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Gene Section
Review

AQP2 (aquaporin 2)

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Abstract

Review on aquaporin-2 (AQP2), with data on DNA, on the protein encoded, and where the gene is implicated.

Keywords
Aquaporin-2; AQP2; Tissue water balance; Cell migration; Cellular volume regulation; Cell membrane; Channel; Nephrogenic diabetes insipidus; Urine concentration; Collecting duct; Kidney

Identity

Other names: AQP-CD, WCH-CD

HGNC (Hugo): AQP2

Location : 12q13

DNA/RNA

Transcription

There are various splicing forms. Canonical form transcript (hg38), including UTRs: chr12:30,911,694 - 30,925,516, size: 13,823bp on forward (+) strand; coding region: chr12: 49,950,746-49,958,881 size: 8,136bp, according to UCSC.
Four exons: exon1 (nt 1 - 450) codes for amino acids (aa) 1-120, exon2 (nt 3415 - 3579) for aa 121-175; exon3 (nt 3890 - 3970) for aa 176-202, and exon4 (nt 4659 - 8141) for aa 203-271 (nextProt).

Protein

Aquaporins are a family of hydrophobic transmembrane channel proteins involved in transport of water and small molecules in response to osmotic gradients. They are distributed throughout many tissues, with various known roles of production, secretion, reabsorption and regulation of water, but also of cell migration (angiogenesis), signal transduction, and cell proliferation. There are 14 AQPs in humans (and 5 pseudogenes): MIP (previously called AQP0), AQP1, AQP2, AQP3, AQP4, AQP5, AQP6, AQP7, AQP8, AQP9, AQP10, AQP11, AQP12A and AQP12B. They are classified into two families: orthodox aquaporins, that transport water only, and aquaglyceroporins (AQP3, AQP7 and AQP9), which also transport glycerol, urea and other small molecules. AQPs form homo-tetramers (Review in Papadopoulos and Saadoun, 2015). The monomeric units of AQPs are ~30 kDa proteins and consist of 6 transmembrane α-helices (M1, M2, M4 to M6 and M8), 2 intramembrane half helices (M3 and M7), and 5 connecting loops (loops A to E) (Review in Verkman et al., 2014). They bear conserved intramembrane Asn-Pro-Ala (NPA) sequence motifs in the intramembrane domains, and six tilted transmembrane helices per monomer, with linkers (loops A to E). The NPA motifs act as hydrogen-bond donors and acceptors that coordinate the transport of water through the pore (Verkman et al., 2014).

