A Population-based Matched-cohort Study on Insertion/Deletion Polymorphism of the *APOBEC3B* gene and Risk of HIV-1

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Background: The human APOBEC3 (A3) family proteins (A3A-H) potently inhibit replication of HIV-1. In human populations, a high-frequency distribution of the *A3B* deletion genotype is observed. Previously, several groups have reported controversial observations on the effect of *A3B* gene deletion on HIV-1 acquisition and disease progression. Here, in order to verify the effects of A3B on HIV-1 infection *in vivo*, we investigated the insertion (I)/ deletion (D) polymorphism frequencies of the *A3B* gene in a matched cohort in Japan.

Methods: The *A3B* genotype was analyzed by PCR with genomic DNA from blood or buccal membrane. The effect of *A3B* gene deletion on disease progression was evaluated by comparing acquisition of Syphilis, HBV and HCV, as well as $CD4^+$ T cell counts and viral load before starting cART among three genotype groups; deletion-homozygous (D/D), hemizygous (D/I), and no deletion (I/I) genotypes. Susceptibility to HIV-1 infection was assessed based on the frequencies of three genotypes between the infected and uninfected cohorts. HIV-1 replication kinetics and the infectivity were assayed *in vitro* by using healthy donor $CD4^+$ T cells. Fischer exact and Mann-Whitney U tests were used for statistics.

Results: 228 HIV-1-infected patients of Japanese men who have sex with men (MSM) and 207 uninfected Japanese MSM were enrolled. Our *A3B* genotyping analysis showed no significant difference in the ratio of *A3B* genotype between the infected (D/D 8.3%, D/I 44.7%, and I/I 46.9%) and the uninfected (D/D 8.7%, D/I 39.6%, and I/I 51.7%) cohorts ($p=.55$). In addition, the parameters of disease progression resulted in quite similar frequencies among the three genotype groups. These results suggest no significant effect of *A3B* gene polymorphism on the HIV-1 transmission or the disease progression. Furthermore, the *in vitro* kinetics of HIV-1 replication and the infectivities of the virus in $CD4^+$ T cells were comparable between D/D and I/I ($p=.31$ and $p=.86$, respectively).

Conclusion: Our analysis of a population-based matched cohort showed that loss of *A3B* gene is not associated with the risk of HIV-1 susceptibility and disease progression. The results suggest *in vivo*, A3B could play an unknown role,but not in eliminating HIV-1.