Multicystic Dysplastic Kidney and Variable Phenotype in a Family with a Novel Deletion Mutation of PAX2

Jeffery Fletcher,* Min Hu,* Yemima Berman,† Felicity Collins,‡ John Grigg,† Margot McIver,§ Harald Jüppner,‖ and Stephen I. Alexander*

*Centre for Kidney Research, Department of Nephrology, and Departments of †Clinical Genetics and ‡Ophthalmology, The University of Sydney, The Children’s Hospital at Westmead, Westmead, New South Wales, Australia; †Department of Nephrology, Dubbo Base Hospital, Dubbo, New South Wales; and ‖Pediatric Nephrology, Massachusetts’s General Hospital for Children, Harvard University, Boston, Massachusetts

The renal coloboma syndrome (OMIM 120330) is caused by mutations in the PAX2 gene. Typical findings in these patients include renal hypoplasia, renal insufficiency, vesicoureteric reflux, and optic disc coloboma. A family with a novel heterozygous 10-bp deletion in exon 2 of the PAX2 gene leading to a truncating mutation and variable phenotype across three generations is reported. The first presentation of multicystic dysplastic kidney in this syndrome is reported. The possibility that abnormal PAX2 protein in this case may cause a dominant negative effect also is discussed. The finding of multicystic dysplastic kidney in renal coloboma syndrome could suggest that PAX2 may play a role in early ureteric obstruction and subsequent renal maldevelopment.

Renal coloboma syndrome is an autosomal dominant disorder, characterized by renal malformations and optic disc coloboma. Renal and/or ocular anomalies are found in all patients, but the type and the severity of these abnormalities can vary markedly. Commonly observed manifestations that affect the kidneys include renal hypoplasia and vesicoureteric reflux (VUR), both of which can lead to renal insufficiency (1–9). Extrarenal manifestations can include sensorineural hearing loss, Arnold Chiari malformation, seizures of unknown cause, and joint laxity, but these are reported in <20% of patients (1,5,7,10).

Heterozygous mutations in the human PAX2 gene were first described in 1995 in patients with the renal coloboma syndrome (4,8). Studies with Pax2-knockout mice have revealed that homozygous deletions lead to early postnatal death with absence of the kidneys, ureters, and eyes (11,12). The human PAX2 gene is located on chromosome 10q24-25. It comprises 12 exons, with exons 2, 3, and 4 encoding a highly conserved 128–amino acid DNA binding domain (2,13). PAX2 encodes a transcription factor that belongs to the “paired-box” family of homeotic genes. During embryonic development, it is abundantly expressed in the kidney, eye, cochlear (14), pancreas (15), and central nervous system (11,16,17) and is involved in the regulation of several genes, such as WT1 (18), N-my (19), and p53 (19).

PAX2 mutations that cause renal coloboma syndrome have been identified in the exons encoding the DNA binding domain (exons 2 and 3), the octapeptide domain (exon 5), the homeodomain (exon 7), and the transactivation domain (exons 8 and 9). All mutations (Table 1) are recorded in the human PAX2 allele variant database (http://pax2.hgu.mrc.ac.uk/) and include nucleotide substitutions (4,6,20,21), insertions (1,6,7,9,10), and deletions (1,5,7,10,22–24), with a single reported case of a de novo translocation (3,10,13). Although variability is found with differing mutations, there is also phenotypic variability with the same mutation and within the same family. PAX2 mutations have been reported in one patient with isolated renal hypoplasia (20) and in patients with isolated VUR (25,26). No patients with isolated ocular coloboma have been found thus far to have PAX2 mutations (22).

