Familial Neurohypophyseal Diabetes Insipidus—An Update

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Although molecular research has contributed significantly to our knowledge of familial neurohypophyseal diabetes insipidus (FNDI) for more than a decade, the genetic background and the pathogenesis still is not understood fully. Here we provide a review of the genetic basis of FNDI, present recent progress in the understanding of the molecular mechanisms underlying its development, and survey diagnostic and treatment aspects. FNDI is, in 87 of 89 kindreds known, caused by mutations in the *arginine vasopressin* (AVP) gene, the pattern of which seems to be largely revealed as only few novel mutations have been identified in recent years. The mutation pattern, together with evidence from clinical, cellular, and animal studies, points toward a pathogenic cascade of events, initiated by protein misfolding, involving intracellular protein accumulation, and ending with degeneration of the AVP producing magnocellular neurons. Molecular research has also provided an important tool in the occasionally difficult differential diagnosis of DI and the opportunity to perform presymptomatic diagnosis. Although FNDI is treated readily with exogenous administration of deamino-D-arginine vasopressin (dDAVP), other treatment options such as gene therapy and enhancement of the endoplasmic reticulum protein quality control could become future treatment modalities.
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Familial neurohypophyseal diabetes insipidus (FNDI) is a rare inherited disease characterized by severe polyuria and polydipsia. It is caused by postnatal development of a deficient neurosecretion of the antidiuretic hormone, arginine vasopressin (AVP), normally produced by the magnocellular neurons. These specialized neurons are located in the supraoptic and paraventricular nuclei of the hypothalamus and form the neurohypophysis by their long extensions projecting down through the diaphragma sellae. Normal AVP biosynthesis is presumed to involve an ordered line of cellular processes starting with a tightly regulated and cell-specific transcription of the AVP gene in the magnocellular neurons,[1,2] proceeding with heteronuclear RNA processing, and

subcellular messenger RNA transportation.[3] Subsequently, the nascent protein is translocated cotranslationally into the lumen of the endoplasmic reticulum (ER), the signal peptide is cleaved followed by AVP prohormone folding,[4-6] disulphide bridge formation,[7] glycosylation,[8] and dimerization.[9] The final steps of the AVP biosynthesis are believed to involve processing in the Golgi apparatus, aggregation and packaging of the AVP prohormone into secretory vesicles in the trans-Golgi network,[10] enzymatic processing during axonal transportation,[11,12] and secretion of active AVP hormone into the circulation on an appropriate stimulus (ie, hyperosmolarity and hypovolemia). Once secreted and transported by the circulation to its target in the renal collecting ducts, the first step in the antidiuretic action of AVP is binding to the V_2 receptor (encoded by the AVPR2 gene), located on the basolateral membrane of the collecting duct epithelial cells. This initiates a signal-transduction cascade leading to the final step of the antidiuretic function of AVP, the exocytic insertion of a specific water channel, aquaporin 2 (encoded by the AQP2 gene), into the luminal membrane resulting in increased water permeability. AVP also increases the water reabsorption capacity of the kidney by regulating the urea

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Table 1 Hereditary Forms of Diabetes Insipidus

Disease	Inheritance	Chromosomal Location	Gene	Mutations	Kindreds	References
FNDI	Autosomal dominant or recessive*	20p13	AVP	56	87	See Table 2
	Autosomal dominant	20p13†	Unknown†	–	1	56
	X-linked recessive	Xq28‡	Unknown‡	–	1	19,20
NDI	X-linked recessive	Xq28	AVPR2	183	287	14
	Autosomal dominant or recessive	12q12–q13	AQP2	35	40	14

*The clinical characteristics of the autosomal-recessive form differ significantly from those of adFNDI.
†Linkage to a 7-cM interval on chromosome 20p13. Mutations searched in the coding region, the promoter, the introns, and enhancers regions of the AVP gene, as well as in the coding region of the nearby UBCE7IP5 gene and the AQP2 gene.
‡Linkage to the same chromosomal location as the AVPR2 gene (Xq28). Mutations searched in the coding region of the AVP and AVPR2 gene.

transporter, UT1, in the inner medullary collecting duct and the permeability of principal collecting duct cells to sodium.[13] Thus, in the absence of AVP stimulation, the collecting duct epithelia show very low permeability to sodium, urea, and water, permitting the excretion of large volumes of hypotonic urine.

Despite its rather benign nature, FNDI has been the subject of intense research. This partly originates from the remarkable severity of the polyuria and polydipsia in affected patients but also is assignable to the potential value of FNDI as a model for studies of neuroendocrinological diseases. This has generated a substantial knowledge of the clinical and pathophysiological characteristics of FNDI, the biochemical and structural characteristics of the individual hormone precursor domains, and the molecular mechanisms involved in the biosynthetic pathway of AVP. Since the genetic basis of FNDI has been established almost completely and new possible aspects of its pathogenesis have been suggested, it seems that FNDI also provides a suitable model for studies of dominant-negative mutations, the effects of such mutations on the folding of hormone precursors in the ER, and the role of ER protein quality control in the cellular handling of misfolded protein. During recent years, evidence has accumulated indicating that FNDI is caused by cytotoxic accumulation of misfolded mutant protein in the AVP-producing neuron, suggesting that FNDI may share common pathogenic mechanisms with neurodegenerative diseases such as Huntington's, Alzheimer's, Parkinson's, and Creutzfeldt-Jakob disease.

This article aims to review the genetic basis of FNDI, present recent progress in the understanding of the molecular mechanisms underlying its development, and provide insight in the diagnostic and treatment aspects of the disease.