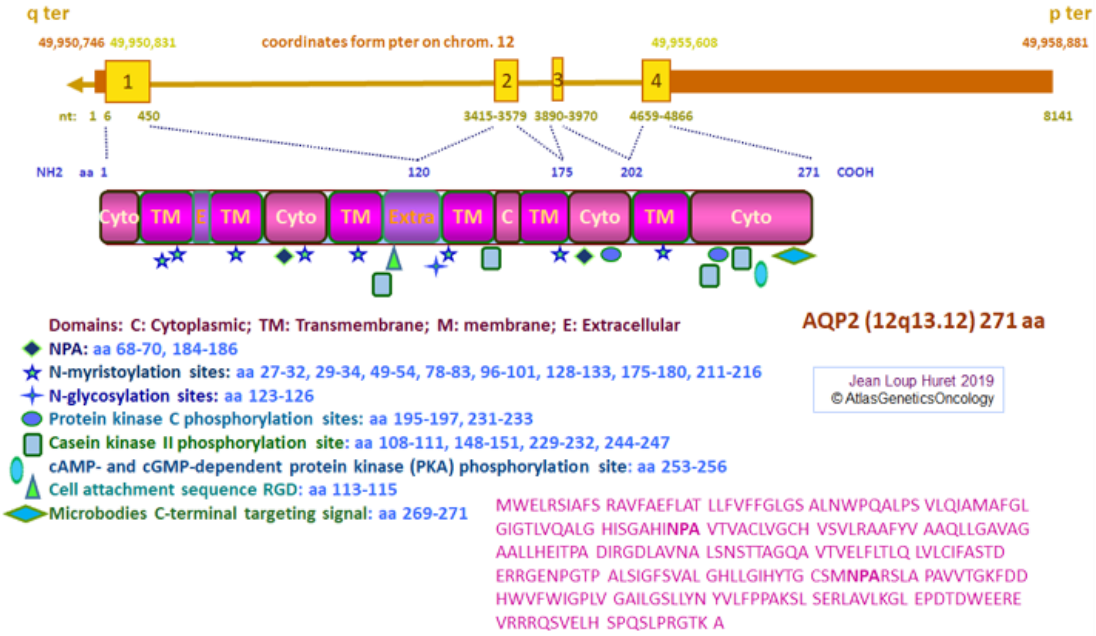

Figure 1. Aquaporin-2 (AQP2) gene exons and protein domains.

Description

Aquaporin-2 canonical form: 271 aa; 28.837kDa; other isoforms; 223, and 244 aa.

AQP2 is a transmembrane protein, with a N-term and a C-term cytoplasmic domains: amino acids 1 - 16 (Cytoplasmic), 17 - 34 (Transmembrane), 35 - 40 (Extracellular ("Loop A")), 41 - 59 (Transmembrane), 60 - 85 (Cytoplasmic ("Loop B")), 86 - 107 (Transmembrane), 108 - 127 (Extracellular ("Loop C")), 128 - 148 (Transmembrane), 149 - 156 (Cytoplasmic ("Loop D")), 157 - 176 (Transmembrane), 177 - 202 (Extracellular ("Loop E")), 203 - 224 (Transmembrane), 225 - 271 (Cytoplasmic) (Figure. 1).

Helical subunits in Loop B and E juxtapose to form a water pore in the monomere. The central pore of the homotetramer (Figure. 2) would be a path for ion and gas (Review in Huber et al., 2012).

Remarkable sites: (Figure. 1)

NPA: aa 68-70, 184-186

N-myristoylation sites (role in membrane targeting): aa 27-32, 29-34, 49-54, 78-83, 96-101, 128-133, 175-180, 211-216.

N-glycosylation sites: aa 123-126.

Protein kinase C phosphorylation sites: aa 195-197, 231-233 (Thr 195 and Ser 231); Casein kinase II phosphorylation site: aa 108-111 (Thr 108), 148-151 (Ser 148), 229-232 (Ser 229), 244-247 (Thr 244); cAMP-and cGMP-dependent protein kinase (PKA) phosphorylation site :aa 253-256.

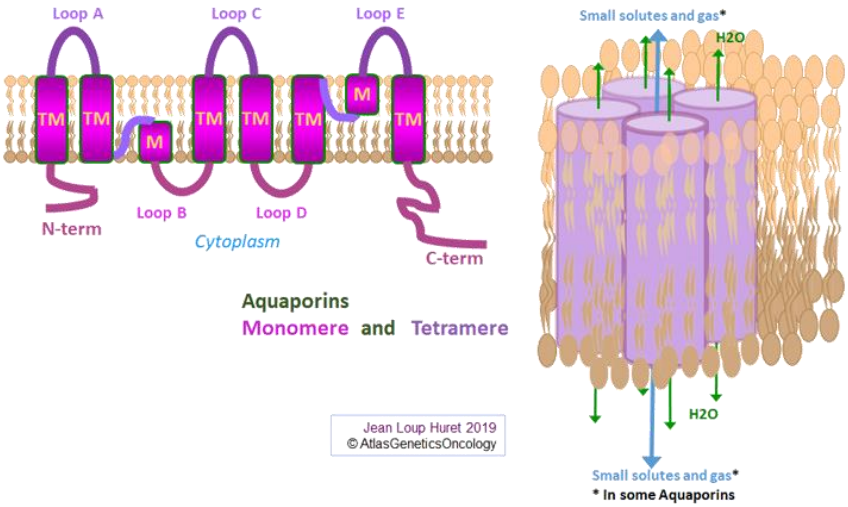

Figure 2. Aquaporins monomere and tetramere. Aquaporins are transmembrane proteins involved in transport of water and small molecules in response to osmotic gradients (water channels).

