IgG and Fc receptor genetic variation associates with functional antibody responses in HVTN108

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BACKGROUND

The HVTN108 trial evaluated the safety and immunogenicity of a DNA prime, adjuvanted protein boost vaccine regimen in the US and South Africa.

PURPOSE OF STUDY: To define the IgG antibody Fc and Fc receptor (FcR) genotypes in the study population and **test our hypothesis** that IgG and FcR genetic variation can affect vaccine-elicited functional antibody responses.

METHODS

- The HVTN108 trial enrolled 334 participants in treatment (n=310) and placebo (n=24) groups.
- IgG Fc and FcRs genotypes were determined by targeted PCR amplification and Illumina next-generation sequencing (**Figure 1**).

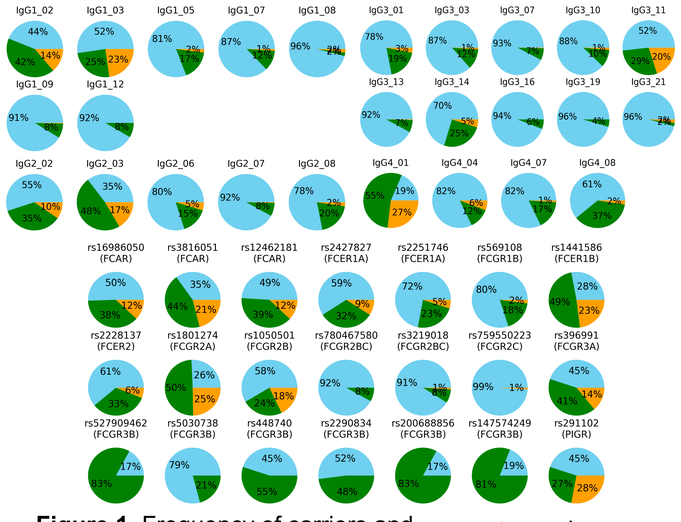


Figure 1. Frequency of carriers and homozygotes for each IgG and FcR genotype in the study cohort.

- Binding antibody multiplex assay (BAMA), antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP) were measured by HVTN core labs.
- Pearson correlation analysis of IgG and FcR genetic variants was used to identify potential linkage disequilibrium.
- Relationships between genotypes and antibody responses were identified by linear regression controlling for treatment group and region. Variants were deemed to be associated with antibody responses when the p-value was below 0.05 and the Benjamin-Hochberg false discovery rate (FDR) adjusted value below 0.2.

The distribution of multiple IgG and FcR genotypes significantly differs in the US and South Africa and several of these genotypes associate with levels of functional antibody responses post-HVTN108 vaccination

RESULTS

1. Was there evidence of linkage disequilibrium among IgG and FcR alleles in the study cohort?

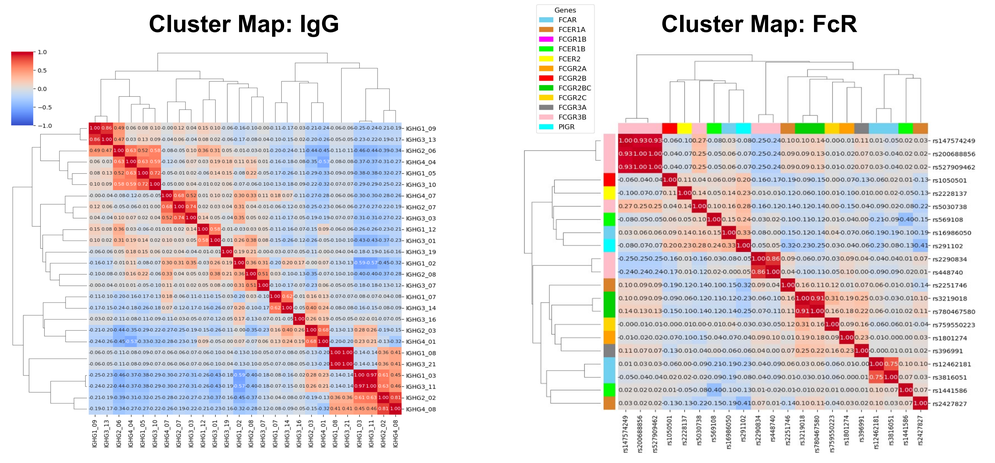


Figure 2. There was evidence of linkage disequilibrium within IgG and FcR alleles.

