CHAPTER V
DISCUSSION

The study of risk association inferred that the NPC development was changed by DNA variation of *PIGR*, nucleotide 1739 would play an important role in several reasons. First, 1739C showed strongly high relative risk in Thai, Chinese, Thai-Chinese and total. Second, haplotype 1093-1739 distribution was significantly distinguished between case and control groups in Thai, Thai-Chinese and total. Third, comparing between GC & AC with another haplotype revealed higher risk than GT & AT, whereas there was no difference between GC and AC. Finally, another nucleotide, except 1739, of *PIGR* could not found the mutation.

The important of deciding SNPs for association study were the consideration in functional SNP. Our data revealed a good example, the physical distance between *PIGR*1093, 1739 and 1773 were 2.5 kb and 30 bp, respectively. Three SNPs were closely linked but 1739C→T only showed significant relative risk. If 1739C→T had not been chosen for this study, the importance of *PIGR* as an NPC susceptibility gene would have been misunderstood.

This study and the previous knowledge regarding the function of this protein leads us to hypothesize that polymorphic *pIgR* plays an important role for NPC development by either enhancing EBV to infect NE or removing EBV from NE less effectively. Interestingly, genotype of this gene can alter this role. Whereas high-risk people with homozygous 1739C have increase their possibility to develop NPC, heterozygous or homozygous 1739T helps protect them. The 1739 T⟶C polymorphism is a missense mutation changing amino acid from alanine to valine. This codon locates in exon 7, which is near endoproteolytic cleavage site of the pIgR extracellular domain.[55,96] How this mutation altering cellular movement of IgA complex remains to be elucidated. Nevertheless, this study has led to speculate the role of this polymorphism. Whereas individual from high-risk ethnic with homozygous 1739C has higher chance for IgA-EBV complex transcytosis failure, this process can be fixed by the contribution of only one 1739T allele.

Though pIgR may involve in entering or removing process of EBV, the variation of the protein function does not significantly related to the onset of the disease. Probably, this may be influenced by several other factors, for example, the age of the patient when infected by EBV as well as the frequency of exposure to carcinogenic promotors. It is important to note that the 1739C→T can also be found among lower risk ethnic groups, such as the Caucasian. This data led to an interesting speculation that even though the 1739C susceptibility was not the ethnic specific mutation that explained the endemic distribution of this disease, pIgR was crucial for the NPC development process. Furthermore, the age of onset of NPC was relatively young and some patients were within active reproductive period. Consequently, high risk people with the susceptibility 1739C would have relative lower fitness than the 1739T group. As a result of this population evolution history, the gene frequency of 1739 susceptible allele would gradually decrease in oriental people but would not be altered in low risk population such as in Caucasian.

Not only that pIgR plays a crucial role in immunizing the mucosa against EBV, but also against pneumococcal infection by transporting polymeric immunoglobulins across the mucosal epithelium. The human pIgR can bind to a major pneumococcal adhesion and enhanced pneumococcal adherence and invasion.[97] In another words, there are two important human pathogenic organisms, EBV and pneumococcus, sharing the same human antibody transport protein, pIgR, to cause two common human diseases at the same tissue type, NE. How these two organisms and host (DNA) variation interact in vivo and what is the consequence to the global evolutionary scale will be interesting for further investigation.