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The Universal Blood Donor Typing array for large-scale genotyping of red cell, platelet and leukocyte antigens shows high concordance with test-of-record in an international multi-ethnic donor cohort

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Background: Matching for blood cell antigens between donor and recipient is important to prevent alloimmunisation and haemolytic transfusion reactions. To facilitate extended matching, the Blood transfusion Genomics Consortium (BGC) has developed the Axiom Total Blood Typing Solution to simultaneously genotype human erythrocyte (HEA), platelet (HPA) and leukocyte (HLA) antigens.

Aims: To determine assay accuracy and reproducibility in a multi-ethnic cohort of two Axiom genotyping arrays and the accompanying integrated analysis package (IAP) designed for blood donor typing in a real-world setting of three blood service laboratories.

Methods: DNA samples were collected from blood services from Australia, Canada, England, Finland, the Netherlands, U.S. and South Africa. Identical sets of 6946 samples were genotyped using the GeneTitan-MC instrument (Thermo Fisher) at two blood centers with a 20,000 probe Universal Blood Donor Typing array (UBDT_PC1). 3,938 samples were typed with the UK Biobankv2.2 array which includes the UBDT_PC1 transfusion focused probes. The array genotypes were analysed using IAP-v2.0. Ancestry was inferred from the data to determine performance within the major ethnic groups. HEA, HPA, and HLA class I/II types were inferred by the IAP bloodTyper and HLA*IMP:02 modules and results were compared to the donor test-of-record. Resolution of sample discordances was performed by SNP-based tests and/or gene sequencing.

Results: Inferred phenotypes of 6,775 samples passing the IAP quality control were compared to donor record types. For HEA, concordance levels of 99.89%, 99.90% and 99.88% across 124,030, 124,629 and 78,092 phenotypes were observed between three test sites. For HPA, concordance was 99.64%, 99.57% and 99.65% across 1389, 1417 and 1433 comparisons although HPA-3 was not able to be determined. For 767 samples with previous HLA results, concordance was 99.7%, 98.7% and 99.7% for HLA class I A, B and C and 96.9%, 99.9%, 98.9% for class II DPB1, DQB1 and DRB1. Lower concordance for DPB1 was due to an outdated reference table. Reproducibility of genotype calls for 53 HEA antigens across 369,181 comparisons in a unified dataset consisting of 6,672 of the samples was 99.93%. Comparison of the 53 HEA and 8 HPA types with donor records resulted in 181 discordances in 165 samples with 44 in RH, 32 in MNS, 29 in DO, 25 in FY, 21 in JK, 10 in LU, 8 in CO, 4 in KEL, 2 in LW and 6 in HPA-1,2,5 and 15. Most (54%) were incorrect donor record types and 38% due to incorrect array interpretations requiring reprogramming.

Summary / Conclusions: We present data that the transfusion genotype module incorporated in UBDT_PC1 and UKBB_v2.2 AxiomTM arrays can produce highly accurate HEA, HPA and HLA genotypes simultaneously and at scale. Both arrays have been trialled using an ancestrally diverse panel of DNA samples, with 34.8% (2,417/6,946) samples from donors of non-European ancestry determined by genotype. A high level of reproducibility for both the genotype calls and inferred phenotypes between the typing labs for 6,672 repeated samples has been shown with 99.93% and 99.98% concordance, respectively. Importantly, all genotyping in this study has been conducted in accredited blood service molecular laboratories, demonstrating that this technology can be implemented for routine donor typing. The

development and validation by BGC of a comprehensive genotyping array to densely type donors of the main ancestry groups for HEA, HPA and HLA will support blood services to issue better matched blood.