Receptors for the crystallisable fragment (Fc) of immunoglobulin (Ig) G, Fcγ receptors (FcγRs), link the humoral and cellular arms of the immune response, providing a diverse armamentarium of antimicrobial effector functions. Findings from HIV-1 vaccine efficacy trials highlight the need for further study of Fc-FcR interactions in understanding what may constitute vaccine-induced protective immunity. These include host genetic correlates identified within the low affinity Fcγ-receptor locus in three HIV-1 efficacy trials – VAX004, RV144, and HVTN 505. This perspective summarizes our present knowledge of FcγR genetics in the context of findings from HIV-1 efficacy trials, and draws on genetic variation described in other contexts, such as mother-to-child HIV-1 transmission and HIV-1 disease progression, to explore the potential contribution of FcγR variability in modulating different HIV-1 vaccine efficacy outcomes. Appreciating the complexity and the importance of the collective contribution of variation within the FCGR gene locus is important for understanding the role of FcγRs in protection against HIV-1 acquisition.

Keywords: FCGR genes, Fc gamma receptor (FcγR), variant, polymorphism, copy number, HIV - human immunodeficiency virus, vaccine, disease progression

INTRODUCTION

Despite enormous research efforts over 30 years, a highly efficacious preventative HIV vaccine remains elusive. Nonetheless, each vaccine efficacy trial provided new insight. Only one HIV-1 vaccine trial has shown some level of protection against HIV-1 acquisition. The RV144 vaccine trial (1), conducted in Thailand, achieved modest vaccine efficacy at 31.2%, while 6 other efficacy trials – VAX003 (2), VAX004 (3), HVTN502 (the Step trial) (4), HVTN503 (the Phambili trial) (5), HVTN505 (6), and HVTN702 (the RV144 follow-on trial) (7) – failed to prevent HIV-1 acquisition in vaccinees, and even increased risk in some individuals (4, 8). Many differences could account for the efficacy outcomes, including the vaccine regimen (design, virus subtype, and adjuvant), diversity of circulating virus strains, sex, modes of transmission, different risk populations, geography, and host genetics.

The initial immune correlate analysis from RV144 (9) provided the impetus for more detailed study of immune correlates to better understand vaccine-induced immune protection against...
HIV-1. These subsequent studies and analyses have revealed the inordinately complex nature of immunological mechanisms that collectively act to provide protection against acquisition of HIV-1 [reviewed in (10)]. In particular, they have highlighted many HIV-specific antibody parameters as correlates of HIV-1 acquisition risk (9, 11–14), many of which bind Fc\textgamma Rs to mediate their functions. Indeed, Fc\textgamma R-mediated effector functions associate with vaccine protection (9, 15). Host genetic correlates further implicating a role for Fc\textgamma Rs have been identified in three efficacy trials, VAX004 (16), RV144 (17), and HVTN505 (18); each conducted in different population groups with distinct allelic variability across Fc\textgamma Rs (19).

Here we summarize our present knowledge of Fc\textgamma R genetics in the context of findings from HIV-1 efficacy trials, and include studies of mother-to-child HIV-1 transmission and HIV-1 disease progression. We highlight the complexity of the FCGR locus, the importance of using validated methods to aid interpretation, the inclusion of FCGR gene copy number determination, and population genetic differences, among other considerations outlined.

### THE LOW AFFINITY FcγRs AND HOST GENETIC VARIABILITY

IgG, elicited through active immunization (infection or vaccination) or transferred passively (intravenous infusion or transplacental), modulates an antiviral response through several mechanisms. The antigen binding fragment (Fab) may neutralize virus infection by binding viral surface proteins and preventing attachment to host receptors, while the antibody Fc domain direct immune mechanisms through the engagement of Fc\textgamma Rs. Cross-linking of Fc\textgamma Rs on the cell surface through multivalent interactions, initiates responses that include antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), oxidative burst, release of inflammatory mediators, and regulation of antibody production (Figure 1A) (21–24).