Inheritance

Familial DI exists in 2 hereditary forms, FNDI and congenital nephrogenic DI (NDI or CNDI), which together account for less than 10% of all DI cases seen in clinical practice.[14] NDI, which is characterized by renal insensitivity to the antidiuretic effect of AVP, is either X-linked and caused by mutations in the gene encoding the V_2 receptor (the AVPR2 gene; Entrez GeneID 554) or autosomal-dominant (or recessive) and caused by mutations in the gene encoding the renal aquaporin 2 water channel (the AQP2 gene; Entrez GeneID 359) (Table 1). Until now, FNDI has been reported in at least 89 kindreds worldwide and in 87 of these, the disease has been linked to mutations in the gene encoding the AVP prohormone (the AVP gene; Entrez GeneID 551) (Table 1). With only a few well-documented exceptions, FNDI is transmitted by autosomal-dominant inheritance (adFNDI) and appears to be largely, if not completely, penetrant.[15] Dominant inheritance is indeed an unexpected feature of a defect in the synthesis of AVP because other isolated deficiencies of pituitary hormones (eg, sexual ateliosis, or isolated growth hormone deficiency) are recessive. In 1 kindred, the transmission of DI is consistent with autosomal-recessive inheritance,[16] however, the clinical characteristics of this variant form differ significantly from those of adFNDI because, for this reason among others, affected individuals do not have abnormally low levels of plasma AVP during fluid deprivation tests. Since the report in 1945 by Forssman,[17] it has been registered in most genetic databases [eg, OMIM (Online Mendelian Inheritance in Man), entry number 304900] that an X-linked recessive form of FNDI existed (xrFNDI). The discovery of this novel form of the disease was based on genealogic and clinical analyses of a huge 9-generation kindred comprising approximately 5,500 family members.[17] Affected members of the kindred showed clear signs of DI with polyuria and polydipsia since birth. When given subcutaneous injections of pituitary extract (3-10 IU), the patients were able to concentrate their urine, thus leading to the diagnosis of FNDI. However, a recent re-investigation including genetic and clinical studies on descendants of the original patients revealed a partial NDI phenotype with a shift to the right of the relationship between concurrent values of plasma AVP and urine osmolality.[18] Affected family members had a normal AVP gene but consistent with the clinical phenotype carried a mutation in the AVPR2 gene (g.310C>T, p.R104C). On the other hand, in another rare report of
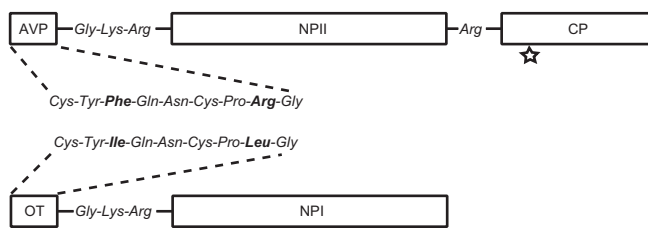
Figure 1 Structural organization of the AVP and oxytocin prohormones. White bars indicate the individual domains. CP, glycosylated protein, copeptin, unique to the AVP prohormone; NPI, oxytocin-associated neurophysin I; NPII, AVP-associated neurophysin II; OT, oxytocin. The hormone moieties also are annotated by their respective amino acid sequence. Both are followed by an amidation and cleavage signal sequence, glycine-lysine-arginine. Neurophysin II is followed by a monobasic cleavage site, an arginine residue. The N-glycosylation site of copeptin is indicated by a star.

xrFNDI, the clinical phenotype in 1 kindred clearly is consistent with that of neurohypophyseal DI and although the disease seems to be linked to the same chromosomal location as the AVPR2 gene associated with NDI, namely Xq28, mutations were neither found in this gene nor in the AVP gene.[19,20]

The AVP Gene

The human AVP gene is located distally at the short arm of chromosome 20 (20p13).[21-23] It covers 2.5 kb and comprises 3 exons encoding, respectively, (1) a signal peptide of 19 amino acid residues, the AVP nonapeptide, a glycine-lysine-arginine linker, and the N-terminal region of neurophysin II (9 amino acid residues); (2) the central, highly conserved region of neurophysin II (67 amino acid residues); and (3) the C-terminal region of neurophysin II (17 amino acid residues), an arginine linker, and a C-terminal glycopeptide, copeptin (39 amino acid residues)[24,25] (Fig 1). The oxytocin gene, encoding oxytocin, another neurohypophyseal hormone closely related to AVP (Fig 1), is linked to the AVP gene[25] with an intergenic region of only 11 kb.[26] The genes have similar gene structures; however, their organization is unusual in that they are transcribed from opposite DNA strands, implying a tail-to-tail orientation. Phylogenetic studies of the primary sequence of the AVP and oxytocin family of related hormones, the structural organizations of their precursors, and their gene structures[25,27-31] have led to the hypothesis that the AVP and oxytocin gene families evolved separately from a common ancestral gene via gene duplication and inversion.[32] In the lowest vertebrates, the cyclostomes, only the vasotocin gene is present, suggesting that the duplication might have occurred after the evolutionary process of the Agnatha.[33-35]

AVP Gene Expression

The AVP and oxytocin genes are expressed in different populations of the hypothalamic magnocellular neurons, defining their identity either as vasopressinergic (AVP-producing) or as oxytocinergic (oxytocin-producing). However, it seems that virtually all the cells also express very low but detectable levels of the other messenger RNA,[36,37] and in lactating rats nearly equivalent amounts of AVP and oxytocin messenger RNA are detected in individual neurons in as many as 15% of the magnocellular neuron population. A number of studies describing the expression of AVP transgenes derived from racine, murine, and bovine sources in both rat and mouse transgenic hosts as well as in organotypic culture models support the hypothesis that cell-specific enhancers of the AVP gene are present in the intergenic region downstream of the AVP gene.[2,38] Recently, DNA sequences in a 178-bp region immediately downstream of exon 3 of the AVP gene were shown to be necessary for cell-specific expression of both the AVP and oxytocin gene in organotypic slice-explant cultures of rat hypothalamus.[39] Furthermore, a 430-bp region immediately downstream of exon 3 of the oxytocin gene seemed to contain a positive regulatory element for cell-specific expression of the oxytocin gene. Within these 2 regions, 4 common DNA motifs were identified as candidate enhancer elements. However, their significance still remains to be tested in *in vivo* models and the apparent physiological regulation of the genes still remains elusive.

The AVP Prohormone

The AVP prohormone encoded by the AVP gene comprises a hormone moiety of only 9 amino acid residues (CYFQNCPRG), which is identical to oxytocin with the exception of the presence of isoleucine in position 3 and leucine in position 8 (Fig 1). Both hormones have an internal disulphide bridge between C1 and C6 that divides the fully processed hormone into a cyclic N-terminal domain and a 3–amino acid residue C-terminal tail. The neurophysin II domain comprising 93 amino acid residues is the largest domain of the AVP prohormone (Fig 1). It is re-
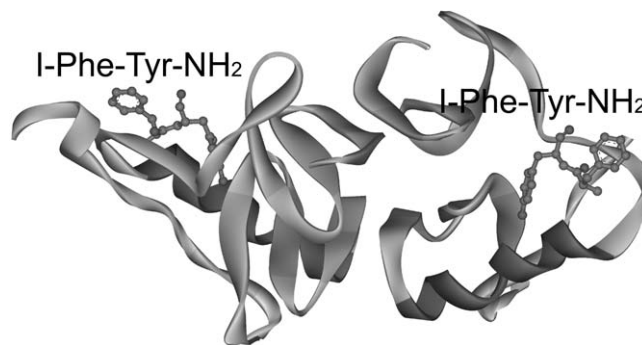

Figure 2 Three-dimensional structural model of a neurophysin II dimer as deduced from the crystal structure of a bovine neurophysin II dipeptide complex[40] using WebLab ViewerLite, version 3.20 (Molecular Simulations Inc., San Diego, CA). Individual atoms of the *para*-iodo-L-phenylalanyltyrosine amide dipeptide (I-Phe-Tyr-NH$_2$) are displayed as balls and sticks. Neurophysin II is displayed as a solid ribbon, colored by secondary structure (α-helices, black and β-strands, gray).

markably well conserved among all vertebrate and invertebrate species, especially with regard to the central region (amino acid residues 10-76) encoded by exon 2.[5] Neurophysin II is divided clearly into 2 domains comprising 2 internal segments with 58% homology to each other (residues 12-31 and 60-79). The 2 related domains, each probably containing 3 disulphide bridges,[7] are linked by the only α-helix predicted to be present in the neurophysin II 3-dimensional structure (Fig 2)[40] and probably by an interdomain disulphide bridge (C10-C54).

