Molecular Biology of Hereditary Diabetes Insipidus

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The identification, characterization, and mutational analysis of three different genes—the arginine vasopressin gene (AVP), the arginine vasopressin receptor 2 gene (AVPR2), and the vasopressin-sensitive water channel gene (aquaporin 2 [AQP2])—provide the basis for understanding of three different hereditary forms of “pure” diabetes insipidus: Neurohypophyseal diabetes insipidus, X-linked nephrogenic diabetes insipidus (NDI), and non–X-linked NDI, respectively. It is clinically useful to distinguish two types of hereditary NDI: A “pure” type characterized by loss of water only and a complex type characterized by loss of water and ions. Patients who have congenital NDI and bear mutations in the AVP2 or AQP2 genes have a “pure” NDI phenotype with loss of water but normal conservation of sodium, potassium, chloride, and calcium. Patients who bear inactivating mutations in genes (SLC12A1, KCNJ1, CLCNKB, CLCNKA and CLCNKB in combination, or BSND) that encode the membrane proteins of the thick ascending limb of the loop of Henle have a complex polyuro-polydipsic syndrome with loss of water, sodium, chloride, calcium, magnesium, and potassium. These advances provide diagnostic and clinical tools for physicians who care for these patients.


A nyone who passes large volumes of urine might be said to be experiencing diabetes insipidus. Years ago, the initial distinction made by physicians in evaluating patients with polyuria was whether their urine was sweet (diabetes mellitus) or not (diabetes insipidus) (1). Diabetes insipidus is a disorder characterized by the excretion of abnormally large volumes (>30 ml/kg body wt/d for adults) of dilute urine (<250 mmol/kg). This definition excludes osmotic diuresis, which occurs when excess solute is being excreted, for example, glucose in the polyuria of diabetes mellitus. Four basic defects can be involved: (1) deficient secretion of the antidiuretic hormone arginine vasopressin (AVP), which is the most common defect and is referred to as neurohypophysial (also known as neurogenic, central, or hypothalamic) diabetes insipidus; (2) renal insensitivity to the antidiuretic effect of AVP, which is known as nephrogenic diabetes insipidus (NDI); (3) excessive water intake that can result in polyuria, which is referred to as primary polydipsia; and (4) increased metabolism of vasopressin during pregnancy, which is referred to as gestational diabetes insipidus. The hereditary forms of diabetes insipidus account for <10% of the cases of diabetes insipidus seen in clinical practice. The purpose of this review is to examine recent developments in the understanding and molecular biology of the hereditary forms of diabetes insipidus. Here we use the gene symbols approved by the HUGO Gene Nomenclature Committee (http://www.gene.ucl.ac.uk/nomenclature) and provide OMIM entry numbers (2). Not included in this review are acquired forms of NDI; for further information, see references 3–5.

Genes Involved in “Pure” Diabetes Insipidus AVP

The regulation of the release of AVP from the posterior pituitary is primarily dependent, under normal circumstances, on tonicity information relayed by osmoreceptor cells in the anterior hypothalamus (6). AVP and its corresponding carrier, neurophysin II, are synthesized as a composite precursor by the magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus (for review, see 7). The precursor is packaged into neurosecretory granules and transported axonally in the stalk of the posterior pituitary. En route to the neurohypophysis, the precursor is processed into the active hormone. Prepro-vasopressin has 164 amino acids and is encoded by the 2.5-kb AVP gene located in chromosome region 20p13 (8,9). The AVP gene (coding for AVP and neurophysin II) and the OXT gene (coding for oxytocin and neurophysin I) are located in the same chromosome region, at a very short distance from each other (12 kb in humans) in head-to-head orientation. Data from transgenic mouse studies indicate that the intergenic region between the OXT and the AVP genes contains the critical enhancer sites for cell-specific expression in the magnocellular neurons (7). It is phylogenetically interesting to note that cis and trans components of this specific cellular expression have been conserved between the Fugu isotocin (the homolog of mammalian oxytocin) and rat oxytocin genes (10). Exon 1 of the AVP gene encodes the signal peptide, AVP, and the NH2-terminal region of neurophysin II. Exon 2 encodes the central region of neurophysin II, and exon 3 encodes the COOH-terminal region of neurophysin II and the glycopeptide.
Pro-vasopressin is generated by the removal of the signal peptide from prepro-vasopressin and from the addition of a carbohydrate chain to the glycopeptide. Additional posttranslational processing occurs within neurosecretory vesicles during transport of the precursor protein to axon terminals in the posterior pituitary, yielding AVP, neurophysin II, and the glycopeptide. The AVP–neurophysin II complex forms tetramers that can self-associate to form higher oligomers (11). Neurophysins should be seen as chaperone-like molecules facilitating intracellular transport in magnocellular cells. In the posterior pituitary, AVP is stored in vesicles. Exocytotic release is stimulated by minute increases in serum osmolality (hypernatremia, osmotic regulation) and by more pronounced decreases in extracellular fluid (hypovolemia, nonosmotic regulation). Oxytocin and neurophysin I are released from the posterior pituitary by the suckling response in lactating women.

