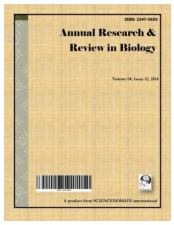

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AQP2 Genes and Nephrogenic Diabetes Insipidus: A Review

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Authors' contributions

This work was carried out in collaboration between both the authors. Author MS designed the review with the consent of author AP. Author MS managed the literature searches and produced the initial draft. Author AP gave final shape to the article. Both the authors read and approved the final manuscript

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ABSTRACT

Nephrogenic Diabetes insipidus (NDI) is an issue coming about because of lacking against diuretic hormone (ADH) activity and is described by the entry of extensive measures of exceptionally dilute urine. This problem must be separated from other polyuric states, for example, essential polydipsia, osmotic diuresis and diabetes mellitus. Diabetes insipidus is a condition when a person is passing urine with excess of water, this condition arise due to improper re-absorption of water during urine formation. Aquaporins (AQPs) play a important role in absorption of water. AQP2 is quite dominant than other isoforms.

This article provides nutshell information about Diabetes Insipidus and role of Aquaporin-2 gene in its physiology.

Keywords: AQP2; Nephrogenic diabetes insipidus; Vesopressin.

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1. INTRODUCTION

Aquaporins (AQPs) assume various part in human body, like urine formation, counteractive action from drying out in covering epithelia, outflow, molding of the physical framework, cell motility and metastasis, development of cell intersections and fat digestion system. AQPs are broadly disseminated among microscopic organisms, plants and creatures [1]. Out of AQP isoforms, AQP2 is predominant vasopressin-regulated water channel of the kidney gathering conduits and is vital for centralization of urinary [2]. Aquaporin2 protein shaped after the direction given by AQP2 gene. This protein shapes a channel that transports water particles crosswise over cell membranes.

Aquaporin-2 (AQP2) is the antidiuretic hormone regulating water channel protein and its sequence mutations area unit proverbial to cause the defect in urine concentrating ability leading to somebody's disease, Nephrogenic Diabetes Insipidus [3]. Transformations in the aquaporin-2 water channel quality are in charge of the autosomal latent and uncommon predominant manifestations of NDI [4]. For intracellular trafficking of AQP2, a few cell models have been created, which can be grouped into non-mammalian and mammalian frameworks. The primary gathering joins the heterologous representation of non-mammalian AQP2 in Xenopuslaevis oocytes and yeast. The second gathering embodies essential societies of vital cells secluded from inward medullary gathering pipe (IMCD) tubules [5], the deified mouse gathering conduit cell line (mpkCCD) and distinctive cell lines steadily transfect with cDNA encoding AQP2.

Nephrogenic Diabetes Insipidus is described by inability to concentrate the urine, which brings about polyuria (extreme pee creation) and polydipsia (over the top thirst). Influenced untreated new-born children normally have poor bolstering and inability to flourish, and fast onset of extreme lack of hydration with ailment, hot environment, or the withholding of water. Short stature and auxiliary dilatation of the ureters and bladder from the high urine volume is basic in untreated people [6]. The distinguishing proof of the distinctive atomic reasons for Congenital Nephrogenic Diabetes Insipidus, an issue portrayed by renal harshness to the antidiuretic impact of arginine vasopressin, has been of irreplaceable significance for comprehension the cell courses of action included in diuresis and antidiuresis [7].

2. NEPHROGENIC DIABETES INSIPIDUS (NDI)

Diabetes is a Greek word signifying "siphon"; it is become from the verb diabainein, which signifies "to remain with legs separated (as in urination) or to experience." Insipidus is a Latin word signifying "without taste." rather than diabetes mellitus, which includes the discharge of sweet urine, diabetes insipidus includes the death of urine that is vapid in view of its moderately low sodium content [8]. Diabetes insipidus is a neuro-endocrine issue that has the most noteworthy prevalence. This issue can be found in all nations around the globe.

