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Identification of High Frequency Antigen-negatives and High Demand Phenotypes using the Universal Blood Donor Typing array

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Introduction – High Frequency Antigens

HFA-negatives: HEA types absent from the red cells of less than 1 in 1000

- Wide range in frequencies
  - Ranging from 1 in 1,000 individuals to below 1 in 500,000

- HFA-negative is a population-specific event
  - Vel-negative; *SMIM1*64_80del* allele
    - Freq. Caucasian pop.: 1.46% (95% CI 1.17% - 1.74%)
    - Freq. African pop.: 0.56% (95% CI 0.15% – 0.98%)
    - Freq. Chinese pop.: 0.60% (95% CI 0.01% – 1.19%)

L. Haer-Wigman et al. Transfusion. 2015

Introduction - High Demand Phenotypes

Propensity to use the frequency of HFA-negatives in donors of EUR ancestry as a point of reference

- Fy(a-b-): 68% in AFR, not occurring in EUR
  - Up to 99% in some AFR countries

- K- C- E- Fy(a)- Jk(b)- S-: 20% required in SCD, <1% in EUR

Donors in donor record SQ	Expected after extended genotyping	ECs ordered in the last 10 years	ECs ordered in 2022
1.852	5.221	7.070	942

Tend to refer to those types as ‘high demand phenotypes’

- Blood services must be able to meet demand for blood which is negative for the different HFA and HDP types to support patients with antibodies

- Blood services make immense efforts to identify those donors

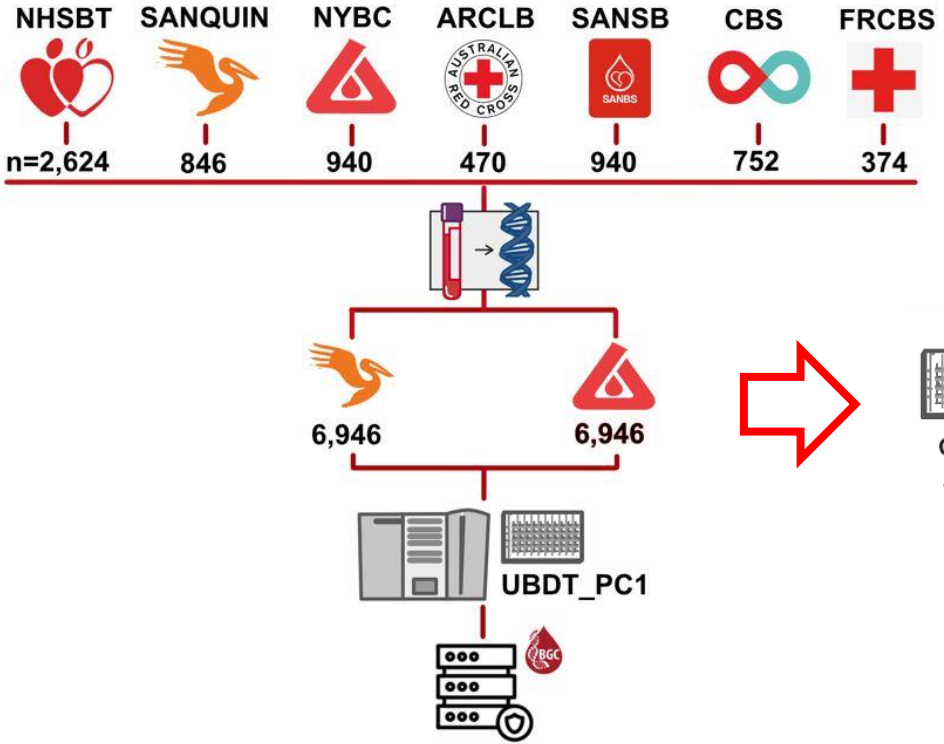
- Extended genotyping will significantly simplify the identification of the rare donors

Aim of the study

To identify HFA-negative and HDP donors in the five main ancestry groups in an international multi-centre validation study using the UBDT_PC1 genotyping array (BloodGenomiX)