The C-terminal domain of the AVP prohormone, copeptin, comprises a sequence of 39 amino acid residues and contains a putative N-glycosylation site (Fig 1). It seems that this C-terminal domain, which is absent in the oxytocin prohormone (Fig 1), evolved in mammals into a well-conserved glycosylated domain that undergoes proteolytic processing. Its physiological function remains unknown, however, it seems possible that glycosylated copeptin plays an important role by assisting refolding of misfolded AVP prohormone monomers through its interaction with the calnexin-calreticulin system in the ER.[41] Its absence in the oxytocin prohormone can be explained by a higher conformational stability of the oxytocin-neurophysin I precursor.

AVP Biosynthesis

The AVP preprohormone encoded by the AVP gene is translocated cotranslationally into the ER lumen owing to the presence of the signal peptide. In the ER lumen, the unique oxidizing environment allows the formation of disulphide bridges and the presence of enzymes and precursors necessary for biosynthesis and transfer of N-linked oligosaccharides enables its glycosylation. Furthermore, the AVP prohormone encounters other components of the so-called ER protein quality control comprising various chaperones and folding enzymes (eg, Grp78, Grp94, calnexin, and calreticulin). These chaperones promote folding of the newly synthesized protein by facilitating folding, preventing untimely intrachain and interchain interactions, and by preventing intracellular trafficking of misfolded and/or unassembled proteins.[42,43] ER chaperones also are involved in the targeting of misfolded proteins to degradation by the cytosolic proteasome.[44]

On exit from the ER to the Golgi apparatus, the AVP prohormone is sorted into the regulated secretory pathway probably by selective aggregation and packaging into dense cores in the trans-Golgi network.[45] It is likely that the aggregation occurs spontaneously owing to the physiochemical properties of the AVP prohormone, local high concentrations of the prohormone, the local pH (pH 6.3), and the local Ca^{2+} concentration (10 mmol/L).[46,47] Recent evidence obtained by heterologous expression of truncated AVP prohormone associated with the enhanced green fluorescent protein in cell lines suggests that a sorting signal resides within amino acid residue 10 to 27 of neurophysin II[10,48] and other studies in cells also have shown that the hormone domain is essential for proper trafficking of the AVP prohormone.[49]

Processing of AVP prohormone into biologically active AVP can be initiated in the ER and/or Golgi complex but is accomplished primarily in the large dense-core secretory vesicles.[50] Furin,[51] which appears to be the main endopeptidase responsible for the proteolytic cleavage events that occur in the ER and/or Golgi complex, is capable of cleaving copeptin from neurophysin II as adjudged from its preferential cleavage motifs. The remaining key prohormone processing enzymes are contained in the secretory granules[12] and they exert their function, probably within the secretory granule, during axonal transport.[52] The processing enzymes act successively and include the following: (1) a lysine-arginine calcium-dependent endopeptidase (prohormone convertase) that is capable of cleaving at the dibasic signal sequence in the prohormone; (2) a carboxypeptidase B-like enzyme that is capable of removing the C-terminal basic amino acid residues that remain after endopeptidase cleavage; (3) a peptidyl-glycine monooxygenase; and (4) an amidating peptidyl-hydroxyglycine lyase, which together are capable of converting the remaining C-terminal glycine residue into a C-terminal α-amide. The resulting biologically active AVP hormone probably retains reversible noncovalent interactions with neurophysin II while contained within the secretory vesicles, but once secreted into the circulation, from the axon termini in the posterior pituitary, they dissociate.[53]

The Genetic Basis of FNDI—An Update

Until now, FNDI has been associated with 56 different mutations in the AVP gene (Table 2 and Fig 3). All but one of these mutations (g.1919+1delG) are located in the coding region of the AVP gene. In concordance with the inheritance pattern of the disease, they affect only 1 allele in the autosomal-dominant form and 2 alleles in the recessive.[16] Almost all the mutations identified are single base substitutions (49 of 56) and except for 2 dinucleotide substitutions (g.1890_1891GC>CT and g.2106_2107CG>GT), the remaining mutations are deletions of either 1 (g.227delG and g.1919+1delG) or 3 nucleotides (g.288_290delTTC, 1774_1776delCGC, and g.1827_29delAGG). With regard to their deduced consequence at the protein level, they are very heterogeneous in type and location (Table 2 and Fig 3). This is evident in that they either predict amino acid substitutions, deletions, or truncations, the latter by introducing premature stop codons, and in that they are located either in the signal peptide, the AVP moiety, or the neurophysin II domain of the AVP preprohormone, encoded by the gene. No mutations predicting changes in the linker regions connecting the different AVP prohormone domains or in the C-terminal copeptin domain have been identified so far. Based on reverse-transcription polymerase chain reaction analysis of RNA isolated from peripheral lymphocytes, the intronic g.1919+1delG mutation is predicted to cause retention of intron 2 during splicing.[54] This causes frameshift from codon

