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Gene Section
Review

SLC9A3R1 (solute carrier family 9 (sodium/hydrogen exchanger), member 3 regulator 1)

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Identity

Other names: EBP50; NHERF; NHERF1; NPHLOP2

HGNC (Hugo): SLC9A3R1

Location: 17q25.1

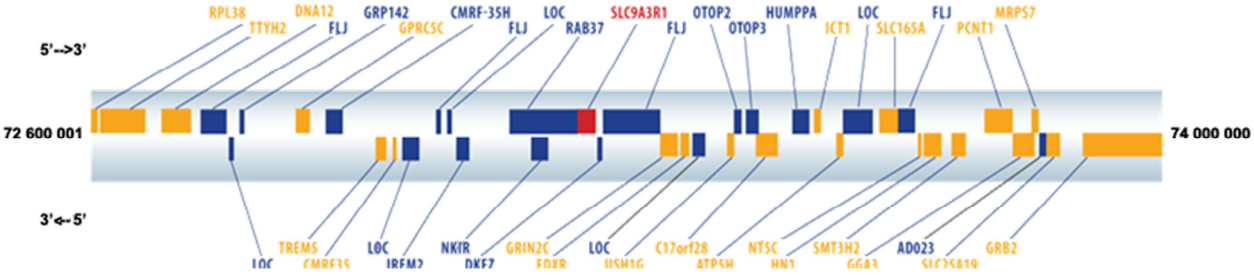
DNA/RNA

Description

The SLC9A3R1 gene is comprised of 6 exons and spans approximately 20.7 kb of genomic DNA.

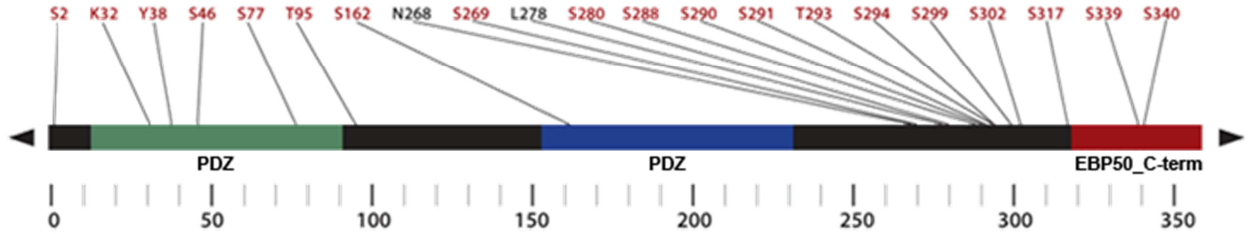
Transcription

The SLC9A3R1 gene encodes a 1978 bp mRNA transcript.
Reported regulatory transcription factor binding sites upstream of the SLC9A3R1 promoter region include: NF-kappaB1, HNF-4alpha2, COUP-TF1, NF-kappaB, NRSF form 2, NRSF form 1, FOXD1, PPAR-gamma2, PPAR-gamma1, GATA-1.



SLC9A3R1 Physical Map.

DNA size 20.71 Kb; mRNA size 1978 bp; 6 exons.



NHERF (human)-358 aminos acids.

Protein

Description

The SLC9A3R1 protein is composed of 353 amino acids (389 kDa).
Post-transcriptional regulation of SLC9A3R1 occurs via Serines S77-p, S162-p, S339-p, S340-p.
SLC9A3R1 is also phosphroylated on T95-p.
SLC9A3R1 has two PDZ (DHR) domains.
SLC9A3R1 can exist as a homodimer or heterodimer with SLC9A3R2.

Expression

SLC9A3R1 is expressed in liver, salivary glands, kidney, pancreas, trachea, small intestine, stomach, prostate and brain.

Localisation

SLC9A3R1 is a cytoplasmic protein. SLC9A3R1 translocates from the cytoplasm to the apical cell membrane in a PODXL-dependent manner. SLC9A3R1 colocalizes with actin in microvilli-rich apical regions of the syncytiotrophoblast. SLC9A3R1 has been found in microvilli, ruffling membrane and filopodia of HeLa cells. SLC9A3R1 is also been discovered in lipid rafts of T-cells.
Subcellular localization is present in cells with apical specialized structure such as micorvili and cilia. SLC9A3R1 also has a membranous expression in cells of non-epithelial origin (astrocytes) and hematopoietic stem cells and has been found in membrane rafts in lymphocytes and at the rear edge of neutrophils.

