

Gene Section

Review

ENPP7 (ectonucleotide pyrophosphatase/phosphodiesterase 7)

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Published in Atlas Database: August 2007

Online updated version: <http://AtlasGeneticsOncology.org/Genes/ENPP7ID44055ch17q25.html>
DOI: 10.4267/2042/38490

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Identity

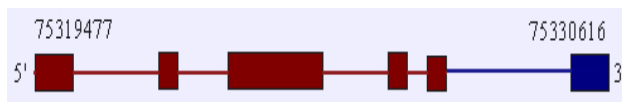
Hugo: ENPP7

Other names: ALK-SMase (Alkaline sphingomyelinase); E-NPP7; MGC50179; NPP-7

Location: 17q25.3

Local order: Upstream to a hypothetical protein LOC146743 and downstream to CBX2.

DNA/RNA



Description

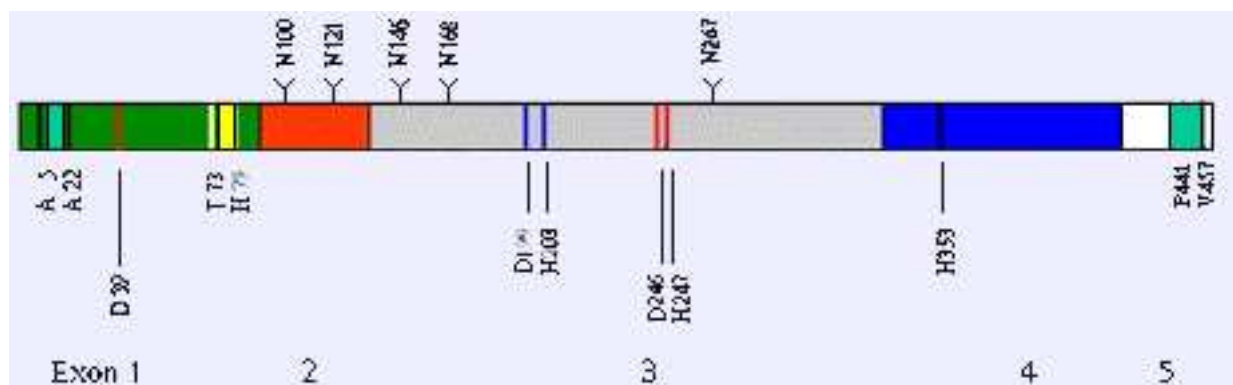
The ENPP7 gene is 11.139 bp in length and is composed of 6 exons in the size of 1841 bp. The first 20 bp in exon 1, the last 17 bp in exon 5 and the exon 6 are not translated.

Transcription

Besides the wild type transcript shown above, different transcripts have been identified. The first is the one with exon 4 deletion, which has been found in HepG2 liver cancer cells and some human colon and liver cancer tissues. The second one also deletes exon 4 but inserts 7 foreign amino acids due to the shift of the splice site. This transcript was identified in human HT29 colon cancer cells. The third one has a larger exon 1 than the wild type, which includes upstream another starting codon (219 bp upstream), and was identified in one liver tumor. Some factors such as ursodeoxycholic acid and psyllium have been found to stimulate the expression of ENPP7 whereas high fat diet decreases ENPP7 expression.

Pseudogene

LOC401847.



The structure of ENPP7 protein. The regions with green, red, gray, blue and white colors indicate the amino acids coded by different exons. The five N-glycosylation sites are shown above the bar and two metal binding sites formed by 6 amino acids are shown under the bar. Two hydrophobic domains (from T5 to A22, and P441 to V457) and the predicted catalytic site (T73-H79) are indicated.

Protein

Description

The wild type ENPP7 contains 458 amino acids, which shares 30-36% identity to other members of the NPP family. The protein has a signal peptide at the N-terminal, which is cleaved in the mature enzyme, and a transmembrane domain at the C-terminal, which anchors the enzyme on the plasma membrane. The rest part of the enzyme is located outside the cells. The enzyme has 5 N-glycosylation sites and glycosylation is important for both transport of the enzyme to the plasma membrane and for enzyme activity. Similar to other NPP members, ENPP7 has two metal binding sites formed by 6 amino acids. These sites are predicted to serve as substrate binding site.