Table 2 Mutations in the AVP Gene Causing FNDI

Nucleotide Change*	Exon	Amino Acid Change†	Peptide‡	Alleles	Population§	References
g.225A > G	1	p.M1_T4del‖	SP-19-16	1	Be	15
g.227delG	1	p.M1_T4del‖	SP-19-16	1	Sw	113
g.227G > A	1	p.M1_T4del‖	SP-19-16	1	Cz	15
g.274C > T	1	p.S17F	SP-3	1	Da	55
g.279G > A	1	p.A19T	SP-1	9	Am, Ja, Da, Sp, Br, Ge	15, 55, 81, 136–140
g.280C > T	1	p.A19V	SP-1	6	Am, Le, Ge, Ja, Nz	15, 55, 114, 115, 141
g.285T > C	1	p.Y21H	AVP2	1	Tu	106
g.288_290delTTC	1	p.F22del	AVP3	1	Am	107
g.301C > T¶	1	p.P26L	AVP7	1	Pa	16
g.1730G > C	2	p.G45R	NP14	1	Is	55
g.1740G > T	2	p.G48V	NP17	1	Du	142
g.1748C > T	2	p.R51C	NP20	1	Au	55
g.1751T > C	2	p.C52R	NP21	1	Am	143
g.1757G > C	2	p.G54R	NP23	3	Ge, Am	15, 114, 127
g.1757G > A	2	p.G54R	NP23	1	Sp	144
g.1758G > T	2	p.G54V	NP23	1	It	145
g.1761C > T	2	p.P55L	NP24	2	Am	138, 146
g.1770G > T	2	p.C58F	NP27	1	Ge	147
g.1772T > C	2	p.C59R	NP28	1	Am	19
g.1773G>A	2	p.C59Y	NP28	1	Cy	148
g.1774_1776delCGC	2	p.C59_A60delinsW	NP28–29	1	Sw	149
g.1797T > C#	2	p.V67A	NP36	1	Am	15
g.1827_1829delAGG	2	p.E78del	NP47	6	Ja, Am, Au, Ch	15, 55, 56, 150
g.1829G > A	2	p.E78K	NP47	1	Ja	151
g.1830A > G	2	p.E78G	NP47	2	En, No	15, 55
g.1839T > C	2	p.L81P	NP50	1	Da	55
g.1857C > T	2	p.S87F	NP56	1	Am	152
g.1859G > A	2	p.G88S	NP57	3	Ja, Am, Ar	55, 138, 153
g.1859G > C	2	p.G88R	NP57	1	Am	55
g.1872G > C	2	p.C92S	NP61	2	Am, Ge	55, 154
g.1872G > A	2	p.C92Y	NP61	2	Am	127, 152
g.1873C > A	2	p.C92X	NP61	2	No, Cz	15, 55
g.1874G > T	2	p.G93W	NP62	1	Ja	155
g.1883G > T	2	p.G96C	NP65	2	Am, Au	15, 55
g.1884G > T	2	p.G96V	NP65	3	Ja, Ge	85, 156, 157
g.1884G > A	2	p.G96D	NP65	1	Se	15
g.1886C > T	2	p.R97C	NP66	1	Am	158
g.1887G > C	2	p.R97P	NP66	1	Ge	159
g.1889T > G	2	p.C98G	NP67	1	Am	160
g.1889T > A	2	p.C98S	NP67	1	It	161
g.1890_1891GC > CT	2	p.C98S	NP67	2	En	162
g.1891C > A	2	p.C98X	NP67	1	Ja	155
g.1892G > C	2	p.A99P	NP68	1	Br	112
g.1907T > G	2	p.C104G	NP73	1	Cz	15
g.1908G > T	2	p.C104F	NP73	1	Am	163
g.1910T > C	2	p.C105R	NP74**	1	Am	127
g.1911G > A	2	p.C105Y	NP74	1	Ja	164
g.1919+1delG	Intron 2	p.E108fs††	NP77	1	Ko	54
g.2094C > A	3	p.C110X	NP79	1	Du	55
g.2101G > T	3	p.E113X	NP82	1	Sp	144
g.2106_2107CG > GT	3	p.E115X‡‡	NP84#	1	Fr	55
g.2107G > T	3	p.E115X	NP84**	1	Ge	154
g.2110T > G	3	p.C116G	NP85	1	Du	165
g.2110T > C	3	p.C116R	NP85	1	Du	57
g.2112C > G	3	p.C116W	NP85	1	It	15
g.2116G > T	3	p.E118X	NP87	1	Am	55

*Numbers refer to the gDNA sequence of the AVP gene, GenBank accession number M11166.1. Numbering from original reports changed according to recommendations[166] and to http://www.hgvs.org/mutnomen/.

†Numbers refer to codons (initiator ATG = codon 1). Numbering from original reports changed according to recommendations[166] and to http://www.hgvs.org/mutnomen/.

‡Numbers refer to the position in the individual peptides originating from the AVP pre-prohormone. NP, neurophysin II; SP, signal peptide.

§Am, American; Ar, Argentine; Au, Austrian; Be, Belgian; Br, Brazilian; Ch, Chinese; Cy, Cypriot; Cz, Czech; Da, Danish; Du, Dutch; En, English; Fr, French; Ge, German; Is, Israeli; It, Italian; Ja, Japanese; Ko, Korean; Le, Lebanese; No, Norwegian; Nz, New Zealand; Pa, Palestinian; Sp, Spanish; Se, Swedish; Sw, Swiss; Tu, Turkish.

‖Based on expression in COS7 cells and in vitro translation of the g.227delG mutation,[88] mutations affecting the initiator ATG are predicted to result in translation initiation at an alternative downstream ATG (codon 5). This will cause a deletion of the first 4 amino acid residues.

¶Mutation associated with autosomal-recessive inheritance of FNDI.

#Mutation associated with inheritance suggesting incomplete penetrance.

**NP74 and NP84 were published originally as, respectively, NP73[127] and NP83.[154]

††Based on reverse-transcription polymerase chain reaction analysis of RNA isolated from peripheral lymphocytes, the mutation is predicted to cause retention of intron 2 during splicing.[54] This will cause frameshift from codon 108.
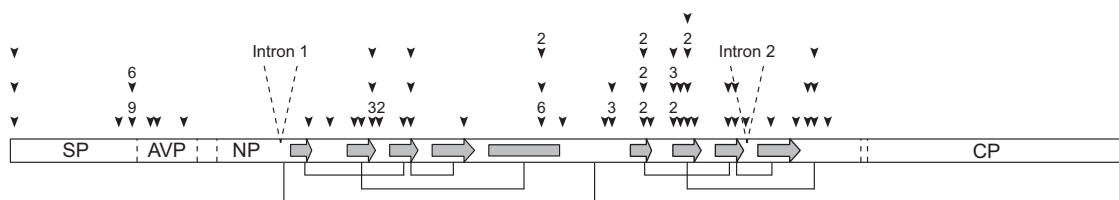
‡‡Originally published as p.P114X and NP83.[55]

Figure 3 Schematic structure of the AVP gene. The location in the AVP gene of all known mutations associated with FNDI is shown by arrowheads. Each arrowhead represents a single unique mutation at the nucleotide level. Numbers above the arrows indicate the number of different alleles identified to carry the same mutation (ie, the number of apparently unrelated kindreds identified to carry the same mutation). No number above an arrow indicates that only 1 allele has been identified. The individual domains of the AVP preprohormone encoded by the AVP gene and the location of the 2 introns are indicated. Vertical dashed bars indicate the cleavage sites for the enzymes responsible for AVP preprohormone processing. The secondary structures identified in the resulting neurophysin II domain are displayed on top of the schematic structure of the AVP gene; shaded block arrows indicate the 8 β-strands and the shaded box indicates the α-helix.[40] The brackets show the 7 disulfide bridges presumed to be present in the neurophysin II domain. CP, copeptin; NP, neurophysin II; SP, signal peptide.