Diabetes insipidus is because of either inadequate emission of AVP, additionally referred to as antidiuretic hormone (ADH), by the pituitary gland or renal tubular lethargy to ADH Nephrogenic DI. As a rule, NDI is X-linked and created by changes in the vasopressin type 2 receptor (V2R) gene. X-linked NDI is for the most part an uncommon malady in which the influenced male patients don't think their urine after organization of AVP. Since this structure is an uncommon, passive X-linked sickness, females are unrealistic to be influenced, however heterozygous females display variable degrees of polyuria and polydipsia on account of X inactivation [8].

3. TYPES OF NEPHROGENIC DIABETES INSIPIDUS

The identification, characterization, and mutational analysis of three different genes, namely the pre & pro-arginine-vasopressin-neurophysin II gene (*pre/ pro-AVP-NPII*), the arginine-vasopressin receptor 2 gene (*AVPR2*) and the vasopressin-sensitive water channel gene (aquaporin-2, *AQP2*), are responsible for three different hereditary forms of diabetes insipidus [9,10] which are described as below:

3.1 Autosomal Dominant Nephrogenic Diabetes Insipidus

Autosomal dominant Neurogenic DI, found in a couple of families, is brought about by transformations that influence the intracellular trafficking of the protein. Every single mutation recognized so far are situated inside the C-terminus of AQP2, which is a locale, vital for the regulation of intracellular trafficking [11]. It is crucial for patients to compensate the water loss by acceptable offer of fluid, joined with a low salt eating regimen, to diminish the commit water

discharge [11,12]. The consolidated treatment with thiazide and inhibitors of cyclooxygenases, for example, indomethacin, diminishes the urinary volume more adequately than thiazides alone. Be that as it may, this treatment may bring about extreme symptoms, including dysregulation of particle homeostasis and gastrointestinal unsettling influences [12]. Dominant mutations cause maintenance of AQP2 in the golgibody, late endosomes/ lysosomes or baso-lateralmembrane because of the development of heterotetramers of typical and unusual AQP2 [13].

3.2 X-linked Nephrogenic Diabetes Insipidus

X-linked type is caused by loss-of-function mutations within the AVPR2 [14]. This way could be a rare, recessive X-linkeddisease, females are unlikely to be affected, on the other heterozygous females exhibit variable degrees of nephrosis and thirst due to X inactivation. The explanation of untreated disease includes symptom, physiological state, slowness, and continual episodes of dehydration in early infancy. In X-linked NDI, loss of mutant alleles from the population happens due to the upper mortality of affected males compared with traditional males, whereas gain of mutant alleles happens by mutation. If affected males with a rare sex chromosome recessive illness don't reproduce and mutation rates are equal in mothers and fathers, then, at genetic equilibrium, one third of latest cases of affected males are owing to new mutations [15].

Eleven distinctive AVPR2 mutations were seen in more than one free NDI family, proposing that there are problem areas for mutations. Extra proof for intermittent mutation is the perception that the change happens on distinctive haplotypes characterized by markers in or near to the AVPR2 quality [16]. Seven of the 11 mutations (V88M, R113W, R137H, S167L, R181C, R202C, and R337X) were single nucleotide substitutions at a CpG dinucleotide. Methylated CpG dinucleotides are perceived problem areas for mutation [17,18]. Thirteen of 18 little cancellation or insertion changes (1 to 35 bp) included immediate or corresponding rehashes (2 to 9 bp) or strings of 4 to 6 guanines demonstrated in Fig. 1 and Fig. 2. This finding proposes that these deletions, in the same way as other that have been portrayed in different qualities, came about because of DNA strand slippage and mispairing amid replication [18,19,20,21].

3.3 Autosomal Recessive Nephrogenic Diabetes Insipidus

Autosomal recessive form is created by mutation in the gene encoding the aquaporin protein that forms the water channels in the distal nephron. Recessive missense mutations cause misfolding of AQP2 and maintenance in the Endoplasmic Reticulum [23]. The recessive AQP2 mutants are held in the Endoplasmic Reticulum, due of misfolding, and are debased here. Regularly, patients have two indistinguishable mutations in both AQP2 alleles. The concentrating capacity of the kidneys of these patients is emphatically lessened (<100 mos ml every Kg H2O) [24]. 39 changes have been accounted for of which 32 reason latent NDI (Table 1).