Fc\textgamma Rs are a complex family of activating and inhibitory receptors, comprising three classes of molecules and different isoforms: Fc\textgamma R\textalpha, Fc\textgamma R\textalpha/b/c, and Fc\textgamma R\textgamma/\textdelta (Figure 1B). All Fc\textgamma Rs are glycoproteins belonging to the Ig superfamily and consist of a ligand-binding \( \alpha \)-chain with two (Fc\textgamma R\textII and Fc\textgamma R\textIII) or three (Fc\textgamma R\textI) extracellular Ig-like domains, a transmembrane domain, and intracytoplasmic domain. The activating or inhibitory signaling motifs are located either within the \( \alpha \)-chain (Fc\textgamma R\textI) or associated signaling subunits (Fc\textgamma R\textII and Fc\textgamma R\textIII) (25). Unique to the Fc\textgamma R family, Fc\textgamma R\textIIId attaches to the cell membrane with a glycosylphosphatidylinositol anchor. Despite lacking intrinsic cytoplasmic signaling domains, Fc\textgamma R\textIIb induces several cell responses (26–28). Each Fc\textgamma R is expressed on specific cell types, either constitutively or induced, and has particular affinities for IgG and its subtypes (IgG1–4). The genes that encode Fc\textgamma Rs – FCGR1A, FCGR2A/B/C, and FCGR3A/B – are further subject to considerable allelic variation, resulting from segmental genomic duplications/deletions or single nucleotide polymorphisms.

Fc\textgamma R2C, FCGR3A, and FCGR3B occur at different gene copies due to the gain or loss of defined copy number regions (CNR1-5, Figure 1C). The number of FCGR genes per diploid genome directly correlate with Fc\textgamma R surface density and function (29, 30). In addition to this gene dosage effect, duplications/deletions create chimeric FcGRs that alter the cellular distribution, expression, and function of Fc\textgamma Rs. A deletion of CNR1, present in 7.4-18.1% of individuals depending on ethnicity, juxtaposes the 5’-regulatory sequences of FCGR2C with the coding sequence of FCGR2B, creating the chimeric FCGR2B and expression of Fc\textgamma RIIb on cytotoxic NK cells where it inhibits cell activation and ADCC (31, 32). A CNR2 deletion, present in <1.5% of individuals, leads to an FCGR2A/2C chimera that result in reduced Fc\textgamma RIIa surface levels and oxidative burst response (32, 33). Conversely, a CNR2 duplication, present in 1.6-4.5% of individuals, leads to an FCGR2C/2A chimeric gene that increases Fc\textgamma RIIc expression levels.

Allelic variation for Fc\textgamma R\textI is low. In contrast, several single nucleotide variants with a known phenotypic or functional consequence exist for Fc\textgamma R\textI/b/c and Fc\textgamma R\textIId/a/b (34). Distinct amino acid changes in the membrane proximal Ig-like domain of Fc\textgamma R\textIIa and Fc\textgamma R\textIId alter their affinity for IgG subtypes and associated effector functions, including Fc\textgamma R\textIIa-p.H166R (alias H131R, rs1801274) and Fc\textgamma R\textIId-p.F176V (alias F158V, rs396991) (35–38). Conversely, in the transmembrane domain of Fc\textgamma R\textIId, the p.L232T variant (rs1050501) alters its inclusion in lipid rafts and inhibitory signaling (39). In Fc\textgamma R\textIId, a combination of six amino acid changes determine the human neutrophil antigens (HNA) 1a/b/c – molecules that are antigenically distinct and modulate neutrophil phagocytosis and oxidative burst (40). Unlike other FCGRs, FCGR2C occurs predominantly as a pseudogene, where a combination of FCGR2C minor alleles – p.X57Q (alias X13Q) and c.798+1A>G (rs76277413) – determine its surface expression (20, 41). Other co-inherited single nucleotide variants (haplotypes) within the promoter region of FCGR2B/C and spanning FCGR3A modulate surface expression levels of Fc\textgamma RIIb/c and Fc\textgamma RIIId, respectively (42–44).