Cell attachment sequence RGD (plays a role in cell adhesion): aa 113-115.
Microbodies C-terminal targeting signal (targeting to organelles such as peroxisomes): aa 269-271.

Expression

AQPs are widely expressed. AQP2 is mainly expressed in the kidney.
Renal collecting duct principal cells
Extra-renal localizations: Ear, epididymis, vas deferens, vagina. Both AQP1 and AQP2 are expressed in the endometrium. AQP2 endometrial expression is menstrual cycle-dependent (high at the proliferative and midsecretory phases).

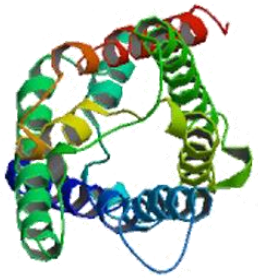

Figure 3. ModBase predicted comparative 3D structure.

Localisation

AQP2 undergoes a constitutive recycling: its trafficking from intracellular vesicles into the plasma membrane and endocytic retrieval to its intracellular storage site. AQP2 forms homotetramers in the endoplasmic reticulum, passes through the Golgi apparatus and is stored in intracellular vesicles in the perinuclear region. Under resting conditions, AQP2 binds monomeric G-actin (ACTG1). F-actin destabilization facilitates translocation of AQP2 to the apical plasma membrane and water reabsorption (Vukićević et al., 2016).

Function

AQPs main's role is to maintain tissue water balance. AQPs also facilitate cell migration, cell proliferation and cell adhesion. Cell migration: AQPs concentrate at the leading end of migrating cells and facilitate the formation of the lamellipodium (Papadopoulos and Saadoun, 2015). Cell proliferation: AQPs may activate transduction pathways such as the mitogen-activated protein kinase pathways or the Wnt/beta-catenin (CTNNB1) signaling.
AQP2 key physiological role is water reabsorption in collecting duct of the kidney to concentrate urine.
Vasopressin / vasopressin receptor / aquaporin-2 axis
In the kidney, AVP 46535 (vasopressin) binds to AVPR2 732 (type 2 vasopressin receptor (V2R)) located in the basolateral membrane of the principal cells of the collecting ducts and increases osmotic water transport through the regulation of the aquaporin-2 water channel localized in the kidney connecting tubules and collecting ducts. Upon binding of vasopressin to AVPR2, the cAMP/PKA (PRKAR1A 387) signal is activated, PRKAR1A is recruited to the vesicles through PRKAR1A-anchoring proteins (AKAPs) (AKAP7 46846 co-localizes with AQP2) and results in phosphorylation in the C-terminus of AQP2 at serines 256, 264, and 269, withdrawing it from F-actin.
AQP2 is subsequently translocated to the apical plasma membrane, and the water luminal permeability to increase water reabsorption from urine. Vasopressin also triggers increases in intracellular calcium required for AQP2 trafficking (Reviews in Jung and Kwon 2016; Ando and Uchida 2018; De Ieso and Yool 2018; Ranieri et al., 2019).
However, cAMP-independent mechanisms for AQP2 trafficking also exist.
Nuclear receptors, especially PPARG (Peroxisome proliferator-activated receptor gamma), NR1H2 (LXRB, Liver X receptor beta), NR1H4 (FXR, Farnesoid X receptor), NR3C1 (GR, Glucocorticoid receptor), NR3C2 (MR, Mineralocorticoid receptor) and ESR1 (Estrogen receptor alpha) regulate AQP2 abundance and membrane translocation. PPARG induces increased AQP2 expression, sodium and water retention and edema. NR3C1 and NR1H4 also activate AQP2 expression. NR3C2 and NR1H2 reduce AQP2 expression. ESR1 mediates the inhibitory effect of estradiol on AQP2 expression (Zhang et al., 2016).
Other factors capable of regulating AQP2: extracellular osmotic pressure, insulin (INS), nuclear factor kB (NFkB), renin/angiotensin/aldosterone system, kinins, nitric oxide, adenosine, ATP and endothelins. PTGER2 (Prostaglandin E receptor 2) also controls AQP2 expression. The phosphorylated activation of CREBBP upregulates AQP2 gene transcription (reviewed in Zhang et al., 2016).
Actin-polymerization/depolymerization
Actin-depolymerization promotes AQP2 trafficking to the plasma membrane. TPM3 and MSN (Tropomyosin 3 and Moesin) result in F-actin destabilization. MLCK (Myosin light chain kinase) also facilitates AQP2 trafficking to the plasma membrane by regulating actin filament organization. RHOA stimulates actin polymerization, which inhibits AQP2 trafficking to the plasma membrane.
Transcription
FOSB (FosB proto-oncogene, AP-1 transcription factor subunit), CREBBP, calcineurins (protein phosphatase 3 subunits) MAPK3 / MAPK1 (so called "ERK1/ERK2") and NFAT5 (nuclear factor of activated T cells 5) increase AQP2 transcription, while NFkB reduces AQP2 gene transcription.
Endocytosis/ubiquitination/degradation
FOSB/ TFAP2A (transcription factor AP-2 alpha (activating enhancer binding protein 2 alpha)) (AP1/AP2) mediates clathrin-mediated endocytosis of AQP2.

