# Classification and Gene Structure of Aquaporins

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Long Xu, Xiangdong Guo, Weidong Wang, and Chunling Li

**Abstract**

Aquaporins (AQPs) are a family of membrane water channels that basically function as regulators of intracellular and intercellular water flow. To date, 13 AQPs, distributed widely in specific cell types in various organs and tissues, have been characterized in humans. A pair of NPA boxes forming a pore is highly conserved among all aquaporins and is also key residues for the classification of AQP superfamily into four groups according to primary sequences. AQPs may also be classified based on their transport properties. So far, chromosome localization and gene structure of 13 human AQPs have been identified, which is definitely helpful for studying phenotypes and potential targets in naturally occurring and synthetic mutations in human or cells.

**Keywords**

Aquaporin · NPA boxes · Gene

L. Xu · X. Guo · C. Li (✉)
Department of Physiology, Zhongshan School of Medicine, Sun Yat-Sen University, Guangzhou, China
e-mail: lichl3@mail.sysu.edu.cn

W. Wang (✉)
Department of Pathophysiology, Zhongshan School of Medicine, Sun Yat-Sen University, Guangzhou, China
e-mail: wangwd6@mail.sysu.edu.cn

## 1.1 Classification of Aquaporins

A large number of evidences have shown an unexpected diversity of aquaporins (AQPs) in both prokaryotic and eukaryotic organisms [1, 2] since the discovery of AQP1. More than 300 different aquaporins have been discovered so far in which 13 isoforms have been identified (AQP0–AQP12) in human. AQPs are integral, hydrophobic, transmembrane proteins that primarily facilitate the passive transport of water depending on the osmotic pressure on both sides of membrane. Subsequent studies show that AQPs can transport not only water molecules but also other small, uncharged molecules, i.e., glycerol, urea, down their concentration gradients.

Structural analysis of several AQPs has established that these protein channels share a common structural feature. The functional aquaporin unit is a homotetramer, which comprises six α-helix transmembrane domains with two conserved asparagine–proline–alanine (NPA) motifs embedding into the plasma membrane, a signature sequence of water channels (see Chap. 3). Conformational changes of AQP protein permit other molecules passing through plasma membrane, i.e., urea, glycerol, $H_2O_2$, $NH_3$, $CO_2$, etc.

According to their structural and functional similarities, AQPs are initially subdivided into two subfamilies, classical AQPs (water-selective) and aquaglyceroporins (glycerol channel, Glps) aquaporins. However, further studies revealed



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that both the subfamilies overlap functionally, for examples, some classical AQPs transport water and other small solutes, e.g., glycerol. In addition, a new group of AQPs discovered showed that their structure is highly deviated from the previous AQPs especially around the AQP NPA box [3–5]. This subfamily was later named superaquaporin (also called unorthodox aquaporin) as it has very low homology with the previous two subfamilies [4]. This classification was usually accepted in physiology.

Later, it was found out that several members, e.g., AQP8 and AQP6 in classical AQP family have unique characteristics. Aquaporins are therefore organized into four categories, classical aquaporins, unorthodoxaquaporins, Aqp8-type aquaammoniaporins, and aquaglyceroporns, according to the phylogenetic tree or phylogenetic topology inferred from Bayesian inference (Fig. 1.1) [2, 4, 6]. This classification is identified based on the transport functions and properties of aquaporins.

The first subfamily is that of aquaporins, the water selective or specific water channels, also named as "orthodox," "classical" aquaporins, including AQP0, AQP1, AQP2, AQP4, AQP5, and AQP6. This subfamily of AQPs has been extensively studied, which help us define regulation of AQP expression in the body and their potential roles in physiological and pathophysiological states. Evidence, however, appears to suggest that AQP6 be classified as unorthodox aquaporins, due to low water permeability of AQP6 [7, 8].

The second subfamily of related proteins has low conserved amino acid sequences around the NPA boxes unclassifiable to the first two subfamilies [4]. Mammalian AQP11 and AQP12 are the only two members in this subfamily, which have been called "superaquaporins" or "unorthodox aquaporins." The NPA boxes of these two AQPs are highly deviated from those of other classical AQPs with homology less than 20%, indicating that they belong to a supergene family of AQPs. The signature sequence for these AQPs is the cysteine residue at the nine residues downstream of the C-terminal of the second NPA, which is exposed on the surface of the protein at the periplasmic side of the membrane [9, 10]. The structure and function of AQP11 and AQP12 are currently poorly understood. As this subfamily focuses on deviated NPA itself and unconventional functions, AQP6 and AQP8 are also included previously [11].

