The p. Ser267Phe NTCP variant in SLC10A1 is associated with resistance to chronic Hepatitis B

With the support by the National Natural Science Foundation of China and the National Science and Technology Program Project, Prof. Gao Zhiliang and Prof. Wang Yiming's group at the Department of Infectious Diseases, Third Affiliated Hospital, Sun Yat-sen University, showed the evidence supporting that NTCP was a cellular receptor for HBV in chronic Hepatitis B, which was published in *Hepatology* (2015, 61: 1251—1260).

In the past 50 years there have been considerable efforts to identify the cellular receptor of hepatitis B virus (HBV). Recently, *in vitro* evidence from several groups has shown that the sodium-taurocholate cotransporting polypeptide (NTCP, which is encoded by SLC10A1 and transports bile acids into hepatic cells in enterohepatic recirculation) is a strong candidate. In particular, *in vitro* the p. Ser267Phe variation of SLC10A1 results in loss of HBV receptor function. We tested the role of NTCP as a receptor for HBV in chronic hepatitis B patients using a genetic association study. We selected SLC10A1 variants from 189 exomes. We used Sanger sequencing to follow up the association of the various SLC10A1 variants in a Han Chinese cohort of 1899 chronic hepatitis B patients and 1828 healthy controls. We further investigated the potential impact of the p. Ser267Phe variant on NTCP function using structural analysis. The p. Ser267Phe variant was associated with healthy status ($P = 5.7\times10^{-23}$, odds ratio = 0.36) irrespective of hepatitis B virus surface antibody status ($P = 6.2\times10^{-21}$ and 1.5×10^{-10}, respectively, when the cases were compared with hepatitis B virus surface antibody-positive and-negative controls). The variation was also associated with a lower incidence of acute-on-chronic liver failure ($P = 0.007$). The estimated heritability explained by this single variation was~3.2%. The population prevented fraction was around 13.0% among the southern Chinese. Our structural modeling showed that the p. Ser267Phe variant might interfere with ligand binding, thereby preventing HBV from cellular entry. In a conclusion, we prove that the p. Ser267Phe NTCP variant is significantly associated with resistance to chronic hepatitis B and a lower incidence of acute-on-chronic liver failure. Our results support that NTCP is a cellular receptor for HBV in human infection.

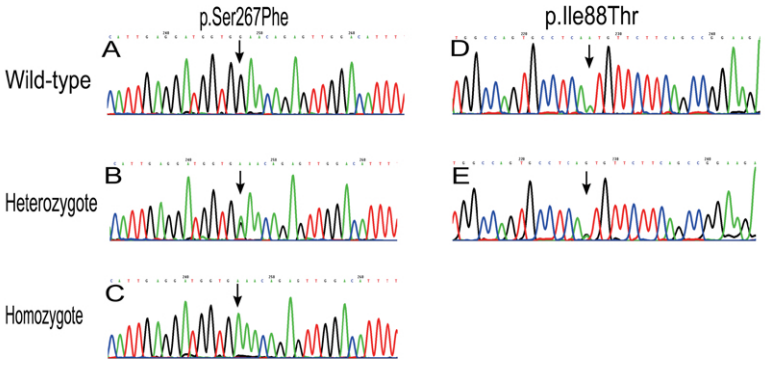

Figure 1 Partial sequences of SLC10A1 variants by Sanger sequencing. (A-C) The p. Ser267Phe variant. (D, E) The p. Ile88Thr variant. Arrows point to the wild-type nucleotide as well as the heterozygous and homozygous variations.

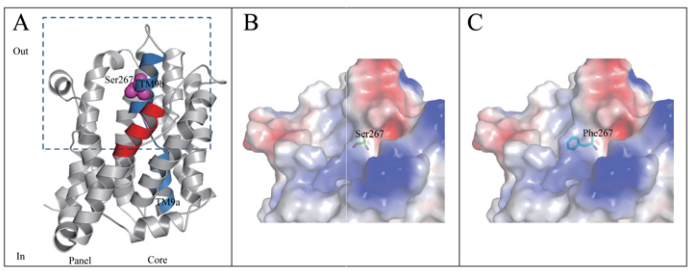

Figure 2 The outward-open model of human NTCP. (A) The ribbon representation of the outward-open model of wild-type human NTCP. The p. Ser267 variant is shown as magenta spheres. Transmembrane domain 9b (TM9b) is colored blue, and the motif of 157—165 critical for HBV binding is in red. (B, C) Surface representation of the model in the dashed-line box in A. (B) Wild-type NTCP model. (C) Mutant p. Ser267Phe model. Both p. Ser267 and p. Phe267 are in stick representation.