VTA1 (vesicle trafficking 1) facilitates AQP2 lysosomal degradation. MAPK14 (p38-MAPK) phosphorylates AQP2 to induce ubiquitination and proteasomal degradation of AQP2. Protein kinases C induce ubiquitination, endocytosis and degradation of AQP2 (Review in Vukićević et al., 2016).

Mutations

Germinal

AQP2 is responsible for nephrogenic non-X-linked diabetes insipidus, a disease characterized by the kidney's inability to concentrate urine (see below).

Implicated in

Dysregulation and dysfunction of AQP2 cause many disorders related to water balance in humans and animals, including polyuria and dilutional hyponatremia (Zan et al., 2016).

Nephrogenic diabetes insipidus.

Nephrogenic diabetes insipidus is characterized by the kidney's inability to concentrate urine even with normal or elevated concentration of vasopressin. Polyuria/polydipsia and electrolyte imbalance is present from birth.
The antidiuretic peptide hormone arginine-vasopressin (AVP) is synthesized in the hypothalamus. Vasopressin binds its receptor AVPR2 (arginine vasopressin receptor 2) in the basolateral membrane of cells of the renal collecting ducts, inducing the vasopressin / vasopressin receptor / aquaporin-2 axis.
Nephrogenic diabetes insipidus occurs either when:
AVPR2 is mutated (90% of cases, "X-linked nephrogenic diabetes insipidus": AVPR2 locates in Xq28), or when
AQP2 is mutated (10% of cases, "nephrogenic non-X-linked diabetes insipidus"; both dominant and autosomal recessive forms have been reported. Patients with recessive forms are either homozygous, or compound heterozygous).
Nephrogenic diabetes insipidus can also be induce by lithium, demethylchlortetracycline or other drugs (Ranieri et al., 2019).

Uterus endometrial carcinoma

There was an increased expression level of AQP2 in endometrial carcinoma, in relation to estradiol level. AQP2 was mainly located in glandular epithelial cells. An estrogen response element was found in the promoter of AQP2. In AQP2 knockdown endometrial carcinoma cells, there was an alteration of the cell morphology by decreasing the expression of ANXA2 (Annexin A2) and F-actin (Zou et al., 2011).

