論文の内容の要旨

論文題目：Genetic Study for Host Susceptibility to Tuberculosis in Javanese (Indonesia)

論文題目の和訳：インドネシア国ジャワ人における結核の宿主遺伝要因に関する研究

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Tuberculosis remains the major health problem in the world, including Indonesia. The genetic studies of tuberculosis (TB) have been conducted in Javanese, a major population in the country. In this study, I started with describing the genetic affinity and comparison between the studied population and other Asian populations based on the polymorphisms of HLA class I and II genes. The possible association of HLA-A, -B and -DRB1 with TB was also analyzed both in primary TB and in recurrent TB patients. Another genetic study on TB was also done in this Javanese population by conducting a high-density association mapping of a candidate region for young-onset TB based on the result of a genome-wide linkage study in Thai (Mahasirimongkol et al., 2009). Thai is a Southeast Asian population with close genetic affinity with the Javanese (Indonesia) population. Two genes newly reported to be associated with TB especially for young-onset TB were found.

Human leukocyte antigen (HLA) genes are the most polymorphic genes in the human genome with the major role in the presentation of variety antigen peptides to lymphocyte T cells. The unique characteristics of HLA genes and their essential function in the immune system serve as the important candidate gene for disease susceptibility and make the genes as useful tool for population study. In the present study, the allele and haplotype frequencies of

HLA-A, HLA-B and HLA-DRB1 were examined in 237 unrelated healthy western Javanese (Indonesia) by the high resolution PCR-Luminex method. A total of 18 A, 40 B and 20 DRB1 alleles were identified. The most frequent HLA-A, -B and -DRB1 alleles were HLA-A*24:07 (21.6%), HLA-B*15:02 (11.6%) and HLA-B*15:13 (11.2%) and DRB1*12:02 (37.8%), respectively. The most frequent 2-locus haplotypes were HLA-A*24:07-B*35:05 (7%) and HLA-B*15:13-DRB1*12:02 (9.2%), and for 3-locus haplotypes were HLA-A*34:01-B*15:21-DRB1*15:02:01 (4.6%), HLA-A*24:07-B*35:05-DRB1*12:02 (4.3%) and HLA-A*33:03:01-B*44:03:02-DRB1*07:01:01 (4.2%). HLA allele and haplotype frequencies in addition to phylogenetic tree and principal component analyses based on the 4-digit sequence level allele frequencies for HLA-A, HLA-B and HLA-DRB1 revealed the evidence of close genetic affinity between Western Javanese (Indonesia) with other Southern group of East Asian, especially Southeast Asian populations.

The association of HLA-A, -B, and -DRB1 alleles and haplotypes with TB was also studied to ascertain their role in susceptibility/resistance to primary and recurrent TB in 257 TB patients (216 primary and 41 recurrent TB patients) and 236 ethnically matched healthy controls in Western Javanese (Indonesia). HLA-B*40:06 was associated with primary TB ($p=0.044$, p_{adj}=ns), whereas HLA-B*18:02 was associated with recurrent TB ($p=0.014$, $p_{adj}=0.024$ for recurrent TB vs control, $p=0.013$, $p_{adj}=0.016$ for primary TB vs recurrent TB). Two other alleles: HLA-B*40:01 and HLA-DRB1*11:01 showed significant association with recurrent TB only in the comparison between recurrent TB and primary TB ($p=0.015$, $p_{adj}=0.028$ and $p=0.008$, $p_{adj}=0.027$, respectively). Except for HLA-B*40:06, those associations remained significant after adjustment for age and sex by logistic regression analysis, although they were disappeared after correction for multiple testing. The possible role of HLA-B*18:02 was further supported by the observation that the presence of HLA-B*18:02-DRB1*12:02 haplotype was associated with susceptibility to recurrent TB ($p=0.014$,

OR=3.8 (1.18-12.27)). On the other hand, HLA-DRB1*12:02 in the absence of HLA-B*18:02 showed a significant association with resistance to recurrent TB ($p= 8.2\times10^{-4}$, OR= 0.32 (0.16-0.64)), suggesting that stronger susceptibility effect of HLA-B*18:02 masked the protective effect of HLA-DRB1*12:02.

Finally, the high-density association mapping of a candidate region for young-onset TB in chromosome 20p13 was performed in the present study in 275 cases (155 young-onset, 120 late-onset) and 250 control of Javanese (Indonesia). Of 135 analyzed SNPs, two SNPs located in the *OXT* and *AVP* gene region showed significant association event after correction for multiple testing (rs6084265(T): $p_{allele}=7.19\times10^{-6}$, OR=2.00 (1.48-2.72) and rs2770381(C): $p_{allele}=4.58\times10^{-5}$, OR= 1.83(1.37-2.45)) in young-onset TB. Moreover, the two-locus haplotype analysis of rs2770381-rs6084265 showed higher significant association with the disease (global $p_{haplotype}=2.68\times10^{-8}$). In contrast, significant association was not observed in late-onset TB group. These results suggest that the association observed in rs6084265 and rs2770381 could be due to other primary SNP in strong LD with it. Oxytocin and arginine vasopressin are neuroendocrine hormones that involve in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis. HPA response through glucocorticoids modulates the immune/inflammatory reaction. It was hypothesized that the variation in the *OXT-AVP* gene region mediated by rs2770381(A)-rs6084265(C) haplotype increase the activity of the gene, consequently activate the HPA-axis and subsequently increase the glucocorticoid production and lead to the shift of immunological balance from T helper (Th) 1 to Th2 that decrease the capability of individuals to respond mycobacterium infection and confer the susceptibility to young-onset TB. This finding is novel and I believe that this work would contribute to better understanding of TB etiology and better strategy to combat the disease. Further study to confirm this finding in other Asian and non Asian populations would be of great important to evaluate the global role of the genes.