GENOME-WIDE SEARCH FOR DISEASE MODIFIER GENES IN β-THALASSEMIA

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Ph.D. (BIOCHEMISTRY)

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ABSTRACT

Despite similar genetic backgrounds, β-thalassemia/Hb E patients show a remarkable phenotypic diversity. The reasons underlying this clinical heterogeneity remain largely obscure.

To identify disease modifier genes, a large-scale association study with approximately 110,000 single nucleotide polymorphisms (SNPs) located within 99 percent of known and predicted human genes was performed in mild and severe β-thalassemia/Hb E patients. Allele frequencies for all tested SNPs were estimated in DNA pools of patients with extremely mild and severe courses, and 4,175 SNPs suggesting significant differences (\(P\)-value <0.02) were selected for verification by repeated pooled DNA analysis. In order to determine precise allele and genotype frequencies, 620 significant SNPs (\(P\)-value <0.05) from a second scan were selected for genotyping of the 503 individual patient DNA. This study observed associations of severe of β-thalassemia with 210 variants in 160 genes/regions, particularly in genes included in proteolysis, apoptosis, signal transduction and regulation of gene expression. Further validation in an independent cohort is required to confirm the evidence of association and functional studies are required to confirm the importance of these variants as modifiers of β-thalassemia phenotype.

One of the candidate loci identified was located within the β-globin gene cluster on chromosome 11p15.5. High-density SNP mapping and haplotype analysis further revealed that 45 SNPs located in the LCR through the δ-globin gene have strong linkage disequilibrium with each other. All variants also conferred association with disease severity in β-thalassemia with an odds ratio between 2.04 to 2.22 and \(P\)-value less than 1×10\(^{-9}\). Association of specific haplotype with up-regulation of γ-globin gene was observed from a quantitative gene expression study. This finding suggests that further biological function exploration of this region would be valuable and could yield a better understanding of γ-globin gene regulation and variation of Hb F in β-thalassemia.

KEY WORDS: β-THALASSEMIA/ Hb E/ GENOTYPE-PHENOTYPE INTERACTION/ ASSOCIATION STUDY/ GENOME-WIDE SCAN