The third subfamily is AQP8-type aquaammoniaporins. The structure and function of AQP8 indicate that AQP8 should not be regarded as either a conventional water channel or an aquaglyceroporin. In AQP8, both NPA motifs are conserved (although the first motif is followed by VS, instead of VT). AQP8 has the highest homology to the plant AQP, γTIP, than any mammalian AQPs [11]. AQP8 is characterized as a $Hg^{2+}$-inhibitable water channel when expressed in Xenopus oocytes [12–14]. AQP8 is unique due to its permeability of $NH_3/NH_4^+$ [15, 16] in Xenopus oocytes and in AQP8-containing proteoliposomes [17]. While more evidence suggests that AQP8 is not the only aquaporin transporting ammonia, some other classical aquaporins (AQP1, −6) and aquaglyceroporins are also capable of facilitating ammonia transport.

The fourth subfamily is represented by aquaglyceroporins that are permeable to water and other small uncharged molecules (ammonia, urea, in particular glycerol). They also facilitate the diffusion of arsenite and antimonite and play a crucial role in metalloid homeostasis [18]. The aquaglyceroporins, including AQP3, AQP7, AQP9, and AQP10, can be distinguished from aquaporins based on amino acid sequence alignments [19]. The aspartic acid residue in the second NPA box is the signature key for AQP members of this subfamily. This residue is located just the downstream of the arginine forming the aromatic residues/arginine (Ar/R) narrowest filter for the selective water permeation [20]. The aspartic acid residue enlarges this pore constriction and makes more hydrophobic, permeating small molecules larger than water [10]. AQP3 is the first mammalian aquaglyceroporin to be cloned, and it is permeable to glycerol and water [21, 22]. AQP7, AQP9, and AQP10 transport water, glycerol, and urea

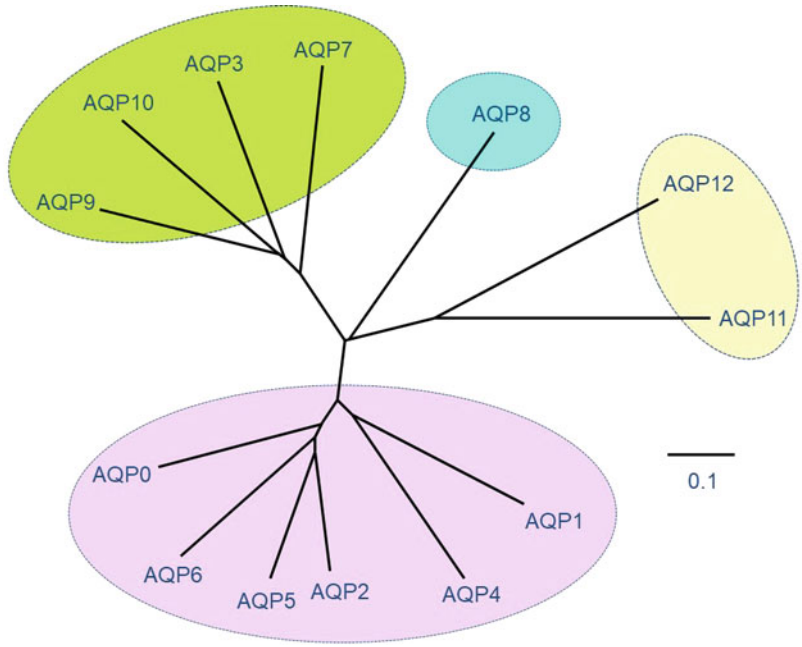


**Fig. 1.1** The phylogenetic tree of 13 human AQPs. The tree shows the classical AQPs (AQP0, AQP1, AQP2, AQP4, AQP5, and AQP6) (light pink oval); the aquaammoniaporin AQP8 (light blue oval); the aquaglyceroporins (AQP3, AQP7, AQP9, AQP10, light green oval); and the superaquaporins (AQP11, AQP12, light yellow oval). (Modified from [4])

when expressed in Xenopus oocytes [23–25]. AQP9 is also permeable to a wide range of other solutes in oocytes [25]. Most aquaglyceroporins that transport glycerol and urea are less understood yet.

Additionally, a few isoforms, for example, AQP1, AQP3, AQP8, also facilitate hydrogen peroxide membrane permeation and are called peroxiporins.

