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Gene Section
Review

SLC22A3 (Solute carrier family 22 member 3)

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Abstract

Review on SLC22A3, with data on DNA, on the protein encoded, and where the gene is implicated.

Keywords
SLC22A3; Hepatocellular carcinoma; Prostate cancer; Renal cell carcinoma; Colon cancer

Identity

Other names: EMT, OCT3

HGNC (Hugo): SLC22A3

Location: 6q25.3

Location (base pair)
Starts at 160769405 and ends at 160873611 bp

Note
The length of SLC22A3 gene is 3.499 base-pair (bp) with an open reading frame of 1.653 bp (Verhaagh et al., 1999). Genes encoding the members of solute carrier family 22a locate at human chromosome 6q26-q27 as a conserved gene cluster between apolipoprotein(a), APO(a)-like gene and tumor suppressor gene IGF2R (Figure 1; Verhaagh et al., 1999; Tregouet et al., 2009; Heise et al., 2012).

DNA/RNA

Note
SLC22A3 is one of three members of cation transporter genes located on chromosome 6. SLC22A3 is involved in the transportation of a variety of organic cations. Organic transporters have been included into the family of solute carrier proteins due to their homologies and third member of this family which was previously called organic cation transporter 3, OCT3, and the extraneuronal monoamine transporter, EMT, renamed as SLC22A3 (Verhaagh et al., 1999; Wieland et al., 2000; Verhaagh et al., 2001).

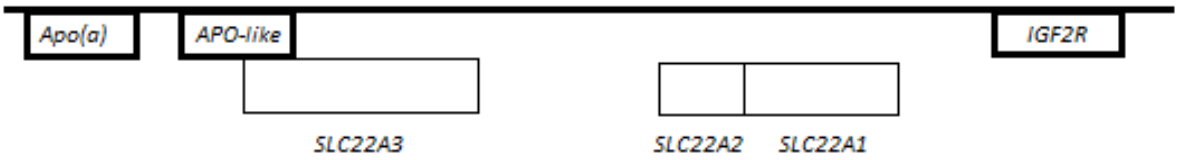

Figure 1. Localization of human SLC22A3 gene on chromosome 6q26-q27 (as depicted in Verhaagh et al., 2009).IMAGE_FISH

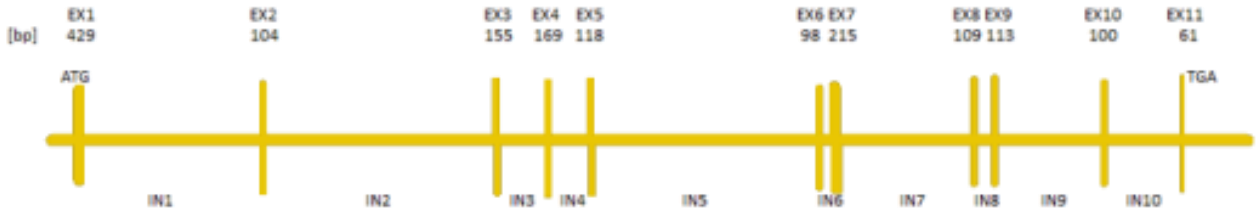

Figure 2. Gene structure of human SLC22A3 (as depicted inWieland et al., 2000).

Description

The SLC22A3 gene consists of 11 exons and 10 introns, and encodes a 551 amino acid long membrane protein that comprises 12 predicted ?-helical transmembrane domains (TMDs). Intron/exon boundaries have the conserved gt/ag consensus splice sites (Figure 2). The exon 1 encodes N-terminus together with the first TMD and the exon 8 encodes TMD 10. The other SLC22A3 exons encode more than one TMDs (Wieland et al., 2000). SLC22A3 displays a structure conserved in members of solute carrier proteins (OCT1, OCT2, ORCTL2, ORCTL3, ORCTL4; Wieland et al., 2000) and in different organisms (rat, murine, mouse, and human; Burckhardt& Wolff, 2000; Wieland et al., 2000).

Transcription

It is reported that a large noncoding RNA (ncRNA), Air, silences cis-linked distal paternal Slc22a3 gene (mouse SLC22A3 gene) allele-specifically by interacting Slc22a3 promoter and H3K9 histone methyltransferase in placenta (Nagano et al, 2008). Studies indicate that the basal promoter of SLC22A3 contains a large CpG island which extends into exon 1, and abnormal methylation decreases SLC22A3 expression in human prostate cancer (Chen et al., 2013).

Protein

Description

The SLC22A3 protein is composed of 551 amino acids with a 61 kDa molecular mass (Kekuda et al., 1998). The protein is predicted to be composed of 12 TMDs and both NH2 and COOH termini of the protein locate at the cytoplasmic site of the plasma membrane (Kekuda et al., 1998; Burckhardt Wolff, 2000). There are three potential N-linked glycosylation sites (positions 72, 99 and 114) within a large extracellular loop (106 amino acids) located between TMDs 1 and 2. Another N-linked glycosylation site is localized at position 199 in an extracellular loop formed between TMDs 3 and 4. SLC22A3 also contains putative phosphorylation sites for protein kinase C (Ser-286, Thr-292 and Thr-459) and protein kinase A (Thr-346 and Thr-544) (Kekuda et al., 1998).

Expression

SLC22A3 is expressed in a wide range of tissues including the first-trimester and term placenta, skeletal muscle, prostate, liver, aorta, fetal lung, salivary gland, adrenal gland (Verhaagh et al., 1999), sympathetically innervated tissues (Lazar et al., 2003), heart, brain (Vialou et al., 2004; Chen et al., 2010), central nervous system (Zhu et al., 2012) and kidney (Wu et al., 2000).

