A common polymorphism in the bile acid receptor farnesoid X receptor is associated with decreased hepatic target gene expression

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The farnesoid X receptor (FXR or NR1H4) is an important bile-acid-activated, transcriptional regulator of genes involved in bile acid, lipid, and glucose homeostasis. Accordingly, interindividual variations in FXR expression and function could manifest as variable susceptibility to conditions such as cholesterol gallstone disease, atherosclerosis, and diabetes. We performed an FXR polymorphism discovery analysis of European-, African-, Chinese-, and Hispanic-Americans and identified two rare gain-of-function variants and a common single nucleotide polymorphism resulting in a G-1T substitution in the nucleotide adjacent to the translation initiation site (FXR*1B) with population allelic frequencies ranging from 2.5 to 12%. In cell-based transactivation assays, FXR*1B (-1T) activity was reduced compared with FXR*1A (-1G). This reduced activity for FXR*1B resulted from neither decreased translational efficiency nor the potential formation of a truncated translational variant. To further define the relevance of this polymorphism, gene expression was examined in a human liver bank to reveal that levels of the FXR target genes small heterodimer partner and organic anion transporting polypeptide 1B3 were significantly reduced in livers harboring an FXR*1B allele. These findings are the first to identify the presence of a common genetic variant in FXR with functional consequences that could contribute to disease risk or therapeutic outcomes.
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