As AQPs are present in three domains of life including bacteria, eukaryotes, and archaea, a generally accepted classification will be useful to obtain an overview of widely distributed AQP family in every kingdom of lives. AQP superfamily may therefore be classified based on the primary sequence around highly conserved a pair of NPA boxes, which is critical for the function of AQPs. Four AQP subfamilies are identified: AQP1-like, AQP3-like, AQP8-like, and AQP11-like. Compared to the above, consistency of primary sequence is emphasized in this classification. For example, the presence of Asp (D) in the second NPA box is the key for AQP3-like, while Cys (C) at nine residues downstream of the second NPA box is the key for AQP11-like.

## 1.2 Isoforms of AQPs

To date, at least 13 isoforms of AQPs have been discovered in humans (Table 1.1). The biological roles of these proteins have been thoroughly investigated in the past 30 years after the discovery of the first water channel AQP1. We have learned substantial base of knowledge on the structure, cellular localization, biological function, and potential pathophysiological significance of these mammalian AQPs, although there are some questions still need to answer.

### 1.2.1 Classical Aquaporins

#### 1.2.1.1 AQP0

AQP0 is the protein in the fiber cells of the eye lens where it is required for homeostasis and transparency of the lens [26]. AQP0 showed lower water permeability than AQP1, about to 1/40 that of AQP1 [27]. AQP0 in lens also functions as peroxiporins to facilitate membrane transport of hydrogen peroxide [28]. The water transport via AQP0 is regulated by C-terminal

**Table 1.1** Genes of human AQPs

| Aquaporins | Exon numbers | Location | OMIM |
|---|---|---|---|
| AQP0 | 8 | 12q13.3 | 154,050 |
| AQP1 | 7 | 7p14.3 | 107,776 |
| AQP2 | 4 | 12q13.12 | 107,777 |
| AQP3 | 6 | 9p13.3 | 600,170 |
| AQP4 | 6 | 18q11.2-q12.1 | 600,308 |
| AQP5 | 5 | 12q13.12 | 600,442 |
| AQP6 | 4 | 12q13.12 | 601,383 |
| AQP7 | 10 | 9p13.3 | 602,974 |
| AQP8 | 6 | 16q12 | 603,750 |
| AQP9 | 6 | 15q21.3 | 602,914 |
| AQP10 | 6 | 1q21.3 | 606,578 |
| AQP11 | 3 | 11q14.1 | 609,914 |
| AQP12 | 4 | 2q37.3 | 609,789 |

References from www.ncbi.nlm.nih.gov/gene/, and omim.org/entry/

cleavage [29]. Deletion of amino acids at the C-terminal end of AQP0 impairs lens fiber organization, integrity, mechanical properties, and lens development [30–32]. AQP0 is also regulated by pH and $Ca^{2+}$/calmodulin (CaM) [33]. Lowering internal $Ca^{2+}$ concentration or inhibiting calmodulin increased AQP0 water permeability. The molecular dynamics and functional mutation studies reveal that binding to calmodulin inhibits AQP0 water permeability by allosterically closing the cytoplasmic gate of AQP0 [34]. Emerging evidence showed that AQP0 could be a marker of erythroid differentiation and play a critical role of AQP0 in erythropoiesis [35].

#### 1.2.1.2 AQP1

AQP1 is the first water channel discovered [36–38] and the first AQP that was found to function as a gas channel [39, 40]. AQP1 is a widely distributed water channel in the body [41], where it plays a central role in the regulation of water transport through those tissues. Aside of facilitating water movement, studies have revealed that AQP1 could enhance $CO_2$ and $NH_3$ permeability [7, 42] and function as a non-selective monovalent cation channel when activated by intracellular cGMP [43]. Phosphorylation of tyrosine Y253 in the C-terminus is involved in the regulation of AQP1 as a cGMP-gated cation channel [44]. Early evidence showed that threonine and serine protein kinase also regulate AQP1 ion channel activity [45]. Recent studies revealed a role of human AQP1 in the facilitated transport of $H_2O_2$ in smooth muscle [46] and cardio myocytes cell [47] hypertrophy.

#### 1.2.1.3 AQP2

AQP2 is an arginine vasopressin (AVP)-regulated aquaporin which is probably the most thoroughly studied to date. AQP2 displays permeability only to $H_2O$ but not any other small molecules. AQP2 is expressed in principal cells of the collecting ducts and is abundant both in the apical plasma membrane and subapical vesicles [48–50] in the kidney where it deeply involved in urine concentration. Translocation of AQP2 from intracellular compartment to the apical membrane is dependent on the binding of vasopressin to its V2 receptor [49, 50] located in the basolateral plasma membrane, by which vasopressin increases the water permeability.

