Abstract

In the present, we examined the linkage of glycogen synthase 1 (GYS1) and glycogen-targeting subunit of protein phosphatase 1 (PPP1R3) genes in Thai affected sibling pairs with type 2 diabetes. Associations of these genes with metabolic covariates were also examined. Subjects consisted of 197 adults with type 2 diabetes from 86 families forming 140 affected sibling pairs. Additional 103 non-diabetic subjects as defined by normal oral glucose tolerance test were recruited as controls. Polymorphisms of GYS1 and PPP1R3 genes were determined by PCR-RFLP. Shared alleles in affected sibpairs were analysed by non-parametric methods using SPLINK program. Data were expressed as mean ± SD.

The age of the subjects was 56.5 ± 9.8 years with an average age at onset of 47.8 ± 8.9 years. Eighty six were males and 111 were females. There was a correlation between age at diagnosis among sibling pairs ($r = 0.34$, $p < 0001$). Likewise, the HbA1c of siblings was also correlated ($r = 0.24$, $p < 0.01$). Regarding body habitus, there were also correlations among siblings in body weight ($r = 0.36$, $p < 0.0001$), height ($r = 0.26$, $p < 0.01$), BMI ($r = 0.39$, $p < 0.0001$), waist circumference ($r = 0.33$, $p < 0.01$) and hip circumference ($r = 0.40$, $p < 0.0001$). Moreover, there were correlations in serum total cholesterol ($r = 0.24$, $p < 0.01$), LDL-cholesterol ($r = 0.29$, $p < 0.001$), HDL-cholesterol ($r = 0.33$, $p < 0.0001$). No association between GYS1 polymorphism and metabolic covariates was found. On the contrary, there were associations between PPP1R3 polymorphism with serum total cholesterol ($r = -0.31$, $p < 0.001$), LDL-cholesterol ($r = -0.32$, $p < 0.001$), triglyceride ($r = 0.25$, $p < 0.01$), waist circumference ($r = 0.27$, $p < 0.01$) and hip circumference ($r = 0.26$, $p < 0.01$) in females but not in males. The genotype distributions of the GYS1 and PPP1R3 polymorphisms were different between diabetics and controls ($p < 0.01$). However, analysis of sibling pairs sharing GYS1 alleles identical by descent revealed that the estimated probability of sibpairs sharing 0 allele was 0.18; 1 allele, 0.5 and 2

allleles, 0.32. No evidence of linkage to diabetes was found (LOD score = 0.37). Likewise, the probability of shared 0, 1 and 2 alleles of PPP1R3 were 0.22, 0.44 and 0.34, respectively and no evidence of linkage to type 2 diabetes was demonstrated (LOD score = 0.49).

Conclusions Our study does not support a major role of GYS1 or PPP1R3 genes in the pathogenesis of type 2 diabetes in Thais. The study, however, suggests the influence of PPP1R3 gene in lipid abnormality in females with type 2 diabetes mellitus.