Accuracy of HLA Eplet Mismatch Analysis with Imputed HLA Typing

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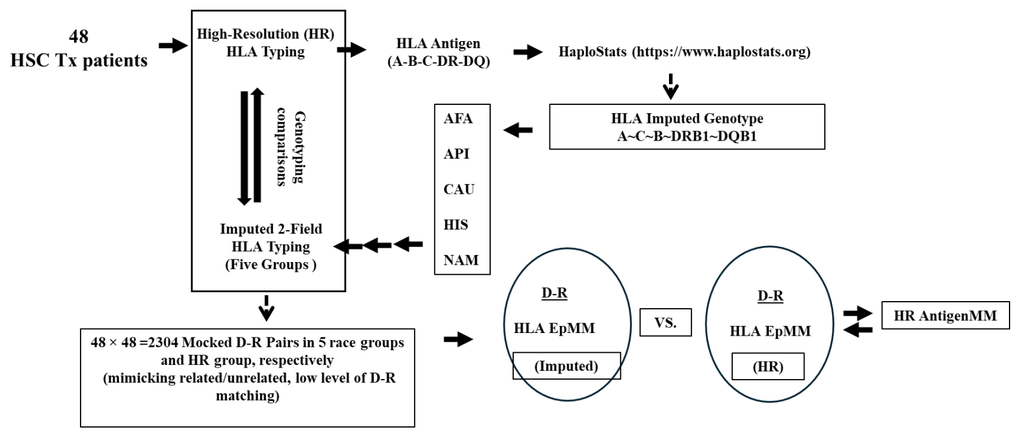
INTRODUCTION

High-resolution HLA typing is essential for accurate eplet mismatch (EpMM) assessment in predicting the development of de novo DSA and rejection post-transplant. However, two-field high resolution HLA typing is not often available for solid organ transplant recipients. EpMM has been reported by using imputation from existing low or intermediate resolution genotyping instead. This study aimed to evaluate the accuracy of EpMM using imputed versus high-resolution donor-recipient (D-R) typing in a larger cohort than we previously studied and presented in ASHI 2023.

METHODS



Summary of the mocked 2,304 donor-recipient (D-R) pairs generated, resources, methods of HLA haplotype imputation, and the analyses performed: (1) High-resolution HLA typing (HR) obtained from 48 hematopoietic stem cell transplant patients (HSC Tx). (2) Patient HLA-A-B-C-DRB1-DQB1 serology were used for imputation. (3) Genotypes were compared between imputed and high-resolution typing in 48 subjects; (4) Mocked 2,304 D-R pairs were made from 48 patients. (5) Association of HLA eplet mismatches (EpMMs) and antigen mismatches (AntigenMM) were analyzed in the high-resolution group for 2,304 D-R pairs. (6) HLA eplet mismatches were compared across 2,304 D-R pairs between the high-resolution group and each imputed group; (7) Δ#AbVEpMM between imputed and high-resolution was calculated for Class I/DRB1/DQB1; and the distribution of Δ#AbVEpMM in D-R pairs were analyzed across race. All EpMM and AbVEpMM were analyzed, AbVEpMM results are shown here. [AFA: African American; API: Asian or Pacific Islander; CAU: Caucasian; HIS: Hispanic; NAM: Native American]

CONCLUSIONS

Despite a high frequency of incorrect allele assignments using imputation, #AbVEpMM didn't change significantly in the mocked imputed D-R pairs compared to high-resolution D-R pairs at the group level, and the previously reported trend was reproduced.

There is a potential possibility to apply imputation for eplet mismatch analysis for studies focusing on overall trend of observations. However, we observed that 3.00 ± 0.81% of D-R pairs had DQB1 Δ#AbVEpMM ≥ 4; the maximum observed difference was 4 in Class I, and 11 in DQB1. Such discrepancies could place pairs on opposite sides of published risk thresholds. Thus, caution is warranted when applying imputation-based typing for eplet mismatch analysis in clinical settings. For accurate assessment, high-resolution typing remains essential.

RESULTS

Table 1. Subject Numbers with Genotype Mismatches _ Imputed vs. High-resolution

Race/Ethnicity	AFA	API	CAU	HIS	NAM	Mean	SD
Subject # (%)_Class I	29 (60.4)	27 (56.3)	22 (45.8)	22 (45.8)	26 (54.2)	25 (52.9)	3 (6.7)
Subject # (%)_Class II	27 (56.3)	26 (54.2)	26 (54.2)	22 (45.8)	26 (54.2)	25 (52.9)	2 (4.1)

In total, 25±3 (53±7%)/25±2 (53±4%) patients showed that one & more imputed Class I and Class II alleles were different from high-resolution alleles, regardless of race. (N=48; AFA: African American; API: Asian or Pacific Islander; CAU: Caucasian; HIS: Hispanic; NAM: Native American)