Expression

The enzyme has so far been found to express in the intestinal mucosal cells of many species and additionally human liver cells. The expression in liver may be restricted to human, because no activity or mRNA of ENPP7 could be found in the bile or liver of many other species. The expression is associated with differentiation of both intestinal and hepatic cells. ENPP7 is developed early in the fetus and high activity has been found in the meconium of human fetus at the age of 23 week gestation.

Localisation

The enzyme is localized at the apical part but not basolateral part of intestinal epithelial cells. The enzyme can be dissociated from the membrane by bile salt and by pancreatic trypsin and released into the lumen in fully active form. Along the intestinal tract, the activity is low in the duodenum, high in the

jejunum, and rapidly decreasing in the distal part of ileum and colon. The enzyme is also found in human bile, which is expressed in the liver and released to the bile.

Function

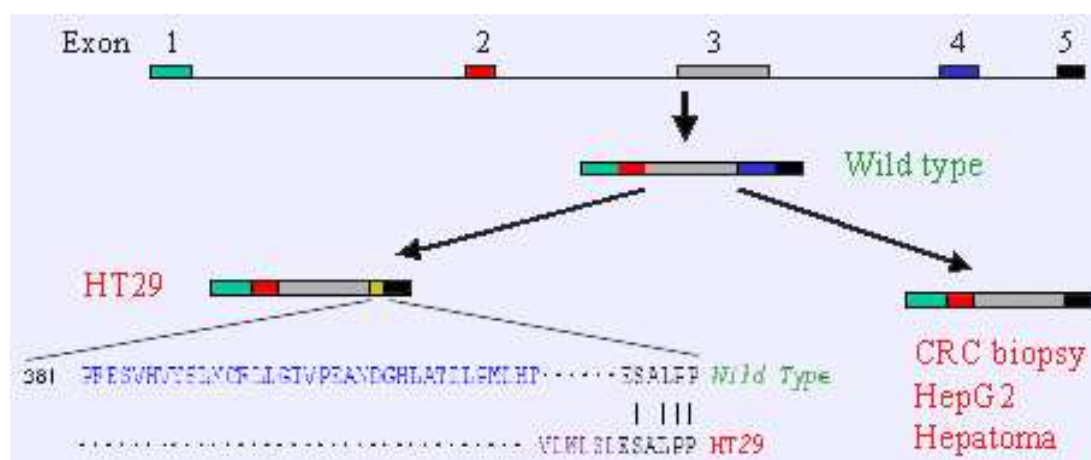
ENPP7 is a member of the ecto-nucleotide pyrophosphatase/phosphodiesterase (NPP) family with specific activity against lipids with positively charged phosphocholine headgroup including sphingomyelin, lysophosphatidylcholine and platelet activating factor (PAF). It hydrolyzes sphingomyelin to generate ceramide, a potent antiproliferative and proapoptotic molecule. It hydrolyzes lysophosphatidylcholine to monoglyceride and therefore competes with lysophospholipase D to reduce the formation of lysophosphatidic acid, a potent factor for inflammation and angiogenesis. It hydrolyzes PAF to 1-O-alkyl-2-acetyl-sn-glycerol and inhibits PAF-induced inflammatory responses. ENPP7 has been proposed as a tumor suppressor protein.

In addition, ENPP7 may influence cholesterol absorption by hydrolyzing sphingomyelin in the intestinal lumen and on the apical surface of microvilli, as the levels of sphingomyelin in the intestinal tract affect cholesterol absorption.

Homology

ENPP7 shares 30-35% homology with other members of ENPP family. Regard to ENPP7, human ENPP7 shares 85% identity with rat form (NP_001012484), 82% with the mouse form (NP_001025462.1), and 82% with fowl form (XP_423912.1). The N-glycosylation sites, the amino acids forming the metal coordinate sites and active core are all conserved in the forms mentioned above.

Mutations



The figure shows the aberrant transcript forms of ENPP7 identified in colon and liver cancers. The first is the one with deleted exon 4, which was found in HepG2 liver cancer cells and human liver cancer and colon cancer tissues. The second is similar as the first one but with an insertion of 7 foreign amino acids due to the shift of the splice site. The third one has a larger exon 1 than the wild type, which includes another starting codon, and was identified in one liver tumor (not shown in the figure). Formation of these aberrant forms are not caused by genomic mutation, but alternative splicing.

