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Gene Section
Mini Review

SEL1L (sel-1 suppressor of lin-12-like (C. elegans))

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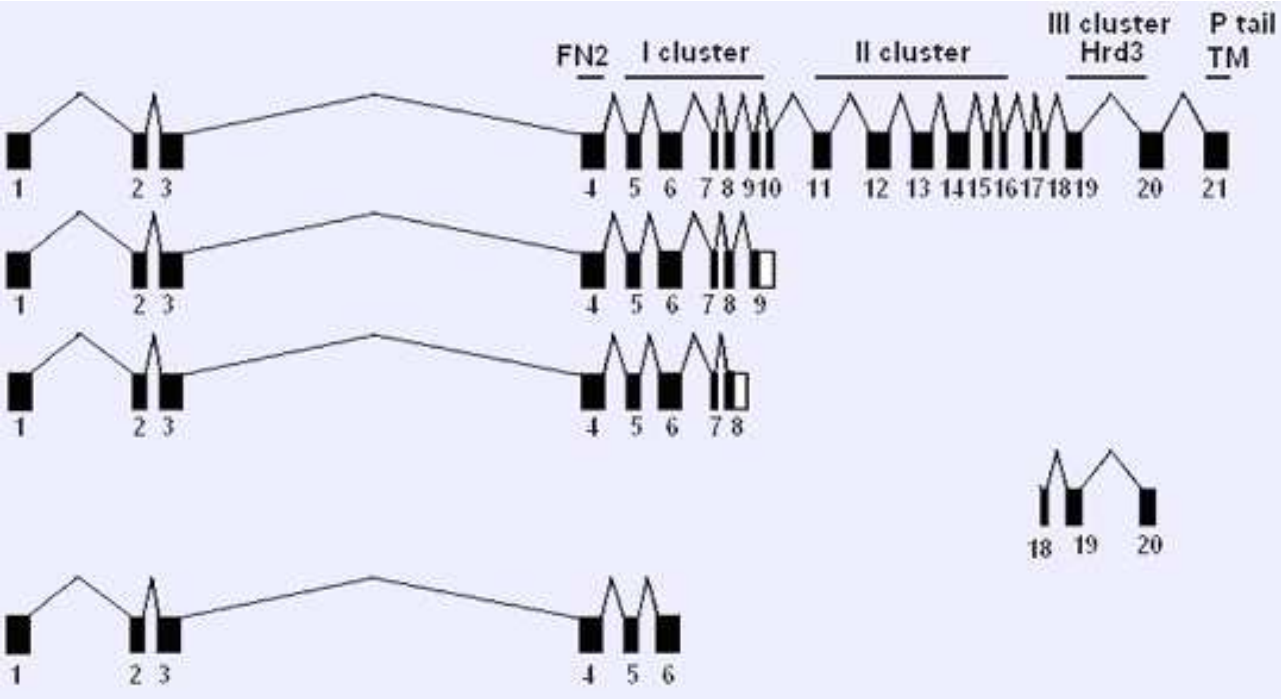
Identity

Hugo: SEL1L
Other names: IBD2; SEL1-like
Location: 14q24.3-q31
Local order: SEL1L is located within a 'Gene Desert area' or 'Genome Deserts'; centromeric to FLRT2 (fibronectin leucine rich transmembrane protein 2) and telomeric to GTF2A1 (general transcription factor IIA) and TSHRq31 (thyroid stimulating hormone receptor).
Note: SEL1L is the human ortholog of the C.Elegans sel-1 (suppressor enhancer of lin-12) gene. It shows a high degree of cross-species conservation in its nucleotide and protein sequence.

DNA/RNA

Description

SEL1L genomic size is of 62,24 Kb localized from 81069886 to 81007646. 3' the first exon lies the basal core of the promter, a TATA-less promoter containing four SP1 binding sites and a CAAT box. A CpG island



A graphical representation of SEL1L isorforms. The black numbered rectangles correspond to the exons, while the white rectangles correspond to the intronic sequence which is retained in the alternative isoforms. The SEL1L domains are indicated on the top of the isoforms. (FN2=fibronectin type II domain; I, II and III clusters of SEL-1 like repeats; Hrd3; TM=transmembrane; P= proline rich domain).

is located between -550bp and the start codon. SEL1L embryonic kidney cells. The C-terminal tail consists of over 5,0Kb untranslated sequences likely containing key regulatory elements.

