Abstract

The *C*arboxyl *E*ster *L*ipase, *CEL*, gene-Evolutionary implications on structure, organization and transcriptional regulation

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The bile salt stimulated carboxyl ester lipase (CEL) is important for the digestion and absorption of dietary lipids, and is highly expressed in the exocrine pancreas and the lactating mammary gland. Low levels of CEL expression are also at hand in the liver, in macrophages, in endothelial cells and in eosinophils.

At the human chromosomal location 9q34.3 both a functional *CEL* gene as well as a truncated ψ*CEL* pseudogene are at hand. A 30 kb long cosmid fragment confirms the presence of both *CEL* genes in close proximity. They are oriented in a head to tail orientation approximately 11 kb apart with the functional *CEL* gene being the most 5' one. The duplication of the genes is proposed to be the result of an over-replication of an 11719 bp long fragment, followed by a transposition like event. At the insertion site a 364 bp long target site duplication was generated. The duplication of the *CEL* gene was estimated to have occurred during primate evolution some 23 million years ago. To investigate if the ψ*CEL* is at hand in other species than man, we decided to analyze the gorilla genome for the presence of two *CEL* genes. The gorilla genome is shown to comprise one functional g*CEL* gene and one ψg*CEL* pseudogene, with the same internal orientation as that found in man. The gorilla *CEL* genes show the same exon distribution as in man, with the functional gene being divided into 11 exons and the pseudogene missing exons 2 through 7 due to a 5 kb deletion. The genomes of chimpanzee, orangutan (Hominoidae), macaque (Old World monkeys) and weeper capuchin (New World monkeys) were also analyzed for the presence of two *CEL* genes. The truncated form of the *CEL* pseudogene is shown to be at hand in the, great apes and man only, while macaques and capuchin monkeys are shown to comprise duplicated *CEL* genes. These findings indicate that the inactivation, through deletion of six exons, rather than the duplication of the original *CEL* gene occurred after the separation of the Hominoids from Old World monkeys some 23 million years ago.

Previous studies on transcriptional regulation of the *CEL* gene in mouse and man mainly reveal differences concerning important *cis*-regulatory elements, involved in transcriptional activation of *CEL*. Notwithstanding, we here report on the identification of one common E-box element, in the proximal promoter at –47/-52, that is important for the overall *CEL* gene expression in monocytic THP-1 cells, the mouse mammary epithelial cell line HC11 and the rat pancreatoma AR42J cells. Electrophoretic mobility-shift assays reveal the binding of upstream stimulatory factors 1 and 2 to the E-box.

Keywords: Carboxyl Ester Lipase, gene structure, pseudogene, locus, evolution, duplication, primate, transcriptional regulation, monocyte, mammary gland, USF 1 & 2.

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