［課程－２］

審査の結果の要旨

氏名　中内　彩香

The present study aims to find any unreported susceptibility genes to young tuberculosis (TB) in the candidate region on chromosome (Chr.) 20 in Thai population. TB is one of the three major infectious diseases worldwide and is known to be a complex disease that both genetic and environmental factors contribute to its development. A number of genetic studies in various populations have been carried out but there has been little consistency among them. Thus, more genetic studies are needed and this study is important in that it contributes better understanding of host genetic factors and TB pathogenesis.

The Ph.D candidate focused on a 1Mb region within Chr. 20p13-12.3, which was previously observed to have significant linkage with earlier onset of TB in Thai genome-wide linkage analysis. In order to overcome the limitations that a previous genome-wide association study could have missed some possible candidates due to insufficient data about variants and their frequencies, as well as the lack of Thai population information in available public databases, next-generation sequencing (NGS) was performed to screen variants and case-control association analysis was carried out for selected candidate polymorphisms. Results are as follows:

1. NGS performed in 13 young patients from Thai multi-case families detected 1,878 variants within the targeted 1Mb region. Among the variants, 3 non-synonymous SNPs (rs1127354, rs2280090, rs17857295) and 2 other functionally interesting SNPs on *ITPA* gene (rs6115814, rs13830) were selected as candidates for the further case-control association studies.

2. Among the candidate SNPs, rs13830 in the 3' untranslated region (UTR) and rs1127354 in the exon region of *ITPA* showed association (p=4.4E-3; OR=0.67, and p=0.015; OR=0.71, respectively) in Thai young patients (< 45 years old).

3. For fine-mapping of *ITPA* region, additional genotyping and analysis of 3 tagSNPs; rs11087570, rs8362 and rs6139034 was carried out. The results showed that only the initial SNPs, rs13830 and rs1127354 had associations in young patients. In the studied young Thai population, the two SNPs showed high linkage disequilibrium (r^2=0.88) and no effective SNP interaction was concluded in the gene region according to the result of haplotype analysis.

4. After genotyping with an additional sample set to increase statistical power, rs13830 and rs1127354 showed lower p-values (p=5.1E-5; OR=0.66, and p=1.3E-03; OR=0.72, respectively) in Thai young patients (< 45 years old).

5. *In silico* expression quantitative trait loci (eQTL) analysis was carried out and eQTL on *ITPA* gene showed a significant association with rs13830 ($p < 0.01$) within a 2 Mbp region around the SNP. In addition, a significant correlation between mRNA level of *ITPA* and the genotypes of rs13830 was observed (permutated p-value=0.0045), displaying higher expression in accordance with the number of minor allele. From the results, it may be speculated that the minor allele of rs13830 may serve to increase the stability of the mRNA transcript and increase expression of the gene, which in turn may lead to better functioning of the cells involved in the immune response against the TB pathogen.

This study is the first attempt in using NGS to gain insight into host genetic factors associated with TB and being the first to report a significant association of *ITPA* with young onset TB. The study not only contributes a better understanding of host genetic factors and TB pathogenesis but also demonstrates the effectiveness of NGS in searching for susceptibility genes in common diseases. For these reasons, we consider the candidate is worthy of a Ph.D degree.