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PBC 進行に関わる PGC-1α 遺伝子多型の *CYP7A1* 転写への影響

◯朱　赤[1], 稲嶺　達夫[1], 野口　扶美枝[1], 佐々木　万莉[1], 平　佳代[1], 近藤　新二[1], 中村　稔[1,2], 大曲　勝久[3], 塚元　和弘[1]([1]長崎大院医歯薬, [2]長崎医療センター, [3]長崎県大)

Background PBC (primary biliary cirrhosis) is a multifactor-induced autoimmune disease, which is characterized by a decrease of the small bile ducts in the liver, resulting in cholestasis, cirrhosis, and liver failure. In this study, to identify genetic factors involved in PBC progression, we examined an association of genetic polymorphisms of *PPARGC1A*, which encodes a co-activator of nuclear receptor regulating energy metabolism and bile acid synthesis including CYP7A1, with PBC progression in Japanese patients.

Methods Single nucleotide polymorphisms (SNPs) of *PPARGC1A* were genotyped by polymerase chain reaction-restriction fragment length polymorphism. Subsequently, genotype distributions were compared between early-stage and late-stage group in 315 Japanese PBC patients. Furthermore, we also performed a reporter gene assay using HepG2 cells to investigate the functional consequence of the PBC progression-associated SNPs to the transcriptional activity of *CYP7A1*, which is a target gene of PGC-1α and encodes a rate-limiting enzyme of bile acid synthesis.

Results In SNP association studies, The G/G genotype of rs8192678 (Gly482Ser) of *PPARGC1A* indicated the protective effect upon PBC progression ($P < 0.01$, odds ratio = 0.44). Furthermore, in functional analysis, the *CYP7A1*-promotor reporter co-transfected with *PPARGC1A* carrying a G allele of rs8192678 revealed a decrease in the transcriptional activity in comparison to that with *PPARGC1A* carrying another A allele.

Conclusion The association study indicates that PBC patients with the G/G genotype of rs8192678 in *PPARGC1A* may imply the lack of susceptibility to PBC progression. The functional analysis also suggests that the protective effect of the G/G genotype against the progression may be attributed to lesser activation of *CYP7A1* promoter, resulting in diminution of bile acids in hepatic cells.