#### 1.2.1.4 AQP4

AQP4 is a predominant AQP located in central nervous system and is permeable to water [51, 52] and $CO_2$ [7]. Phosphorylation of AQP4 at cytosolic serine residues (Ser111 and Ser180) is indicated mediating water permeability by gating [53]. AQP4 possesses $Ca^{2+}$-dependent calmodulin-binding domains at both its cytosolic N- and C-termini. The S276 residue of AQP4 was able to be phosphorylated in vivo and was linked

to $Ca^{2+}$-CaM-dependent, reversible translocation of AQP4 to the cell surface during extracellular hypotonic challenge of astrocytes [54, 55]. Phosphorylation at AQP4 C-terminus by protein kinase C (PKC) is required for Golgi transition [56].

#### 1.2.1.5 AQP5

AQP5 expression was described in the digestive, renal, respiratory, integumentary, and reproductive systems as well as in sense organs [57]. AQP5 is permeable to water and $CO_2$ [7, 58]. AQP5 can be directly phosphorylated at Ser156 and Thr259 by protein kinase A (PKA) in the cytoplasmic loop and the C-terminus [59, 60]. However, it increases intracellular $Ca^{2+}$, but not PKA-induced phosphorylation, that induces AQP5 trafficking to plasma membrane [61, 62].

#### 1.2.1.6 AQP6

AQP6 colocalizes with the $H^+$-ATPase in intracellular vesicles in the renal collecting duct type-A intercalated cells [8], indicating that AQP6 may functionally interact with $H^+$-ATPase in the vesicles to regulate intravesicle pH. In response to acid–base changes $H^+$-ATPase in the intercalated cells is observed translocating from the cytoplasmic vesicles to the apical plasma membrane [63], where no AQP6 is found, indicating that AQP6 lacks intracellular trafficking and functions exclusively at the intracellular sites. The lack in intracellular trafficking of AQP6 is likely due to its intracellular retention [64]. A region within loop C of AQP6 that is responsible for severely hampering plasma membrane expression was recently identified. Serine substitution corroborated that amino acids present within AQP6 194–213 of AQP6 loop C contribute to its intracellular endoplasmic reticulum (ER) retention [64]. This signal may preclude proper plasma membrane trafficking and severely curtail expression of AQP6 in heterologous expression systems [64]. AQP6 appears impermeable to $H_2O$ [7, 65], but in the presence of $HgCl_2$ or at acidic pH (<5.5), the water and anion permeability of AQP6 in oocytes was rapidly increased [8]. Moreover, AQP6 also enables transport of urea, glycerol, and nitrate [66, 67]. The N-terminus of AQP6 seems critical for the trafficking of the protein to the intracellular sites and intracellular vesicles localization [68]. Calcium signals may be involved in internalization of AQP6 as calmodulin can bind AQP6 in a calcium-dependent manner at the N-terminus [69].

### 1.2.2 Superaquaporins

#### 1.2.2.1 AQP11

AQP11 has a conventional N-terminal Asn-Pro-Ala (NPA) signature motif and an unique amino acid sequence pattern that includes an Asn-Pro-Cys (NPC) motif, which appears essential for full expression of molecular function [3]. Recent evidence strongly suggests that Cys227 of AQP11 plays an important role in the formation of its quaternary structure and molecular function [70]. One reconstruction vesicle study has clearly shown that AQP11 is indeed a water channel that transports water as efficient as AQP1 [71, 72]. Although detailed subcellular localization of AQP11 remains clarified, it has been observed that AQP11 colocalizes with markers of the endoplasmic reticulum [73] and HA-tagged AQP11-transgenic mice [74]. Recent studies showed that AQP11 colocalized to the mitochondrial-associated membrane (MAM) which regulates essential signal transduction [75]. AQP11 facilitates specifically $H_2O_2$ transport to ER [75] and thus AQP11 constitutes an important regulator of renal and hepatic ER redox homeostasis and signaling. Deficiency or downregulation of AQP11 is associated with endoplasmic reticulum stress and apoptosis in the kidney proximal tubules [73] and in adipocytes [76].

#### 1.2.2.2 AQP12

AQP12 is more closely related to AQP11 than to other aquaporins. With regard to the signature motifs, the first NPA motif of AQP12 is substituted by an Asn-Pro-Thr (NPT) motif and the C-terminal NPA motif is conserved [5, 9]. AQP12 seems to be expressed specifically

in pancreatic acinar cells and retained in intracellular structures [5]. The osmotic water permeability measured by using vesicles from the AQP12 knockout and wild-type mouse pancreas showed only a small nonsignificant difference [77]. One study suggests that AQP12 may function as controlling the proper secretion of pancreatic fluid following rapid and intense stimulation [77].