Transcription

The sequence is composed of 21 exons and produces at least five different alternative transcripts (A-E) which originate from alternative splicing and putative promoter usage. Exons 1-6 are common to forms A-B-C-E.

Pseudogene

No known pseudogenes

Protein

Note: SEL1L is a multimodular protein consisting of several domains and signal sequences that confer the multifaceted specificities to the molecule.

Description

SEL1L is not a member of a vast family of proteins but the several described isoforms (over 4) give the appearance of belonging to a multifamily of molecules having perhaps redundant functions.

Expression

Ubiquitously expressed only in fetal and neoplastic tissues. In normal adult tissues is highly expressed in the acini and in the alpha cells of the pancreas; in general is highly represented in secretory cells such as plasma cells.

Localisation

SEL1L protein can have a nuclear, cytoplasmic and nuclear-cytoplasmic location.

Function

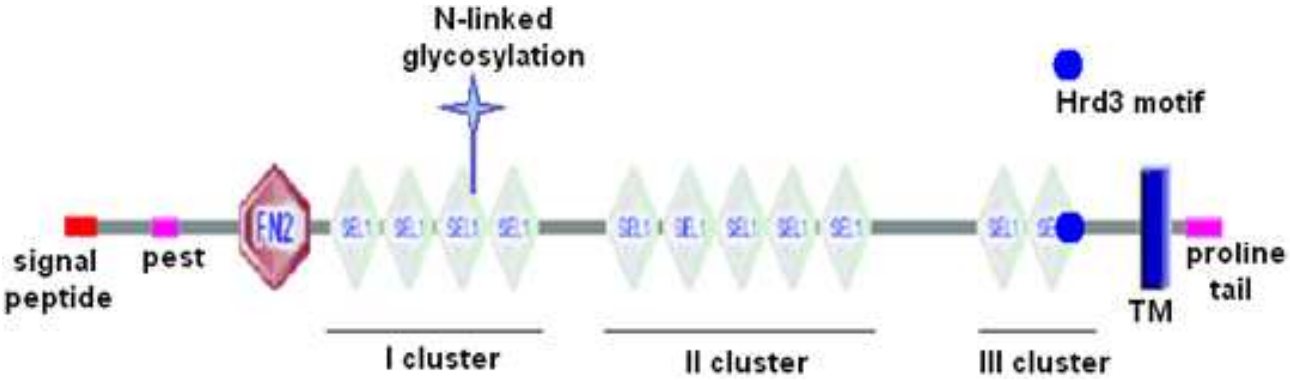
May have a role in the ER-associated protein degradation (ERAD) system (similarity with Hrd3).
Negative regulator of the NOTCH pathway in C. Elegans.
May play a role in TGF beta signalling.
In breast and pancreatic tumor decrease tumor growth and aggressiveness, possibly involving cell-matrix interaction.

Homology

Comparative sequence analysis across different regna, including metazoa, fungi, viridiplantae and bacteria, revealed the remarkable conservation of its primary sequence, although the gene structural complexity increased in evolution. Among mammals, SEL1L shares strict amino acid identity with chimpanzee (99%), dog (97%), hamster (92%), mouse (93%) and rat (92%). It also shows a good similarity with the model organisms such as xenopus (82%), chicken (83%), zebrafish (73%), Drosophila melanogaster (51%) and C. elegans (46%) (Table 1). Arabidopsis thaliana and Saccharomyces cerevisiae display lower similarity (34% and 28%, respectively).

Mutations

Note: Neither causative nor functional mutations were found except for the presence of two base substitutions in the minimal promoter region in two well differentiated lung adenocarcinoma that led to a significant increase in the transcription. A polymorphic base substitution was reported in the fibronectin type II domain of the gene in children affected by persistent hyperinsulinemic hypoglycemia (insulinoma) of infancy which induces a major change in the amino acid composition.



SEL1L protein structure: SEL1L is a multimodular protein containing several structural and functional domains as well as signal sequences. The signal peptide (from 1 to 22 amino acid residues) and the Pest sequence (from 80 to 102 amino acid residues) are represented by red and pink rectangles. The fibronectin type II domain (from 120 to 168 residues) is symbolized by the hexagon (FNII), the SEL-1-like repeats are represented by rhombi and are distributed in tandem along the central portion of the protein in three large clusters (I cluster: 183-326; II cluster: 373-554 and III cluster: 664-675 residues). The Hrd3 like motif is located within the last SEL-1-like repeat (664-675 residues) and is represented by an circle. The transmembrane region (TM) (739-761 residues) and the proline-rich tail (770-793 residues) are symbolized by a blue rectangle. The N-linked glycosilation is also underlined.

