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CORRESPONDENCE

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Prognostic impact of donor mitochondrial genomic variants in myelodysplastic neoplasms after stem-cell transplantation

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Abstract

Mitochondrial DNA (mtDNA) variants in patients with myelodysplastic neoplasms (MDS) are shown to be prognostic of outcomes after allogeneic hematopoietic cell transplantation (allo-HCT). However, the prognostic impact of donor mtDNA variants is unknown. Here, we performed whole-genome sequencing on 494 donors who were matched to MDS patients enrolled in the Center for International Blood and Marrow Transplant Research (CIBMTR). We evaluated the impact of donor mtDNA variants on recipients' transplantation outcomes, including overall survival, relapse, relapse-free survival, and transplant-related mortality. The optimism-adjusted bootstrap method was employed to evaluate the prognostic performance of models that include donor mtDNA variants alone and combined with MDS- and HCT-related clinical factors. In the entire donor cohort, we identified 1,825 mtDNA variants, including 67 potential pathogenic variants. Genetic variants on *MT-CYB* and *MT-ND5* genes were identified as independent predictors of posttransplant outcomes. Integration of donor mtDNA variants into the models based on the International Prognostic Scoring System-Revised (IPSS-R) could capture more prognostic information for MDS patients. Sensitivity analysis in 397 unrelated donors obtained similar results. More importantly, we found that incorporating donor mtDNA variants with donor age and the degree of HLA-matching could help to identify "suboptimal" younger HLA-well-matched unrelated donors and "optimal" older HLA-partially/mismatched unrelated donors. Our study shows that mtDNA variants in donors, including those from unrelated donors, hold prognostic value for MDS patients undergoing allo-HCT and augment the prognostic stratification of current scoring systems. These findings present an opportunity to refine donor selection strategies and improve posttransplant outcomes for MDS patients.

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To the Editor,

Allogeneic hematopoietic stem-cell transplantation (allo-HCT) is the only curative therapy for myelodysplastic neoplasms (MDS) [1]. However, disease relapse and transplant-related mortality (TRM) remain the main obstacles limiting the success of allo-HCT. Donor-related factors, such as donor age and genetic susceptibility, have been reported to be independent prognostic factors of posttransplant survival in MDS [2–4]. Despite mitochondria playing a critical role in MDS pathogenesis [5], few studies have investigated the effects of donor mitochondrial DNA (mtDNA) variants on posttransplant outcomes in MDS. Using whole-genome sequencing (WGS), we profiled the prognostic landscape of mtDNA mutations in 494 European ancestry patients with MDS who underwent allo-HCT [6]. Here, we performed WGS on their 494 donors (Supplementary Table 1) and investigated the prognostic impact of donor mtDNA variants.

A total of 1,825 mtDNA variants were identified, with the median number of 32 (ranging from 6 to 88) per donor. Sixty-seven mtDNA variants were predicted to be pathogenetic. Among them, four heteroplasmic rare variants were associated with at least one of the four post-transplant outcomes (i.e., overall survival (OS), relapse, relapse free survival (RFS), and TRM) ($P<0.05/67=7.46\times10^{-4}$) (Supplementary Table 2). Common variants that were associated with posttransplant outcomes at P values <0.05 were listed in Supplementary Tables 3–6. Gene-based analysis showed that donor *MT-ND5* was associated with RFS ($P=1.02\times10^{-4}$), relapse ($P=6.10\times10^{-5}$) and TRM ($P=3.60\times10^{-4}$), and *MT-CYB* was associated with relapse ($P=9.44\times10^{-4}$) after Bonferroni correction ($P<0.05/16=3.13\times10^{-3}$) (Table 1). *MT-ND5* is a mitochondrial respiratory complex I subunit and a genetic hotspot for many cancers, including MDS [6, 7]. Genetic alterations in complex I genes may cause the generation of ROS, impair oxidative phosphorylation (OXPHOS), and reduce the ATP synthesis, all of which could promote tumorigenesis [8]. *MT-CYB* is fundamental for the assembly and function of OXPHOS complex III. Genetic variants on *MT-CYB* resulting in complex III deficiency have reported in association with blood disorders [9, 10]. Additional significantly associated mitochondrial genes were observed in burden test and/or SKAT (Supplementary Tables 7 and Supplementary Figs. 1–4). No significant association was observed for OS. Similar results were observed when adjusting for patients' clinical factors (i.e., IPSS-R, MDS type and pre-transplant treatments) with minor differences (Supplementary Table 8).

