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Novel Functional Impaired Single Nucleotide Polymorphism of Na^+-taurocholate Taurocholate Cotransporte Polypeptide (NTCP) in Korea Population

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Background: Na^+-taurocholate cotransporting polypeptide (NTCP, SLC10A1) is the key transporter responsible for hepatic uptake of bile acids from portal circulation. This study was designed to identify common SLC10A1 genetic variants and determine their in vitro functional change.

Methods: Genetic variants in exons and upstream domain of the gene were detected by direct sequencing in 50 Korean subjects. The novel nonsynonymous was further screened by pyrosequencing in Chinese and Vietnamese population. Transfected MDCK cells of human NTCP were used for in vitro uptake study. [3H] Taurocholic acid and [3H] extrone sulfate were selected as probe substrates.

Results: Sequence analysis revealed 2 SLC10A1 upstream SNPs and 4 code region SNPs, including a novel nonsynonymous SNP G190A (Ala64Thr) with 1% allele frequency in Korean (n=150). However, this SNP was not found in 360 Chinese and 152 Vietnamese subjects. The alleles frequency of reported C800T (Ser267Phe) SNP were found 5%, 7.8% and 9.2% in Korean, Chinese and Vietnamese subjects respectively. Ser267Phe variant, which has been reported to exhibit near complete loss of function for bile acid uptake, fully normal transport function for estrone sulfate. Otherwise, Ala64Thr variant showed decreased uptake activity of both [3H] Taurocholic acid and [3H] estrone sulfate substrates when compared with wild type though they had same expression level. However, both variants (Ala64Thr, Ser267Phe) and wild type showed the similar response to the known NTCP inhibitor (taurocholic acid, bromosulfalein and cyclosporin A).

Conclusion: Novel nonsynonymous SNP was found in SLC10A1 gene, which showed ethnic specificity, suggesting that this position may be part of a region in the transporter critical and specific for bile acid substrate recognition. Our study indicates functionally important polymorphisms in NTCP exist and that the likelihood of being carriers of such polymorphisms is dependent on ethnicity.