Because of the commonly associated finding of ureteric atresia, multicystic dysplastic kidney (MCDK) is thought to arise from congenital ureteral obstruction during early nephrogenesis (27). Some forms of unilateral renal agenesis could also be due to the involution of early MCDK (27). Anatomic and structural studies have suggested that the anomalies observed in MCDK arise from malformation of the ureteric bud branches and ampullae (28). MCDK has not previously been reported in patients with renal coloboma syndrome; however, unilateral renal agenesis has been reported in two patients and is observed in 1 to 6% of mice with the Pax2Nou mutation (1,12,21,29). Renal agenesis, unilateral kidney cysts, dilated ureters, and cystic changes within the renal medulla have also been observed in small numbers of Kidney and Retinal Defects (Krd) transgenic mice (12).

We now describe a family who have renal coloboma syndrome and a novel heterozygous 10-bp deletion in exon 2 of PAX2, which leads to a shift in the open reading frame and thus a chimeric protein that comprises PAX2 residues 1 to 46 fol-
Table 1. Reported PAX2 mutations in the human PAX2 allelic variant database (http://pax2.hgu.mrc.ac.uk/) and clinical phenotype associated with each mutation

<table>
<thead>
<tr>
<th>Mutation Type</th>
<th>Mutation</th>
<th>Location (Nucleotide)</th>
<th>Renal Phenotype</th>
<th>Ocular Phenotype</th>
<th>Other</th>
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<tr>
<td>Substitution</td>
<td>n.769C&gt;A Missense</td>
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<td>Mild renal impairment</td>
<td>Mild eye anomalies</td>
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<td>Exon 7 (1228)</td>
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<td>Exon 7 (1249)</td>
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<td>Asymptomatic right optic nerve atrophy</td>
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<td>20</td>
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<tr>
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<td>n.1497C&gt;A Nonsense</td>
<td>Exon 9 (1497)</td>
<td>Isolated renal hypoplasia; neonatal renal insufficiency; bilateral small kidneys; bilateral vesicoureteric reflux</td>
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<td>Insertions</td>
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<td>Exon 2 (619)</td>
<td>Renal tubular atrophy; interstitial fibrosis; proteinuria; end-stage renal failure</td>
<td>Bilateral optic nerve coloboma</td>
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<td>Exon 2 (619)</td>
<td>Bilateral renal hypoplasia; end-stage renal failure; focal segmental glomerulosclerosis</td>
<td>Bilateral optic nerve coloboma</td>
<td></td>
<td>10</td>
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<td>Exon 2 (619)</td>
<td>Bilateral renal hypoplasia; end-stage renal failure</td>
<td>Left optic nerve aplasia; right optic disc hypoplasia with optic pit; chorioretinal coloboma; capsular opacities; microphthalmos; retrobulbar cyst</td>
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<td>Bilateral optic nerve coloboma</td>
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<td>Bilateral abnormal optic discs; left macular hypoplasia; right morning glory syndrome</td>
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<td>n.619insG Frame shift</td>
<td>Exon 2 (619)</td>
<td>Oligomeganehphronia; papillary dysplasia</td>
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<td>Bilateral optic nerve coloboma</td>
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<tr>
<td></td>
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<td>Bilateral optic nerve coloboma; myopia</td>
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<td>Exon 2 (619)</td>
<td>Small kidneys; progressive renal failure</td>
<td>Bilateral optic nerve coloboma with retinal detachment</td>
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<td>Severe visual impairment</td>
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<td>Bilateral optic nerve coloboma with retinal detachment</td>
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<td>Rickets; umbilical and right inguinal hernia</td>
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<td>Bilateral renal hypoplasia; left kidney VUR</td>
<td>Bilateral optic nerve coloboma</td>
<td></td>
<td>22</td>
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<tr>
<td></td>
<td>n.619delG Frame shift</td>
<td>Exon 2 (619)</td>
<td>Bilateral renal hypoplasia; left kidney VUR; VUR</td>
<td>Nystagmus; esotropia</td>
<td></td>
<td>7</td>
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<td></td>
<td>n.619delG Frame shift</td>
<td>Exon 2 (619)</td>
<td>Bilateral optic nerve coloboma; VUR</td>
<td>fourth and fifth digit clinodactyly</td>
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<td>Bilateral optic nerve coloboma; severe myopia</td>
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<td>Exon 5 (1104)</td>
<td>Bilateral renal hypoplasia; nonfunctional right kidney; renal failure; grade IV VUR</td>
<td>Bilateral optic nerve coloboma</td>
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<td>De novo translocation</td>
<td>Chr 10; Chr 13</td>
<td>Renal tubular atrophy; glomerulosclerosis; mild renal dysfunction with proteinuria</td>
<td>Bilateral optic nerve coloboma; cataracts</td>
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aVUR, vesicoureteral reflux.

