MBD4, RUNX1, SRP72, TERC/TERT,* and *TP53*. This absence of findings can be attributed to both the content of the Exome Chip and our criteria for selecting variants. For example, despite the presence of 39 *ANKRD26* missense variants on the Exome Chip, 18 of which were found in DISCOVeRY-BMT, none were LPV/PV. Similar scenarios occurred with other commonly recognized genes; in addition, there were LPV/PV variants present on the Exome Chip but were undetected in DISCOVeRY-BMT.

Table 2. Autosomal dominant pathogenic and likely pathogenic variant allele frequencies in DISCOVeRY-BMT AML and MDS patients and HLA matched unrelated donors

Gene/rsid	Chr: BP (hg38)	Clinical Sig.	Pubmed ID	Alleles ref/alt	Amino acid	AML C1/C2	MDS C1/C2	Donors C1/C2	AML freq.	MDS freq.	Donor freq.
APC/rs1801155	5: 112175211	Con. Inf./LP/P	24429628, 29489754, 29625052, 26556299, 28199314, 2658044	T/A	Ile1307Lys	6/0	3/0	5/4	0.00394	0.00649	0.00401
ATM /rs139770721	11: 108186638	LP/P	24429628, 29489754, 29625052, 26556299, 2819931	G/A	Arg2032Lys	0/0	1/0	0/0	0	0.00216	0
CHEK2 /rs28909982	22: 29121326	LP/P	28199314,25503501 22419737, 24429628, 24763289, 26556299, 21244692, 29489754, 26681312, 29625052, 18725978, 12454775, 16982735, 12610780, 16835864, 27553368, 27595995, 28503720, 27798748 ,28125075, 29922827, 29945567, 30256826, 30128536,29659569	T/C	Arg117Gly	0/0	1/0	2/0	0	0.00216	0.00089
CHEK2 /rs17879961	22: 29121087	LP	24429628, 29489754, 29625052, 26556299, 28199314	A/G	Ile157Thr	4/3	2/1	14/5	0.0046	0.00649	0.00846
DDX41 /rs141601766	5: 176943944	LP/P	26712909, 27795557, 27210295, 27133828, 28600339,31484648, 30963592, 32098966, 33585199, 28104920	C/T	Met1Ile	8/3	4 / 2	0 / 0	0.00722	0.01299	0
DDX41 /rs142143752	5: 176942767	LP/P	28600339, 26712909	G/A	Arg164Trp	1/0	0 / 0	1 / 0	0.00066	0	0.00045
FANCC /rs121917783	9: 97912338	P	24429628, 28600339, 29489754, 29625052, 26556299, 28199314,23028338, 8128956,20509860, 26681312	G/A	Arg185Ter	0/0	0/0	1/0	0	0	0.00045
FANCD2 /rs201811817	3: 10115047	P	31980526, 26689913, 30676620, 30609409, 22829014, 17436244, 24448499, 28678401, 25239263, 25525159, 25703294, 28386063, 28600339, 29489754, 29625052, 28199314	G/A	N/A	1/0	0/0	1/0	0.00066	0	0.00045
FANCM /rs147021911	14: 45658326	LP/P	28600339, 29489754, 29625052, 28199314	C/T	Gln1701Ter	0/0	0/0	3/0	0	0	0.00134
FANCM /rs144567652	14: 45667921	LP/P	28600339, 29489754, 29625052, 28199314, 28702895, 28837162, 26822949, 30426508, 23409019, 28687971, 28591191, 30267214, 23585368	C/T	Arg1931Ter	2/0	0/0	2/0	0.00131	0	0.00089
LRRK2 /rs34637584	12: 40734202	P	15726496	G/A	Gly2019Ser	0/0	0/0	1/0	0	0	0.00045
MITF /rs149617956	3: 70014091	LP/P	29489754, 29625052, 26556299, 28199314	G/A	Glu425Lys	11/2	2/0	6/4	0.00854	0.00433	0.00445
TSHR /rs121908869	14: 81422146	P	29625052, 26556299, 28199314	G/C	Cys41Ser	0/0	0/0	1/0	0	0	0.00045
Total						32/8	13/3	37/13	0.0263	0.0346	0.0223

Chr: Chromosome; bp: base-pair; hg38: genome build; Clinical Sig.: clinical significance; C1: cohort 1; C2: cohort 2; ref: reference allele; alt: alternate allele; AML: acute myeloid leukemia; MDS: myelodysplastic syndromes; Freq.: allele frequency.