**AVPR2 and AQP2**

The transfer of water across the principal cells of the collecting ducts is now known at such a detailed level that billions of molecules of water that traverse the membrane could be represented and are useful teaching tools (http://www.mpibpc.gwdg.de/abteilungen/073/gallery.html; http://www.ks.uiuc.edu/research/aquaporins). The 2003 Nobel Prize in chemistry was awarded to Peter Agre and Roderick MacKinnon, who solved two complementary problems presented by the cell membrane: How does a cell let one type of ion through the lipid membrane to the exclusion of other ions? How does it permeate membrane: How does a cell let one type of ion through the lipid membrane of the kidney collecting tubule has been designated as the water channel of the apical membrane of the collecting duct (16–18). The human gene that codes for the carrier neurophysin II (23). The polyuric symptoms are also observed in heterozygous di/h rats. Homozygous Brattleboro rats may still demonstrate some V2 antidiuretic effects, because the administration of a selective nonpeptide V2 antagonist (SR121463A, 10 mg/kg intraperitoneally) induced a further increase in urine flow rate (200 to 354 ± 42 ml/24 h) and a decline in urinary osmolality (170 to 92 ± 8 mmol/kg) (24). Oxytocin, which is present at enhanced plasma concentrations in Brattleboro rats, may be responsible for the observed antidiuretic activity (25,26). Oxytocin is not stimulated by increased plasma osmolality in humans. The Brattleboro rat model therefore is not strictly comparable with the rarely observed human cases of autosomal recessive neurohypophyseal diabetes insipidus (27).

Patients with autosomal dominant neurohypophyseal diabetes insipidus retain some limited capacity to secrete AVP during severe dehydration, and the polyuro-polydipsic symptoms usually appear after the first year of life (28), when the infant’s demand for water is more likely to be understood by adults.

More than 50 AVP mutations segregating with autosomal dominant or autosomal recessive neurohypophyseal diabetes insipidus have been described (see http://www.medicine.mcgill.ca/nephros for a list of mutations). The mechanisms by which a mutant allele causes neurohypophyseal diabetes insipidus could involve the induction of magnocellular cell death as a result of the accumulation of AVP precursors within the endoplasmic reticulum (29–31). This hypothesis could account for the delayed onset of the disease. In addition to the cytotoxicity caused by mutant AVP precursors, the interaction between the wild-type and the mutant precursors suggests that a dominant negative mechanism may also contribute to the pathogenesis of autosomal dominant diabetes insipidus (32). The absence of
symptoms in infancy in autosomal dominant neurohypophyseal diabetes insipidus is in sharp contrast with NDI secondary to mutations in \( \text{AVPR2} \) or in \( \text{AQP2} \), in which the polyuric-polydipsic symptoms are present during the first week of life. Of interest, errors in protein folding represent the underlying basis for many inherited diseases (33–35) and are also pathogenic mechanisms for \( \text{AVP} \), \( \text{AVPR2} \), and \( \text{AQP2} \) mutants. Why \( \text{AVP} \) misfolded mutants are cytotoxic to \( \text{AVP} \)-producing neurons is an unresolved issue. Protein misfolding, an “unfolded protein response” in cells, and the accumulation of excess misfolded protein leading to apoptotic cell death are well documented for autosomal dominant retinitis pigmentosa (36).

Three families with autosomal recessive neurohypophyseal diabetes insipidus in which the patients were homozygous or compound heterozygotes for \( \text{AVP} \) mutations have been identified (27,37). Two of these families are characterized phenotypically by severe and early onset in the first 3 mo of life with polyuria, polydipsia, and dehydration. As a consequence, early hereditary diabetes insipidus can be neurogenic or nephrogenic.