Materials and Methods

Genomic DNA was extracted from patients’ peripheral blood samples (2 to 5 ml) using the SDS-protease K method. DNA from patient II-3 was extracted from a Papanicolaou-smear that was stored at room temperature using the QiAamp DNA Mini Kit (Qiagen Pty Ltd, Doncaster, Australia) method.

PAX2 exon 2 was amplified from genomic DNA by PCR. Oligonucleotide primers for exon 2 were designed using the Primer 3 software of Bionavigator. The forward primer was 5’-TGTTGTTGGGTTGT-GTGT-3’ and was FAM-labeled at the 5’ end. The reverse primer was 5’-GGAAGTGCAAGGCTGCTC-3’. Both primers incorporated in-tronic DNA flanking exon 2; the expected PCR product was 253 bp in length. Primers were purchased from Invitrogen Life Technologies (Melbourne, Australia). The PCR was performed in a final volume of 50 µl, which contained 10X Taq buffer (5 µl), 0.2 mM dNTP (4 µl), TaqDNA polymerase 0.5 U (0.4 µl), 20 ng of genomic DNA (2 µl), 0.25 µM of each primer (2 µl), and H2O (34.6 µl). The PCR profile using three-step cycling for 35 cycles was denaturation at 95°C for 30 s,
was also suggestive of MSK. She subsequently developed sponge kidney (MSK) was made. Renal biopsy at 29 yr of age mal calyces, and at the time a diagnosis of right medullary bilaterally small kidneys with right tubular defects and abnor- 

sequenced using an ABI PRISM 310 genetic analyzer. The samples were incubated at 37°C overnight. Colonies with insertions of the PCR product were identified. Nucleotide sequence analysis was performed on independent bacterial colonies using the Big Dye terminator cycle sequence ready reaction kit (Applied Biosystems). The samples were sequenced using an ABI PRISM 310 genetic analyzer.

Subcloning and DNA Sequencing

PCR products were purified using a QIAquick PCR purification kit (Qiagen) and cloned into the pGEM-T Easy vector system (Promega, Madison, WI) and transformed into Escherichia coli JMS09 competent cells. After the bacterial cells were transformed in SOC medium, 100 µl of the suspension was plated on lysogeny broth medium that contained ampicillin (100 µg/ml), IPTG (0.5 nM), and X-Gal (80 µg/ml). Plates were incubated at 37°C overnight. Colonies with insertions of the PCR product were identified. Nucleotide sequence analysis was performed on independent bacterial colonies using the Big Dye terminator cycle sequence ready reaction kit (Applied Biosystems). The samples were sequenced using an ABI PRISM 310 genetic analyzer.

Twin Zygosity Determination

Assessment for zygosity was undertaken in patients IV-2 and IV-3. Molecular zygosity determination was performed using the PowerPlex 1.2 System (Promega).

Results

Family pedigree is shown in Figure 1.

Patient 1

Patient II-3 presented at age 21 yr with right pyelonephritis. Investigations revealed mild proteinuria (0.2 g/L) and an elevated creatinine (166 µmol/L). Intravenous pyelogram showed bilaterally small kidneys with right tubular defects and abnormal calyces, and at the time a diagnosis of right medullary sponge kidney (MSK) was made. Renal biopsy at 29 yr of age was also suggestive of MSK. She subsequently developed chronic renal impairment (serum creatinine 250 µmol/L). Ophthalmoscopy and fluorescein angiography revealed optic disc coloboma (Figure 2A). Audiometry revealed bilateral high-tone sensorineural and mild conductive hearing loss. She died at the age of 51 yr after complications from ischemic heart disease.