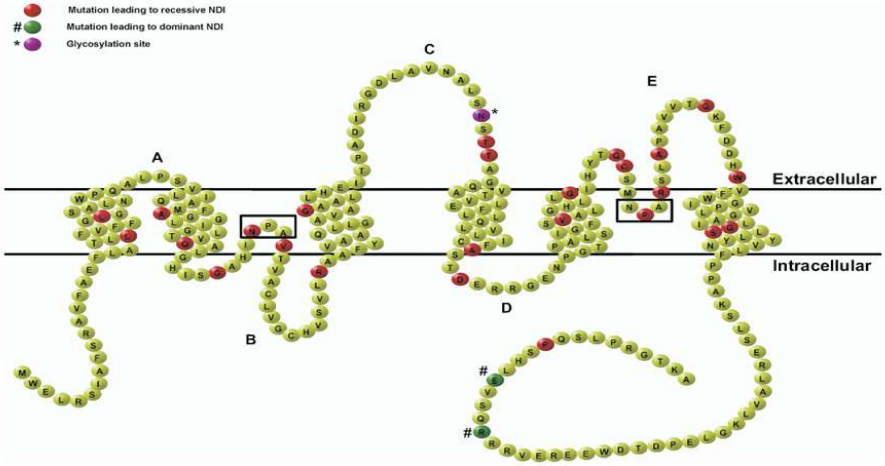

Fig. 1. Schematic representation of human AQP2 [22]

Functional analyses of various mutants uncovered that more than 50% of mutations distinguished in acquired infections are class II mutations. With class II transformations, the interpretation of the protein is finished, yet the strange protein neglects to be sent out from the endoplasmic reticulum. Correspondingly, representation in oocytes of missense AQP2 mutants in passive NDI uncovered that most were impeded in their fare from the ER. As opposed to these class II AQP2 mutation, depicted two mutations in recessive [25].

4. AQUAPORIN-2: THE GENE

The AQP2 is likewise usually named as ADH water channel protein or collecting ducts water channel protein or water channel aquaporin-2 [26]. AQP2 is found in the apical cell membranes of the kidney. The human AQP2 gene is situated in chromosome section 12q13 and has four exons and three introns [23,27,28]. It is expected to code for a polypeptide of 271 amino-acid proteins that is composed into two rehashes arranged at 180 to each other and that has six

Table 1. List of nephrogenic diabetes insipidus-causing mutations in AQP2 [22]

Nucleotides	Amino acids	Homozygous/ Heterozygous	Substitutions	Function-ality
64C>G	L22V	he3	R	P.(60%)
83T >C	L28P	Ho	R	
140C>T	A47V	Ho	R	P.(60%)
170A >C	Q57P	he5	R	NF
190G >A	G64R	Ho	R	P.(20%)
197–198 del CA	Frameshift	he9	R	
293A >G	N68S	Ho	R	NF
211G >A	V71M	Ho	R	NF
253C >T	R85*	Ho	R	
298G >A	G100R	Ho	R	
299C >T	G100* (stop codon)	Ho	R	
299G >T	G100V	he5	R	NF
369delC	Frameshift	Ho	R	
374C >T	T125M	ho,he8	R	P.(25%)
377C >T	T126M	Ho	R	P.(20%)
439G >A	A147T	Ho	R	Funct.
450T >A	D150E	he7,he10	R	NF
502G >A	V168M	he4,ho	R	P.(60%)
523G >A	G175R	he8,ho	R	NF
537G >A	G180S	Ho	R	
543C >G	C181W	he3	R	NF
553C >G	P185A	Ho	R	NF
559C >T	R187C	ho,he1	R	NF
643G >T	G215C	he10	R	
928G >A	A190T	he2	R	NF
587G >A	G196D	he7	R	NF
606G >T	W202C/splice	Ho	R	
c606+1G>A	Splice	he6,all.2	R	
646T >C	S216P	he1, he4	R	NF
652delC	Frameshift	He6,all.1	R	
721delG	Frameshift	He	D	F
727delG	Frameshift	He	D	F
761G >T	R254L	He	D	F
763–772del	Frameshift	He	D	F
772G >A	E258K	He	D	F
779–780insA	Frameshift	He	D	F
785C >T	P262L	he2	R	F
812–818del	Frameshift	He	D	F
1502G >A	Transition splice site	he9	R	

