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Research Communication

Impact of MICA-129 Mismatch on Hematopoietic Stem Cell Transplantation Outcomes: Evidence from a Large European Cohort and Meta-Analysis

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Matching for HLA antigens is the gold standard in allogeneic hematopoietic stem cell transplantations (HSCT), but even a full match does not suffice to avoid complications such as graft-versus-host disease (GvHD). Other genetic factors in non-HLA genes may also affect HSCT outcome. One promising novel histocompatibility factor is the major histocompatibility complex class I chain-related gene A, *MICA*.

MICA encodes a transmembrane glycoprotein, also expressed in the bone marrow and GvHD tissues, which is a ligand for the activating NKG2D receptor on NK cells and subsets of T cells, where it triggers cytotoxicity and cytokine secretion or acts as a co-stimulator. MICA-129 (rs1051792) polymorphism affects binding affinity and NKG2D signaling [1,2]. We studied the effect of *MICA* polymorphism and matching on HSCT outcomes and performed a meta-analysis on *MICA* results on HSCT.

Our HSCT study cohort was retrospective and multipopulational, from Finland, the UK, Spain, and Poland. Approval for data collection and usage was granted by the Ethical Review Boards of each collaborating hospital. The total number of recipients available for the analysis was 2175, with 1492 donors and 1409 donor-recipient pairs. MICA-129 variant rs1051792 was extracted from genotyped and imputed data, while *MICA* alleles were imputed using variants in the HLA region.

We tested MICA-129 mismatches, MICA-129 donor and recipient genotypes, and *MICA* allele mismatches for their effect on aGvHD, cGvHD, relapse, overall survival (OS), and relapse-free survival (RFS) using univariate Kaplan–Meier

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survival analyses, log-rank tests, multivariate Cox regression, and multivariate logistic regression, and corrected for multiple testing with a false discovery rate (FDR) of 0.1. Mismatches were analyzed only in unrelated-donor HSCTs, whereas MICA-129 genotypes were analyzed in all data. We combined our survival results for MICA-129 mismatches with studies identified in a literature search [3–5]. Further details on the HSCT cohort and methods are provided in the Supplementary Materials and methods, Supplementary Tables S1 and S2, and Supplementary Figure S1.

Patient and donor characteristics are summarized in Supplementary Table S3. The number of MICA-129 mismatches, MICA-129 genotypes, and *MICA* allele mismatches are presented in Supplementary Table S4. MICA-129 mismatches were observed in 3% (n = 39) of the donor-recipient pairs, while *MICA* allele mismatches were observed in 6% (n = 81) of the pairs. MICA-129 genotype Val/Val (GG) was the most frequent in patients (45%, n = 982) and donors (46%, n = 691), followed by Val/Met (GA; 42%, n = 920 for patients; 41%, n = 614 for donors), and Met/Met (AA; 11%, n = 231 for patients; 11%, n = 168 for donors).

MICA-129 mismatch led to inferior RFS (Figure 1A) with hazard ratio (HR) = 1.80 (95% confidence interval [CI] 0.88 to 3.69, P value .11). The effect was stronger in multivariate analysis (HR = 4.18, 95% CI 1.29 to 13.53, P value .02, FDR value 0.84). In accordance with our result for RFS, MICA-129 mismatch was associated with an increased risk for relapse (OR = 4.62, 95% CI 0.80 to 26.80, P value .09, FDR value 0.84), although this was not statistically significant. In contrast, MICA-129 matching had no effect on OS (Figure 1B) or GvHD (Supplementary Table S5). MICA-129 genotypes and *MICA* allele mismatches had no effect on aGvHD, cGvHD, relapse, RFS, and OS (Supplementary Tables S6 to S9).

Our multivariate MICA-129 mismatch results for RFS and OS were combined with all relevant studies identified in a literature search [3–5] in a meta-analysis (Figure 1C,D). The pooled effect for RFS was HR = 1.63 (95% CI 0.91 to 2.91, P value .10), and HR = 1.47 (95% CI 0.94 to 2.30, P value .09) for OS.