Patient 2

Patient III-3 received a diagnosis at 3 years of age of bilateral grade III to IV VUR and right secondary ureteropelvic junction (UPJ) obstruction. Renal ultrasound showed bilaterally small kidneys. An ophthalmologist’s examination revealed bilateral optic disc coloboma and normal visual acuity. Proteinuria at 4 yr of age was significant at 0.8 g/L per d. Serial urinalyses using “combur 10” test strips (Roche Diagnostics, Castle Hill, New South Wales) showed persistent heavy (4+) proteinuria. He was treated for hypertension and developed left ventricular hypertrophy diagnosed by echocardiography. Renal osteodys- trophy was treated with oral vitamin D supplementation. He- modialysis was commenced at the age of 14 yr, and he died at age 16 yr after a cardiac arrest associated with overwhelming sepsis. Autopsy was not performed.

Patient 3

Patient III-4 is a 24-yr-old woman who was noted at age 18 mo to have mild proteinuria and an elevated creatinine (80 µmol/L). Renal ultrasound and micturating cystogram were normal. An ophthalmologist’s examination revealed bilateral optic disc coloboma. She currently has stable chronic renal impairment (creatinine 320 µmol/L), normal visual acuity, and normal hearing. A 24-h urinary protein assessment shows significant proteinuria of 4.56 g/L, and her mild hypertension (BP 140/95 mmHg) is currently managed with a calcium channel blocker. She has received genetic counseling advising a risk of 50% transmission in subsequent pregnancies and has since undergone a tubal ligation.

Patient 4

Patient IV-1 is a 3-yr-old boy who received a diagnosis antenatally of bilaterally small kidneys. Postnatal ultrasounds confirmed bilateral renal hypoplasia, and he has mild chronic renal impairment (creatinine 100 µmol/L). An ophthalmologist’s examination showed bilateral optic disc coloboma. Urinalysis using “combur 10” test strips (Roche Diagnostics) at age 4 yr shows no evidence of proteinuria, and he remains normo- tensive. Initial hearing screening using visual reinforcement orientation audiometry is normal.

Patient 5

Patient IV-2 is a 6-mo-old twin girl who received a diagnosis antenatally of bilaterally small dysplastic kidneys, confirmed on postnatal ultrasound. She has mild renal impairment (creatinine 57 µmol/L) and an asymmetrical right optic disc coloboma (Figure 2B). Urinalysis using “combur 10” test strips (Roche Diagnostics) at age 8 mo shows no evidence of proteinuria, and she is currently being treated for mild hypertension with a calcium channel blocker (BP 104/65 mmHg). Initial

![Figure 1](image-url)
hearing screening using visual reinforcement orientation audiometry is normal.

Patient 6

Patient IV-3 is a 6-mo-old twin girl who received a diagnosis antenatally of a small left dysplastic kidney and right MCDK. An antegrade nephrostogram performed postnatally confirmed noncommunicating cysts, which are consistent with MCDK (Figure 3, A through C). She has moderate renal impairment (serum creatinine 99 μmol/L) and an asymmetrical right optic disc coloboma (Figure 2C). Renal ultrasound performed at 8 mo of age shows enlargement of a single cyst in the right kidney (Figure 2D). Spot urine protein shows significant proteinuria of 0.96 g/L, and she is currently treated for mild hypertension with a calcium channel blocker (BP 102/68 mmHg). Initial hearing screening using visual reinforcement orientation audiometry is normal.

Patients IV-2 and IV-3 are monozygotic with identical alleles for all nine microsatellite markers tested. Spectratype analysis showed the twins to be heterozygous at four alleles and homozygous at five alleles.