2. Was there evidence of regional biases in the distribution of genetic polymorphisms in the two vaccine trial sites -- US and South Africa?

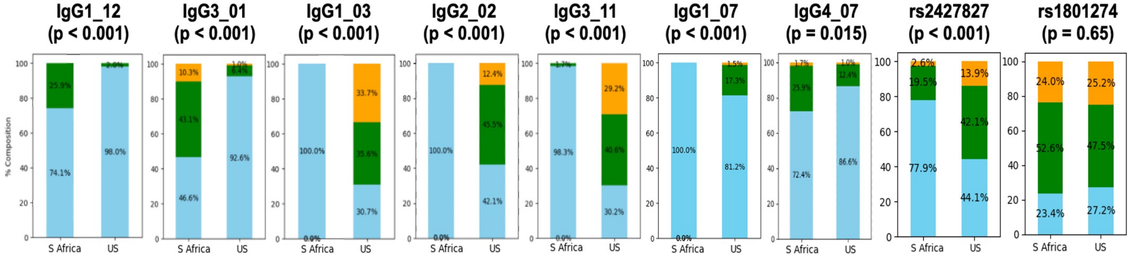


Figure 3. Multiple IgG and FcR alleles display a significant divergence in genetic distribution between the US and South Africa. Fisher's exact test.

3. Did any IgG or FcR genotypes associate with levels of vaccine-elicited functional antibody responses?

Relationships between genotypes and antibody responses were identified by linear regression controlling for treatment group and region within the subset of the cohort tested for functional antibody responses (IgG, n=41; FcR, n=55).

Allele	Coefficient	FDR corrected P-Value	Assay	
IgG1_12	5.2885	0.0097	ADCC: Titer	TV1 GTL
	9.4589	0.0269	ADCC: Activity Peak	TV1 GTL
IgG3_01	2.1680	0.1265	ADCC: Titer	TV1 GTL
	4.4176	0.1023	ADCC: Activity Peak	TV1 GTL
IgG1_03	-1.8407	0.0277	ADCC: Titer	TV1 GTL
	-3.3172	0.0499	ADCC: Activity Peak	TV1 GTL
IgG2_02	-2.1117	0.0320	ADCC: Titer	TV1 GTL
	-3.3983	0.1023	ADCC: Activity Peak	TV1 GTL
IgG3_11	-1.8639	0.0277	ADCC: Titer	TV1 GTL
	-3.3687	0.0499	ADCC: Activity Peak	TV1 GTL
IgG1_07	2.8695	0.0320	ADCC: Titer	TV1 GTL
	5.1091	0.0714	ADCC: Activity Peak	TV1 GTL
IgG4_07	2.8115	0.0636	ADCC: Titer	TV1 GTL
	4.6800	0.1333	ADCC: Activity Peak	TV1 GTL
rs2427827	3.0283	0.1273	ADCC: Activity Peak	1086C LUC
rs1801274	1.6982	0.0655	BAMA	C V1V2

Table 1. Several IgG and FcR alleles were significantly associated with immune responses (FDR corrected p-values < 0.2). Red and purple brackets indicate genotypes that are in linkage disequilibrium.

CONCLUSIONS

Multiple IgG genotypes and FcR mutations were associated with ADCC and binding antibody levels after HVTN108 vaccination when controlling group and region. Genetic variation in antibodies and FcRs contributes to vaccine-induced humoral responses but there were significant differences in their distribution, suggesting that regional development of vaccines may be scientifically appropriate.

ACKNOWLEDGEMENTS

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