108 and introduction of a premature stop codon in exon 3 (according to the recent AVP genomic sequence, GenBank accession number AL160414.18).

There is no real prevalent adFNDI mutation in the AVP gene but 1 mutation is nonetheless more frequent than all others, namely the g.279G>A substitution (predicting an A19T amino acid substitution) (Table 2 and Fig 3), which has been identified in 9 kindreds with no known relationship to each other. Another mutation affecting the same codon, namely the g.280C>T substitution (predicting a p.A19V amino acid substitution) together with the g.1827_1829delAGG deletion (predicting a p.E78del amino acid deletion), are the 2 second most frequent mutations (Table 2 and Fig 3), each identified in 6 apparently unrelated kindreds. No polymorphisms have been identified in the coding region of the AVP gene among 296 normal alleles from healthy controls, patients with idiopathic neurohypophyseal DI, and healthy relatives in kindreds with a family history of FNDI.[15] However, this does not fully exclude their existence.

In a recent study, we have searched for mutations in the AVP gene in 15 unrelated kindreds in which DI appeared to be segregating.[15] The ratio of recurrent mutations identified was 9 of 15 (60%), which is significantly higher than the 4 of 17 (23.5%) identified in 1 of our previous studies.[55] This could reflect the fact that the mutation spectrum in FNDI now almost is revealed.

The genetic basis of FNDI remains unknown in 2 reported kindreds (Table 1).[19,20,56] In the first one reported, FNDI appears to be transmitted in a xrFNDI mode and preliminary linkage analysis suggests that the disease gene is located at the end of the long arm of the X-chromosome (Xq28).[19,20] In the second one, a Chinese family with adFNDI, it has been reported that the disease showed linkage to a 7-cM interval on chromosome 20p13 containing the AVP gene; however, unexpectedly no mutations could be detected in the coding region, the promoter, or the introns of the AVP gene (Table 1). Moreover, no mutations were found in the downstream regions reported to comprise critical enhancer elements for the cell-specific

expression of the AVP gene in animal models (see earlier)[39] and, furthermore, no mutations were identified in the coding region of the nearby UBCE7IP5 gene encoding an ubiquitin protein ligase that could be involved in the degradation of the AVP prohormone. To investigate whether the disease in this family actually represented an atypical nephrogenic DI, the coding region of the AQP2 gene (located on chromosome 12) was investigated, however, no mutations were found. Thus, the exact genetic basis of the disease in this family remains unknown. Ye et al[56] suggest that other genes or enhancers located between the D20S199 and D20S849 markers on chromosome 20 are involved in the development of adFNDI in the family. However, it is not possible to rule out the presence of a mutation in the AVP gene completely, although not recognized by the applied methods, as a mutation by itself or a polymorphism at one of the primer sites in the introns that segregates with the mutation could impair proper polymerase chain reaction amplification of the mutant allele, thereby producing a homozygous wild-type pattern. A homozygous mutant pattern initially was observed in heterozygous adFNDI patients in a Dutch kindred as a result of such a methodologic problem.[57]

Pathogenesis of FNDI

Autosomal-Dominant FNDI

The pathogenesis of adFNDI has been studied intensively in different model systems during the past few years. Several hypotheses explaining the molecular mechanisms underlying the development of the disease have been proposed,[58-61] all of which are based on the unique clinical, biochemical, and pathologic characteristics of the disease. To go over the main points, adFNDI is associated with mutations in 1 allele of the AVP gene and is caused by postnatal development of deficient AVP secretion proposed to be owing to selective degeneration of the magnocellular neurons normally producing the hormone. The AVP deficiency appears to develop progressively and the age of onset seems to be the only inter-

kindred variable. Finally, adFNDI is caused by mutations in 1 allele of the AVP gene in.

To explain how such a vast variety of mutations as those identified in the AVP gene (Table 2 and Fig 3) cause a disease with such minimal variation in clinical phenotype, it has been hypothesized that the mutations solely involve amino acid residues important for proper folding and/or dimerization of the neurophysin II domain of the AVP prohormone.[58] Neurophysin II (and neurophysin I) contain a single hormone-binding site to which oxytocin and AVP can bind with virtually identical affinity and binding kinetics.[62] Neurophysin has the ability to self-associate by dimerization and aggregation and hormone binding is indeed the principal factor affecting these processes. In vitro binding studies of the intermolecular interactions between mature hormone (or smaller peptides) and neurophysin as well as studies of the intramolecular interaction within their common precursor have provided detailed knowledge about the structural requirements for neurophysin folding and hormone binding.[53,63-66] Most of the proposed interactions are confirmed and further characterized by nuclear magnetic resonance (NMR) investigations[67,68] as well as by the determination of the crystal structure of a bovine neurophysin II dipeptide complex (Fig 2),[40] a neurophysin I oxytocin complex,[69] and a bovine neurophysin II–lysine-vasopressin (LVP) complex and its unliganded state.[70] The ordered formation of 8 disulphide bridges seems to govern the initial folding of the hormone domain and the stepwise folding of the neurophysin domain into a metastable state.[71] Subsequent insertion of the cyclic N-terminal domain of the hormone into the binding pocket of neurophysin[40,72,73] stabilizes the prohormone in its correct conformation and enhances dimerization.[74] Among the structural requirements important for hormone binding, the α-amino group and the phenyl ring of tyrosine in position 2 in the hormone are most critical. The 3–amino acid tail of the hormone participate, at best, very weakly in the binding process.

Based on this knowledge, all mutations identified to date can indeed be predicted to affect folding and/or dimerization (Fig 3). Furthermore, based on the presumed causes of their effects, the mutations fall into 1 or more of the following 4 categories: (1) those predicted to interfere with the binding of the AVP moiety to neurophysin II either by impairing or misdirecting signal peptide cleavage, changing amino acid residues in the N-terminal region of the AVP moiety, or changing the conformation of the neurophysin II binding pocket; (2) those predicted to interfere with disulphide bridge formation by eliminating or introducing cysteine residues; (3) those predicted to interfere with the flexibility or rigidity of the peptide backbone by eliminating or introducing, respectively, glycine or proline residues; and (4) those predicted to encode a truncated neurophysin II domain by introducing premature stop codons.