Implicated in

Colon cancer, inflammatory bowel diseases, and liver cancer

Disease

ENPP7 may have implications in colon cancer, inflammatory bowel diseases such as ulcerative colitis, necrotizing enterocolitis, and liver cancer. Significant reduction of ENPP7 activity has been found in human longstanding ulcerative colitis, sporadic colon cancer and familial adenomatous polyposis. The reduction may be caused by formation of the aberrant transcripts, which cause the inactivation of ENPP7, and have been found in human HT29 colon cancer cells, HepG2 liver cancer cells and also in human colon and liver cancer tissues. The frequency of such mutations is unknown. ENPP7 may also affect the pathogenesis of atherosclerosis as it influences the sphingomyelin levels in the gut and thus affect cholesterol absorption.

Prognosis

The enzyme activity is easy to be determined in the feces. Fecal activity reflects the total enzyme levels in the intestinal tract and has been shown to be decreased in colonic inflammation and cancer.

References

Nilsson A. The presence of sphingomyelin- and ceramide-cleaving enzymes in the small intestinal tract. *Biochim Biophys Acta* 1969;176:339-345.

Duan RD, Nyberg L, Nilsson A. Alkaline sphingomyelinase activity in rat gastrointestinal tract: distribution and characteristics. *Biochim Biophys Acta* 1995;1259:49-55.

Duan RD, Hertervig E, Nyberg L, Hauge T, Sternby B, Lillienau J, Farooqi A, Nilsson A. Distribution of alkaline sphingomyelinase activity in human beings and animals. Tissue and species differences. *Dig Dis Sci* 1996;41:1801-1806.

Nyberg L, Duan RD, Axelson J, Nilsson A. Identification of an alkaline sphingomyelinase activity in human bile. *Biochim Biophys Acta* 1996;1300:42-48.

Duan RD, Nilsson A. Purification of a newly identified alkaline sphingomyelinase in human bile and effects of bile salts and phosphatidylcholine on enzyme activity. *Hepatology* 1997;26:823-830.

Hertervig E, Nilsson A, Nyberg L, Duan RD. Alkaline sphingomyelinase is decreased in human colorectal carcinoma. *Cancer* 1997;79:448-453.

Duan RD. Sphingomyelin hydrolysis in the gut and clinical implications in colorectal tumorigenesis and other gastrointestinal diseases. *Scand J Gastroenterol* 1998;33:673-683 (Review).

Duan RD, Cheng Y, Tauschel HD, Nilsson A. Effects of ursodeoxycholate and other bile salts on levels of rat intestinal alkaline sphingomyelinase: an potential implication in tumorigenesis. *Dig Dis Sci* 1998;43:26-32.

Cheng Y, Tauschel HD, Nilsson A, Duan RD. Ursodeoxycholic acid increases the activities of alkaline sphingomyelinase and

caspace 3 in the rat colon. *Scand J Gastroenterol* 1999;34:915-920.

Hertervig E, Nilsson A, Bjork J, Hultkrantz R, Duan RD. Familial adenomatous polyposis is associated with a marked decrease in alkaline sphingomyelinase activity: a key factor to the unrestrained cell proliferation?. *Br J Cancer* 1999;81:232-236.

Nilsson A, Duan RD. Alkaline sphingomyelinase and ceramidase of the gastrointestinal tract. *Chem Phys Lipids* 1999;102:97-105. (Review).

Liu JJ, Nilsson A, Duan RD. Effects of phospholipids on sphingomyelin hydrolysis induced by intestinal alkaline sphingomyelinase: an in vitro study. *J Nutr Biochem* 2000;11:192-197.

Nyberg L, Duan RD, Nilsson A. A mutual inhibitory effect on absorption of sphingomyelin and cholesterol. *J Nutr Biochem* 2000;11:244-249.

Cheng Y, Nilsson A, Tomquist E, Duan RD. Purification, characterization, and expression of rat intestinal alkaline sphingomyelinase. *J Lipid Res* 2002;43:316-324.

Liu JJ, Nilsson A, Duan RD. In vitro effects of fat, FA and cholesterol on sphingomyelin hydrolysis induced by rat intestinal alkaline sphingomyelinase. *Lipids* 2002;37:469-574.

Sjöqvist U, Hertervig E, Nilsson A, Duan RD, Ost A, Tribukait B, Löfberg R. Chronic colitis is associated with a reduction of mucosal alkaline sphingomyelinase activity. *Inflamm Bowel Dis* 2002;8:258-263.