**X-Linked NDI (OMIM 304800) as a Result of Mutations in \( \text{AVPR2} \)**

X-linked NDI is generally a rare disease in which the affected male patients do not concentrate their urine after administration of \( \text{AVP} \) (38). Because this form is a rare, recessive X-linked disease, female individuals are unlikely to be affected, but...
heterozygous female individuals can exhibit variable degrees of polyuria and polydipsia because of skewed X chromosome inactivation. In Quebec, the incidence of this disease among male individuals was estimated to be approximately 8.8 in 1,000,000 male live births (39). A founder effect of two particular AVPR2 mutations (40), one in Ulster Scot immigrants (the “Hopewell” mutation, W71X) and one in a large Utah kindred (the “Cannon” pedigree), results in an elevated prevalence of X-linked NDI in their descendants in certain communities in Nova Scotia, Canada, and in Utah (40). These founder mutations now have spread all over the North American continent. To date, we have identified the W71X mutation in 42 affected male individuals who reside predominantly in the Maritime Provinces of Nova Scotia and New Brunswick and the L312X mutation in eight affected male individuals who reside in the central United States. We know of 98 living affected male individuals of the Hopewell kindred and 18 living affected male individuals of the Cannon pedigree. To date, 183 putative disease-causing AVPR2 mutations have been published in 287 NDI families (Figure 1).

We propose that all families with hereditary diabetes insipidus should have their molecular defect identified. The molecular identification underlying X-linked NDI is of immediate clinical significance because early diagnosis and treatment of affected infants can avert the physical and mental retardation that results from repeated episodes of dehydration. Affected premature male infants may experience less severe polyuric symptoms and may need only increased hydration during their first week without a need for hydrochlorothiazide treatment. Water should be offered every 2 h day and night, and temperature, appetite, and growth should be monitored. Admission to hospital may be necessary for continuous gastric feeding. The voluminous amounts of water kept in patients’ stomachs will exacerbate physiologic gastrointestinal reflux in infants and toddlers, and many affected boys frequently vomit. These young patients often improve with the absorption of an H2 blocker and with metoclopramide (which could induce extrapyramidal symptoms) or with domperidone, which seems to be better tolerated and efficacious. All polyuric states (whether neurogenic, nephrogenic, or psychogenic) can induce large di-

Figure 2. (A) Schematic representation of aquaporin 2 (AQP2) and identification of 35 putative disease-causing AQP2 mutations. The locations of the conserved asparagine-proline-alanine (NPA) boxes and the protein kinase A (PKA) phosphorylation site (Pa) are indicated. The extracellular, transmembrane, and cytoplasmic domains are defined according to Deen et al. (17). Solid symbols indicate the location of the missense or nonsense mutations. There are 25 missense, two nonsense, six frameshift deletion or insertion, and two splice-site mutations. (B) A monomer is represented with six transmembrane helices, A through F. *Where the molecular pseudo-2-fold symmetry is strongest (89).
lutions of the urinary tract and bladder (41–43), and bladder function impairment has been well documented in patients who bear AVPR2 or AQP2 mutations (44,45). Chronic renal failure secondary to bilateral hydronephrosis has been observed as a long-term complication in these patients. Renal and abdominal ultrasound should be done annually, and simple recommendations, including frequent urination and “double voiding,” could be important to prevent these consequences.

Classification of the defects of naturally occurring mutant human V2 receptors can be based on a similar scheme to that used for the LDL receptor (46). Mutations have been grouped according to the function and subcellular localization of the mutant protein whose cDNA has been transiently transfected in a heterologous expression system. Using this classification, type 1 mutant V2 receptors reach the cell surface but display impaired ligand binding and are consequently unable to induce normal cAMP production. The presence of mutant V2 receptors on the surface of transfected cells can be determined pharmacologically. By carrying out saturation binding experiments using tritiated AVP, the number of cell surface mutant V2 receptors and their apparent binding affinity can be compared with that of the wild-type receptor. In addition, the presence of cell surface receptors can be assessed directly by using immunodetection strategies to visualize epitope-tagged receptors in whole-cell immunofluorescence assays.

