主論文の要旨

Association of *APOBEC3G* genotypes and CD4 decline in Thai and Cambodian HIV-infected children with moderate immune deficiency

（タイ・カンボジアにおける HIV 未治療感染児の *APOBEC3G* 遺伝子型は CD4 陽性細胞の減少と相関する）

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【Introduction】

Disease progression to acquire immune deficiency syndrome (AIDS) is multifactorial and affected by host genetics and viral factors. Apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G (*APOBEC3G*) is a host factor potently controls HIV-1 replication. Human *APOBEC3G* is located on chromosome 22q13.1-13.2. Association of *APOBEC3G*, CD4 and HIV-RNA levels in HIV-infected adults has been reported. A genetic variant of *APOBEC3G*; H186R in GG, was significantly associated with a decline in CD4 T cells and higher HIV-RNA among antiretroviral therapy (ART)-naïve African HIV-infected adults. However, its effect on HIV/AIDS disease progression in ART-naïve perinatally HIV-infected children remains unclear.

【Methods】

This is a sub-study of the Pediatric Randomized Early versus Deferred Initiation in Cambodia and Thailand study (The PREDICT study, a multicentre, randomised, open-label trial of early ART in perinatally HIV-infected children, clinicaltrials.gov identification number NCT00234091). The inclusion criteria for PREDICT study were ART-naïve HIV-infected children, aged 1-12 years, Center for Disease Control and Prevention (CDC) clinical classification N (no HIV symptoms) A (mild HIV symptoms) or B (moderate HIV symptoms), CD4 15%-24%, hemoglobin ≥ 7.5 g/dL and no active opportunistic infections at screening visit. The children were followed CD4 every 12 weeks and plasma HIV-RNA every 24 weeks until 144 weeks. Children in the deferred-arm were started ART when either the CD4% declined to < 15% or CDC classification C events developed.

We used blood samples from all children in the deferred-arm of the PREDICT study. The genomic DNA was isolated from buffy coats of each child using the Invisorb® Spin Blood Mini kit (Invitek, Berlin, Germany). The *APOBEC3G* genotypes for three polymorphisms (186H/H, 186H/R and 186R/R) were determined by polymerase chain reaction (PCR)-Restriction Fragment Length Polymorphism (RFLP) described in previous reports.

The PCR reaction was performed to amplify 409-bp DNA fragment of *APOBEC3G* H186R region using the *APOBEC3G* forward primer: 5'-acctgtgggtctgctctgat-3' and *APOBEC3G* reverse primer: 5'-caggagggaaggcaggag-3'. The APOBEC3G genotypes were reported as genotype AA (186H/H), AG (186H/R), or GG (186R/R).

This study was approved by the local and the Ministry of Public Health Institutional Review Boards. All caregivers gave consent prior to the enrolments.

【Results】

We enrolled 147 ART-naïve HIV-infected children, 35% male, median (IQR) age 6.5 (4.3-8.8) years. The median (IQR) baselines of CD4%, CD4 count and HIV RNA were 20 (17-23)%, 605 (460-846) cells/mm^3 and 4.7 (4.3-5.0) log_{10}copies/mL, respectively. Table 1 shows details of baseline characteristics. The frequencies of *APOBEC3G* genotypes AA (186H/H), AG (186H/R) and GG (186R/R) were 86% (n = 127), 12% (n = 17) and 2% (n = 3), respectively.

During baseline to week 144, 30 children progressed to the CDC classification B (e.g. bacterial pneumonia, thrombocytopenia, herpes zoster, herpes simplex) and 2 girls progressed to CDC classification C. A total of 69 children had started ART and 78 children were still ART-naïve at week 144. The reasons to started ART were worsening of clinical criteria in 3 children (1 *Pneumocystis jiroveci* pneumonia and 2 severe thrombocytopenia) and immunologic criteria in 66 children (63 for CD4 <15% and 3 for CD4 <20%).

The proportion who started ART because of CD4 decline/clinical progression among children with *APOBEC3G* genotypes AA, AG, and GG were 60/127 (47%), 7/17 (41%) and 2/3 (67%) respectively (p=0.71). No significant association between the *APOBEC3G* genotypes and the CDC classification B/C was found (p=0.49).

By random-effect linear regression analysis, after adjustment by baseline CD4%, CD4 count and study week, it was demonstrated that the *APOBEC3G* genotype GG was associated with significant decline from baseline to week 144 in CD4% (95% confidence interval) -5.1% (-8.9 to -1.2%), p<0.001, and CD4 counts -226 (-415 to -34) cells/mm^3, p<0.001.

Figure 1 shows the decline of CD4% over 144 weeks of each *APOBEC3G* genotypes. No significant associations of *APOBEC3G* genotypes with HIV-RNA changes overtime (p=0.16) was observed.

【Discussion】

In this study, the association of a genetic variant of *APOBEC3G* genotypes, H186 in GG, with the decline in CD4% and the CD4 count over time in Thai and Cambodian ART-naïve HIV-infected children with moderate immune deficiency was demonstrated. However, no significant association of the *APOBEC3G* genotypes with changes of HIV-RNA log_{10} overtime or progression of CDC classification was found.

From previous published data, *APOBEC3G* genotypes have been associated with significant decline in CD4 count in ART-naïve African HIV-infected adults. In our

study, we also found the association of *APOBEC3G* genotypes with significant decline in CD4% and CD4 count. This association needs more study in a larger sample size or other ethnicity as the mechanism is unclear and warrants further investigation.

Majority of Thai and Cambodian children had *APOBEC3G* genotype AA which is similar to previous publications that *APOBEC3G* genotype AA is more common than genotype GG.

In summary, our data showed that a genetic variant of *APOBEC3G* genotypes, H186 in GG, was significantly associated with decline in CD4% and the CD4 count over time in Thai and Cambodian ART-naïve HIV-infected children with moderate immune deficiency.