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Gene Section
Review

ABCC11 (ATP-binding cassette, sub-family C (CFTR/MRP), member 11)

Akimitsu Yamada, Kazuaki Takabe, Krista P Terracina, Takashi Ishikawa, Itaru Endo

Department of Breast and Oncological Surgery, Yokohama City University School of Medicine, Kanagawa, Japan (AY, IE), Department of Surgery, Virginia Commonwealth University, Richmond, Virginia, USA (AY, KT, KPT), Department of Breast and Thyroid Surgery, Yokohama City University Medical Center, Yokohama, Kanagawa, Japan (TI)

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Abstract

Review on ABCC11, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: EWWD, MRP8, WW

HGNC (Hugo): ABCC11

Location: 16q12.1

DNA/RNA

Note

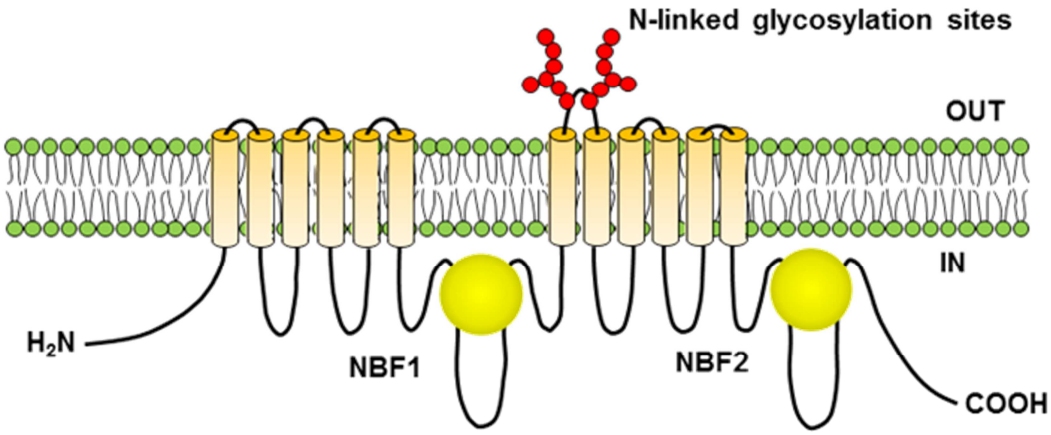
In 2001, three research groups independently cloned two novel ATP-binding cassette transporters named ABCC11 and ABCC12 from the cDNA library of human adult liver (Bera et al., 2001; Tammur et al., 2001; Yabuuchi et al., 2001). These two genes have been found to be located at human chromosome 16q12.1. Phylogenetic analysis determined that ABCC11 and ABCC12 are derived by duplication, and are closely related to the ABCC5 gene (Tammur et al., 2001). ABCC11 has overall 42% identity and 51% similarity with the MRP5 sequence and the predicted amino acid sequences of gene products show high similarity to those of ABCC5 (Bera et al., 2001). Thus these two genes were classified into the multidrug resistant-associated protein (MRP) family.

Description

The ABCC11 gene is encoded by a 68 kb gene consisting of 30 exons (Yabuuchi et al., 2001). According to the August 2013, NCBI database, there are three ABCC11 variants. Variant 1 consists of 4576 bp (NM_032583.3) while variant 2 consists of 4862 bp (NM_033151.3). Both variant 1 and 2 genes encode an ABCC11 protein (isoform a) consisting of 1382 amino acids. Variant 3 (isoform b) consists of 4462 bp (NM_145186.2) and encodes a protein consisting of 1344 amino acids. This variant 3 lacks an alternate in-frame exon compared to variant 1, resulting in a shorter protein (isoform b), compared to isoform a.

Transcription

Transcript analyses suggest that human ABCC11 mRNA is ubiquitously expressed in human adult and fetal tissues (Tammur et al., 2001; Yabuuchi et al., 2001). ABCC11 mRNA has been detected in several tissues including breast, testis, liver, placenta, and brain (Bera et al., 2001; Tammur et al., 2001; Yabuuchi et al., 2001). Transcripts of ABCC11 genes have been observed in cell lines of carcinoma and adenocarcinoma originating from breast, lung, colon and prostate (Yabuuchi et al., 2001).