Type 2 mutant receptors have defective intracellular transport. This phenotype is confirmed by carrying out, in parallel, immunofluorescence experiments on cells that are intact (to demonstrate the absence of cell surface receptors) or permeabilized (to confirm the presence of intracellular receptor pools). In addition, protein expression is confirmed by Western blot analysis of membrane preparations from transfected cells. It is likely that these mutant type 2 receptors accumulate in a pre-Golgi compartment, because they are initially glycosylated but fail to undergo glycosyl-trimming maturation.

Type 3 mutant receptors are ineffectively transcribed and lead to unstable mRNA, which are rapidly degraded. This subgroup seems to be rare, because Northern blot analysis of cells expressing most mutant V2 receptors showed mRNA of normal quantity and molecular size.

Most of the AVPR2 mutants that we and other investigators have tested are type 2 mutant receptors. They did not reach the cell membrane and were trapped in the interior of the cell (47–50). Other mutant G protein–coupled receptors (51) and gene products that cause genetic disorders are also characterized by protein misfolding. Mutations that affect the folding of secretory proteins; integral plasma membrane proteins; or enzymes destined to the endoplasmic reticulum, Golgi complex, and lysosomes result in loss-of-function phenotypes irrespective of their direct impact on protein function because these mutant proteins are prevented from reaching their final destination (52). Folding in the endoplasmic reticulum is the limiting step: Mutant proteins that fail to fold correctly are retained initially in the endoplasmic reticulum and subsequently often degraded (Figure 3). Key proteins involved in the urine countercurrent mechanisms are good examples of this basic mechanism of misfolding. AQP2 mutations that are responsible for autosomal recessive NDI are characterized by misrouting of the misfolded mutant proteins and are trapped in the endoplasmic reticulum (53). Mutants that encode other renal membrane proteins that are responsible for Gitelman syndrome (54), Bartter syndrome (55,56), and cystinuria (57) are also retained in the endoplasmic reticulum.

The AVPR2 missense mutations are likely to impair folding and to lead to rapid degradation of the misfolded polypeptide and not to the accumulation of toxic aggregates (as is the case for AVP mutants), because the other important functions of the principal cells of the collecting duct (where AVPR2 is expressed) are entirely normal. These cells express the epithelial sodium channel (ENaC). Decreased function of this channel results in a sodium-losing state (58). This has not been observed in patients with AVPR2 mutations. By contrast, another type of conformational disease is characterized by the toxic retention of the misfolded protein. The relatively common Z mutation in α1-antitrypsin deficiency not only causes retention of the mutant protein in the endoplasmic reticulum but also affects the secondary structure by insertion of the reactive center loop of one molecule into a destabilized β sheet of a second molecule (59). These polymers clog up the endoplasmic reticulum of hepatocytes and lead to cell death and juvenile hepatitis, cirrhosis, and hepatocarcinomas in these patients (60).

If the misfolded protein/traffic problem that is responsible for so many human genetic diseases can be overcome and the mutant protein transported out of the endoplasmic reticulum to its final destination, then these mutant proteins could be sufficiently functional (34). Therefore, using pharmacologic chaperones or pharmacocinerones to promote escape from the endoplasmic reticulum is a possible therapeutic approach (35,52,61). We used selective nonpeptide V2 and V1 receptor antagonists to rescue the cell-surface expression and function of naturally occurring misfolded human V2 receptors (47). Because the beneficial effect of nonpeptide V2 antagonists could be secondary to prevention and interference with endocytosis, we studied the R137H mutant previously reported to lead to constitutive endocytosis (62). We found that the antagonist did not prevent the constitutive β-arresting-promoted endocytosis (48). These results indicate that as for other AVPR2 mutants, the beneficial effects of the treatment result from the action of the pharmacologic chaperones. In clinical studies, we administered a nonpeptide vasopressin antagonist SR49059 to five adult patients who have NDI and bear the del62–64, R137H, and W164S mutations. SR49059 significantly decreased urine volume and water intake and increased urine osmolality, whereas sodium, potassium, and creatinine excretions and plasma sodium were constant throughout the study (63). This new therapeutic approach could be applied to the treatment of several hereditary diseases resulting from errors in protein folding and kinesis (34,35). Alternatively, bypassing the V2 receptor and stimulating AQP2 insertion independent of AVP stimulation could be a new, interesting avenue to pursue (64,65).