Function

SLC9A3R1 is a scaffold protein that connects plasma membrane proteins with members of the ezrin/moesin/radixin family and thereby helps to link them to the actin cytoskeleton to regulate their surface expression. SLC9A3R1 has been shown to be necessary for recycling of internalized ADRB2. SLC9A3R1 regulates SLC9A3 as well as its subcellular location. SLC9A3R1 is required for cAMP-mediated phosphorylation and inhibition of SLC9A3R1. SLC9A3R1 interacts with MCC. SLC9A3R1 may participate in HTR4 targeting to microvilli. SLC9A3R1 has been shown to play a role in the WNT signaling pathway.

Induction: SLC9A3R1 can be induced by estrogen.
SLC9A3R1 has been show to have binary interaction with the following proteins: CFTR, CLCN3, MSN, NF2, RDX.

Mutations

Note

SLC9A3R1 has been shown to have three natural variants.
Natural variant 110L --> V in NPHLOP2; the mutant expressed in cultured renal cells increases the generation of cyclic AMP (cAMP) by parathyroid hormone (PTH) and inhibits phosphate transport.
Natural variant 153R --> Q in NPHLOP2; the mutant expressed in cultured renal cells increases the generation of cAMP by PTH and inhibits phosphate transport.
Natural variant 225E --> K in NPHLOP2; the mutant expressed in cultured renal cells increases the generation of cAMP by PTH and inhibits phosphate transport.

Implicated in

Cancer progression

Note

There is growing evidence SLC9A3R1 plays an important role in cancer progression. SLC9A3R1 functions as an adaptor protein to control cell transformation. In addition, recent evidence suggests that SLC9A3R1 has a dual role either acting as a tumor suppressor when it is localized as the cell membrane or as an oncogenic protein when it is localized in the cytoplasm (Georgescu et al., 2008).

Glioblastoma

Note

The invasive nature of glioblastoma multiforme presents a clinical problem rendering tumors incurable by conventional treatment modalities such as surgery, ionizing radiation, and temozolomide.
SLC9A3R1 has been implicated to play a role in sustaining glioma cell migration and invasion. SLC9A3R1 has been shown to be over-expressed in invading glioma cells as compared to the tumor core (Kislin et al., 2009).

Breast cancer

Note

Increased cytoplasmic expression of SLC9A3R1 in breast tumors suggests a key role of its localization and compartmentalization in defining cancerogenesis, progression, and invasion. SLC9A3R1 overexpression has been associated with increasing tumor cytohistological grade, aggressive clinical behavior, unfavorable prognosis, and increased tumor hypoxia. Moreover, SLC9A3R1 co-localizes with the oncogenic receptor HER2/neu in HER2/neu-overexpressing carcinoma and in distant metastases (Mangia et al., 2009).

The switch from apical membranous to cytoplasmic expression is compatible with a dual role for NHERF1 as a tumour suppressor or tumour promoter dependent on its subcellular localization (Georgescu et al., 2008).

Cystic fibrosis

Note

The inherited disease cystic fibrosis is one of the most common chronic lung diseases in children and young adults and may lead to an early death.

Cystic fibrosis transmembrane regulator (CFTR) functions as a cAMP-regulated chloride channel, and mutations in CFTR are contributory in cystic fibrosis. CFTR contains a C-terminal SLC9A3R1 consensus sequence affording the two proteins to bind with high affinity. Recent experiments have postulated two roles for SLC9A3R1 in CFTR function. Guggino, Stanton, and coworkers have proposed that NHERF functions as a membrane retention signal for CFTR (Moyer et al., 1999).

Raghuram et al. suggest that SLC9A3R1 facilitates the dimerization of CFTR leading to its full expression of chloride channel activity (Raghuram et al., 2001).

Lastly, ss2-adrenoceptors have been shown to physically interact with CFTR Na+/H+ Exchanger Regulatory Factor 1 SLC9A3R1 protein. This function of SLC9A3R1 could be a new therapeutic target in CF patients to facilitate the trafficking of mutated CFTR to plasma membrane (Bossard et al., 2011).

Hypophosphatemia and nephrolithiasis

Note

SLC9A3R1 plays an important role in tumor phosphorous transport. Inactivating missense mutations in SLC9AR1 have been identified in patients with hypercalciuria and neprolithiasis (Karim et al., 2008).

To be noted

Note

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