

Gene Section

Review

SEP15 (15 kDa selenoprotein)

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Identity

Location: 1p22.3

Local order: According to NCBI Map Viewer, SEP15 gene is located between: SH3GLB1 (SH3-domain GRB2-like endophilin B1), RPL17P5 (ribosomal protein L17 pseudogene 5) (in telomeric position), HS2ST1 (heparan sulfate 2-O-sulfotransferase 1) and potential gene LOC339524 (in centromeric position).

Note: SEP15 is one of the 25 genes encoding human selenoproteins. The product of this gene, 15 kDa selenoprotein contains selenocysteine (Sec), which is encoded (like in the case of all selenoproteins) by the UGA codon, normally serving as stop/termination codon. Due to specific mechanism involving selenocysteine insertion sequence (SECIS), a secondary DNA structure common for all selenoproteins, UGA codon is being recognized as Sec codon.

DNA/RNA

Note

Genetic locus of SEP15, 1p31 is commonly mutated or deleted in human cancer.

Description

The genomic DNA of SEP15 spans about 52 kb. The gene consists of 5 exons, with the Sec codon being placed in exon 3 (codon 93). Specific stem loop structure called SECIS element is present within 3'-untranslated region of mRNA. Second stem loop structure close to SECIS element was identified, but it is not active (does not take part in the translation process). Structure of 15-kDa selenoprotein cDNA sequence is presented in figure 1. Single nucleotide polymorphism (SNP) within SEP15 SECIS element was identified, which is associated with G/A transition at position 1125 (rs5859). SEP15 1125G/A polymorphism was shown in in vitro studies to influence the efficiency of Sec codon (UGA) readthrough during translation process.

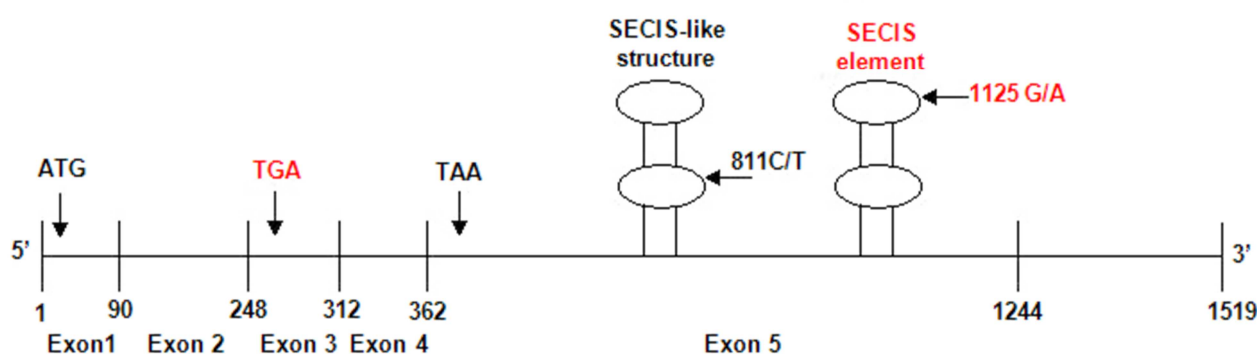


Figure 1. Structural organization of the human SEP15 cDNA sequence with the relative positions of ATG initiation and the TGA Sec codons, the TAA termination signal, the detected polymorphisms (C811T in the SECIS-like structure and G1125A in the SECIS element), alternative 3'-end sequences (position 1244 or 1519 within the cDNA) of exon 5. Short vertical lines correspond to the last nucleotides in the preceding exons (adapted with minimal modification from Kumaraswamy et al., 2000).

Other investigated SNPs within SEP15 gene: rs5845, rs479341, rs56104, rs527281, rs1407131.

Transcription

Two alternative transcripts of SEP15 exist. Transcript variant 1 is longer and consists of 5 exons. Transcript variant 2 lacks an exon in the 3' coding region. Compared to isoform 1, the isoform 2 has a shorter and distinct C-terminus.

Pseudogene

According to Entrez Gene, no SEP15 pseudogene was identified.

Protein

Note

15 kDa selenoprotein was described for the first time in 1995 by Kacklosch et al., who found the protein in rat prostate. In 1998 the protein was identified in humans, by Gladyshev et al.

SEP15 possesses enzymatic activity of oxidoreductase and catalyzes disulfide bonds formation. The protein contains one atom of selenium which is present in the form of selenocysteine. Selenium is involved in human cancer development, playing dual role in this process - from protection to promotion. It is supposed that role of selenium in cancer may be partially associated with selenoproteins, including SEP15.

Description

162 amino acids, with size of 17790 Da. Possesses redox activity due to Cys-X-Sec motif (similar to Cys-X-X-Cys motif present in thioredoxin).

Expression

Highly expressed in prostate, liver, brain, kidneys and testis. The protein expression was shown to be increased in colon cancer and decreased in liver cancer and prostate cancer.

Localisation

Endoplasmic reticulum lumen.

Function

Studies in vitro suggest that SEP15 is involved in the process of posttranslational protein folding. It forms a 1:1 complex with the UDP-glucose: glycoprotein glucosyltransferase (UGGT), an enzyme that is responsible for quality control in the endoplasmic reticulum by oxidative folding and structural maturation of N-glycosylated proteins. It is supposed that SEP15 serves as a disulfide isomerase of glycoproteins targeted by UGGT. Due to redox activity it may also function as an antioxidant.

Homology

SEP15 is a distant sequence homolog of other human

selenoprotein, SelM. Intraspecies homologs of SEP15 are highly conserved and were identified in dog, cow, mouse, rat, chicken, zebrafish, fruit fly, mosquito, *C. elegans*, *A. thaliana* and rice.