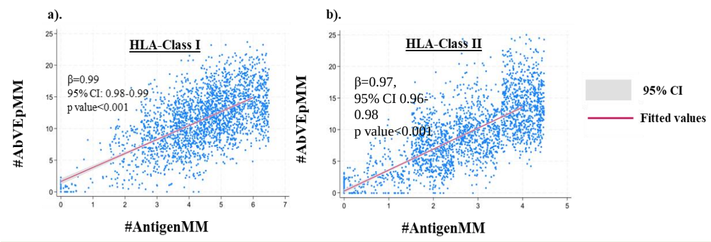


Fig. 1. Association of the number of AbVEpMM and AntigenMM in D-R pairs (N=2304) in high-resolution group. Fig.1a. Class I; Fig.1b. Class II. A strong and statistically significant correlation was observed.

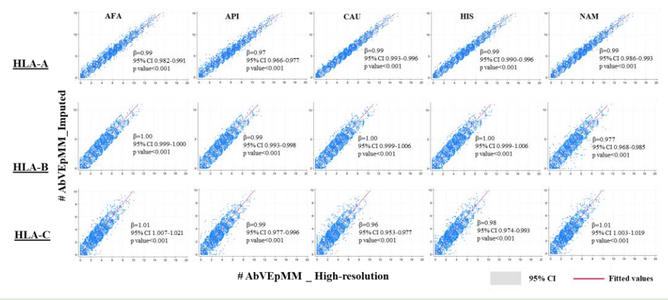


Fig. 2. Correlations of #AbVEpMM between the high-resolution group and each imputed group (N=2,304) by race at Class I specific loci _ HLA-A-B-C. The association was significant.

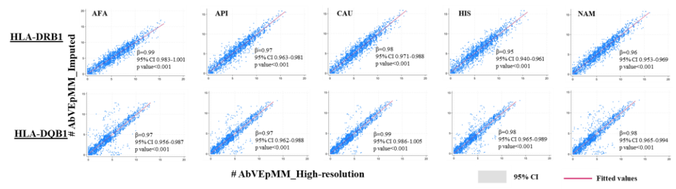
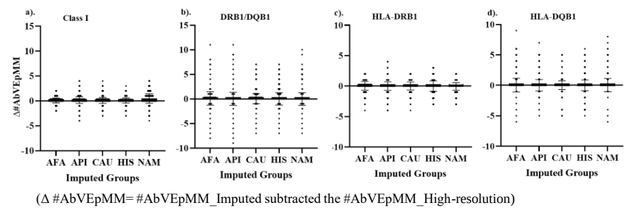


Fig. 3. Correlations of #AbVEpMM between the high-resolution group and each imputed group (N=2,304) by race at Class II specific loci _ HLA-DRB1-DQB1. The association was significant.



(Δ #AbVEpMM= #AbVEpMM_Imputed subtracted the #AbVEpMM_High-resolution)

Fig. 4. Δ#AbVEpMM between imputed and high-resolution. Fig.4a. Class I; Fig.4b. DRB1/DQB1; Fig.4c. DRB1; Fig.4d. DQB1. In each of the interested targets, both the mean and median Δ#AbVEpMM were 0. However, the maximum observed difference was 4 in class I, and 11 in DQB1.

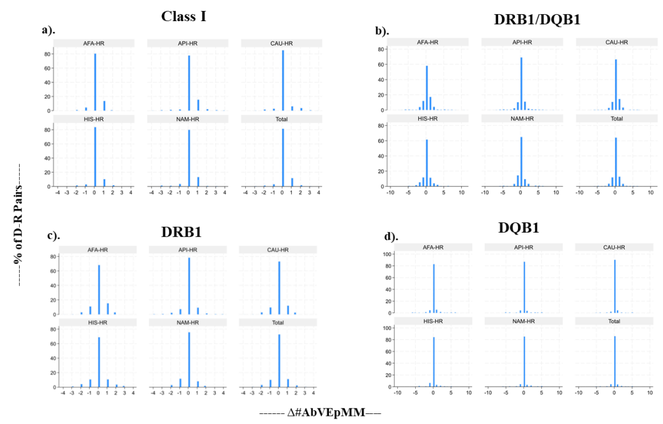


Fig. 5. Distributions of Δ#AbVEpMM in D-R pairs (N=2,304). Fig.5a, Class I; Fig.5b, DRB1/DQB1; Fig.5c DRB1, Fig.5d, DQB1. For Class I, over 81% of pairs had a Δ#AbVEpMM of 0 between the imputed and high-resolution (HR) groups, with very few showing any differences. However, in Class II (DRB1/DQB1), about 40% of pairs showed differences. A similar pattern was observed at the DRB1 and DQB1 loci.

- **Disclosure: There is no disclosure.**