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Molecular cloning and characterisation of the 5'-untranslated region and promoters in human peroxisome proliferator-activated receptor alpha (hPPARα)

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Peroxisome proliferator-activated receptor alpha (PPARα) is a ligand-activated transcription factor which belongs to the nuclear receptor superfamily and regulates gene transcription by heterodimerising with retinoid X receptor (RXR). PPARα has attracted considerable attention since it was demonstrated to be pivotal regulators of lipoprotein metabolism, vascular inflammation, atherosclerosis and carcinogenesis. To date, studies addressing the regulation of human PPARα (hPPARα) gene expression remain largely unexplored. In order to understand the structure and molecular mechanisms governing hPPARα regulation, it is vital to identify and characterise the 5'-untranslated region (UTR) and promoter region of the hPPARα gene. In this study, six alternatively spliced variants and three new novel exons at the 5'-UTR of hPPARα gene designated as Exon A, Exon B and Exon 2b were identified. The putative transcriptional start site of each variant was identified, leading to the discovery of four promoters in the hPPARα gene which are responsible for transcribing these alternatively spliced variants. Three of these four promoters, named promoter B, promoter C and promoter D, were successfully cloned and sequenced. Sequence analysis revealed potential binding sites for transcriptional factors in all three promoters B, C and D. Finally, transient transfections using luciferase reporter constructs into HepG2 cells showed that all three promoters B, C and D are functional promoters, with promoter B being the most potent and strongest promoter. Deletion analysis of the hPPARα promoters identified a possible negative regulatory element located between the regions -341 to -1147 of promoter B, -413 to -967 of promoter C, and -395 to -934 of promoter D.