Eighteen mitochondrial haplogroups were predicted in donors. Within our expectation, haplogroup H was the most common haplogroup in our study population [6]. Compared to H, haplogroup V was significantly associated with shorter OS (HR, 1.95; 95% CI, 1.05–3.62; $P=0.03$) and worse TRM (HR, 2.28; 95% CI, 1.03–4.99; $P=0.04$) (Supplementary Table 9).

Table 1 Associations between donor mitochondrial genes and MDS outcomes after allo-HCT

Gene	No. of MDS	No. of Death	No. of Relapse	No. of TRM	OS	RFS	Relapse	TRM
Control region	494	278	178	136	0.02	0.18	0.19	6.44×10^{-3}*
Complex I	494	278	178	136	0.11	1.21×10^{-3}*	0.20	0.27
ND1	448	251	162	121	0.29	0.37	0.51	0.17
ND2	483	272	176	131	0.26	0.37	0.02	0.64
ND3	145	91	53	45	0.57	0.33	0.56	0.35
ND4	309	179	108	92	0.14	0.14	0.01	0.08
ND4L	81	46	30	26	0.38	0.93	0.29	0.82
ND5	494	278	178	136	0.44	1.02×10^{-4}*	6.10×10^{-5}*	3.60×10^{-4}*
ND6	190	105	74	47	0.01	0.08	0.28	0.01
Complex III	493	277	177	136	0.08	0.04	9.44×10^{-4}*	0.69
CYB	493	277	177	136	0.08	0.04	9.44×10^{-4}*	0.69
Complex IV	402	219	140	109	0.04	0.14	0.43	0.27
CO1	346	194	120	98	0.02	4.06×10^{-3}	0.01	0.01
CO2	139	66	40	36	0.10	0.19	0.01	0.32
CO3	180	102	67	46	0.15	0.03	0.05	4.86×10^{-3}
Complex V	491	276	176	136	0.27	0.20	5.12×10^{-4}*	0.44
ATP6	490	276	176	136	0.34	0.22	2.84	0.55
ATP8	48	30	15	17	0.28	0.36	0.14	0.36
rRNA	489	275	176	135	0.07	0.58	0.04	0.54
tRNA	245	133	88	66	0.08	0.37	0.39	0.08

Models are adjusted for donor age, sex, type and first 10 principal components.

*Significant *P* values after Bonferroni correction.