Over the past few years, research identified several new FCGR variants of clinical relevance in the context of HIV-1 (described below). Although, linkage disequilibrium (co-occurring variants) in the FCGR locus has impeded identification of potential causal variants (19, 45, 46). Studying FCGR variants in different population groups in the same and/or different context may help define a role for specific variants, since linkage disequilibrium is inconsistent between geographical populations (19). Of note, describing new FCGR variants and assigning them to specific Fc\textgamma Rs warrants caution, since high nucleotide sequence homology between FCGRs could lead to inaccurate assignment of variants to specific genes (34); thus, highlighting the need for validated genotyping methods. In general, for the description of new and conventional FCGR variants, we encourage the use of a single international genotypic variation nomenclature as described by the Human Genome Variation Society (HGVS) to enable cross-referencing of FCGR variants between studies (34, 47). We include here the HGVS name for all variants.
A FcyR-mediated mechanisms

Antibody-dependent cell cytotoxicity

NK cell

Phagocyte

Antibody-dependent cellular phagocytosis

Phagocyte

Oxidative burst

B cell regulation

B FcyR family

| Protein | Ectodomain | Signalling motif | Cellular distribution | IgG affinity (K_{D} × 10^6 M^{-1}) |
|---------|------------|-----------------|----------------------|----------------------------------|
| FcγRI   | ITAM       | Y6G              | Monocytes, Macrophages, Neutrophils* | H131, R131, F176, V176, Q57, HNA1a |
| FcγRIIa | ITAM       | Y6G              | Dendritic cells, Macrophages, Mast cells* | H131, R131, F176, V176, Q57, HNA1a |
| FcγRIIb | ITAM       | Y6G              | NK cells, T cells, Macrophages, Mast cells* | H131, R131, F176, V176, Q57, HNA1a |
| FcγRIIc | ITAM       | Y6G              | NK cells, T cells, Macrophages, Basophils* | H131, R131, F176, V176, Q57, HNA1a |
| FcγRIIIa| GPI anchor | Y6G              | Neutrophils* | H131, R131, F176, V176, Q57, HNA1a |
| FcγRIIIb| GPI anchor | Y6G              | Basophils* | H131, R131, F176, V176, Q57, HNA1a |

C Genomic structure and variation

Intragenic haplotype

Four variants

Increased surface levels

rs1801274
p.H166R
Binding affinity

rs396991
p.F176V
Binding affinity

p.X57Q
Expression

rs76277413
c.798+1A>G
Expression

rs10505611
p.I123T
Increased expression

rs8862172
c.798+1A>G
Increased expression

rs10505611
p.I123T
Subcellular localization

Gene dosage

FCGR copy number = FcyR surface expression = function

Chimeric FCGR genes

| Gene | Copy number variation | Gene dosage | Chimeric FCGR genes | FCGR expression | Functional |
|------|-----------------------|-------------|---------------------|-----------------|------------|
| FCGR1A | Chr. 1q21.2 | CNR1 | CNR2 | CNR3 | CNR4 | CNR5 |
| FCGR2A | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR2B | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3A | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3B | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3C | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3D | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3E | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3F | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3G | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3H | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3I | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3J | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3K | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3L | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3M | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3N | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3O | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3P | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3Q | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3R | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3S | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3T | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3U | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3V | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3W | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3X | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3Y | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3Z | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3{1} | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |
| FCGR3{2} | Chr. 1q23.3 | CKNR3 | CKNR4 | CKNR5 | CKNR6 | CKNR7 |