membrane spanning domains, with both terminal closures found intracellularly, and conserved Asn-Star Ala boxes Fig. 1. These highlights are normal for the major inborn protein family [28]. There is 48% amino acid sequence identify in the middle of AQP2 and the human channel–forming basic protein of 28 kDa (CHIP28 or aquaporin-1), a water channel in erythrocytes and in the kidney proximal and descending tubules [29]. Without vasopressin, AQP2 is restricted in vesicles in the sub apical locale of the cell. The channels are recovered by endocytosis on evacuation of vasopressin [30-32].

There are thirteen different AQPs are expressed in the kidneys, to be specific AQP0 to AQP12 have been acknowledged. AQPs are classified into three sub families: the aquaporin subfamily, aqua glyceroporin subfamily and super-aquaporin subfamily [33].

- The aquaporin subfamily is specified to water permeation and is made up of AQP0, AQP1, AQP2, AQP4, AQP5, AQP6, and AQP8.
- Aqua-glyceroporin serves in the transfer of water as well as small molecules such as glycerol and urea and is made up of AQP3, AQP7, AQP9, and AQP10.
- The super aquaporin subfamily is composed of AQP11 and AQP12, which show a low homology (>20%) with other AQPs and have poorly conserved NPA boxes. Out of 11 mammalian AQP isoforms, AQP2 is the predominant vasopressin-regulated water channel [34,35].

4.1 Role of AQP2 in Water Metabolism

Aquaporin-2 (AQP2) is the antidiuretic hormone regulated water channel protein. The antidiuretic hormone vasopressin (AVP) is a basic controller of water homeostasis by controlling the water development from lumen to the interstitium for water reabsorption and modifying the urinary water excretion. One of the first models to study the AVP-dependent water transport was the amphibian urinary bladder, which compares practically to the mammalian collecting duct [36]. Incitement of this epithelium with AVP builds the water penetrability and results in the presence of intracellular film particles on the apical cell surface. Freeze-fracture electron microscopic studies, first in the land and water proficient urinary bladder and later in disengaged renal gathering channels, demonstrated that these particles were limited in clathrin-covered pits and may contain AVP-controlled water [36]. Vasopressin is in charge of managing the body's maintenance of water by acting to build water assimilation in the collecting ducts of the kidney nephron [37].

Vasopressin has significant impacts by which it adds to expanded urine osmolarity (expanded focus) and diminished water discharge. Expanding the water permeability of distal tubule and collecting duct cells in the kidney, accordingly permitting water reabsorption and discharge of more focused urine, i.e., antidiuresis. This happens through insertion of water channels (Aquaporin-2) into the apical layer of distal tubule and gathering channel epithelial cells [38]. Aquaporins permit water to move down their osmotic slope and out of the nephron, expanding the measure of water reabsorbed from the filtrate (shaping pee) over into the circulation system [39]. AVP ties to V2 receptors, which are G protein-coupled receptors on the basolateral plasma membrane of the epithelial cells, couple to the heterotrimeric G-protein, which initiates adenylyl cyclases III and VI to change over ATP into cAMP, in addition to 2 inorganic phosphates (Fig. 2). The ascent in cAMP then triggers the insertion of aquaporin-2 water channels by exocytosis of intracellular vesicles, reusing endosomes [40].

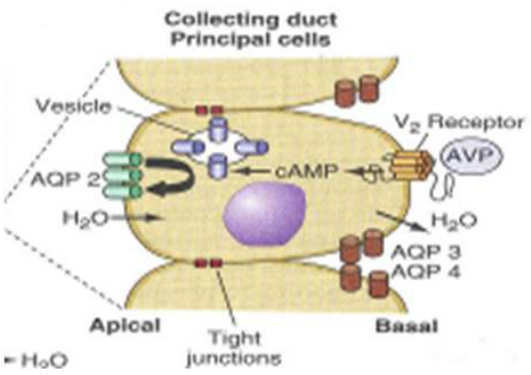

Fig. 2. Higher water permeability in the collecting duct and driven by an osmotic gradient, pro- urinary water then passes the membrane through AQP2 and leaves the cell on the basolateral side via AQP3 and AQP4 water channels, which are constitutively expressed on the basolateral side of these cells. When isotonicity is restored, reduced blood AVP levels results in AQP2 internalization, leaving the apical membrane water tight again [38]