Implicated in

Considering the overall results published on SEL1L by various investigators working in different organisms, it can, perhaps, safely be deduced that this gene plays a fundamental role in eukaryotic intracellular protein degradation processes. Protein degradation is becoming a central theme in cancer biology and recently therapeutic approaches that use inhibitors of proteins belonging to ubiquitin-proteosoma pathway have been developed in solid tumors and haematological diseases. A survey of the expression of SEL1L mRNA as well as its encoded protein on a series of cancerous and pre-neoplastic lesion, revealed the role of SEL1L in cancer progression. Furthermore, its expression in breast cancer correlated with patient¹s survival. In vitro studies indicated that SEL1L protein affects those pathways which regulate signalling (cell-cell and or cell-matrix) interactions. Available data derived from several organisms indicate that it may function in the protein degradation processes through ubiquitin-proteosome system and perhaps in regulating important pathways such as Notch and TGF-beta. The fundamental question raised by the observation that SEL1L gets up-modulated during the early steps of tumor transformation is of paramount importance for early diagnosis. Currently it is only possible to hypothesize that the increased SEL1L levels are required in order to meet the advent of genetic and/or genomic structural alterations acquired during cancer initiation or to influence intra-cellular signalling. Its presence may be important in protecting cellular homeostasis from genetic mutations.

References

Biunno I, Appierto V, Cattaneo M, Leone BE, Balzano G, Socci C, Saccone S, Letizia A, Della Valle G, Sgaramella V. Isolation of a pancreas-specific gene located on human chromosome 14q31: expression analysis in human pancreatic ductal carcinomas. Genomics 1997;46(2):284-286.

Donoviel DB, Donoviel MS, Fan E, Hadjantonakis A, Bernstein A. Cloning and characterization of Sel-1l, a murine homolog of the C. elegans sel-1 gene. Mech Dev 1998;78(1-2):203-207.

Donoviel DB, Bernstein A. SEL-1L maps to human chromosome 14, near the insulin-dependent diabetes mellitus locus 11. Genomics 1999;56(2):232-233.

Harada Y, Ozaki K, Suzuki M, Fujiwara T, Takahashi E, Nakamura Y, Tanigami A. Complete cDNA sequence and genomic organization of a human pancreas-specific gene homologous to Caenorhabditis elegans sel-1. J Hum Genet 1999;44(5):330-336.

Biunno I, Bernard L, Dear P, Cattaneo M, Volorio S, Zannini L, Bankier A, Zollo M. SEL1L, the human homolog of C. elegans sel-1: refined physical mapping, gene structure and identification of polymorphic markers. Hum Genet 2000;106(2):227-235.

Cattaneo M, Orlandi R, Ronchini C, Granelli P, Malferrari G, Menard S, Biunno I. The expression of SEL1L and TAN-1 in normal and neoplastic cells. Int J Biol Markers 2000;15(1):26-32.

Cattaneo M, Sorio C, Malferrari G, Rogozin IB, Bernard L, Scarpa A, Zollo M, Biunno I. Cloning and functional analysis of SEL1L promoter region, a pancreas-specific gene. DNA Cell Biol 2001;20(1):1-9.

Ban Y, Taniyama M, Tozaki T, Yanagawa T, Tomita M, Ban Y. SEL1L microsatellite polymorphism in Japanese patients with autoimmune thyroid diseases. Thyroid 2001;11(4):335-338.

Cattaneo M, Zollo M, Malferrari G, Orlandi R, D'Angelo A, Menard S, Biunno I. Allelic polymorphisms in the transcriptional regulatory region of human SEL1L. Mutat Res 2001;458(3-4):71-76.

Larsen ZM, Angelo AD, Cattaneo M, Nerup J, Biunno I, Zollo M, Pociot F. Complete mutation scanning of the human SEL 1L gene: a candidate gene for type 1 diabetes. Acta Diabetol 2001;38(4):191-192.