Duan RD, Bergman T, Xu N, Wu J, Cheng Y, Duan J, Nelander S, Palmberg C, Nilsson A. Identification of human intestinal alkaline sphingomyelinase as a novel ectoenzyme related to the nucleotide phosphodiesterase family. *J Biol Chem* 2003;278:38528-38536.

Duan RD, Cheng Y, Hansen G, Hertervig E, Liu JJ, Syk I, Sjöstrom H, Nilsson A. Purification, localization, and expression of human intestinal alkaline sphingomyelinase. *J Lipid Res* 2003;44:1241-1250.

Hertervig C, Nilsson A, Duan RD. Purified intestinal alkaline sphingomyelinase inhibits proliferation without inducing apoptosis in HT29 colon carcinoma cells. *J Cancer Res Clin Oncol* 2003;129:577-582.

Lillienau J, Cheng Y, Nilsson A, Duan RD. Development of intestinal alkaline sphingomyelinase in rat fetus and newborn rat. *Lipids* 2003;38:545-549.

Cheng Y, Ohlsson L, Duan RD. Psyllium and fat in diets differentially affect the activities and expression of colonic sphingomyelinases and caspases in mice. *Br J Nutr* 2004;91:715-723.

Wu j, Cheng Y, Nilsson A, Duan RD. Identification of one exon deletion of intestinal alkaline sphingomyelinase in colon cancer HT29 cells and a differentiation-related expression of the wild-type enzyme in Caco-2 cells. *Carcinogenesis* 2004;25:1327-1333.

Wu J, Liu F, Nilsson A, Duan RD. Pancreatic trypsin cleaves intestinal alkaline sphingomyelinase from mucosa and enhances the sphingomyelinase activity. *Am J Physiol* 2004;287:G967-973.

Di Marzio, L.Di Leo, A, Cinque, B, Fanini D, Agnifili A, Berloco P, Linsalata M, Lorusso D, Barone M, De Simone C, Cifone MG. Detection of alkaline sphingomyelinase activity in human stool: proposed role as a new diagnostic and prognostic marker of colorectal cancer. *Cancer Epidemiol Biomarkers Prev* 2005;14:856-862.

Duan RD. Anticancer compounds and sphingolipid metabolism in the colon. *In Vivo* 2005;19:293-300. (Review).

Wu J, Cheng Y, Palmberg C, Bergman T, Nilsson A, Duan RD. Cloning of alkaline sphingomyelinase from rat intestinal mucosa and adjusting of the hypothetical protein XP_221184 in GenBank. *Biochim Biophys Acta* 2005;1687:94-102.

Wu J, Hansen GH, Nilsson A, Duan RD. Functional studies of human intestinal alkaline sphingomyelinase by deglycosylation and mutagenesis. *Biochem J* 2005;386:153-160.

Duan RD. Alkaline sphingomyelinase: an old enzyme with novel implications. *Biochim Biophys Acta* 2006;1761:281-191 (Review).

Liu F, Cheng Y, Wu J, Tauschel HD, Duan RD. Ursodeoxycholic acid differentially affects three types of sphingomyelinase in human colon cancer Caco-2 cells. *Cancer Lett* 2006;235:141-146.

Nilsson A, Duan RD. Absorption and lipoprotein transport of sphingomyelin. *J Lipid Res* 2006;47:154-171. (Review).

Wu J, Nilsson A, Jönsson BA, Stenstad H, Agace W, Cheng Y, Duan RD. Intestinal alkaline sphingomyelinase hydrolyses and inactivates platelet-activating factor by a phospholipase C activity. *Biochem J* 2006;394:299-308.

Duan RD, Cheng Y, Jönsson BA, Ohlsson L, Herbst A, Hellström-Westas L, Nilsson A. Human meconium contains significant amounts of alkaline sphingomyelinase, neutral ceramidase, and sphingolipid metabolites. *Pediatr Res* 2007;61:61-66.

Duan RD, Verkade HJ, Cheng Y, Havinga R, Nilsson A. Effects of bile diversion in rats on intestinal sphingomyelinases and ceramidase. *Biochim Biophys Acta* 2007;1771:196-201.

This article should be referenced as such:

Duan RD. ENPP7 (ectonucleotide pyrophosphatase/phosphodiesterase 7). *Atlas Genet Cytogenet Oncol Haematol*.2008;12(2):96-99.