Mutations

Note

No mutations in SEP15 gene have been identified yet.

Implicated in

Breast cancer

Disease

Hu et al. (2001) found statistically significant difference in SEP15 allelic distribution for rs5859 between breast cancer individuals (DNA obtained from tumours, n=60) and cancer-free individuals (DNA obtained from lymphocytes, n=490) among African Americans.

Studies conducted by Nasr et al. (2003) also suggest possible role of SEP15 in breast cancer development among African American women. The authors used four highly polymorphic microsatellite markers on the chromosome 1 region that includes SEP15 gene, to assess the difference in heterozygosity index at studied loci between DNA obtained from breast cancer tumours (n=61) and DNA obtained from lymphocytes of cancer-free individuals (n=50). Significant reduction of heterozygosity was found for locus that was most tightly linked to SEP15 gene.

Head and neck cancer

Disease

Hu et al. (2001) found statistically significant difference in SEP15 allelic distribution for rs5859 between head and neck cancer individuals (DNA obtained from tumours, n=33) and cancer-free individuals (DNA obtained from lymphocytes, n=490) among African Americans.

Mesothelioma

Disease

Apostolou et al. (2004) reported that SEP15 gene expression was downregulated in malignant mesothelioma (MM) cell lines (14 out of 23 cell lines examined) and mesothelioma tumours (3 out of 5 tissue specimens examined). The authors examined also the effect of selenium in MM cell lines on the growth inhibition and apoptosis. They observed that suppression of SEP15 expression by siRNA affected the response of cells to selenium, making them more resistant to the microelement. The growth inhibition and apoptosis effects followed by selenium treatment were also less pronounced in cells with variant alleles of SEP15 (SEP15 1125A, rs5859) as compared to cells with wild type allele (SEP15 1125G).

Lung cancer

Disease

In the case control study (238 cases, 340 controls), Jablonska et al. (2008) observed a modifying effect of SEP15 polymorphism (rs5859) on lung cancer risk associated with selenium status. The high risk of lung cancer in the studied group was associated with low as well as with high plasma selenium concentration. After stratifying the data according to SEP15 genotype, it was found that among individuals with high selenium status, the risk of lung cancer was increased among those possessing at least one wild type allele, whereas in those with both variant alleles, the risk was decreased (figure 2).

No expression change for SEP15 was observed between malignant and non-malignant lung tissue (study of 33 non-small cell lung cancer patients, conducted by Gresner et al., 2009).

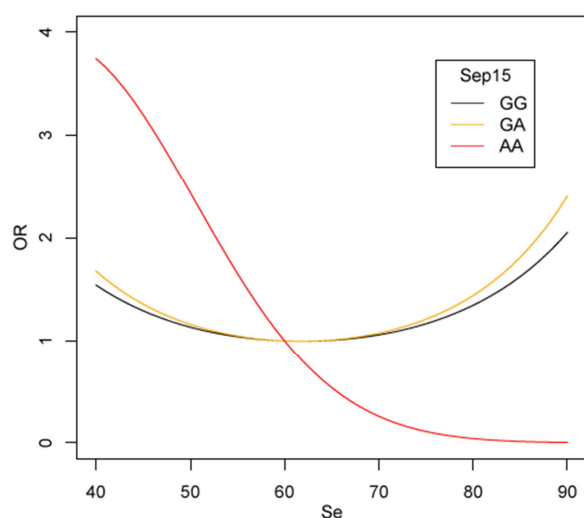


Figure 2. Joint effect of plasma selenium concentration and SEP15 1125G/A polymorphism for lung cancer development. OR - Odds Ratio for lung cancer risk. SEP15 genotypes: 1125GG (black line), 1125GA (yellow line), 1125AA (red line). Test for trends in SEP15 genotypes: $p=0.038$ for GG, $p=0.035$ for GA, $p=0.030$ for AA. Test for trend differences: AA vs. GG: $p=0.049$, AA vs. GA: $p=0.025$ (results of this study were published in Jablonska et al., 2008).

Bladder cancer

Disease

Reszka et al. (2009) indicated that SEP15 was down expressed in the blood leucocytes of bladder cancer patients (33 males) as compared to healthy controls (47 males). SEP15 expression was positively correlated with tumour grade.

Prostate cancer

Disease

Penney et al. (2010) conducted nested case control study among 1286 cases and 1267 controls to assess the relationship between five SEP15 polymorphisms (rs5859, rs479341, rs561104, rs527281, rs1407131), selenium status and prostate cancer risk and survival.

Authors did not find any association between SEP15 polymorphisms and prostate cancer risk. However they observed that three variants (rs479341, rs1407131 and rs561104) were significantly associated with prostate cancer mortality and one of the SNPs (rs561104) was shown to modify prostate cancer survival in association with selenium status.

Colon/colorectal cancer

Disease

Studies conducted in mice by Irons et al. (2010), showed that down regulation of SEP15 inhibited colon cancer development induced by injection of mouse CT26 colon cancer cells. Authors suggest that targeted down regulation of SEP15 in colon cancer cells may protect them from tumorigenesis.

Meplan et al. (2010) conducted case control study including 832 cases and 705 controls, in which they assessed the association between colorectal cancer and several SNPs within genes encoding selenoproteins and also other proteins. They found significant two-loci interaction between SEP15 (rs5859) and other selenoprotein (Sepp1) associated with colon cancer risk.

In a similar study, involving 827 cases and 733 controls, Sutherland et al. (2010) found two SNPs within SEP15 (rs5845 and rs5859) to be associated with colorectal cancer risk.

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