In addition to AD variants in known cancer susceptibility genes, we also identified PV variants in DNA Cytosine-5-Methyltransferase (*DNMT3A*), rs147001633 (p.R882H, c.2645G>A) and rs144689354 (p.R635W, c.1903G>A). While germline PVs in *DNMT3A* are associated with Tatton-Brown-Rahman

Syndrome, an extremely rare overgrowth syndrome[29], the p.R882H mutation is the most common site of *DNMT3A* acquired mutations in AML and this variant should be viewed as a somatic finding in 45 AML patients[30,31]. This variant was also identified in four donors; the presence of p.R882H in these otherwise young healthy donors could represent clonal hematopoiesis of indeterminate potential (CHIP)[32]. The second *DNMT3A* PV, rs144689354 (p.R635W, c.1903G>A), was seen in one AML patient and one donor; as with p.R882H, the PV in the donor likely represents CHIP[31]. Thirty-four LPV/PVs in 22 genes for autosomal recessive (AR) conditions were identified in 211 AML and MDS patients (11.1%) and 246 donors (11%). Supplementary Table 2 shows the carrier frequency of mutations in patients and donors in genes associated with AR conditions. These include cancer phenotypes such as MUTYH-associated polyposis (*MUTYH)* and Schwachman-Diamond Syndrome (*SBDS).* While mutation carriers do not exhibit the AR disorder or show associations with other solid tumors, there are increased screening recommendations for *MUTYH* carriers with a family history of colon cancer[33].

Variant associations with survival

Cox proportional hazard models were performed for the most frequent LPV/PV in recipients (*DDX41*) and donors (*CHEK2* and collectively the variants in the FA genes). Patients with a *DDX41* mutation did not differ in survival during the first year after transplant compared to those without a *DDX41* mutation ($P = 0.30$). Donor *CHEK2* LPV/PV was not related to recipient survival ($P = 0.25$). In contrast, patients with donors with a LPV/PV in a FA gene had significantly lower survival (HR = 2.38, 95%CI: 1.06-5.31, $P = 0.035$), compared to patients whose donors did not have an LPV/PV variant. All seven recipients of donors with an LPV/PV FA variant died within two years of transplant and five died within the first year. Overall survival for these patients ranged from 0.46 months to 21.3 months, with a median survival of 4.9 months. An adjudication panel reviewed all cause-specific recipient deaths within 12 months of transplant[12]; two recipients died due to disease in less than seven months following transplant, two recipients died due to infection/organ failure within one month, and one recipient died due to GvHD within six months of transplant. Supplementary Figure 1 shows patients with a donor who had an FA LPV/PV were almost 2.5 times more likely to die within the first year following transplant.

DISCUSSION

Autosomal dominant acting LPV/PV cancer variants were identified in both pre-transplant AML and MDS patients and donors. We identified 18 patients and 1 donor with LPV/PV in the known myeloid leukemia gene *DDX41*. Recently, a large-scale study on *DDX41* mutations in 5,609 multi-ethnic patients with AML or MDS showed that germline or somatic mutation in *DDX41* was seen in 202 of the 5,609 patients (3.6%)[34]. These data also show that if a *DDX41* variant is present in a patient's NGS marrow biopsy, there is a 78% chance of a germline mutation; in contrast, without a somatic *DDX41* mutation, the probability of a germline DDX41 variant is around two percent. When considering a history of cytopenia, family history of cancer, or personal history of another cancer, it is almost certain the patient will have a germline *DDX41* pathogenic variant if a somatic mutation is present[35]. These studies provide genetics professionals with concrete numbers to discuss the risks of having a germline PV in *DDX41* before and after NGS testing, irrespective of family or personal history.

While there was no distinction made for those undergoing transplant in Makishima *et al.*, the 1% *DDX41* mutation frequency in DISCOVeRY-BMT is attributable to only two mutations[34]. Variant coverage on the exome chip represents a fraction of the data available with sequencing, so unsurprisingly, this fraction is lower in our study. Our sex finding, showing a higher *DDX41* LPV/PV frequency in males versus females, and age results, that patients with *DDX41* mutations were significantly older than AML and MDS patients without the mutation, are in line with previously published literature and Makishima *et al.*'s findings[34,36]. In

the future, sex-specific information could be used to further refine estimates of mutation likelihood following bone marrow biopsy results for counseling patients with AML and MDS.