FIGURE 1 | FcyR function, structure and variability. (A) FcyRs activate or inhibit immune mechanisms that include killing of infected cells through antibody-dependent cellular cytotoxicity, clearance of immune complexes through phagocytosis, release of reactive oxygen species [superoxide anion (O^{-2}) and hydrogen peroxide (H_{2}O_{2})], and regulation of B cell activation through co-engaging the B cell receptor and inhibitory FcyRllb by immune complexes. (B) FcyRs comprise a family of receptors: FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb; also known by their cluster of differentiation (CD) markers CD64, CD32a, CD32b, CD32c, CD16a, and CD16b, respectively. The FcyRs IgG binding chain activates or regulates immune responses depending on its association with or inclusion of an immunoreceptor tyrosine activation motif (ITAM) or inhibitory motif (ITIM). Unique among FcyRs, FcγRIIIb attaches to the cell membrane with a glycosylphosphatidylinositol (GPI) anchor. Each receptor has a specific cell expression profile and affinity for IgG and its subtypes (K_{D}1-4), shown as affinity constants (K_{D} × 10^6 M^{-1}); -, no binding. Expression patterns: *inducible expression; † in individuals bearing the FCGR2C expression variants (20); *very low expression or expressed by rare subsets; *expressed in individuals bearing a FCGR2C-FCGR3B gene deletion. (C) The cluster of FCGR2A/B/C and FCGR3A/B genes on chromosome 1q23.3 that encode FcγRIIa/b/c and FcγRIIIa/b are polymorphic. Variants include nonsynonymous single nucleotide polymorphisms that alter the receptor’s binding affinity for certain IgG subtypes, determine expression of an otherwise pseudogene, increase surface expression, glycosylation, and subcellular localization. Large segmental duplications and deletions in the FCGR cluster further modify FcγR expression levels and create chimeric genes that yield FcyRs with altered cellular distribution and/or function. Created with BioRender.com.
FcγR GENE VARIANTS AND HIV VACCINE EFFICACY TRIALS

In HIV-1 vaccine efficacy trials, studies have shown clear associations between FcγR-mediated effector functions and risk of HIV-1 acquisition following vaccination (9, 15, 16, 48). To dissect further, three vaccine efficacy studies to date have investigated FcγR variation as a modifier of antibody Fc-mediated effector functions and HIV-1 acquisition risk (Figure 2A).

The VAX004 trial evaluated a recombinant envelope protein (AIDSVAX B/B) prime-boost regimen in predominantly Caucasian men who have sex with men (3). Vaccine recipients who remained uninfected had higher antibody-dependent cell-mediated virus inhibition (ADCVI) responses, which encompass ADCC, ADCP and the induction of soluble antiviral factors, than...
those who became infected (48). The magnitude of ADCVI responses inversely correlated with the HIV-1 acquisition rate, but only in individuals bearing low affinity alleles for FcγRIIa-p.H166R (HR/RR genotypes) and FcγRIIIa-p.F176V (FF genotype) (48) (Figure 2Aii). When adjusted for linkage disequilibrium between the two variants, an independent association with FcγRIIa-p.H166R remained. However, the FcγRIIa-p.H166R variant itself did not predict acquisition rate (16). Conversely, in the low risk behavioral group, vaccinees homozygous for the p.176V allele were at greater rate of acquiring HIV-1 compared to those who received the placebo (hazard ratio 4.51), suggesting enhanced infection from the use of AIDSVAX B/B in this genotype group (16).

The RV144 trial, which evaluated a heterologous ALVAC-HIV (vCP1521) canary pox vector prime and AIDSVAX B/E protein boost regimen, demonstrated modest vaccine efficacy (31.2%) in Thai individuals (1). The primary determinants of vaccine efficacy were binding IgG to the variable loops 1 and 2 (V1V2) region of gp120 and binding of plasma IgA to envelope (9). In a secondary analysis, the combination of high levels of ADCC and low plasma anti-HIV-1 envelope IgA antibodies inversely correlated with HIV-1 acquisition risk (9). Variants within FcγRIIa, the major FcγR involved in NK cell-mediated ADCC, did not associate with HIV-1 acquisition risk (17) (Figure 2Aii). Conversely, three single nucleotide variants within FCGR2C significantly modified vaccine efficacy that include FCGR2C 126C>T (HVGs name: c.134-96C>T, rs114945036), c.353C>T (p. T118I, rs138747765), and c.391+111G>A (rs78603008) (17). All variants were in complete linkage disequilibrium in Thai RV144 trial participants, forming a haplotype. Possession of the haplotype associated with an estimated vaccine efficacy of 91% against CRF01 AE 169K HIV-1 and 64% against any HIV-1 strain, compared to 15% and 11% in the absence of the haplotype, respectively. The functional significance of the variant is unrelated to FcγRIIc surface expression, since only one study participant carried an FcγRIIc-p.57Q allele that predicts expression (17). Alternatively, the haplotype locates within a weak transcriptional enhancer (49). The minor alleles likely abrogate binding of repressor proteins within the regulatory motif and increase mRNA expression. Indeed, in Epstein-Barr virus transformed lymphoblastoid B-cell lines from European Caucasians, the minor allele haplotype associated with increased expression of FCGR2A and/or FCGR2C exon 7 (50). Other FCGR2C variants in complete linkage disequilibrium with the haplotype include c.113-1058T>C (rs2169052/rs115953596) and c.113-684C>T (rs111823862) (49) were not genotyped in RV144 participants and warrant further investigation. Of significance, two components of the haplotype, p.T118I (rs138747765) and c.391+111G>A (rs78603008), are rarely polymorphic in Africans (19), where the RV144 follow-up trial HVTN 702 failed to protect against HIV-1 infection (7).

