To the editor:

Limited role of MHC class I chain–related gene A (MICA) typing in assessing graft-versus-host disease risk after fully human leukocyte antigen–matched unrelated donor transplantation

We read the manuscript by Parmar with interest. In an exploratory analysis, these investigators found that mismatching of major histocompatibility complex class I–related chain A (MICA) between donor and recipient was associated with gastrointestinal (GI) acute graft-versus-host disease (aGVHD).[1] Based on the polymorphism of this protein, the constitutive expression on the GI epithelium and the T- and natural killer (NK)–cell immune activating function,[2,3] we too have hypothesized a role for MICA in GI aGVHD. To address this we developed a high-resolution MICA typing method (see supplemental Table 1 and supplemental Figure 1, available on the *Blood* website; see the Supplemental Materials link at the top of the online article). MICA alleles were determined in 38 donor-recipient pairs after human leukocyte antigen (HLA) 12/12 matched unrelated donor transplantations. One-half of these recipients developed severe (grade II-IV) GI aGVHD, whereas the other half did not. All but one donor-recipient pair were matched at the MICA locus. Thus in this setting, MICA mismatching was rare. This is likely due to tight linkage disequilibrium with HLA B (D′0.99484, $P < .001$). Given that the single MICA mismatch occurred in a patient *without* aGVHD, this also suggests that MICA mismatching per se did not uniformly lead to severe GI aGVHD.

In reconsidering our hypothesis, we reasoned that the important interaction might be between the immune receptor NKG2D (on donor T and NK cells) and recipient MICA (on the GI tract). MICA amino acid substitutions at position 129 (methionine or valine) are associated with "weak" or "strong" NKG2D binding.[4] We thus hypothesized that strong NKG2D:MICA binding might be associated with GI aGVHD. However no association between recipient MICA allele binding affinity and GI aGVHD was observed (not shown). An additional exploratory analysis examined whether certain recipient MICA alleles were associated with GI aGVHD protection or risk. There was a trend toward less aGVHD for recipients with MICA*008 ($P = .07$). Similarly, a possible increase in severe GI aGHVD was noted in recipients with an amino acid motif encoded by MICA*004, *006, *009, *044, or *049 ($P = .075$).

Given that MICA is tightly linked to HLA-B, we examined whether certain recipient HLA-B alleles (based on MICA linkage) are associated with GI aGVHD. Using a second cohort of 1676 recipients of myeloablative, HLA 8/8 matched unrelated donor transplantation, we tested whether recipient HLA-B alleles correlated with transplantation-associated outcomes. HLA-B alleles were divided into low and high risk based on linkage to MICA*008 or *004, *006, *009, *044, and *049, respectively (described in Table 1 footnotes). All other HLA-B alleles were considered to have intermediate aGVHD risk. As shown in Table 1, in multivariate analysis there were no differences in transplantation outcomes between the high-, intermediate-, and low-risk groups.

In contrast with the data presented by Parmar et al, our studies do not support the concept that donor-recipient MICA mismatching plays a role in GI aGVHD. In addition, these data also do not suggest that certain recipient MICA alleles are associated with GI aGVHD. While the reasons for the differences between our study and that of Parmar et al are not entirely clear, potential explanations may include registry versus

Table 1. Impact of HLA-B alleles on transplantation-related outcomes based on linkage to high- and low-risk HLA alleles

Clinical endpoint	Odds ratio (95% CI)	*P*
GI aGVHD (grade II-IV)*		.059
2 low-risk alleles	1	
Intermediate	1.04 (0.75-1.46)	
≥ 1 high-risk allele	0.63 (0.38-1.04)	
GI aGVHD (grade III-IV)*		.88
2 low-risk alleles	1	
Intermediate	0.90 (0.58-1.40)	
≥ 1 high-risk allele	0.80 (0.44-1.44)	
Overall aGVHD (grade II-IV)*		.41
2 low-risk alleles	1	
Intermediate	0.99 (0.79-1.24)	
≥ 1 high-risk allele	1.18 (0.89-1.57)	
Overall aGVHD (grade III-IV)*		.60
2 low-risk alleles	1	
Intermediate	0.90 (0.68-1.19)	
≥ 1 high-risk allele	1.05 (0.73-1.51)	
Chronic aGVHD*		.15
2 low-risk alleles	1	
Intermediate	1.15 (0.89-1.48)	
≥ 1 high-risk allele	1.38 (1.0-1.90)	
Relapse*		.17
2 low-risk alleles	1	
Intermediate	1.35 (0.94-1.93)	
≥ 1 high-risk allele	1.01 (0.63-1.60	
Treatment-related mortality*		.11
2 low-risk alleles	1	
Intermediate	0.76 (0.59-0.98)	
≥ 1 high-risk allele	0.80 (0.58-1.12)	
Disease-free survival†		.64
2 low-risk alleles	1	
Intermediate	0.96 (0.84-1.11)	
≥ 1 high-risk allele	0.91 (0.76-1.10)	
Overall survival†		.45
2 low-risk alleles	1	
Intermediate	0.95 (0.82-1.10)	
≥ 1 high-risk allele	0.89 (0.73-1.07)	

