Functional assessment of genetic variants located in the promoter of SHP1 (NR0B2)

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Small heterodimer partner 1 (SHP1, NR0B2) is a member of the superfamily of nuclear receptors (NRs). Even if this orphan receptor, unlike other NRs, lacks the DNA-binding domain, it is capable of regulating transcription by repressing the activity of other NRs by direct protein-protein interaction. Accordingly, SHP1 is part of negative feedback loops of the transcriptional regulation of genes involved in drug metabolism and various metabolic pathways including bile acid and glucose homeostasis. Although it is known that several interacting partners of SHP1 also modulate its expression, there is little information about genetic variability of this regulatory mechanism. Our study aimed to identify genetic variants in the NR0B2 promoter region and to determine their impact on NR0B2 transcription. For this, DNA samples originating from 119 participants of the population-based cohort Study of Health in Pomerania were analyzed by Sanger sequencing revealing four genetic variants: NR0B2:c.-594T(rs71636795), NR0B2:c.-414G(newly identified), NR0B2:c.-423C(rs78182695), and NR0B2:c.-224delCTGA (rs145613139) localized in the 5' untranslated region of NR0B2. The impact of these variants on transactivation of the NR0B2 promoter by NRs known to be regulators of SHP1 expression (hepatocyte nuclear factor 4α, liver receptor homolog-1, and farnesoid X receptor) was assessed in a cell-based reporter gene assay, showing that transactivation by hepatocyte nuclear factor 4α and liver receptor homolog-1 was significantly decreased in the presence of the genetic variant NR0B2:c.-594T, even though this effect was cell specific. However, SHP1 mRNA expression in a small collection of human kidney samples was not affected by these genetic variants.
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