Because most human gene-therapy experiments using viruses to deliver and integrate DNA into host cells are potentially dangerous (66), other treatments are being actively pursued. Schöneberg and colleagues (67) used aminoglycoside
antibiotics because of their ability to suppress premature termination codons (68). They demonstrated that geneticin, a potent aminoglycoside antibiotic, increased AVP-stimulated cAMP in cultured collecting duct cells prepared from E242X mutant mice. The urine-concentrating ability of heterozygous mutant mice was also improved.

Autosomal Recessive (OMIM 222000) and Dominant (OMIM 125800) NDI as a Result of Mutations in AQP2 (OMIM 107777)

On the basis of desmopressin infusion studies and phenotypic characteristics of both male and female individuals who are affected with NDI, a non–X-linked form of NDI with a postreceptor (post cAMP) defect was suggested (69–71). A patient who presented shortly after birth with typical features of NDI but exhibited normal coagulation and normal fibrinolytic and vasodilatory responses to desmopressin was shown to be a compound heterozygote for two missense mutations (R187C and S217P) in the AQP2 gene (17). To date, 35 putative disease-causing AQP2 mutations have been identified in 40 NDI families (Figure 2). The oocytes of the African clawed frog (Xenopus laevis) have provided a most useful experimental system for studying the function of many channel proteins. This convenient expression system was key to the discovery of AQP1 by Agre (72) because frog oocytes have very low permeability and survive even in freshwater ponds. Control oocytes are injected with water alone; test oocytes are injected with various quantities of synthetic transcripts from AQP1 or AQP2 DNA (cRNA). When subjected to a 20-mOsm osmotic shock, control oocytes have exceedingly low water permeability but test oocytes become highly permeable to water. These osmotic water permeability assays demonstrated an absence or very low transport for all of the cRNA with AQP2 mutations. Immunofluorescence and immunoblot studies demonstrated that these recessive mutants were retained in the endoplasmic reticulum.

AQP2 mutations in autosomal recessive NDI, which are located throughout the gene, result in misfolded proteins
that are retained in the endoplasmic reticulum. In contrast, the dominant mutations reported to date are located in the region that codes for the carboxyl terminus of AQP2 (73–75). Dominant AQP2 mutants form heterotetramers with wt-AQP2 and are misrouted. Investigation of P262L, the only recessive mutation in the carboxyl terminus, provided new insights into the loss of function and oligomerization of AQP2 proteins. Functional analysis in oocytes of P262L cRNA indicated that, unlike other AQP2 mutants in recessive NDI, it is a functional water channel and that trafficking to the plasma membrane was not impaired (76). Furthermore, unlike other AQP2 recessive mutants, P262L cRNA forms heterotetramers with wt-AQP2 and is routed to the apical membrane and thus in cellular experimental systems has

![Figure 4.](image-url)

Measurements on two sisters with Bartter syndrome compared with a patient with nephrogenic diabetes insipidus (NDI). The two sisters with polyuria, polydipsia, hypokalemia, hypocalcemia, and nephrocalcinosis are homozygous for the A177T mutation in the KCNJ1 gene (55; M.-F. Arthus, M. Lonergan, and D.G.B., unpublished data). Both sisters were born as preterm infants after severe polyhydramnios. The dDAVP infusion tests (91) were done at 9 yr (patient 1, left) and 11 yr (patient 2, middle) of age. Indomethacin treatment was discontinued 1 wk before testing; water was not restricted during the test. Plasma vasopressin was very low (<0.5 pg/ml) during the test, but plasma renin activity was elevated (20 ng/ml per h in patient 1, 10 ng/ml per h in patient 2). By contrast, patients with AVPR2 (4-yr-old patient with NDI and the AVPR2 A132D mutation [40], right) or AQP2 mutations generally have low urine osmolality unresponsive to dDAVP, normal plasma potassium, high vasopressin levels, and normal plasma renin activity.
most of the features of AQP2 mutants in dominant NDI. Carriers of the P262L mutation seem to be asymptomatic, but more precise measurements are needed to determine whether there is a partial NDI phenotype.

