**Disease modifier genes in beta thalassemia/HbE**

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Beta-thalassemia/HbE disease is one of the most common thalassemias in Southeast Asia. The clinical expression of this disease is remarkable variable, ranging from nearly asymptomatic to severe, transfusion-dependent disease. A number of additional genetic modifier genes may account for this variability. To identify genetic modifiers influencing severity among 1060 beta0-thalassemia/HbE patients, we use MassARRAY spectrometry to conduct a genome-wide association study involving approximately 110,000 gene-based single nucleotide polymorphisms (SNPs). A number of SNPs showed evidence for association with disease severity, including several in reported quantitative trait loci (QTLs) associated with fetal hemoglobin HbF levels. We finally identify armored 150 SNPs (with potential 100 candidate genes), which are different between the mild end severe β-thalassemia/HbE patients. The most strongly associated SNPs were within a region on chromosome 11 distinct from the beta globin gene cluster, within which most analysis to date has focused. In this study we will search for disease modifier genes, base on our SNPs data, by 1) resequencing the DNA/gene near the SNPs that have strongest associations with the disease severity, 2) functional study in the candidate genes with known biological functions. and 3) an information-based approach, relying on ability to mine public genomic resources and databases, will be undertaken to define relationships of these SNPs to other known genes.

The project will result in a number of publications in international, peer-reviewed journals. We expect at least 3 to 5 publications within the period of funding. In addition, the project is expected to produce 2 Ph.D. degree and 2 to 4 MSc degree students. The project proposed herein also offers the prospect of commercialization of the results and by patenting of potential applications such as a rapid protease assay kit useful for erythrocyte samples. A potential endpoint of this basic research project would be the development of small molecule drugs that are eventually suitable to stimulate HbF production or proteolytic activity in the erythrocytes of the patients and thereby would ameliorate disease severity.