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Fibroblast growth factor receptor 4 Gly388Arg polymorphism associated with severity of gallstone disease in a Chinese population

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ABSTRACT. The etiology of gallstone disease is multifactorial; supersaturation of bile with cholesterol is a primary cause for gallstone formation. In previous studies, we found that fibroblast growth factor receptor 4 (FGFR4) plays an important role in maintaining bile acid homeostasis by regulating the expression of cholesterol 7α-hydroxylase (CYP7A1), a rate-limiting enzyme for bile acid biosynthesis. The Gly388Arg (G-388R) polymorphism of *FGFR4* affects stabilization and activation of FGFR4. Consequently, we studied the *FGFR4* gene as a candidate gene for genetic susceptibility to gallstone disease. We found that overexpression of FGFR4, especially the G-388R mutant of *FGFR4*, inhibits luciferase activity of CYP7A1 reporter in HepG2 cells, indicating that the G-388R mutant of *FGFR4* may have greater inhibitory activity against bile acid biosynthesis. To investigate the association of *FGFR4* polymorphism with gallstone disease, 117 patients with gallstone

disease and 457 controls were genotyped for *FGFR4* polymorphism G-388R by PCR-RFLP. Although the incidence of gallstone disease was not greater in patients with the *FGFR4* RR genotype, the ratio of gallstone patients with acute cholecystitis in the *FGFR4* RR genotype (42%) was significantly higher than that in other genotypes of *FGFR4* (P = 0.019). In conclusion, the *FGFR4* polymorphism is a genetic risk factor contributing to aggravation of gallstone disease.

Key words: Fibroblast growth factor receptor 4; Polymorphism; Gallstone disease