Complex Polyuro-Polydipsic Syndrome

In contrast to a “pure” NDI phenotype, with loss of water but normal conservation of sodium, potassium, chloride, and calcium, in Bartter syndrome, patients’ renal wasting starts prenatally and polyhydramnios often leads to prematurity. Bartter syndrome (OMIM 601678, 241200, 607364, and 602522) refers to a group of autosomal recessive disorders caused by inactivating mutations in genes (SLC12A1, KCNJ1, CLCNKB, CLCNKA and CLCNKB in combination, or BSND) that encode membrane proteins of the thick ascending limb of the loop of Henle (for review, see 77,78). Although Bartter syndrome and Bartter’s mutations are commonly used as a diagnosis, it is likely, as explained by Jeck et al. (79), that the two patients with a mild phenotype originally described by Dr. Bartter had Gitelman syndrome, a thiazide-like salt-losing tubulopathy with a defect in the distal convoluted tubule (79). As a consequence, salt-losing tubulopathy of the furosemide type is a more physiologically appropriate definition.

Thirty percent of the filtered sodium chloride is reabsorbed in the thick ascending limb of the loop of Henle through the apically expressed sodium-potassium-chloride co-transporter NKCC2 (encoded by the SLC12A1 gene), which uses the sodium gradient across the membrane to transport chloride and potassium into the cell. The potassium ions must be recycled through the apical membrane by the potassium channel ROMK (encoded by the KCNJ1 gene). In the large experience of Seyberth and colleagues (80), who studied 85 patients with a hypokalemic salt-losing tubulopathy, all 20 patients with KCNJ1 mutations (except one) and all 12 patients with SLC12A1 mutations were born as preterm infants after severe polyhydramnios. Of note, polyhydramnios is never seen during the pregnancy that leads to infants bearing AVPR2 or AQP2 mutations. The most common causes of increased amniotic fluid include maternal diabetes mellitus, fetal malformations and chromosomal aberrations, twin-to-twin transfusion syndrome, rhesus incompatibility, and congenital infections (81). Postnatally, polyuria was the leading symptom in 19 of the 32 patients. Renal ultrasound revealed nephrocalcinosis in 31 of these patients. These patients with complex polyuro-polydipsic disorders are often poorly recognized and may be confused with “pure” NDI. As a consequence, congenital polyuria does not suggest automatically AVPR2 or AQP2 mutations, and polyhydramnios, salt wasting, hypokalemia, and nephrocalcinosis are important clinical and laboratory characteristics that should be assessed. In patients with Bartter syndrome (salt-losing tubulopathy/furosemide type), the dDAVP test (Figure 4) will indicate only a partial type of NDI. The algorithm proposed by Peters et al. (80) is useful because most mutations in SLC12A1 and KCNJ1 are found in the carboxyl terminus or in the last exon and, as a consequence, are amenable to rapid DNA sequencing.

Conclusion

The study of diabetes insipidus has been a fascinating journey for >100 yr since Magnus and Schaffer (82), as early as 1901, demonstrated that posterior pituitary extracts had oxytocic, pressor, and antidiuretic activities. This was followed by Farini (83) and von den Velden (84), who successfully used posterior pituitary extracts to treat diabetes insipidus in 1913. du Vigneaud (85) received the 1955 Nobel Prize in chemistry for the first synthesis of a polypeptide hormone AVP. Sachs and Takabatake (86) proposed the remarkable concept that AVP and neurophysin might be synthesized on ribosomes via a common precursor protein. This was proved by Land et al. (87) in 1982. After the discovery that loss-of-function mutations in the rhodopsin gene cause retinitis pigmentosa (OMIM 180380), numerous examples of other human diseases caused by loss-of-function mutations in G protein–coupled receptors were identified, including X-linked NDI. The small sizes of the genomic and coding regions of the genes involved (AVP, AVPR2, and AQP2) allows for relatively easy mutation analysis, thereby allowing for carrier, prenatal, and perinatal testing. We conclude that hereditary diabetes insipidus is a good model system that could bring further insights into various basic biologic processes and approaches to treatment of disease.

Acknowledgments

This research was supported by grants from the Canadian Institutes of Health Research (MOP-8126), the Kidney Foundation of Canada, and the Network of Centres of Excellence Program—the Canadian Genetic Diseases Network (to Kenneth Morgan). D.G.B. holds a Canada Research Chair in Genetics of Renal Diseases. We thank our co-workers, Marie-Françoise Arthus, Danielle Binette, Michèle Lonergan, and Kenneth Morgan, and many colleagues who contributed families and ideas to our work.

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