Localisation

SLC22A3 is localized on the plasma membrane (Kekuda et al., 1998; Burckhardt Wolff, 2000).

Function

SLC22A3 is a potential-sensitive organic cation transporter and activated by inside-negative membrane potential (Kekuda et al., 1998). The main function of the protein is to uptake and to eliminate clinically used drugs, endogenous organic cations (dopamine, norepinephrine and histamine; Wu et al., 2000) and toxic substances in the kidney, placenta and liver by uptake-2 transport system, which is the high-capacity and low-affinity transport system (Hayer-Zillgen et al. 2002; Vialou et al., 2004; Sakata et al., 2010). SLC22A3 uptakes catecholamines and neurotoxic organic cations in glial cells (Wieland et al., 2000). It also carries out the clearance of monoamines by co-localizing with other enzymes in placenta (Verhaagh et al., 2001). The mouse homolog Slc22a3 is shown to be involved in regulating salt-uptake (Vialou et al., 2004) and is a regulator of neurotransmission by controlling the transportation of dopamine, norepinephrine, 5-hydroxytriptamine, epinephrine and histamine in the central nervous system (Zhu et al., 2012).
The activity of SLC22A3 is selectively inhibited by corticosterone, progesterone and 17?-estradiol, O-methylisoprenaline (OMI) and decynium22 (Hayer-Zillgen et al., 2002).

Homology

SLC22A3 shares homology with the other members of organic cation transporter OCT1 and OCT2; at amino acid sequence level, the identity ranges between 30-51% (Kekuda et al., 1998). SLC22A3 also shows conserved amino acid sequences in

mammals (Burckhardt& Wolff, 2000; Wu et al., 2000).

Mutations

It is reported that there are six single-nucleotide substitutions and one deletion within the core promoter, exonic and intronic sequences and 3' untranslated region without any amino acid changes in Caucasians, suggesting that the mutations would be as the result of demographic differences (Lazar et al., 2003).

A non-synonymous substitution in SLC22A3 gene, Mel370Ile, may be related to obsessive-compulsive disorder (Lazar et al., 2008). Of the reported five nonsynonymous SNPs (T44M, A116S, T400I, A439V and G475S; NCBI dbSNP, http://ncbi.nlm.nih.gov/SNP; Sakata et al., 2010), A116, A439 and G475 are found only in the SLC22A3 gene while the others are also found in other organic cation transporter genes. The variations in the amino acid sequence result in a reduced substrate uptake and functionality (Sakata et al., 2010).

It is also reported that T44M, P84P, A116S, R102R, T400I, A411A, L498L SNPs in the coding regions of SLC22A3, as well as SNPs in intronic regions, may result in alterations in substrate specificity (Chen et al., 2010).

Implicated in

Hepatocellular carcinoma

SLC22A3, as SLC22A1, is downregulated in human hepatocellular carcinoma.

The downregulation of SLC22A3 is associated with tumor progression and poor patient survival (Heise et al. 2012).

Prostate cancer

Studies with 12 known risk polymorphisms in risk allele status for prostate tissue suggest that 4 of 12 prostate cancer risk variants are related to five transcripts, one of which is SLC22A3.

Studies suggest that the expression of SLC22A3 is reduced in prostate cancer cells due to the aberrant methylation of the promoter region, an indication that the reduced level of SLC22A3 expression may be involved in the progression of prostate cancer (Chen et al., 2013).

Renal cell carcinoma

Kidneys are important for the excretion of xenobiotic compounds and consequently are highly susceptible for tumor development.

Renal cell carcinomas are mainly resistant to chemotherapies, which appear to be dependent upon the expression of transporter proteins that include SLC22A3 (Shnitsar et al., 2009).

Distal colon cancer

Genome-wide studies suggest that the genetic variant rs7758229 in SLC22A3 is associated with colorectal cancer susceptibility in Japanese population (Cui et al, 2011), the same variant, on the other hand, shows no association for colorectal cancer risk in a Chinese cohort (Zhu et al., 2013).

Coronary artery disease (CAD)

Genome-wide haplotype association studies suggest that SLC22A3-LPAL2-LPA gene cluster constitutes a strong susceptibility locus for CAD (Tregouet et al., 2009).

Methamphetamine (MAP) use disorder

MAP is an amphetamine derivative and illicit psycho-stimulant. MAP dependence, an important social problem, is thought to be influenced by genetic factors. Due to the ability of SLC22A3 to transport MAP (Wu et al., 1998), it is suggested that polymorphisms in SLC22A3 gene may be correlated with MAP dependence (Aoyama et al., 2006).

Obsessive-compulsive disorder (OCD)

OCD is primarily linked with abnormalities in serotonergic system. The observations that genome-wide linkage of OCD (6q26) overlaps with SLC22A3 (6q26-q27) provides a support for a role of SLC22A3 in OCD. Two novel mutations, Met370Ile and -106/107delAG which cause 40% reduction in norepinephrine transport in patients, could underlie the modulatory role of SLC22A3 in OCD (Lazar et al., 2008).

Depression

Clearance of neurotransmitters for the homeodynamic regulation of the central nervous system is mediated by uptake-1 and uptake-2 systems. The uptake-2 is a low-affinity and high-capacity system within which SLC22A3 plays a significant role (Schildkraut and Mooney, 2004). SLC22A3 transports various neurotransmitters including dopamine, norepinephrine, epinephrine, 5-hydroxytryptamine and histamine (Wu et al., 2000). Anti-depressants currently used in clinics include selective 5-HT and 5-HT-NE inhibitors. Studies suggest that the inhibition of SLC22A3-mediated neurotransmitter uptake is a critical contributor for the effects of antidepressants, underlying the importance of SLC22A3 in depression progression and protection (Baganz et al., 2008; Mooney et al., 2008; Zhu et al., 2012).

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