We identified several AR inherited PVs in donors and patients, including those responsible for Fanconi Anemia in a homozygous state and solid tumors in a heterozygous state[21,24,25,37,38]. FA mutation carriers do not exhibit the AR disorder; however, there is evidence that heterozygous Fanconi Anemia gene carriers may be at increased risk of developing MDS and AML[38]. The identification of the donor FA association with recipient survival and our previous publications on exome and genome-wide significant associations with survival in DISCOVeRY-BMT provide strong evidence that non-HLA genetics is relevant to patient survival and replication of these findings in additional cohorts could have implications for patient clinical care and for counseling patients around outcomes following transplant[10,11,39]. At present, there are no NCCN or WHO guidelines on germline testing for survival outcomes following transplant. New genes and PVs with biological relevance will likely continue to be identified and validated and may need to be considered in the context of donor selection, strategies for transplant timing and/or pre-transplant conditioning intensity. While a larger and more diverse cohort with sequence data and follow-up time greater than 1 year will be necessary to definitively answer these questions, this is an arena where genetic counselors could play a role in patient care.

Given the presence of both AD and AR pathogenic variants in our AML and MDS patients, it is also worth considering questions that arise around the return of results, which have direct implications for related family as individuals and as potential donors to their affected relatives. First, hematologic malignancy prevention strategies for unaffected, mutation-positive at-risk relatives are not well defined[6]. Medical management often utilized in the care of families affected by a predisposition to solid tumors, such as prophylactic surgeries, is not feasible in mitigating leukemia risk. For example, a prophylactic BMT in an unaffected individual is not an acceptable medical prevention for AML or MDS due to the high morbidity and mortality after BMT and the increased risk of t-AML or t-MDS following transplant. A second issue centers around family members serving as blood or marrow donors for related or haplo-identical transplants[9]. While unrelated donors must be 18 years of age, this is not true of related donors; a sibling, child, or related donor who is a minor may further add to families' psychological and financial difficulties at the time of diagnosis. A systematic review of 16 studies across 1,023 related hematopoietic stem cell donors on experiences around information and psychosocial support found few studies addressed donors' unmet needs. Importantly, genetic testing in the context of cancer predisposition contribution to psychosocial stressors has not been measured or evaluated in published literature[40]. For mutations associated with adult age at onset of disease, such as *DDX41*, this could translate to testing for a mutation with average onset decades later and why the National Society of Genetic Counselors (NSGC) does not encourage genetic testing for adult-onset diseases in individuals < 18. This, and more broadly the issue of testing coercion that could arise due to lack of matched unrelated donors, may disproportionately impact individuals of African, Asian, Native American, Pacific Islander, and mixed genomic ancestries given the likelihood of finding an unrelated match is substantially reduced due to a smaller donor pool coupled with more human leukocyte antigen (HLA) diversity[41]. In January of 2023, the NMDP initiated a policy that allows donors to receive results about genetic variation detected in a recipient following transplant, but this information is not made available at donation[42].

Previous DISCOVeRY-BMT variant and gene-based analyses were performed irrespective of variant pathogenicity and were the first to identify rare and common variations related to one-year survival following transplant[10-12]. The analyses herein focus on LPV/PV variants in a select list of genes related to cancer and demonstrate that germline mutations in known cancer susceptibility genes with medical

management recommendations are present at low frequency in unrelated donors. While broad unrelated donor germline screening is not standard practice, it is imperative that research on the psychosocial implications of germline testing for hereditary hematologic malignancies keep pace with genomic discovery and the framework for donor disclosure is continually developed and refined[43]; it is only in this way that we will be able to effectively incorporate appropriate genomic testing.