- *Specificity and sensitivity*

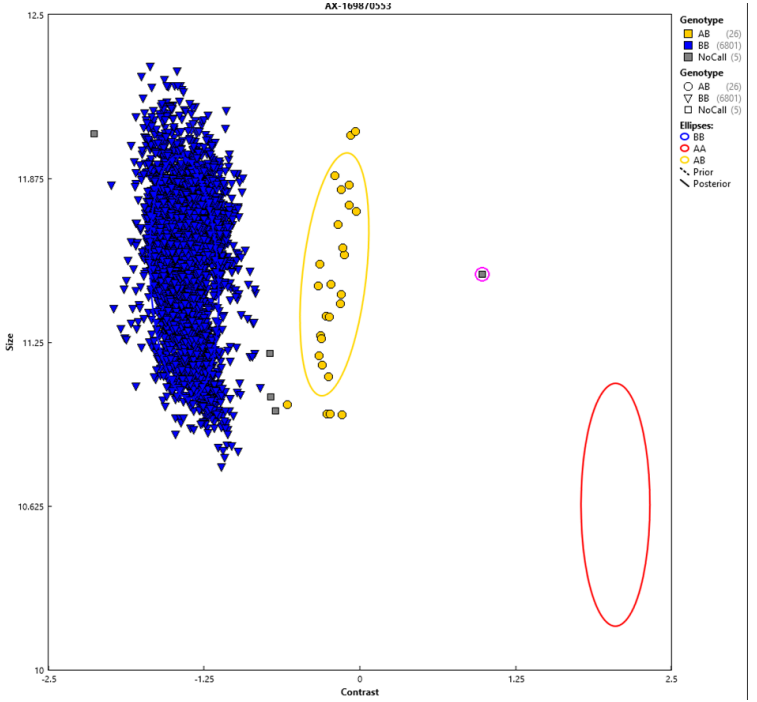
Methods



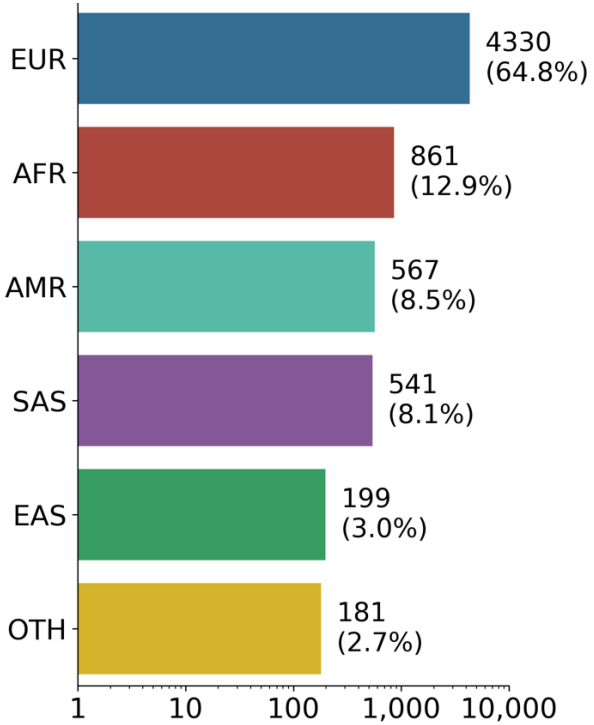
Additional sample set

Methods

- Electronic donor record
- Genotyping result as HFA-neg in SQ and/or NYBC: confirmation by Sanger sequencing
- Visual inspection of all no calls: sequencing of samples with signal more close to minor allele then to major allele



Ancestry distribution of the unified dataset (n=6,679)



35.2% of the samples were from non-European blood donors

System	Category	Phenotype	Registred in electronic donor record	Identified by array	Increase in number of HFA-negative/HDP donors
MNS	HFA	U-	4	4	0
LU	HFA	Lu(a)+_Lu(b)-	4	8	4
KEL	HFA	Js(a)+_Js(b)-	5	8	3
KEL	HFA	K+_k-	8	36	28
KEL	HFA	Kp(a)+_Kp(b)-	0	1	1
~~FY~~	~~HDP~~	~~Fy(a)_Fy(b)~~	~~312~~	~~629~~	~~317~~
~~JK~~	~~HDP~~	~~Jk(a)_Jk(b)~~	~~0~~	~~5~~	~~5~~
DI	HFA	Di(a)+_Di(b)-	0	1	1
DI	HFA	Wr(a)+_Wr(b)-	0	0	0
YT	HFA	Yt(a)-_Yt(b)+	2	12	10
SC	HFA	Sc1-_Sc2+	0	0	0
DO	HFA	Hy-	1	2	1
DO	HFA	Jo(a-)	3	7	4
CO	HFA	Co(a)-_Co(b)+	1	17	16
LW	HFA	LW(a)-_LW(b)+	1	1	0
KN	HFA	Kn(a)-_Kn(b)+	0	4	4
KN	HFA	McC(a)-_McC(b)+	0	55	55
VEL	HFA	Vel-	0	1	1
			341	791	**450**