Glioma

The expression of both ESR2 (Estrogen Receptor 2 (ER beta)) and AQP2 was low in glioma cells from patient tissues and glioblastoma cell lines.
AQP2 promoted the transcriptional activity of LAX1 (Lymphocyte transmembrane adaptor 1) and inhibited cell invasion.
ESR2 may function as AQP2 promoter in the nucleus to sustain cells stability while ESRRA (Estrogen-related receptor alpha) would acts as an antagonist of AQP2 (Wan et al. 2018).

Kidney adenocarcinomay

A t(3;12)(p13;q13) AQP2/ FOXP1 has been found in adenocarcinoma of the kidney (Hu et al., 2018).

To be noted

Aquaporin-targeted drugs: Heavy metal ions (mercury, silver, gold) are inhibitors of aquaporin-1. The Henle loop diuretic bumetanide and analogues AqB013 and AqF026 also inhibit aquaporin-1.
The quaternary ammonium compound tetraethylammonium is an inhibitor of aquaporin-1 water permeability (Verkman et al., 2014; Tomita et al., 2017).

References

Ando F, Uchida S. Activation of AQP2 water channels without vasopressin: therapeutic strategies for congenital nephrogenic diabetes insipidus. Clin Exp Nephrol. 2018 Jun;22(3):501-507

De Ieso ML, Yool AJ. Mechanisms of Aquaporin-Facilitated Cancer Invasion and Metastasis. Front Chem. 2018;6:135

Hu X, Wang Q, Tang M, Barthel F, Amin S, Yoshihara K, Lang FM, Martinez-Ledesma E, Lee SH, Zheng S, Verhaak RGW. TumorFusions: an integrative resource for cancer-associated transcript fusions. Nucleic Acids Res. 2018 Jan 4;46(D1):D1144-D1149

Huber VJ, Tsujita M, Nakada T. Aquaporins in drug discovery and pharmacotherapy Mol Aspects Med 2012 Oct-Dec;33(5-6):691-703

Jung HJ, Kwon TH. Molecular mechanisms regulating aquaporin-2 in kidney collecting duct Am J Physiol Renal Physiol 2016 Dec 1;311(6):F1318-F1328

Papadopoulos MC, Saadoun S. Key roles of aquaporins in tumor biology Biochim Biophys Acta 2015 Oct;1848(10 Pt B):2576-83

Ranieri M, Di Mise A, Tamma G, Valenti G. Vasopressin-aquaporin-2 pathway: recent advances in understanding water balance disorders F1000Res 2019 Feb 4;8

Verkman AS, Anderson MO, Papadopoulos MC. Aquaporins: important but elusive drug targets Nat Rev Drug Discov 2014 Apr;13(4):259-77

Vukićević T, Schulz M, Faust D, Klussmann E. The Trafficking of the Water Channel Aquaporin-2 in Renal Principal Cells-a Potential Target for Pharmacological Intervention in Cardiovascular Diseases Front Pharmacol 2016 Feb 11;7:23

Wan S, Jiang J, Zheng C, Wang N, Zhai X, Fei X, Wu R, Jiang X. Estrogen nuclear receptors affect cell migration by altering sublocalization of AQP2 in glioma cell lines Cell Death Discov 2018 Oct 17;4:49

Yoshihara K, Wang Q, Torres-Garcia W, Zheng S, Vegesna R, Kim H, Verhaak RG. The landscape and therapeutic relevance of cancer-associated transcript fusions Oncogene 2015 Sep 10;34(37):4845-54

Zhang XY, Wang B, Guan YF. Nuclear Receptor Regulation of Aquaporin-2 in the Kidney Int J Mol Sci 2016 Jul 11;17(7)

Zou LB, Zhang RJ, Tan YJ, Ding GL, Shi S, Zhang D, He RH, Liu AX, Wang TT, Leung PC, Sheng JZ, Huang HF. Identification of estrogen response element in the aquaporin-2 gene that mediates estrogen-induced cell migration and invasion in human endometrial carcinoma J Clin Endocrinol Metab 2011 Sep;96(9):E1399-408

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