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Identification of high-frequency antigen-negative blood donors using the Universal Blood Donor Typing and UK Biobank genotyping arrays

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Background: A High-Frequency Antigen (HFA) is defined as an antigen absent from the red blood cells of less than 1 in 1000 donors. Most HFA have limited antigenicity, but on rare occasions, a HFA-negative patient may form an alloantibody after transfusion or in pregnancy. To be able to supply compatible units, blood services make immense efforts to identify HFA-negative donors. Genotyping for clinically relevant blood groups will significantly simplify the identification of rare donors. The BGC has developed the Axiom Universal Blood Donor Typing (UBDT_PC1) and Axiom UK Biobank (UKBB_v2.2) arrays to genotype donors for human erythrocyte, platelet and leukocyte antigens (HEA, HPA and HLA, respectively).

Aims: To identify HFA-negative donors in the five main ancestry groups in an international multi-centre validation study using the UBDT_PC1 array and in the STRIDES NIHR BioResource (SNBR) study using the UKBB_v2.2 genotyping array.

Methods: DNA samples of 6,946 donors were provided by blood services from AU, CA, GB, FI, NL, SA, and US, and were genotyped with the UBDT_PC1 array on a GeneTitan-MC instrument (Thermo Fisher) at the New York Blood Center and SANQUIN. A set of challenge samples enriched for HEA/HPA phenotypes lacking in the 6,946 samples was also selected and genotyped (n=333), including 131 HFA-negative donors. The inferred phenotypes of 53 HEAs (MNS, RH, LU, KEL, FY, JK, DI, YT, SC, DO, CO, LW, CROM, KN and VEL) by the bloodTyper module of the AxiomTM Total Blood Typing Solution were compared to HEA types retrieved from electronic donor records. Finally, 82,000 DNA samples from NHS Blood and Transplant (NHSBT) donors, enrolled in the SNBR study, were genotyped with the UKBB_v2.2 array by the NHSBT.

Results: The dense genotyping results allowed for automated quality control of the samples, and 6,867/6,946 (98.9%) passed. Genotypes were used to infer ancestry, showing that 34.8% of the samples were from non-European (EUR) donors. 156 HFA-negative donors (4 U-, 8 Lu(b-), 36 k-, 1 Kp(b-), 8 Js(b-), 1 Di(b-), 10 Yt(a-), 2 Hy-, 8 Jo(a-), 17 Co(a-), 4 Kn(a-), 54 McC(a-), 3 Vel-) were identified in the 6,867 samples, and 99/156 were newly identified. The 156 HFA-negative donors were from African (AFR, n=72), Admixed American (AMR, n=10), East Asian (EAS, n=1), South Asian (SAS, n=3), and EUR (n=70) ancestry. No Wr(b-), Lw(a-) and Cr(a-) donors were identified, which is in keeping with these types being exceptionally rare.

In the set of selected samples known to be HFA-negative, 126/131 were identified by the array, with the remainder being untyped for their respective HFA-negative antigen. Inspection of genotyping call plots for these five samples revealed that the issue could be rectified by an algorithmic adjustment.

Ancestry inference showed that 3,817 of the first 21,444 SNBR samples were from non-EUR donors, with 3.0%, 3.1%, 1.6%, 9.1% being of AFR, AMR, EAS and SAS ancestry. 160 HFA-negative donors (24 Lu(b-), 27 k-, 3 Js(b-), 24 Yt(a-), 33 Co(a-), 8 Kn(a-), 40 McC(a-), 1 Vel-) were identified.

Summary / Conclusions: The AxiomTM Total Blood Typing Solution is capable of identifying HFA-negative donors, represented in the five major ancestry groups. To determine the specificity of the array, the newly identified HFA-negative donors are presently confirmed by an accredited test. This study illustrates how high-throughput genotyping brings benefits for identifying donors with extremely rare HEA types, including those who are negative for HFA types.