FC GAMMA RECEPTOR GENETIC VARIABILITY IN PAEDIATRIC HIV-1 INFECTION

ABSTRACT

The crystallisable fragment (Fc) region of immunoglobulin G antibodies engages with Fc gamma receptors (FcγRs) to recruit antiviral effector functions of the innate immune system. Allelic variation within the *FCGR* genes that encode FcγRs alter the potency of these effector functions by modulating the receptor surface density, binding affinity, cellular localization, glycosylation and cellular distribution. Genetic association studies of functional FcγR genetic variants can therefore provide insight into the role of Fc-mediated effector functions in affecting disease susceptibility and outcome. This study aimed to investigate FcγR variants in the context of perinatal HIV-1 acquisition, mortality, virological control and latent reservoir size during antiretroviral treatment in the early life of children living with HIV-1. A nested case-control study was conducted, combining *FCGR* genotypic data from five perinatal cohorts at two hospitals in Johannesburg, South Africa. All study participants were black South Africans and received nevirapine for prevention of mother-to-child transmission. Children with perinatally-acquired HIV-1 (cases) were compared to HIV-1-exposed uninfected children (controls). Functional variants were genotyped using a multiplex ligation-dependent probe amplification assay and Sanger sequencing. Their representation compared between groups using regression analyses. Increased odds of perinatal HIV-1 acquisition was associated with the *FCGR2C* c.134-96T-allele, *FCGR3A* gene duplication, homozygous FcγRIIb-232T allele, and FcγRIIIb-HNA1a, but not the common FcγRIIa-H166R and FcγRIIIa-F176V polymorphisms. The low-affinity FcγR variants did not associate with mortality, except for *FCGR3A* copy number variation that demonstrated a positive association. None of the FcγR variants associated with pre-treatment viral load, virologic failure, or size of the HIV-1 DNA reservoir. In contrast to the protective effect observed in the Thai RV144 trial, we found the *FCGR2C* variant c.134-96T-allele associated with increased odds of perinatal HIV-1 acquisition in South African children. These findings, taken together with a similar deleterious association found with HIV-1 disease progression in South African adults, highlight the importance of elucidating the functional relevance of this variant in different populations and vaccination/disease contexts. Our findings suggest that the FcγRIIb-232TT genotype exerts a controlling influence on infant susceptibility to HIV-1 infection. We also show a deleterious role for the less studied *FCGR3A* copy number variation and homozygous HNA1a. These findings provide additional insight into a role for FcγRs in HIV-1 infection in children.

Keywords: Fc gamma receptor, allelic variant, perinatal HIV-1 acquisition, South Africa