The HVTN 505 trial that evaluated another heterologous prime-boost regimen – a multigene, multiclade DNA prime and recombinant adenovirus 5 (rAd5) boost – did not show any efficacy in a cohort of predominantly Caucasian men who have sex with men (6). However, ADCP responses and binding of immune complexes to recombinant FcγRIIa-p.166H inversely correlated with HIV-1 acquisition risk (15) (Figure 2Aiii). The associations increased for individuals without HIV-1 envelope IgA. Intriguingly, in a phase IIa clinical trial of the same DNA/rAd5 regimen (HVTN 204) (51), a different group did not detect ADCP responses (52). The cause of the distinct observations is unclear; both groups used the same assay albeit a different antibody source (isolated IgG vs. serum) and antigen (vaccine clade-specific gp120 vs. Con S gp140) (52). In the HVTN 505 trial participants, targeted sequencing of regions encoding the extracellular domains of FcγRs identified several variants that associated with HIV-1 acquisition risk or Fc-mediated effector functions. An FCGR2A intrinsic variant modified HIV-1 acquisition risk, FCGR2A-intron13-645-G/A (HVGs name: c.742+290G>A, rs2165088) (15). In vaccine recipients bearing the minor allele of c.742+290G>A, the magnitude of ADCP responses and FcγRIIa-p.166H binding to antibody-rgp140 complexes with reduced risk of HIV-1 acquisition (15). The functional consequence of FCGR2A c.742+290G>A is unknown and it does not appear to be in complete or high linkage disequilibrium with other variants in, or flanking, FCGR2A. Inverse correlations between ADCP with HIV-1 acquisition risk similarly occurred for participants bearing minor alleles of two FCGR2B variants (synonymous FCGR2B-exon5-523-G/A; HVGs name: c.336G>A, rs6665610 and FCGR2B-intron14-352-T/G; HVGs name: c.760+267>G, rs6666965) (18). c.336G>A is in high linkage disequilibrium with seven other FCGR2B variants and associated with decreased expression of FCGR2A (18).

Furthermore, in HVTN 505 participants, a four-variant FCGR2C haplotype and three-variant FCGR3B haplotype associated with increased HIV-1 acquisition risk (hazard ratio 9.79 and 2.78, respectively) (18) (Figure 2Aiii). The FCGR2C haplotype comprise two of the three FCGR2 variants identified as protective in the RV144 vaccine trial (p.T118I, rs138747765; and c.391+111G>A, rs78603008). The lack of association with the third FCGR2 variant (c.134-96C>T, rs114945036) is likely due to incomplete linkage disequilibrium of the three FCGR2C variants in Caucasians (49), the predominant ethnicity of HVTN 505 participants. Additional FCGR2C variants were in complete linkage disequilibrium in HVTN 505 participants, FCGR2C-intron15-403-C/T (HVGs name: c.760+81C>T, rs373013207) and FCGR2C-intron14-433-G/A (HVGs name: c.760+111G>A, rs201984478). The functional consequences of these variants remains to be determined. The haplotype within FCGR3B that also associated with increased HIV-1 acquisition comprise three variants in the 5' untranslated region of FCGR3B, 111 to 126 nucleotides upstream of the transcription start site and potentially in the gene promoter region. These include FCGR3B-5'utr222-G/A (HVGs name: c.-111G>T; rs34085961), FCGR3B-5'utr44-T/A (HVGs name: c.-181T>A, rs34322334), and FCGR3B-5'utr99-C/G (HVGs name: c.-126C>G, rs61803026). In individuals with the FCGR3B haplotype, vaccination was less likely to induce potentially protective envelope-specific IgG and/or CD8+ T-cell responses than for individuals without the FCGR3B haplotype.
**FcγR VARIANTS IN OTHER HIV INFECTION AND DISEASE CONTEXTS**