### 1.2.3 AQP8-Type Aquaammoniaporins

#### 1.2.3.1 AQP8

So far, AQP8 is the only member in this family. It is a water channel first found in intracellular domains of the proximal tubule and the collecting duct cells [78]. Several studies showed that AQP8 transports water [7, 79] and ammonia [7, 17]. Although AQP8 was shown ultrastructurally localized at inner mitochondrial membrane (IMM) in the liver and functionally permeable to water [79], this was not supported by water permeability study in AQP8-deleted mouse liver cell IMM [80]. In the kidney, AQP8 facilitates transport of $NH_3$ released from glutamine and glutamate out of the IMM [81] for secretion into the tubule lumen, where the $NH_3$ buffers acid excreted by epithelial cells, particularly during metabolic acidosis [82]. AQP8 may also facilitate the diffusion of hydrogen peroxide across membranes of mitochondrial in situations when reactive oxygen species is generated, e.g., electron transport chain is highly reduced [75, 83, 84].

### 1.2.4 Aquaglyceroporins

#### 1.2.4.1 AQP3

AQP3 has a wide tissue distribution. It is permeable to water, glycerol, and urea. Recent studies revealed the pH gating of human AQP3 on both water and glycerol permeabilities using a human red blood cell model and in silico [85]. AQPs also differ in their capacity to transport various substances, such as urea, glycerol, $H_2O_2$, ions, and gas. Emerging evidence showed that AQP3 is regulated on short-term basis likely via cAMP-PKA pathway [86–88]. In the kidney, the increased basolateral diffusion of AQP3 induced by elevated intracellular cAMP likely altered AQP3 interactions with other proteins or lipids in the plasma membrane, which may be a physiological adaptation to the increased water flow mediated by apical AQP2 [86]. AQP3 was shown to transport $H_2O_2$ through the plasma membrane [84, 89, 90], which likely plays an important role in initiating intracellular signaling in cell migration [91], inflammation [92], and cancer progression [93, 94].

#### 1.2.4.2 AQP7

AQP7 facilitates transport of water, glycerol, urea, ammonia, arsenite, and $NH_3$ [7, 23, 95]. Hydropathy analysis predicts six putative transmembrane domains with the N- and C-terminal localized in the cytosol. Six prospective sites of AQP7 for PKA phosphorylation have been identified based on database analysis [96], but the direct regulation by PKA remains to be elucidated, whereas a potential PKC phosphorylation site is found at residue Thr-174 [23]. AQP7 is abundantly expressed in adipose tissue [97] and pancreatic β-cells [98, 99].

#### 1.2.4.3 AQP9

AQP9 is expressed at the sinusoidal plasma membrane of hepatocytes [100], where it serves as a conduit for the uptake of $NH_3$ and mediates the efflux of newly synthesized urea. AQP9 may also function as a glycerol channel to facilitate glycerol uptake in the liver. AQP9 is also permeable to water, carbamides, $CO_2$, and $NH_3$; moreover, AQP9 is suggested playing a crucial role in metalloid homeostasis by transporting antimonite and arsenite [2, 11]. Interestingly, it also transports much larger substrates such as lactate, purine, pyrimidine [2, 25], probably due to a larger pore size disclosed by a 3D structure analysis [101]. AQP9 facilitates the membrane transport of $H_2O_2$ in mammalian cells and regulates redox-regulated downstream cell signaling [102]. Human AQP9 has a potential N-glycosylation site at Asn142, a potential PKC phosphorylation sites at Ser11 and Ser222, a potential casein kinase II phosphorylation site at

Ser28 [25, 103]. However, little is known about short-term regulation of AQP9.