AdFNDI mutations that involve amino acid residues not as obviously essential for proper folding and/or dimerization of the neurophysin II domain as the others have been investigated by in vitro folding studies of mutant recombinant proteins, either bovine neurophysin I[75] or human AVP pro-
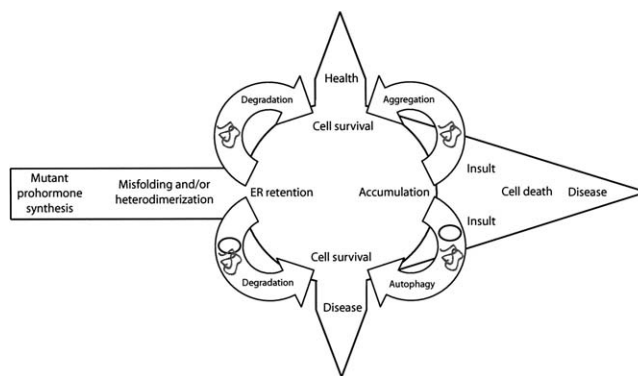

Figure 4 A survey of the molecular and cellular processes presumed to be involved in the pathogenesis of adFNDI. Mutations in the AVP gene result in the synthesis of a mutant AVP prohormone. Because of the mutations it is unable to fold correctly in the ER and it thus is retained by the ER quality control system. Proteosomal degradation of misfolded mutant prohormone (indicated by scrambled threads) or heterodimers protects the cells but in the latter case disease develops as WT prohormone (indicated by ellipses) is eliminated together with the mutant prohormone. If the quality control system is unable to refold and/or degrade the mutant prohormone, it accumulates. On accumulation both aggregation and autophagy would protect the cells but only the latter results in disease because WT prohormone is eliminated together with mutant prohormone during the autophagic process. Cells protected by these means are susceptible to second insults (eg, excitatory stress) and apoptosis is initiated (or maybe initiated by protein accumulation by itself). Disease develops when the cell population decreases to less than the specific number required to produce enough AVP to maintain antidiuresis. Variables such as the rate of AVP prohormone synthesis, mutant prohormone degradation efficacy, cell sensitivity toward second insults, and the number of magnocellular neurons all affect the outcome (survival/death and health/disease) of the processes shown.

hormone.[41] All mutations investigated had structural consequences that diminished the conformational stability and folding efficiency of the mutant proteins and, in addition, several mutations affected dimerization as well. The sole mutation resulting in almost unchanged physical properties of bovine neurophysin I predict a deletion of the last 7 residues of the protein (g.2116G>T, p.E118X) (Table 2 and Fig 3). However, because copeptin by itself seems to participate in stabilizing interactions unique to the human AVP prohormone, the predicted pathogenicity of p.E118X could be owing to the loss of copeptin.[41]

A pathogenic hypothesis addressing the mutation pattern described earlier together with the relatively uniform clinical phenotype in adFNDI with delayed onset and progressive development of the disease, and the autopsy evidence of degeneration of the AVP-producing magnocellular neurons[17,76-80] has been proposed.[19,55,58,59,81] It suggests that the dominant-negative effect exerted by the mutations is caused by the production of a mutant hormone precursor that fails to fold and/or dimerize properly in the ER and, as a consequence, is retained by the ER protein quality control,[42,43] resulting in cytotoxic accumulation of protein in the neurons (ie, a misfolding-neurotoxicity hypothesis) (Fig 4). Ho-

modimer and heterodimer formation between wild-type and mutant AVP prohormones and impairment of wild-type prohormone trafficking by the mutant precursor during heterologous expression in cell cultures has been shown.[60] This suggests that wild-type and mutant prohormones forms abnormally configured heterodimers that are retained in the ER. Their rapid degradation by the cytosolic proteasome could account for the failure of the normal allele to maintain the predicted AVP secretion at 50% of normal,[58] however, this does not account for the progressive and degenerative features of adFNDI. Thus, additional cellular processes almost certainly are involved (Fig 4). In another study, a mutant AVP protein expressed in cell culture seems to be retrotranslocated from the ER to the cytosol and degraded by the proteasome, however, ubiquitination could not be shown.[82] A significant portion of the primary translation products failed to enter the ER lumen at all. Both pathways of degradation, via the ER lumen and directly from the cytosol, were found additionally to some extent for the wild-type protein. These data suggest that mutant AVP prohormone is retained in the ER and degraded to some extent; however; also in this case additional cellular processes must be involved to explain disease development (Fig 4).

The misfolding-neurotoxicity hypothesis implies that the clinical, hormonal, and biochemical phenotype should be similar in all adFNDI kindreds and that the disease is caused exclusively by mutations in the AVP gene affecting amino acid residues important for proper folding and/or dimerization of the neurophysin II domain of the AVP prohormone. With regard to the homogeneity of the phenotype in adFNDI, only relatively subtle differences have been encountered until now, the most prevailing being the interkindred and intrakindred difference in the age at which the DI reportedly began.[83] This variation could reflect that the cytotoxic accumulation of misfolded protein is occurring to variable degrees in different patients or at different times, depending on factors such as the severity of the folding defect, the efficiency of the ER protein quality control, how early the treatment was initiated, and the susceptibility of the AVP-producing magnocellular neurons.[58] The presence of the bright spot on magnetic resonance images (MRIs) in some affected members of adFNDI kindreds could in part be owing to the lack of specificity of the MRI signal[84] but, on the other hand, it is indeed striking that the majority of the reported examples of adFNDI patients having a normal MRI signal are children.[84-86] It can be speculated that the AVP deficiency resulting in complete adFNDI in these children actually precedes the disappearance of the MRI bright spot. With regard to the genetic basis of adFNDI, identification of new mutations in the AVP gene in kindreds with adFNDI continually provides more evidence that they exclusively affect amino acid residues predicted to be important for proper folding and/or dimerization of the neurophysin II domain of the AVP prohormone (see earlier).[15]

The misfolding-neurotoxicity hypothesis additionally implies the following: (1) the mutant AVP preprohormone is retained in the ER by the protein quality control; (2) the ER retention results in lethal accumulation and/or aggregation of mutant protein; (3) the decreased AVP secretion capacity is associated with selective degeneration of the AVP-producing magnocellular neurons; and (4) these neurons are more vulnerable than the parvocellular AVP-producing neurons either because of the higher level of AVP production or because of a less efficient ER protein quality control. Heterologous expression of a variety of different adFNDI mutations in either cell cultures or transgenic animals has been performed to address these questions. The studies consistently have confirmed the misfolding-neurotoxicity hypothesis, at least partly, because all adFNDI mutations investigated until now lead to the production of a mutant AVP prohormone that, compared with the wild type, is retained largely in the ER and to a varying degree is processed inefficiently into AVP and neurophysin II.[59,83,87-94]