Schematic illustration of ABCC11 protein structure. ABCC11 has a total of 12 transmembrane (TM) regions and two intracellular ATP-binding cassettes.

Protein

Note

ABCC11, a plasma membrane ATP-binding cassette transporter, has been implicated in the drug resistance of breast cancer due to its ability to confer resistance to fluoropyrimidines (5-FU), and to efflux methotrexate, and has been found to be expressed in breast cancer tumors. One of the single nucleotide polymorphisms (SNPs) of this gene, 538G>A, determines wet vs. dry earwax type and it also likely has a key role in the function of ceruminous apocrine glands.

Description

The calculated molecular weight of the protein encoded by the ORF is about 150 kDa. The N-linked glycosylated form of ABCC11 is 180 kDa (Toyoda et al., 2009).

Structure: ABCC11 is a full transporter and has two conserved nucleotide binding domains and 12 putative transmembrane domains (Kruh et al., 2007).

Expression

ABCC11 wild type protein with Gly180 is expressed in the cerumen gland, which is one of the apocrine glands (Toyoda et al., 2009). ABCC11 has also been identified as an axonal protein of the central nervous system and peripheral nervous system (Bortfeld et al., 2006).

Localisation

ABCC11 wild type with Gly180 is an N-linked glycosylated protein, which is localized within intracellular granules and large vacuoles as well as at the luminal membrane of secretory cells in the cerumen apocrine gland.

As opposed to the wild type, the SNP variant Arg180 lacks N-linked glycosylation and readily undergoes proteosomal degradation, most probably via ubiquitination. As a consequence, no granular or vacuolar localization is detected in the cerumen apocrine glands of people homozygous for the SNP variant (Toyoda et al., 2009).

When ABCC11 wild type protein was transfected exogenously into Madin-Darby canine kidney cells stain II (MDCK II) cells, the protein was found to be preferentially sorted to the apical membrane of these polarized cells, a finding with a known association to axonal localization within the neuron (Bortfeld et al., 2006).

Function

ABCC11 has been identified as an efflux pump for variety of lipophilic anions including the cyclic nucleotides cAMP and cGMP, glutathione conjugates such as leukotriene C_4 (LTC_4) and S-(2,4-dinitrophenyl)-glutathione (DNP-SG), steroid sulfates such as estrone 3-sulfate (E_13S) and dehydroepiandrosterone 3-sulfate (DHEAS), glucuronides such as estradiol 17-β-D-glucuronide ($E_217βG$), the monoanionic bile acids glycocholate and taurocholate, as well as folic acid and its analog methotrexate (MTX) (Guo et al., 2003; Chen et al., 2005; Bortfeld et al., 2006).

ABCC11 is directly involved in 5-FU resistance by the efflux transport of the active metabolite 5-fluoro-2'-deoxyuridine 5'-monophosphate (FdUMP) (Oguri et al., 2007).

ABCC11 polymorphisms have strong associations with earwax type (Yoshiura et al., 2006), axillary osmidrosis (Yabuuchi et al., 2001; Nakano et al., 2009; Toyoda et al., 2009; Inoue et al., 2010; Martin et al., 2010), and apocrine colostrum secretion from mammary gland (Miura et al., 2007).

Human earwax type is determined by a single nucleotide polymorphism (SNP), 538G>A (re17822931; Gly180Alg), in ABCC11 (Yoshiura et al., 2006; Toyoda et al., 2009).

The G/G and G/A genotypes correspond to the wet type of earwax, whereas A/A corresponds to the dry type (Toyoda et al., 2009).

Frequencies of this allele are known to vary dramatically depending on ethnicity. For example, in Mongoloid populations in Asia, the frequency of the 538A allele is predominantly high, whereas the frequency of this allele is low among Caucasians and Africans. Consequently, earwax type also varies between populations (Yoshiura et al., 2006).
In addition to its association with earwax type, the ABCC11 wild type (G/G and G/A) allele is also intimately associated with axillary osmidrosis, and several studies have already concluded that the genotype at ABCC11 538G>A would be a useful biomarker for the diagnosis of axillary osmidrosis (Yabuuchi et al., 2001; Nakano et al., 2009; Toyoda et al., 2009; Inoue et al., 2010; Martin et al., 2010).
Axillary osmidrosis patients (538G/G homozygote or G/A heterozygote) have significantly more numerous and larger-sized axillary apocrine glands compared to those with A/A homozygote.
Lastly, there is a strong association between human earwax-type according to 538G>A and apocrine colostrum secretion from the mammary gland. In a study in 225 Japanese women, the frequency of women without colostrum among dry-type women was significantly higher than that among wet-type women and the measurable colostrum volume in dry type women was significantly smaller than that found in wet-type women (Miura et al., 2007).