Vasopressin likewise expands the concentration of calcium in the collecting duct cells, by round about discharge from intracellular stores. Vasopressin, acting through cAMP, likewise expands interpretation of the aquaporin-2 gene, in this way expanding the aggregate number of aquaporin-2 gene in collecting duct cells. Cyclic-AMP activates protein kinase A (PKA) by tying to its administrative subunits and permitting them to withdraw from the catalytic subunits. Separation uncovered the reactant site in the chemical, permitting it to add phosphate gatherings to proteins (counting the aquaporin-2 protein), which adjusts their roles [39].

5. RELATIONSHIP BETWEEN NEPHRO-GENIC DIABETES INSIPIDUS & AQP-2

Aquaporin-2 (AQP2) is the vasopressin regulated water channel protein and its gene mutation are known to bring about the imperfection in urine concentrating capacity, causing disease, Nephrogenic Diabetes Insipidus [3]. Mutations in the aquaporin-2 (AQP2) water channel quality are in charge of the Nephrogenic Diabetes Insipidus. Aquaporin is controlled in two courses by the peptide hormone vasopressin: Short-term regulation (minutes) through trafficking of AQP2 vesicles to the apical area where they meld with the apical plasma film and Long-term regulation (days) through an increment in AQP2 quality declaration. Changes in this channel are connected with Nephrogenic Diabetes Insipidus, which can be either autosomal dominant or recessive.

In the basal state, AQP2 is put away in intracellular vesicular compartment however upon ADH incitement, it quickly moves to the apical membrane where it goes about as a water channel for the concentration of urine. Vasopressin acts at V2 receptors in the basolateral plasma layer (BLM) of Compact disc important cells, Initiation of adenyl cycles quickens the creation of cyclic AMP from ATP; the cyclic AMP then ties to the regulatory subunit of protein kinase A (PKA) which initiates the reactant subunit of PKA. PKA then phosphorylates AQP2 in the intracellular vesicles and perhaps other cytosolic or layer proteins. Microtubular engine protein and vesicles focusing on receptors (VAMP-2, Syntaxin-4, and NSF) may take an interest in the specificity of AQP2 focusing to the apical film to build water permeability [41].

Numerous type of mutations in the AVPR2 and AQP2 genes have been accounted for to bring about congenital Nephrogenic Diabetes Insipidus, a disease in which the kidney is not able to gather urine in answer of AVP. Mutations in the AVPR2 gene result in NDI that is acquired as X-linked recessive characteristic, while mutations in the AQP2 gene reason NDI that is acquired as either an autosomal recessive or a dominant attribute [42,43]. Statement examines in oocytes demonstrated that an AQP2 mutant in dominant NDI, AQP2-E258K, was an utilitarian water channel yet was held in the area of the Golgi complex. Misfolding of mambrane proteins assumes an essential part in numerous human diseases, for example, retinitis pigmentosa, inherited deafness and Diabetes insipidus. Single-molecule power spectroscopy is a novel procedure, which measures the power important to haul a protein out of a membrane [5,44]. High-throughput power spectroscopy examinations create several power bends including spurious ones and great bends, which compare to distinctive unfolding pathways [5]. Most AQP2 missense mutants in recessive NDI are held in the endoplasmic reticulum (ER), yet AQP2-T125M and AQP2- G175R were accounted for to be non-useful directs whole in their steering to the plasma membrane [25].

6. CONCLUSION

Aquaporine 2 (AQP2) & Arginin Vasopressin Receptor 2 (AVPR2) are the genes which are responsible as an essential part in the pathogenesis of nephrogenic diabetes insipidus. AQP2 is the quality in which changes are known to bring about autosomal latent and autosomal prevailing nephrogenic diabetes insipidus. A mutation within the Aquporin, a pair of cistron impedes the traditional practicality of the urinary organ water channel, and thus urinary organ became unable to soak up water.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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