Counseling BMT patients and their families can be further complicated by the type of genomic variation identified. While a novel germline *DNMT3A* mutation was recently identified in a mother-son pair with leukemia[44], the two *DNMT3A* variants we identified in AML patients are likely somatic. Those in the five donors are likely CHIP. CHIP is associated with an increased risk of hematologic cancer, an increase in all-cause mortality, decreased overall survival, and susceptibility to heart disease, which makes the finding of these mutations in our young donors of interest[31,45,46]. At present, opinions are divided in the field regarding screening donors for CHIP[47,48]. To understand the impact of donor or recipient CHIP on transplant outcomes, and subsequently make clinical recommendations for donor selection and genetic counseling, larger population studies and clinical trials will be necessary[49,50]. From a patient care and genetic counseling perspective, CHIP highlights unique considerations of caring for transplant patients and their donors. While the identification and clinical implications of CHIP in high-risk populations have recently been explored, there is a paucity of articles on counseling patients with CHIP[51]. An extensive MESH search identified one article written in the last year focusing on counseling older adults with cancer[52].

This study is not without limitations. The patient and donor population in DISCOVeRY-BMT, while representative of HLA-matched unrelated transplants in the United States, is not representative of the racial and/or ethnic diversity of AML or MDS patients. Larger more diverse studies with follow-up time longer than one year are imperative. In addition, patient samples are blood, and while taken pre-transplant from patients in complete remission (CR) helps distinguish between somatic germline, the exclusion of mutations that are only somatic was not possible. The selection of genes with known function-related cancer susceptibility can be viewed as a strength; however, the assumption that genes associated with susceptibility are also associated with one-year survival following treatment is an independent hypothesis. Lastly, while some work has been performed for validation and functional purposes[10,53,54], additional cohorts with full sequencing data and further functional studies are warranted.

We identified LPV/PV across cancer genes in AML and MDS patients and their HLA-matched unrelated blood or marrow donors. These data are the first to demonstrate that collectively, donor PV across Fanconi Anemia genes significantly impacts recipient survival in the first year following transplant. Using a decade of data from CIBMTR on AML and MDS patients and donors, these results highlight the need for genomic science and genetic counseling research around the characterization of susceptibility and survival-correlated germline variation in patients receiving a BMT, donor selection, and the conveyance of this information to the patient and their family.

DECLARATIONS

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Authors' contributions

Wrote the manuscript, designed the research, performed analyses and quality control and generated figures and tables: Sucheston-Campbell L
Performed the genotyping: Pooler L, Haiman C, Sheng X
Performed analyses and quality control: Clay-Gilmour A, Zhu Q
Adjudicated recipient causes of death: Hahn T, McCarthy P, Pasquini M
Contributed to content related to genetic counseling and manuscript writing: Senter L, Brock P, Cooper J
All authors reviewed and approved the manuscript.

Availability of data and materials

De-identified individual participant data that underlie the reported results are available at the Center for International Blood and Marrow Transplant (www.cibmtr.org). Both genotype and phenotype data for the entire DISCOVeRY-BMT cohort will also be made available in dbGaP following NIH requirements or by request from DBMT study team (Contact: Alyssa Clay-Gilmour, claygila@mailbox.sc.edu), excluding 978 recipient-donor pairs for which the informed consent is not compliant with the NIH Genomic Data Sharing Policy.

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Conflicts of interest

McCarthy P: Consulting: BlueBird Biotech, Bristol-Myers Squibb, Celgene, Fate Therapeutics, Janssen, Juno, Karyopharm, Magenta Therapeutics, Sanofi, Takeda; Honoraria: BlueBird Biotech, Bristol-Myers Squibb, Celgene, Fate Therapeutics, Janssen, Juno, Karyopharm, Magenta Therapeutics, Medscape, Takeda; Institutional Research Support: Celgene. Pasquini M: Institutional Research Support: Bristol-Myers Squibb, Novartis, Kite, GlaxoSmithKline; Consulting: Amgen (institution), Bristol-Myers Squibb (personal). Sucheston-Campbell L and Hahn T: report grants from NIH/NHLBI, and grants from NIH/NCI, during the conduct of the study. All other authors have nothing to declare.

Ethical approval and consent to participate

Recipients and donors provided written informed consent for participation in the Center for International Blood and Marrow Transplant Research clinical outcome database and research repository. The biospecimen and database protocols were approved by the National Marrow Donor Program (NMDP) Institutional Review Board (IRB), as well as the individual transplant and donor centers' IRBs. Recipients and donors were not compensated for their participation. This study was reviewed and approved by the Roswell Park Comprehensive Cancer Center and NMDP IRBs. Sucheston-Campbell L, Wang J, Clay-Gilmour A, Zhu Q, Spellman SR, and Hahn T had access to all the data during the duration of the study.

Consent for publication

Not applicable.

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