*Mother-to-child-transmission.* Investigations of FCGR variants and mother-to-child-transmission risk are limited to two Kenyan cohorts and one South African cohort (53–55). In a Kenyan cohort of grouped perinatal HIV-1 transmission routes (*in utero*, intrapartum, and breastfeeding), infants with the FcRRIIa-p.166HH genotype were at increased risk of acquiring HIV-1 compared with infants bearing the p.166HR genotype (53). Studies of a Kenyan cohort with a large representation of breastfeeding HIV-1 transmission and our South African cohort with predominantly *in utero* and intrapartum HIV-1 transmission, did not replicate these findings (55, 56). In the latter two cohorts, the maternal FcRRIIa-F176V variant associated with HIV-1 transmission, although with contrasting findings. In the Kenyan cohort of predominantly breastfeeding women, heterozygous mothers (FV) had an increased risk of transmitting HIV-1 compared to homozygous mothers (combined FF/VV); however, carriage of the 176V allele did not predict HIV-1 transmission (56). If adjustment for multiple comparisons were applied in the study, the association would not have been statistically significant. In contrast, our South African cohort revealed a protective role for the 176V allele in *in utero* transmission, where the association remained significant after adjustment for multiple comparisons (55). A recent study of FCGR2C variability in South African children revealed a protective role for a single gene copy of FCGR2C/3B per diploid genome (57). In contrast, children bearing the minor allele of the FCGR2C variant c.134-96C>T (rs114945036) – identified as protective in Thai RV144 vaccine recipients (17) – were more likely to acquire HIV-1 compared to children homozygous for the c.134-96C allele (57).

*Disease progression.* The FcRRIIa low affinity genotype, p.166RR, predicted a faster CD4 decline compared to p.166HH/HH in the Multicenter AIDS Cohort Study (MACS) of predominantly Caucasian men who have sex with men (58). A similar analysis in Kenyan women – a different host genetic background, sex and route of transmission – showed no effect (59). In addition, the variant did not modify natural control of HIV-1 infection in African Americans (60, 61). Despite convincing evidence for a role for ADCC in natural HIV-1 control [reviewed in (62)], the FcRRIIa-p.176V variant does not appear to modify HIV-1 disease course in Caucasians (58) or African Americans (60) (after adjusting for multiple comparisons). Neither FcRRIIa-p.H166R, FcRRIIa-p.F176V, nor FcRRIIb-p.I232T associated with HIV-1 control in the French multicentric CODEX cohort (63). Of note, the potential for FcγR variants to modify HIV-1 control may only become apparent when considering variability within the ligand, such as IgG γ chain phenotypes (GM allotypes). For example, in individuals bearing the FcRRIIa p.166HH or FcRRIIa p.176VF/VV genotypes, HIV-1 viraeic control was more likely in the absence of the IgG GM21 allotype (61). Beyond the protein-coding region, a variant located 3.1 kilobases upstream of FCGR2A, g.1954 A>G (rs10800309), modified HIV-1 disease progression in a cohort of predominantly Caucasian men and women (63). In particular, homozygosity for g.1954A allele, which associates with increased FcRRIa surface expression on myeloid cells, predicted natural control of HIV-1 independent of HLA-B57 and HLA-B27 (63). Another non-coding variant, the FCGR2C variant c.134-96C>T (rs114945036), predicted HIV-1 disease progression in South Africans (49), the same population where the RV144 follow-on trial, HVTN702, failed to show efficacy (7). However, in the French multicentric CODEX cohort of predominantly Caucasian individuals, the same FCGR2C variant did not associate with disease progression (63). It is unclear whether the different outcomes of RV144 and HVTN702 result from diverse population genetics, that include FCGR2C, or vaccine-associated factors that include differences in HIV-1 subtype envelopes, mismatched circulating strains, adjuvant or additional booster vaccination. Regardless, the collective findings further emphasize the importance of the FCGR2C locus, and additional study in different contexts will help elucidate the underlying protective/deleterious mechanisms.