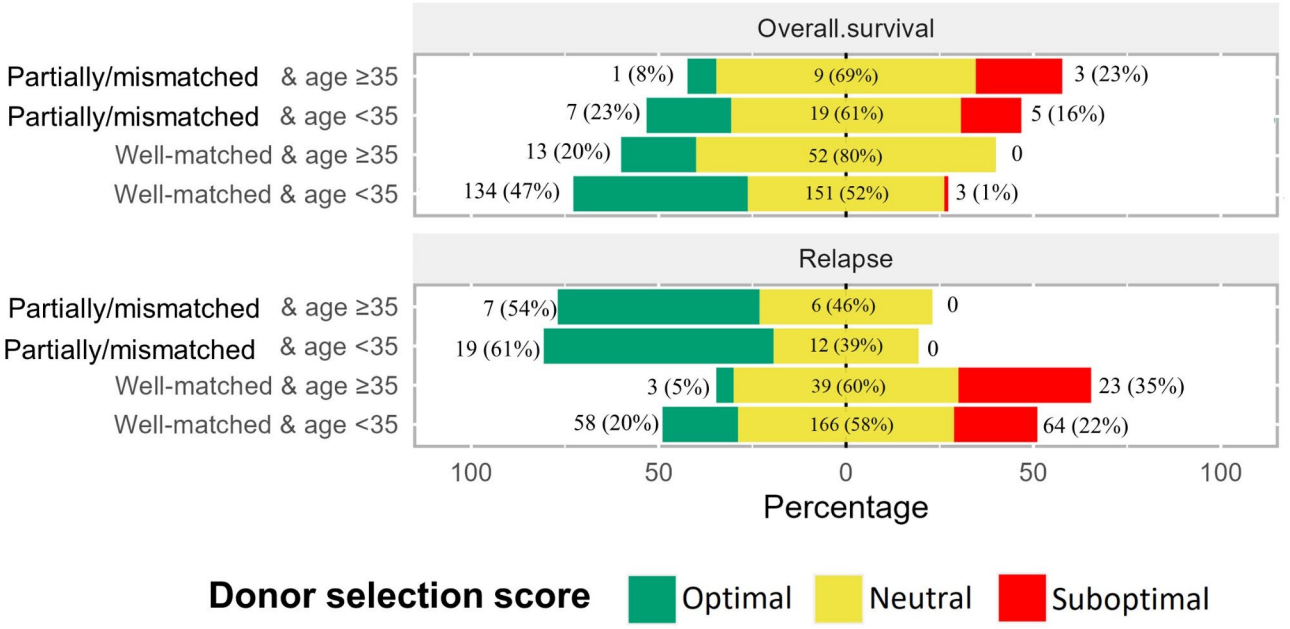

Fig. 1 Clinical implications of donor mtDNA variants in identifying optimal and suboptimal unrelated donors. Donor selection scores were computed based on donor age and the degree of HLA-matching, with and without the inclusion of donor mtDNA variants. "Suboptimal" indicates that incorporating donor mtDNA variants may lead to a shorter OS or a higher risk of relapse for the recipient, compared to considering only the donor's age and the degree of HLA-matching. "Optimal" indicates that incorporating donor mtDNA variants may result in a longer OS or a lower risk of relapse for the recipient, compared to only considering the donor's age and the degree of HLA matching. "Neutral" suggests no differences between the scores with and without the inclusion of donor mtDNA variants. The x-axis represents the number and percentage of donors that classified as "optimal", "neutral" and "suboptimal" after incorporating donor mtDNA into the score. Each row sums to 100%.

We then evaluated whether donor mtDNA variants could predict patient posttransplant outcomes. As shown in Supplementary Fig. 5A, the model based on IPSS-R alone had a low to moderate performance with corrected C-index of 0.58, 0.56, 0.57, and 0.56 to predict OS, relapse, RFS and TRM, respectively. Incorporating donor mtDNA variants into IPSS-R model improved the performance of the IPSS-R model, with the absolute value of corrected C-index increased from 0.58 to 0.59 for OS, from 0.56 to 0.58 for relapse, and from 0.57 to 0.58 for RFS, respectively. However, no improvement was observed in predicting TRM.

To examine whether the prognostic effects of donor mtDNA variants are caused by the shared genetic heritability between related donors and patients, we further conducted a sensitivity analysis in 397 unrelated donors. We observed similar results as those in the entire donor cohort with minor differences (Supplementary Fig. 5B and Supplementary Tables 10–16), suggesting that genetic heritability from unrelated donors could also provide additional information to improve the prognostic stratification of MDS patients undergoing allo-HCT.

To investigate the clinical implications of donor mtDNA variants in optimizing donor selection, we further computed donor selection scores using donor age and the degree of HLA-matching, with and without the inclusion of donor mtDNA variants (Supplementary Methods, Fig. 1). For OS, 1% (n=3) younger HLA-well-matched unrelated donors were categorized as "suboptimal", and 8% (n=1) older HLA-partially/mismatched unrelated donors were considered as "optimal". For relapse, 22% (n=64) younger HLA-well-matched unrelated donors were categorized as "suboptimal", and 54% (n=7) older HLA-partially/mismatched unrelated donors were categorized as "optimal". Our findings highlight that utilizing donor mtDNA variants can assist in decision making of which donor is better than another.

In conclusion, this study lays the groundwork for updating guidelines in donor selection strategies, which may ultimately enhance the likelihood of successful HCT. Future studies focusing on deeper sequencing of targeted genes to evaluate mtDNA in the context of IPSS-M model, and evaluating the interplay between nDNA and mtDNA variants, as well as the interactions between donor and recipient variants, may yield additional insights to further refine prognostic stratification.

Abbreviations

allo-HCT	Allogeneic hematopoietic stem-cell transplantation
MDS	Myelodysplastic syndromes
mtDNA	Mitochondrial DNA
WGS	Whole-genome sequencing
CIBMTR	Center for International Blood and Marrow Transplant Research
OS	Overall survival
RFS	Relapse-free survival
TRM	Transplant-related mortality

IPSS-R	Revised International Prognostic Scoring System
ROS	Reactive oxygen species
OXPHOS	Oxidative phosphorylation
tRNA	Transfer RNA
rRNA	Ribosomal RNA
ETC	Electron transport chain
HF	Heteroplasmic fraction
AF	Allele frequency
SKAT-O	Sequence kernel association test

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Data availability
CIBMTR supports accessibility of research in accord with the National Institutes of Health (NIH) Data Sharing Policy and the National Cancer Institute (NCI) Cancer Moonshot Public Access and Data Sharing Policy. The CIBMTR only releases de-identified datasets that comply with all relevant global regulations regarding privacy and confidentiality.

Declarations

Ethics approval and consent to participate
The study was approved by the Institutional Review Board of CIBMTR and conducted in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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