Enhanced HLA typing performance of Korea Biobank Array with large scale reference panel

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Background: In clinical transplantation, increased human leucocyte antigen (HLA) mismatch between donor and recipient were well-known risk factor for graft survival. However, HLA typing in a large scale genome study is not feasible due to high cost. Alternatively, HLA alleles can be statistically inferred via HLA imputation from single nucleotide polymorphism (SNP) microarray data. Previously, Korea National Institute of Health (KNIH) designed Korea Biobank Array (KBA), a fully customized SNP microarray for Koreans with 10K HLA regional SNPs as optimal set for imputing HLA alleles.

Methods: We assessed HLA typing accuracy of KBA comparing HLA imputed alleles from KBA and HLA typing via high-throughput sequencing. Among Korean Organ Transplantation Registry participants, 254 samples were genotyped using KBA and also HLA typed by HLAaccuTest kit (NGeneBio). For HLA imputation, IMPUTE v4 was used with reference panels of Pan-Asian & Korean (PanREF, n=854) or Han Chinese MHC (HanREF, n=10,689). Accuracy was assessed by comparing four-digit HLA alleles of the imputed and the NGS based typing among *HLA-A*, *HLA-B*, *HLA-C*, *HLA-DRB1*, *HLA-DPA1*, *HLA-DPB1*, *HLA-DQA1*, and *HLA-DQB1* loci.

Results: Imputed HLA alleles were compared its true HLA alleles from NGS typing. For four-digit HLA alleles, accuracy was 88.9% and 93.6% for PanREF and HanREF, respectively. While accuracy for *HLA-DPA1* and *HLA-DPB1* was comparable (95%–96%), *HLA-C* and *HLA-DQA1* showed large difference in accuracy (51.7%–91.5% for PanREF, 82.2%–99.1% for HanREF). However, both panels showed comparable accuracy (about 95%) for *HLA-A*, *HLA-B*, and *HLA-DRB1*, which are the most important three loci for transplantation. Overall, imputed HLA alleles from KBA using HanREF showed enhanced accuracy over PanREF.

Conclusions: Taken together, accuracy for HLA typing of KBA was increased using large reference panel (HanREF). The result showed that KBA is an efficient platform to comprehensively obtain four-digit level imputed HLA alleles with accuracy of about 94%.

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