Allogeneic transplant recipients (n = 1676) were assigned to high-, intermediate-, or low-risk groups based on known linkage between HLA-B and MICA.[5-8] MICA alleles (and the associated HLA-B alleles) that trended toward GI aGVHD protection (*008) were considered low-risk. MICA alleles associated with increased GI aGVHD risk (*004, *006, *009, *044, and *049) were considered high risk. All others were coded as intermediate risk. To investigate risk factors for MICA-associated HLA-B alleles and aGVHD in the cohort analysis, cumulative incidence rates of aGVHD (the chance a patient will have experienced aGVHD event before time *t*, and where death without the aGVHD event is the competing risk) were calculated using methods previously described.[9] Multivariate analyses were applied to adjust for the effects of other covariates on the cumulative incidence of aGVHD using the pseudovalue approach of Klein[10,11] with a logistic link function. A forward stepwise regression model using a generalized linear model for the pseudovalues was used. Shown are the *P* values comparing the clinical endpoint for recipients with 2 low-risk alleles to either intermediate or ≥ 1 high-risk allele.

CI indicates confidence interval.

*Pseudovalue technique.

†Cox regression.

single-center reporting, high- versus low-resolution MICA typing, HLA disparity in the patient cohorts (matched vs potentially mismatched), and differing experimental approaches. As called for by Parmar et al, confirmation of the role of MICA in GI aGVHD in a larger cohort of patients is necessary, particularly using high-resolution typing methods.

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The online version of this correspondence contains a data supplement.

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Response:

MHC class I chain–related gene A (MICA) in unrelated donor transplantation

We thank Anderson et al for their questions regarding our report.[1] In brief, they failed to observe an association of major histocompatibility complex (MHC) class I chain–related gene A (MICA) mismatches and graft-versus-host disease (GVHD). The studies, however, have differences in design. Anderson and coworkers performed MICA typing in 38 donor-recipient pairs selected on the basis of complete matching in alleles of 12 human leukocyte antigen (HLA) loci (HLA-A, B, C, DRB1, DQB1, and DPB1), whereas in our study (n = 236) typing was performed without any bias on the basis of match grade with a subsequent outcome analysis. They had only one case of MICA mismatch, and that case did not develop GVHD.[2] In our cohort MICA mismatch frequency was 8.6%; the incidence of grade II-IV acute GVHD was significantly higher in MICA-mismatched patients after multivariate analysis.

The observed differences may be related to the discrepancy in sample sizes. Both series show the low frequency of MICA mismatches in HLA-A/B/C/DRB1/DQB1–matched subjects, which results from tight linkage disequilibrium between HLA-B and MICA, as demonstrated in our dataset. Furthermore, because we used high-resolution MICA typing as previously described,[2] resolution level should not explain differences in outcomes between the studies. The 38 pairs described by Anderson were matched in all HLA loci including DPB1, whereas in our study only 16% percent of the pairs (26 of 167) that were fully matched in HLA-A/B/C/DRB1/DQB1 in both graft-versus-host (GVH) and host-versus-graft (HVG) directions were also fully matched in HLA-DPB1. The low frequency of mismatch in MICA (2.6%) in their analysis is likely the result of inclusion of patients carrying conserved HLA haplotypes. In contrast, in our set of patients matched in 10/10 alleles in the GVH direction (n = 172), there were 8 examples of mismatches in MICA (4.7%) in the GVH vector. It is important to note that HLA-DPB1 mismatches[3] were proportionally distributed in the MICA-matched and -mismatched pairs in our cohort (74% vs 63%; *P* = not significant), and the association of MICA mismatch with acute GVHD was independent of mismatches in HLA-DPB1.