Long-term cytotoxic effects of accumulation of mutant protein in the ER have been observed in neuronal cell lines stably expressing different adFNDI mutations,[58,59] in 1 of 2 different murine knock-in mouse models of adFNDI,[95] whereas no cell death or atrophy was observed in the magnocellular neurons of transgenic rats manipulated to have cell-specific and dehydration-inducible expression of an adFNDI mutation.[96] In the latter case, the expression of the mutation resulted in the accumulation of mutant gene products in a swollen and distended ER together with endogenous AVP. Based on morphologic observations, Davies and Murphy[61] suggest that these structures represent autophagic vesicles, an interpretation supported by their immunoreactivity against various markers of degradative autolysosomes and the general upregulation of autolysosomal processes as a specific consequence of the expression of the mutation.[61] Further studies in cell cultures recently have shown that autophagy, induced by the accumulation of misfolded mutant AVP prohormone, actually seems to be prosurvival but that a second insult (eg, excitatory stress) triggers autophagy-dependent apoptosis in the cells.[97,98] This could imply that adFNDI is initiated when autophagy as a result of gradual accumulation of mutant AVP prohormone in the ER removes the deranged organelle and thereby also the wild-type prohormone.[61] In fact, this hypothesis does not exclude the misfolding-neurotoxicity hypothesis because, although prosurvival autophagy may be responsible for the initiation of symptoms of adFNDI, it does not rule out the possibility that degeneration of the AVP-producing magnocellular neurons is a long-term consequence. In this context, it is important to note that the transgenic animals that had autophagic structures in the brain on expression of mutant AVP prohormone actually did not develop any clear-cut DI phenotype during 5 cycles of dehydration/rehydration used for the induction of transgene expression, reflecting that the AVP deficiency in the animals was far from complete.

A misfolding-neurotoxicity pathogenesis not only categorizes adFNDI as an ER storage disease[99,100] together with other endocrinopathies as congenital hypothyroid goiter,[101] osteogenesis imperfecta,[102] and hypercholesterolemia,[103-105] but suggests that adFNDI is related closely to certain forms of α1-antitrypsin deficiency and neurodegenerative diseases such as Alzheimer's and Parkinson's.

Autosomal-Recessive FNDI

Autosomal-recessive inheritance of FNDI has been suggested in a kindred comprising asymptomatic first-cousin parents and 3 affected children.[16] All 3 affected children are homozygous and the parents are heterozygous for a g.301C>T mutation in the AVP gene, predicting a substitution of proline for leucine at position 7 in AVP (AVP7), corresponding to position 26 of the AVP preprohormone (p.P26L) (Table 2 and Fig 3). Thus, unlike other patients with FNDI, no normal AVP can be produced in affected members of the kindred, not even at birth. In summary, the affected children are characterized by: (1) postnatal development of DI symptoms; (2) progressive development of disease symptoms as evidenced by the results of repetitive fluid deprivation tests, at least in the 2 eldest children; (3) abnormally low urine osmolality at the end of a fluid-deprivation test, at least in the 2 eldest children; (4) high levels of plasma P26L-AVP before and during a fluid-deprivation test; (5) a significant increase in urine osmolality after administration of dDAVP; (6) a normal bright spot on T1-weighted MRI images solely in the youngest child. Despite the fact that this mutation is situated in close proximity to other adFNDI mutations predicted to change the AVP hormone, p.Y21H (AVP2)[106] and p.F22del (AVP3)[107] (Table 2 and Fig 3), it seems solely to cause clinically significant deficiency in antidiuretic function in the homozygous state. In addition, it looks as if the mutation does not result in degeneration of the neurohypophysis in view of the fact that relatively large amounts of biologically inactive P26L-AVP appear to be produced in the homozygous state.[16] These clinical differences and the fact that P26 has never been identified as important for folding of the AVP prohormone,[69,70,108] suggest that the P26L prohormone, unlike the Y21H and F22del prohormones associated with adFNDI, is folded, dimerized, and transported unhindered from the ER without any interference with the cellular integrity neither in the heterozygous nor the homozygous state. This hypothesis recently has been supported in a study performed by us in which we compared the cellular handling of the P26L and Y21H prohormones on heterologous expression studies in neuronal cell lines.[94] Our investigations showed, as expected, that the cellular handling of the P26L prohormone is unique among all previous findings (eg,[93,107]) in that this specific mutant prohormone seems not to be retained to any detectable degree in the ER and its intracellular trafficking and secretion is not prevented. Our results provide a negative control in support of the idea that autosomal-dominant inheritance of FNDI is caused by mutations in the AVP gene that affect amino acid residues important for proper folding and/or dimerization of the neurophysin II domain of the AVP prohormone.

It remains unclear why the homozygous children developed DI despite the continued secretion of hormone. Our results indicated that the mutation affected the final processing of the prohormone into neurophysin II and hormone,[94] however, the clinical significance of a possible reduced efficiency of the enzymatic processing probably would be insignificant because the antidiuretic activity of mature P26L-AVP by itself, as determined by in vitro functional analyses, was decreased. The postnatal and progressive development of DI in the kindred remains unexplained and, in general, the pathogenesis of this variant form of FNDI remains elusive.

Clinical Aspects of FNDI

The remarkable phenotype of FNDI was noted even in the first descriptions of the disease more than a century ago.[109-111] The familial occurrence of severe polyuria and polydipsia (up to 28 L/24 h[89]), which segregates in an autosomal-dominant pattern and responds readily to exogenous dDAVP, show several intriguing features: the affected family members show a completely normal water balance at birth and during early infancy but develop progressive symptoms of compulsive drinking at some point during childhood. In the few cases in which it has been studied by repetitive fluid-deprivation tests, AVP secretion is normal before the onset of FNDI but diminishes progressively during early childhood.[81,86,112] Once fully developed, the polyuria and polydipsia continue throughout life, however, with the exception that in some elderly patients, symptoms decrease markedly without treatment and with preserved glomerular filtration.[81,113,114] With the recent insight into the molecular pathogenesis of FNDI (Fig 4), the delayed onset of symptoms is explained readily and large interindividual variation in the severity of symptoms within FNDI families truly is expected (see earlier). The explanation behind the age-related decrease of symptoms, however, remains unclear.