Pociot F, Larsen ZM, Zavattari P, Deidda E, Nerup J, Cattaneo M, Chiaramonte R, Comi P, Sabbadini M, Zollo M, Biunno I, Cucca F. No evidence for SEL1L as a candidate gene for IDDM11-conferred susceptibility. Diabetes Metab Res Rev 2001;17(4):292-295.

Biunno I, Castiglioni B, Rogozin IB, DeBellis G, Malferrari G, Cattaneo M. Cross-species conservation of SEL1L, a human pancreas-specific expressing gene. OMICS 2002;6(2):187-198.

Chiaramonte R, Calzavara E, Basile A, Comi P, Sherbet GV. Notch signal transduction is not regulated by SEL1L in leukaemia and lymphoma cells in culture. Anticancer Res 2002;22(6C):4211-4214.

Chiaramonte R, Sabbadini M, Balordi F, Comi P, Sherbet GV. Allele frequency of two intragenic microsatellite loci of SEL1L gene in Northern Italian population. Mol Cell Biochem 2002;232(1-2):159-161.

Orlandi R, Cattaneo M, Troglio F, Campiglio M, Biunno I, Ménard S. Production of a monoclonal antibody directed against the recombinant SEL1L protein. Int J Biol Markers 2002;17(2):104-111.

Orlandi R, Cattaneo M, Troglio F, Casalini P, Ronchini C, Menard S, Biunno I. SEL1L expression decreases breast tumor cell aggressiveness in vivo and in vitro. Cancer Res 2002;62(2):567-574.

Cattaneo M, Orlandini S, Beghelli S, Moore PS, Sorio C, Bonora A, Bassi C, Talamini G, Zamboni G, Orlandi R, Menard S, Bernardi LR, Biunno I, Scarpa A. SEL1L expression in pancreatic adenocarcinoma parallels SMAD4 expression and delays tumor growth in vitro and in vivo. Oncogene 2003;22(41):6359-6368.

Kaneko M, Nomura Y. ER signaling in unfolded protein response. Life Sci 2003;74(2-3):199-205.

Kim SH, Ma X, Klupa T, Powers C, Pezzolesi M, Warram JH, Rich SS, Krolewski AS, Doria A. Genetic modifiers of the age at diagnosis of diabetes (MODY3) in carriers of hepatocyte nuclear factor-1alpha mutations map to chromosomes 5p15, 9q22, and 14q24. Diabetes 2003;52(8):2182-2186.

Mathlouthi R, Aberle S, Schug N, Küpper JH, Schröder K, Seitz G, Blin N. Assessing optimal promoter activity for constructs in gastrointestinal gene. Anticancer Res 2003;23(5A):4011-4015.

Aberle S, Schug N, Mathlouthi R, Seitz G, Küpper JH, Schröder K, Blin N. Promoter selection for the cytosine deaminase suicide gene constructs in gastric cancer. Eur J Gastroenterol Hepatol 2004;16(1):63-67.

Cattaneo M, Canton C, Albertini A, Biunno I. Identification of a region within SEL1L protein required for tumour growth inhibition. Gene 2004;326:149-156.

Diaferia G, Cattaneo M, Saltini G, Proverbio MC, Monferini E, Malferrari G, Albertini A, Biunno I. RNA-mediated interference

indicates that SEL1L plays a role in pancreatic beta-cell growth. DNA Cell Biol 2004;23(8):510-518.

Granelli P, Cattaneo M, Ferrero S, Bottiglieri L, Bosari S, Fichera G, Biunno I. SEL1L and squamous cell carcinoma of the esophagus. Clin Cancer Res 2004;10(17):5857-5861.

Saltini G, Proverbio MC, Malferrari G, Biagiotti L, Boettcher P, Dominici R, Monferini E, Lorenzini E, Cattaneo M, Antonello D, Moore PS, Zamproni I, Viscardi M, Chiumello G, Biunno I. Identification of a novel polymorphism in the fibronectin type II domain of the SEL1L gene and possible relation to the persistent hyperinsulinemic hypoglycemia of infancy. Mutat Res 2004;554(1-2):159-163.

Bianchi L, Canton C, Bini L, Orlandi R, Ménard S, Armini A, Cattaneo M, Pallini V, Bernardi LR, Biunno I. Protein profile changes in the human breast cancer cell line MCF-7 in response to SEL1L gene induction. Proteomics 2005;5(9):2433-2442.

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