#### 1.2.4.4 AQP10

AQP10 is an aquaglyceroporin expressed only in the human gastrointestinal tract, but not in the mouse small intestine where it has been demonstrated to be a pseudogene [24, 104]. AQP10 is able to transport water, glycerol, and urea when expressed in *Xenopus* oocytes [24]. AQP10 is also a glycerol channel expressed in the plasma membrane of human adipocytes [105]. Silence of AQP10 in human differentiated adipocytes resulted in a 50% decrease of glycerol and osmotic water permeability, suggesting that AQP10, together with AQP7, is particularly important for the maintenance of normal or low glycerol contents inside the adipocyte, thus protecting humans from obesity [105]. Three potential glycosylated sites for AQP10 were predicted, at least one of them Asn133 in the extracellular loop of AQP10 was confirmed. Glycosylation at Asn133 may increase thermostability of AQP10 when challenged with low temperature, indicating a stabilizing effect of the N-linked glycan [106]. AQP10 mediated increased glycerol flux activated by acidification in human adipocytes [107], likely by a unique gating mechanism combining complex interaction networks between water molecules and protein residues at the loop interface [108].

## 1.3 Gene Structures of AQPs

Table 1.1 shows chromosome localization and numbers of exons of 13 human AQPs. The gene of AQP0 spans 3.6 kb, contains four exons, and is present in single copy in the haploid human genome. Transcription is initiated from a single site 26 nucleotides downstream from the TATA box [109].

Genomic Southern analysis indicated the existence of a single *AQP1* gene that was localized to human 7p14 by in situ hybridization [110–112]. AQP2 cDNA was cloned as the water channel of the apical membrane of the kidney collecting tubule in the rat [48], which shows 42% identity in amino acid sequence to AQP1. Human AQP2 encodes a deduced protein with 89.7–91% amino acid identity to the rat protein [112–115]. By in situ hybridization, *AQP2* gene was mapped to chromosome 12q13 [113, 115], very close to the site of major intrinsic protein (MIP).

Using a rat AQP3 probe, Ishibashi [116] screened a human kidney cDNA library and isolated a cDNA coding for human AQP3 protein. *AQP3* gene is located at 9p13 and appeared to exist as a single copy with six exons. The initiation site of transcription was identified to be located 64-bp upstream of the first ATG codon. The 5-prime flanking region contained a TATA box, 2 Sp1 sequences, and some consensus sequences including AP-2 sites [117].

Human AQP4 (initially called mercurial-insensitive water channel, MIWC) cDNA cloned from a fatal brain cDNA library showed that the longest open reading frame encoded 301 amino acids with 94% identity to rat AQP4. Analysis of MIWC genomic indicated two distinct but overlapping transcription units from which multiple MIWC mRNAs are transcribed. Later reports revealed that the *AQP4* gene is composed of four exons encoding 127, 55, 27, and 92 amino acids separated by introns of 0.8, 0.3, and 5.2 kb. Genomic Southern blot analysis indicated the presence of a single MIWC gene, localized on chromosome 18q [51, 118].

Human *AQP5* cDNA and gene was isolated and characterized from a human submaxillary gland library, which contained a 795-bp open reading frame encoding a 265-amino acid polypeptide with a transcription initiation site 518 bp upstream of the initiating methionine. *AQP5* gene was mapped to chromosome 12q13 [119].

Ma et al. isolated the cDNA by using degenerate PCR from a human kidney cDNA library that was related to AQP2, having four exons and was organized similarly to AQP0 and AQP2 and later was referred to this gene as *AQP6*, assigned to chromosome 12q13 [120, 121].

Human *AQP7* gene contains 10 exons. An Alu repetitive sequence and binding sites for several different transcription factors within the AQP7 promoter was determined, including a putative

peroxisome proliferator response element and a putative insulin response element, indicating potential involvement of AQP7 in energy metabolism [23, 122, 123].

Like the genes of non-water-selective aquaporins, the *AQP8* gene contains six exons; however, its exon–intron boundaries are different from the boundaries of those other aquaporin genes. *AQP8* gene was mapped to chromosome 16p12 [14, 124].

A partial AQP9 cDNA was isolated by using RT-PCR of leukocyte RNA with primers based on conserved regions of aquaporins [125]. AQP9 shares greater sequence identity with AQP3 and AQP7 than with other members of the family, suggesting that these three proteins belong to a subfamily.

The cDNA encoding AQP10 was isolated from jejunum cDNA library. Sequence analysis predicted that AQP10 is approximately 53% identical to AQP3 and AQP9, Northern blot analysis revealed expression of a 2.3-kb AQP10 transcript in jejunum but not liver [126].

Human *AQP11* gene contains three exons and spans 8 kb and was mapped to chromosome 11q14. Human *AQP12A* gene contains four exons and encodes a 1.5-kb transcript only in pancreas [73, 127].

Genetic variants of AQPs may result in disturbance of molecule selection and transport by AQPs; disruption of the formation of tetramers or arrays; and misfolding, faulty sorting of AQPs, or other dysfunction [81].

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