Mutation Analysis

Heterozygosity for a mutation of exon 2 of PAX2 was identified in all affected family members by an abnormal spectratype pattern showing a normal and a shortened mutant allele. All affected individuals have identical spectratyping patterns showing two peaks; the unaffected father and normal control subjects have a single peak (Figure 4). Nucleotide sequence analysis of independent clones derived from the PCR product comprising exon 2 revealed a 10-bp deletion (nucleotide 682 to 691 of the cDNA), CAGGGTGTGC (Figure 5) within the paired box domain leading to a shift in the open reading frame. The encoded protein thus corresponds to the first 46 amino acids of PAX2, followed by 31 amino acids of unrelated sequence (Figure 6).

Discussion

We present six affected family members who have renal coloboma syndrome and a novel heterozygous missense mutation in the highly conserved exon 2 region of PAX2. A mutation encompassing this region has previously been described in a family with renal coloboma syndrome (10). Both the previously reported nucleotide deletion and the deletion presented in this report lead to a frame shift and an unrelated protein comprising 31 amino acids in length downstream of the deletion (Figure 7, A and B). Figure 7A shows the mutated protein described in this family. As can be seen in Figure 7B, the previously described larger deletion of 22 bp in the same region leads to a

Figure 2. (A) Postnatal renal ultrasound in patient IV-3 showing multiple noncoalescing cystic structures consistent with multicystic dysplastic kidney (MCDK). (B and C) Nephrostogram performed to exclude ureteropelvic junction (UPJ) obstruction on day 2 of life shows two noncommunicating cystic structures again consistent with MCDK (small arrows indicate nephrostogram needle entering two separate cysts, confirming MCDK). (D) Renal ultrasound at 8 mo of age showing increasing size of a single cyst in the MCDK.

Figure 3. Phenotypic features of the eyes in patients II-3 (A), IV-2 (B), and IV-3 (C). A fluorescein angiogram of patient II-3 shows a large typical optic disc coloboma with a sharply delimited excavation occupying an enlarged optic disc. Patients IV-2 and IV-3 show the coloboma occupying the temporal aspect of optic disc with normal nasal neuroretinal rim in each patient. The colobomas were asymmetrical, with the right eye more severely affected in these two patients.
for all tested family members and an unrelated control. This novel protein that is four amino acids shorter but contains the identical novel sequence generated by the frame shift.

The finding of MCDK in patient IV-3 and UPJ obstruction in patient III-3 raises several hypotheses as to the relationship of this novel PAX2 mutation and renal obstruction. First, it strengthens the hypothesis that PAX2 also plays a role in ureteric development, drainage, and early renal obstruction as seen in mouse models of congenital anomalies of the kidney and urinary tract (CAKUT) (30). Second, variable phenotypic expression is well documented in PAX2 mutations in humans and mouse models (see Table 1). The variable expression of MCDK and UPJ obstruction in the PAX2 kindred described here is consistent with the variability found in CAKUT, in which only one kidney is usually affected, whereas the other is typically spared, suggesting that there may be nongenetic factors that contribute to the development of MCDK (30,31). Alternatively, renal obstruction and MCDK may arise in these patients through co-inheritance of a second, unrelated genetic mutation. There are no other reports of digenic inheritance of either MCDK or PAX2 mutations with other disorders. Each condition is rare, with MCDK having an incidence of 1:4300 (32) and only approximately 75 cases of PAX2 mutations reported worldwide (1–2,4–7,9–11,20,22–24,29). Therefore, the possibility of digenic inheritance for these two conditions seems unlikely.