With the discovery of the molecular genetic background behind FNDI arises the question of whether different mutations result in different clinical phenotypes. The answer to this question has, however, been somewhat held back by the lack of sufficient clinical data including measurements of plasma AVP during osmotic challenge in FNDI patients. So far, the only phenotypical variable that has shown some relation to the type of mutation is the age of onset of symptoms, which seems to be higher in kindreds carrying the common signal peptide mutation (g.279G>A, p.A19T) than kindreds with mutations affecting the neurophysin II region (eg, p. L81P).[83,89] This notion is supported by expression studies showing that cells expressing the A19T prohormone are capable of secreting some normal AVP through the regulated secretory pathway.[59,83] Also, the variability in age of onset seem to be larger in kindreds carrying signal peptide mutations, as shown by a kindred reporting an average age of onset of 11.4 years, with a range of 3 to 28 years.[115]

The clinical diagnosis of DI can be made easily by measuring urine osmolality during a fluid-deprivation test, at least when the disease present in its complete form. Both subcategories of primary polydipsia (dipsogenic DI and psycogenic polydipsia) are excluded if significant dehydration induced by fluid deprivation results in lack of urinary concentration. If urine osmolality remains low after subsequent administration of AVP or dDAVP, neurohypophyseal DI is excluded. Gestational DI in a pregnant woman is differentiated from nephrogenic and neurohypophyseal DI by a potent antidiuretic effect of administered dDAVP but not AVP. This reflects that dDAVP is less susceptible to degradation by pla-

central vasopressinase than AVP.[116] There are, however, several pitfalls in the differential diagnostic evaluation and in partial neurohypophyseal DI, partial nephrogenic DI, and primary polydipsia, the differentiation is often not that straightforward because fluid deprivation in all cases results in some degree of urinary concentration. These types usually can be differentiated by measuring plasma AVP levels before and during fluid deprivation and/or hypertonic saline infusion to evaluate their relationship to concurrent levels of, respectively, plasma and urine osmolality.[117]

Reports of specific mutations in the AVPR2 gene resulting in partial DI phenotypes[18,118-124] have added to the differential diagnostic challenge. In such kindreds, affected subjects are able to concentrate their urine to almost normal levels in response to osmotic stimuli or high doses of dDAVP, although the mutation causes a shift to the right of the dose-response relationship between plasma AVP and urine osmolality.[18] There are examples of kindreds with AVPR2 mutations causing partial NDI that have been misdiagnosed as FNDI.[18,123]

One obvious conclusion based on such observations is that molecular genetic evaluation should be performed in all patients with familial occurrence of DI symptoms regardless of the results of clinical tests. Apart from verifying the correct differential diagnosis of the patient in question and possibly adding to the understanding of the genetic background behind familial DI, the molecular genetic analyses can contribute further in the clinical setting. Once the molecular diagnosis is established in FNDI kindreds, it is relatively easy to screen other family members for the mutation. This is particularly relevant in infants at risk of inheriting the mutation because presymptomatic diagnosis thereby is possible, relieving years of parental concern about the disease status of their offspring. Because FNDI is associated with very few symptoms and with a normal quality of life at least when treated appropriately, and because there is little risk of severe central nervous system sequelae[125] compared with NDI, prenatal diagnosis seems not to be indicated.

It has not been clear whether patients with idiopathic neurohypophyseal DI should be tested genetically for de novo mutation in the AVP gene. These patients constitute a relatively large proportion of neurohypophyseal DI cases (20%-50%[126]) and some occur during childhood. In our data for 17 cases with idiopathic neurohypophyseal DI (unpublished) we found 1 with an abnormality in the AVP gene.[15] Other cases have been reported as well.[127] Thus, we suggest that patients with neurohypophyseal DI occurring during childhood, without a family history, and without an identifiable cause (eg, thickening of the pituitary stalk) should be tested genetically.

Treatment Aspects

In contrast to NDI and dipsogenic DI, treatment of FNDI is relatively straightforward because administration of the AVP analog, dDAVP, 2 to 3 times daily eliminates symptoms.[128] Because patients with FNDI have preserved osmoregulation of thirst, only minor fluctuations in plasma osmolality are seen even with irregular medicine intake and the risk of inducing hyponatremia is very small in these patients. Because the dose-response curve of the antidiuretic effect of dDAVP is very steep over a limited concentration range of plasma dDAVP, bioavailabililty is more relevant for the duration of action of a dose rather than its potency.[129] This fact is relevant clinically because the main treatment problem for the patient is the sudden lack of antidiuresis when plasma dDAVP levels decrease below a threshold. To date, no other V_2 receptor agonists have been introduced in the treatment of DI but the delivery method has undergone a significant development from a rhinyle over nasal spray device, and over a common tablet to the very recently introduced sublingual instant melting tablet.[130] Whether such selection of delivery methods results in superior control of polyuria and polydipsia or merely is a matter of subjective preference remains to be shown.

Ideally, treatment of FNDI should provide a long-lasting antidiuresis with the possibility to provide escape in case a higher-than-required fluid intake is desirable, for example, for social reasons. Such a treatment profile could, at least in theory, be obtained with gene therapy providing constantly high levels of AVP through the expression of the AVP gene contained in a viral vector. Several recent studies have shown efficient long-term treatment of DI in the AVP-deficient Brattleboro rat by gene therapeutic approaches such as the injection of viral vectors into the central nervous system[131-133] or skeletal muscles,[134] however, there is still a general concern regarding the safety of such viral approaches. To obtain escape from the constant antidiuresis induced by gene therapy, an antidote could be provided by the recently developed V_2 receptor antagonists (eg, conivaptan).[135]

Concluding Remarks

Although molecular research has contributed significantly over more than a decade, the genetic background and the pathogenesis of FNDI still is not understood fully. The disease segregates in 3 different modes of inheritance, seems to be linked to mutations located on at least 2 different chromosomes, yet to date only 1 specific disease-causing gene, the AVP gene, has been identified in FNDI. In almost all of the reported kindreds (ie, 87/89), the disease is caused by mutations in the AVP gene, the pattern of which seems to be largely revealed because only few novel mutations are emerging. The autosomal-dominant form of the disease has attracted substantial scientific interest because it has a potential role as a simpler (and very well-described) model of protein misfolding, intracellular protein accumulation, and neurodegeneration than more prevalent diseases such as Alzheimer's and Parkinson's. The pattern of adFNDI mutations together with evidence from clinical and expression studies points toward a pathogenic cascade of events that finally lead to degeneration of the AVP-producing magnocellular neurons. Furthermore, molecular research has provided an additional tool in the occasionally difficult differential diagnosis of DI and has provided the opportunity to perform presymptomatic diagnosis in infants. Although the disease is treated

readily with exogenous administration of dDAVP, other treatment options such as gene therapy and enhancement of the ER protein quality control (eg, improvement of the protein degradation and folding) could become future treatment modalities.

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