We studied the effect of MICA-129 mismatches, MICA-129 patient and donor genotypes, and *MICA* allele matching on the outcome of HSCT in a multipopulational cohort. Our results from association and survival analyses did not pass FDR correction, but the most promising result was MICA-129 mismatches leading to inferior RFS. We also performed, to our knowledge, the first meta-analysis on MICA-129 mismatches for OS and RFS, where the pooled effect was consistent with our result, although it was not statistically significant.

Only 3% and 6% of the donor-recipient pairs were mismatched for MICA-129 and *MICA* alleles, respectively. This is slightly smaller than the percentages reported elsewhere, likely due to a larger proportion of related-donor HSCTs in our data. MICA-129 Met/Met was the least common genotype in both recipients and donors, and Met/Val and Val/Val were equally common in both recipients and donors, which is in accordance with previous studies.

MICA could affect HSCT outcome by acting as an additional histocompatibility antigen. Here, MICA-129 mismatches led to inferior RFS, whereas *MICA* allele mismatches had no effect despite there being fewer MICA-129 than *MICA* allele mismatches, indicating the effect of MICA-129 to be more prominent in our data. Many MICA alleles may contain the same MICA-129 genotype, which may, in part, explain this.

Our MICA-129 result on RFS is in line with that of Fuerst et al. [4], who suggested MICA-129 possibly being involved in the maturation or licensing of immune effector cells with NKG2D receptor. The only other study, in addition to the present study, where both MICA-129 mismatches and *MICA* allele mismatches have been tested, is by Carapito et al. [5], who saw neither affecting RFS. Overall, they reported no effect for MICA-129 mismatches, but in their data, *MICA* allele mismatches affected relapse, aGvHD, cGvHD, and NRM/TRM.

MICA-129 genotypes could also affect HSCT outcome. Recipient genotype could reflect the susceptibility of recipient cells, malignant or in GvHD tissues, to NKG2D-mediated cytotoxicity by alloreactive donor cells [2]. Likewise, donor genotype might reflect donor T cell susceptibility, where fewer alloreactive T cells may reduce the risk of GvHD. It has also been suggested that alloreactive donor NK cells could eliminate recipient antigen-presenting cells and immature dendritic cells, leading to reduced GvHD. In our data, MICA-129 genotypes did not affect any of the tested endpoints. Therefore, the effect of MICA-129 mismatch is more evident in our data.

Many previous studies have not yielded statistically significant results, likely due to small datasets, have been single-center studies, have lacked full HLA matching data, or have not always adjusted analyses for covariates or corrected for multiple testing. Others have also included other *MICA*-related variables, such as MICA short tandem repeat mismatches or *MICB* mismatches, in