The possible role of PAX2 in the development of MCDK has previously been postulated (30,33). Woolf (33) hypothesized that congenital obstruction resulting in MCDK involves the upregulation of PAX2 from stretching of the metanephric epithelium after ureteric obstruction. This overexpression of PAX2 may lead to an alteration in BCL2 protein, which may stimulate renal epithelial hyperproliferation, giving rise to the kidney’s multicystic appearance (33,34). This hypothesis is supported by the presence of increased in vitro expression of PAX2 and BCL2 in dysplastic epithelia (32,33). The presence of increased apoptosis in Pax2neo mice heterozygous for PAX2 mutations may also reflect the important role of PAX2 in regulating apoptosis. In addition, increased apoptosis in homozygous congenital polycystic kidney (cpk) mice heterozygous for PAX2 mutations has been suggested to lead to the observed slowing of the progression of renal cystic disease (35,36) in mice that carry the additional PAX2 mutation compared with those without a PAX2 mutation.

The presence of MCDK in patient IV-3 seems contradictory to the hypothesis that upregulation of PAX2 results in the development of MCDK whereas downregulation slows cystic progression. Although the clinical phenotype of renal coloboma syndrome has been attributed to a decreased expression of PAX2, it is possible in this particular case that expression of the truncated and abnormal protein may have a dominant effect resulting in a similar process to upregulation of normal PAX2 with obstruction. This would explain the antiapoptotic effect and cystic changes in this patient. An alternative hypothesis is that the mutant PAX2 gene could be acting independently to cause ureteric obstruction with the development of cysts being a secondary phenomenon.

Other clinical findings in renal coloboma syndrome have raised the possibility of PAX2 being involved in ureteric obstruction. Unilateral renal agenesis has been reported in two patients with renal coloboma syndrome. Right renal agenesis, bilateral optic nerve coloboma, and renal failure were described in a patient with an affected sibling with a less severe renal phenotype (29). This case was not diagnosed as having renal coloboma syndrome at the time of publication, although the patient’s phenotype is highly suggestive of this (29). The second reported patient with renal coloboma syndrome and unilateral renal agenesis was identified to have a mutation involving a single nucleotide deletion at nucleotide position 832 of exon 3 (n. 832 del G) of PAX2. The same mutation in this patient’s father was expressed as a less severe phenotype with renal insufficiency and reduced kidney size (1). This mutation led to truncation of the predicted paired box domain protein as
shown in Figure 7I. The marked clinical variability found within families and between patients with identical mutations in both structural lesions and clinical outcomes is similar to that found in patients with WT-1 gene mutations (37). This may suggest that PAX2 is a spatially and temporally important regulator of renal development and that unilateral renal agenesis in affected patients may be caused by ureteric obstruction during early nephrogenesis, leading to involution of the affected kidney in utero (27,38).

Sanyanusin et al. (5) also report a 15-yr-old boy with a non-functioning right kidney and bilateral reflux. This patient was found to have a single nucleotide deletion in exon 5 (n.1104 del C). This mutation led to the paired box domain's remaining intact, potentially allowing DNA binding with truncation of the
PAX2 protein within the octapeptide sequence (Figure 7J). Potentially, mutations involving exons 3 and 5 and our mutation may allow transcription of enough amino acids to precipitate DNA binding and production of a similar mutant PAX2 protein with aberrant PAX2 function when compared with mutations that lead to shorter amounts of wild-type protein (Figure 7, C through H).

The observed phenotype of UPJ obstruction and MCDK in our reported patients is the first human report of a PAX2 mutation leading to the anomalies of MCDK and UPJ encompassed in CAKUT (30,31). Several genes, including PAX2, have been described in mouse models as having potential roles in the ontogeny of CAKUT; these include Kali, Eya1, and AGTR2 (30). The observed absence of kidneys and ureters in the Pax2 /− mice and renal hypoplasia in the Pax2 +/+ heterozygotes is in keeping with the clinical phenotype of this kindred and supports a role for PAX2 in the ontogeny of CAKUT (30).

In conclusion, we have identified a novel mutation in exon 2 of the PAX2 gene that causes renal coloboma syndrome and is associated with MCDK. These findings, in conjunction with the previous reports of renal agenesis in this syndrome, suggest that PAX2 may play a role in early ureteric obstruction.

Acknowledgments

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References


Access to UpToDate on-line is available for additional clinical information at http://www.jasn.org/