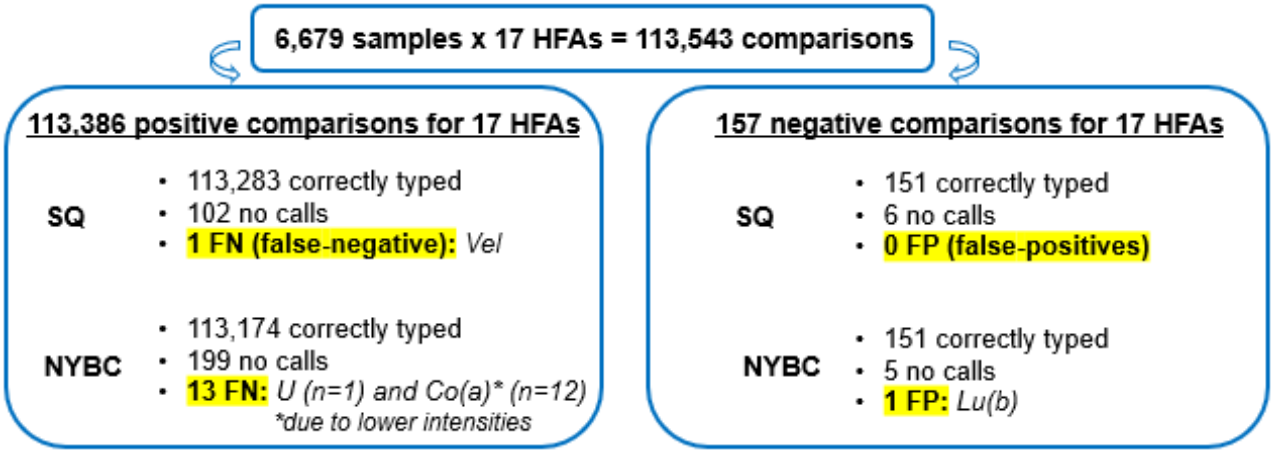
Identification of HFA/HDP phenotypes in the unified dataset (n=6,679)

Factor >5

Factor >2

High specificity of the Axiom™ Total Blood Typing Solution: >99.9%

In the unified dataset (n=6,679) for 17 HFA types



- If the array predicted that the donor was positive for HFA/HDP, this was a correct result in:
  99.989% (NYBC); 113,174/(113,174+13)*100
  99.999% (SQ); 113,283/(113,283+1)*100

- Reproducibility: 99.72%

Robust sensitivity of the Axiom™ Total Blood Typing Solution: 93.7%

System	Negative for HFA	Detected in unified dataset (n=…)	Known and tested from additional dataset (n=…)	Total (n=…)	Concordant (n=…)	Discordant (n=…)	No result (n=...)
MNS	U	4	16	20	20	0	0
LU	Lu(b)	8	6	14	13 SQ / 12 NY	0 SQ / 1 NY	1
KEL	k	36	2	38	38	0	0
KEL	Kp(b)	1	31	32	26	6	0
KEL	Js(b)	8	5	13	13	0	0
DI	Di(b)	1	3	4	3	0	1
DI	Wr(b)	0	6	6	6	0	0
YT	Yt(a)	12	2	14	14	0	0
SC	Sc1	0	0	0	0	0	0
DO	Hy	2	5	7	7	0	0
DO	Jo(a)	7	6	13	12	0	1
CO	Co(a)	17	9	26	25	1	0
LW	LW(a)	1	6	7	5	0	2
CROM	Cr(a)	0	5	5	3	2	0
KN	Kn(a)	4	5	9	7	2	0
KN	McC(a)	55	7	62	62	0	0
VEL	Vel	1	16	17	15	0	2
		157	130	287	269	11	7

Conclusions

- The Axiom™ Total Blood Typing Solution is capable of identifying HFA-negative blood donors, represented in the five main ancestry groups.

- In this multi-ethnic donor cohort, 81.5% of the identified HFA-negative blood donors lacked prior registration in electronic donor records, demonstrating their status as newly identified HFA-negative donors. The HFA-negativity of these donors needs to be confirmed with a serological test as long as this test is the gold standard.

- The Axiom™ Total Blood Typing Solution exhibits 99.9% specificity and a robust sensitivity of 93.7%. Although the sensitivity for Kp(b), Cr(a), and Kn(a) is currently lower, efforts to improve this are ongoing. No Sc1-negative samples have been tested yet, nor identified.

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For Life.