**DISCUSSION**

Many factors affect the host immunological response to immunization and to the pathogen (HIV) encountered. These include i) the route of inoculation and of HIV-1 acquisition, ii) immunogen/virus variability, iii) vaccine regimen (modality, dose, timing, adjuvant), iv) other prior exposures (related or unrelated), comorbidities and pre-existing infections, v) age, vi) sex, vii) geography (population genetics), and viii) genetic variation of the host (Figure 2B). The immune milieu present at antigen encounter is affected by all these factors, which collectively define what could be called “an immunological founder effect” – a measure of an individual’s immune capability that dictates the likelihood of producing a protective response to vaccination or infection. As context matters, the antibody Fc-FcγR axis, implicated in protection from acquisition of HIV-1 in vaccine recipients, would be expected to be modulated by these factors.

Investigations of FcγRs and their variants warrant several considerations. i) There are no association studies of FCGR copy number variation and HIV vaccine outcome. In RV144, ADCC was a correlate of protection. It is therefore plausible that a CNR1 deletion, which results in the expression of the inhibitory FcRRIlb on NK cells and subsequent inhibition of ADCC, may have an effect on vaccine efficacy. ii) Investigations of single nucleotide variants need to adjust for FCGR gene copy number. Certain minor alleles are more prevalent in individuals with more than two gene copies and may confound quantitative trait loci studies of FCGR variants (49). iii) Investigations of Fc-mediated effector functions should consider the autologous FcγR variants since they modulate binding of the receptor to antibodies, surface expression levels of the receptor, and/or cell activation/inhibition (64). iv) FCGR genes are highly homologous. Assigning single nucleotide variants to specific FCGRs requires validated
methods. v) Considerable linkage disequilibrium between single nucleotide variants exist across the FCGR gene region (19, 45, 46), complicating identification of potential causal variants. vi) Increasing evidence suggest a clinical significance for non-coding FCGR variants highlighting potential complex cis- or transgene regulation that warrants characterization and investigation in other contexts. vii) FcγRs often co-occur on the same cell type. Elucidating the role of a single variant requires adjusting for allelic variants in co-expressed FcγRs, since the collective function of all co-expressed FcγRs will determine the effector response. Furthermore, phenotypic and functional analyses of FCGR genotype combinations are highly relevant, as demonstrated by an association of the FCGR2A rs1801274: rs10800309 diplotype with cell-type specific FcγRII expression (65) and FcγRIIa: FcγRIIb haplotypes with neutrophil function (66). viii) FCGR variation – gene copy number variation, single nucleotide variants, and linkage disequilibrium – differ significantly between population groups and genetic association cannot necessarily be extrapolated between groups. ix) Phenotypic and functional consequences of allelic variants should be studied in the disease context and immune milieu of the condition under study, since disease may alter allelic function (67).

In summary, FCGR genetic variants have been associated with protective or deleterious infection and disease outcomes. Much insight can be gained into the potential functional significance of these variants by testing samples from other efficacy trials. For example, HVTN 702, which was non-ef cacious in South Africans immunized with subtype C envelope ALVAC-HIV (vCP2438) prime and an MF59-adjuvanted subtype C bivalent envelope protein boost (7). Similarly, individuals passively immunized with broadly neutralizing antibody (VRC01) in the Antibody Mediated Prevention (AMP) trials (68) provide another informative study model. Harnessing host genetic variation between populations, and studying the collective contribution of FCGR variants in different infection/disease contexts, will provide much needed insights into what constitutes protective immunity to HIV-1. Importantly, the considerations discussed here extend beyond the context of HIV, bearing relevance to other infections and vaccination strategies that encompass endemic [e.g. malaria (69)], epidemic [e.g. influenza and respiratory syncytial virus (70–72)], and emerging/re-emerging infectious diseases [e.g. Ebola (74, 75)].

DATA AVAILABILITY STATEMENT
The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS
RL and CT conceptualized and wrote the article. Figures were generated by RL. All authors contributed to the article and approved the submitted version.

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