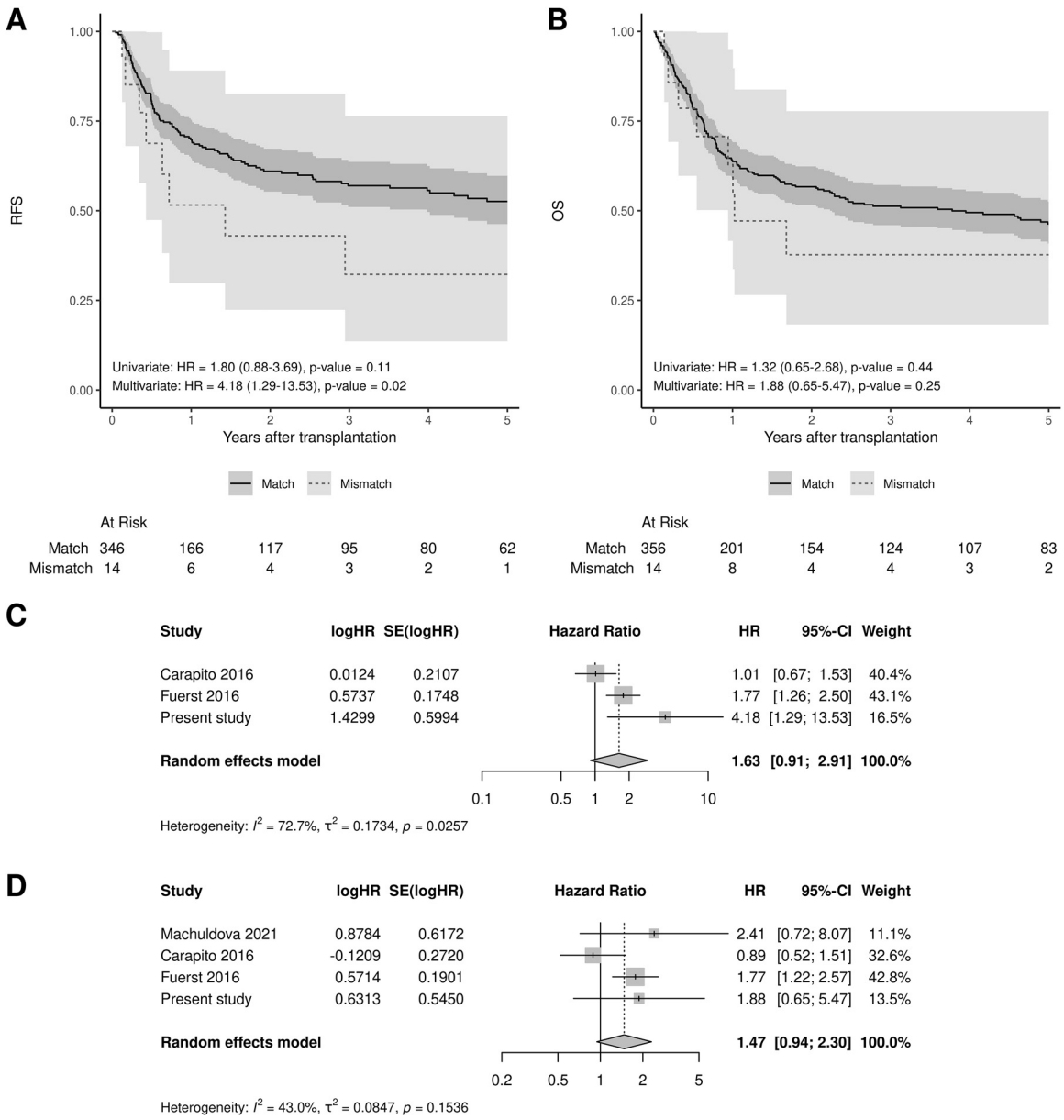

Figure 1. Univariate Kaplan–Meier survival curves for RFS (A) and OS (B) for MICA-129 mismatches in unrelated-donor HSCT. Meta-analysis of multivariate Cox regression results of MICA-129 mismatch on RFS (C) and OS (D) in unrelated-donor HSCT, where *P* values for the pooled effects were .10 for RFS and .09 for OS.

their studies, reporting that they may be more dominant or that the effect attributed to *MICA* might be due to these other variables.

Although our HSCT cohort is rather large, it is multipopulational and retrospective, which introduce heterogeneity. We adjusted for this with many patient, donor, and treatment-related covariates. Different from most studies on *MICA*, half of our data was from related-donor HSCTs, likely resulting in fewer mismatches, which may affect statistical power.

Although *MICA* has been the focus of several studies, its overall role in HSCT has remained elusive. Here, MICA-129 mismatch was found to decrease RFS. In our meta-analysis, the direction of effect for MICA-129 on RFS was consistent in most studies, but the pooled effect was not statistically significant. Therefore, the evidence for *MICA* as an additional, common histocompatibility factor for HSCT, although promising, remains limited and inconclusive. Special attention should be paid on other genetic factors in proximity to *MICA*, covariates potentially confounding results, and adjusting for multiple tests.

DATA STATEMENT

The scripts used for association testing and survival analyses are publicly available in GitHub

(https://github.com/FRCBS/HSCT_MICA). Individual-level genotype, laboratory, or clinical data of HSCT recipients and donors are not publicly available due to restrictions set by the ethical permits, but can be asked for relevant studies from jukka.partanen@veripalvelu.fi.

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Conflict of Interest Statement: Rachel Crossland works part-time for ESP Diagnostics.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2025.08.023.

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