An FCGR2C Polymorphism Associates with HIV-1 Vaccine Protection in RV144 Trial

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The phase III HIV-1 trial RV144 in Thailand tested the efficacy of a vaccine consisting in priming with a canarypox vector carrying three HIV genes (*gag*, *pol* and *env*) and boosting wth the protein gp120 env. The tested vaccine has so far been the only one showing protection from HIV-1 infection, although with a limited efficacy of 31.2% efficacy. Post hoc analyses of the trial results showed that HIV-specific Immunoglobulin (Ig) G binding to the envelope (Env) V1V2 region inversely correlated with infection risk, while the presence of IgA directly correlated with the risk of infection.

This finding led to the hypothesis that IgG protection is not related to their capacity to bind and neutralize the virus, but to their fragment crystallizable (Fc)-mediated function. Antibodies can have functions such as antibody-dependent cellular cytotoxicity, requiring the recognition of Fc by specific receptors (FcR) on effector cells, which can be inhibited by the presence of IgA, recognized by the same FcR.

Prompted by this major finding in HIV research, Drs. Shuying Li and Peter Gilbert from the Vaccine and Infectious Disease Division (VIDD) and their collaborators investigated the correlation between genetic polymorphisms in the FcR-encoding sequences and surrounding areas and vaccine protection. Their results were published in *The Journal of Clinical Investigation*.

The authors evaluated single nucleotide polymorphisms (SNPs) in six different human FcR genes (FCGR2A, FCGR2B, FCGR2C, FCGR3A, FCGR3B, and FCAR) and found that the SNP rs114943036 in FCGR2C was significantly associated with vaccine efficacy. The vaccine was effective against a particular genotype of HIV-1 in 91% of individuals carrying CT or TT genotypes compared with 15% of individuals carrying the CC genotype. Furthermore, they found Env-specific IgG and subclass IgG3 antibodies (Abs), IgG avidity, and neutralizing Abs inversely correlated with the infection risk but only in the vaccine recipients who carried the CT or TT genotype.

These results open new questions regarding the functional significance of this polymorphism, in particular on its effects on FcR structure, function or expression. To this regard, Dr. Sue Li of the Statistical Center for HIV/AIDS Prevention, comments: "Our paper is the first report of an association between FCGR2C 126C>T and prevention efficacy against any clinical outcomes. FCGR2C is a

product of unequal crossover between FCGR2A and FCGR2B. This gene structure is complex and is not well studied in the literature. The functional significance and implication of this association remains to be established. Dr. Daniel Geraghty from the Clinical Research Division is applying for funding to pursue experimental approaches to study the function of the polymorphisms and to distinguish whether the genetic variants detected in this study were themselves causal or in linkage with other causal variations that were not genotyped in this study."

When asked about the significance of this study for HIV research, Dr. Li adds: "Our data suggest a potent role of Fc-γ receptors and Fc-mediated Ab function in conferring protection from transmission risk in the RV144 trial. We hope that new immune correlates of risk identified in host genetic subgroups in this study will inform/direct future experiments and vaccine trials that can increase knowledge about mechanisms of vaccine protections. Understanding the process of Ab-mediated vaccine protection, where virus neutralization and Fc-FcR interaction together achieve immune protection, is critical for HIV vaccine design." Furthermore, "our study demonstrates the importance of considering host immune genetics in assessments of vaccine efficacy, immune correlates of risk, and sieve analysis of viral sequences data."

Li SS*, Gilbert P*, Tomaras GD, Kijak G, Ferrari G, Thomas R, Pyo CW, Zolla-Pazner S, Montefiori D, Liao HX, Nabel G, Pinter A, Evans DT, Gottardo R, Dai JY, Janes H, Morris D, Fong Y, Edlefsen PT, Li F, Frahm N, Alpert MD, Prentice H, Rerks-Ngarm S, Pitisuttithum P, Kaewkungwal J, Nitayaphan S, Robb ML, O'Connell RJ, Haynes BF, Michael NL, Kim JH, McElrath MJ, Geraghty DE.2014 FCGR2C polymorphisms associate with HIV-1 vaccine protection in RV144 trial. *J Clin Invest*. 124(9):3879–3890.

See also: JY Dai, SS Li, PB Gilbert. 2014. Case-only method for cause-specific hazards models with application to assessing differential vaccine efficacy by viral and host genetics. *Biostatistics*. 15(1): 196-203.

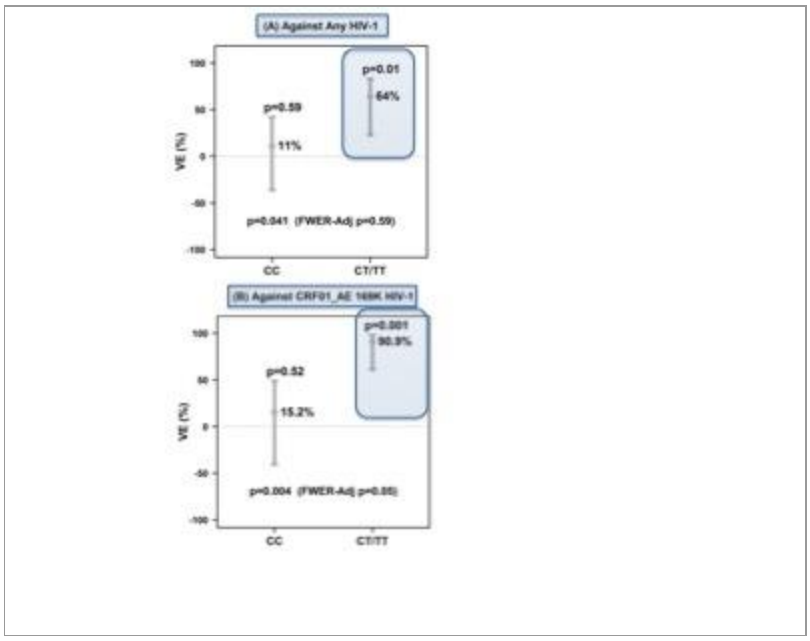

Image provided by Dr. Shuying Li

Association of FCGR2C 126C>T (rs114945036) genotype with vaccine efficacy (VE) against any HIV-1 strains (VE=11% among individuals carrying CC genotype vs. 64% among individuals carrying CT or TT genotype, p-value=0.04) and VE against HIV-1 subtype CRF01_AE with lysine at position 169 (169K) in the V2 loop (VE=15% among individuals carrying CC genotype vs. 64% among individuals carrying CT or TT genotype, p-value=0.004 and 0.05 after multiplicity correction for 28 tag SNPs). The error bars are 95% confidence intervals for the estimated VEs. The numbers on the bottom of each plot are the numbers of infected individuals by vaccine arm (vaccine vs. placebo) and FCGR2C 126C>T genotype group (CC vs. CT or TT). Case-only statistical method (Dai, Li, and Gilbert, 2014) was used to estimate and test the difference of VE between the host genotype groups.