Homology

No gene orthologous to human ABCC11 has been found in mammals except for primates (Shimizu et al., 2003).

Mutations

Note

More than 10 non-synonymous single-nucleotide polymorphisms (SNPs) have been reported in the ABCC11 gene, including R19H, G180R, A317E, T546M, R630W, V648I, V687I, K735R, M970V, and H1344R. There is also a rare deletion mutation, Δ27 (Toyoda et al., 2008; Toyoda et al., 2009).
Among those SNPs, one SNP (rs17822931; 538G>A, Gly180Arg) located on exon 4 is thought to be a clinically important polymorphism described as above.
Further, the wild type allele of the ABCC11 gene (G/G or G/A) is associated with breast cancer risk in the Japanese population (Ota et al., 2010). However, this has not been found to be the case in women of European or Caucasian descent (Beesley et al., 2011; Lang et al., 2011).
Thus it remains controversial whether the 518G allele contributes to a risk factor of breast cancer or not.
A deletion mutation, Δ27, has also been linked to the formation of dry-type earwax (Ishikawa et al., 2012).

Implicated in

Breast cancer

Note

Several studies have reported that ABCC11 mRNA is highly expressed in breast tumors and breast cancer cell lines (Bera et al., 2001; Yabuuchi et al., 2001; Bièche et al., 2004; Park et al., 2006, Szakács et al., 2004).
ABCC11 expression is regulated directly or indirectly by estrogen receptor α, and the prolonged exposure of breast cancer cells to tamoxifen has been associated with up-regulation of ABCC11 (Honorat et al., 2008).
In a study by Park et al., the mRNA of ABCC11 was shown to be increased in the breast tumors of patients with residual disease compared to those who have achieved a complete response from neoadjuvant chemotherapy.
However, ABCC11, in the analysis, was not found to be the ABCC transporter protein most predictive of failure of neoadjuvant chemotherapy (Park et al., 2006).
A tissue microarray analysis of 281 breast cancer samples revealed that high expression of ABCC11 in breast cancer is associated with aggressive subtypes such as HER2 type or triple negative type, and is associated with low disease free survival (Yamada et al., 2013). The mechanism underlying this association with breast cancer patients' survival remains unknown.

Leukemia

Note

Some of the histone deacetylase inhibitors such as SAHA are known to induce the expression of ABC transporters including the ABCC11 gene to make acute myeloid leukemia (AML) cells resistant to a broad-spectrum of drugs (Hauswald et al., 2009).
The efflux of the nucleoside analogue cytosine arabinoside (AraC) metabolite by ABCC11 is one of the mechanisms contributing to resistance of AML. The expression of ABCC11 WT is an important factor affecting AML patient survival (Guo et al., 2009).

Paroxysmal kinesigenic choreoathetosis (PKC) and infantile convulsions with paroxysmal choreoathetosis (ICCA).

Note

ABCC11 and ABCC12 have been mapped to a region harboring genes for paroxysmal kinesigenic choreoathetosis (PKC) (Tomita et al., 1999), and infantile convulsions with paroxysmal choreoathetosis (ICCA) (Lee et al., 1998). The two genes were thought to be represent positional candidates for this disorder; however, it has since

been reported that ABCC11 has been ruled out as the cause of PKC (Du et al., 2008).

Breakpoints

Note

ABCC11 is in a relatively early stage of investigation. The SNP (538G>A) in the ABCC11 gene determines both ear wax phenotype and axillary osmidrosis and plays a key role in the function of apocrine glands. Though ABCC11 transports a variety of organic anions, the endogenous natural substrates for this transporter have not yet been identified that might explain the association between ABCC11 expression in breast cancer and poor prognosis.

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