Eye and Kidney: From Clinical Findings to Genetic Explanations

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Although the study of embryonic eye and kidney development was first studied in the middle of the 19th century, three decades passed until scientists identified the molecular controls of both renal and eye organogenesis. Most of these advances have come from mouse and rodent gene manipulation. Translation of the mouse data to human congenital oculorenal disease has just begun. Examples of these genes include Pax2 and bone morphogenic protein 7 (BMP-7). Others factors that participate in mouse ocular and renal organogenesis, such as epithelial growth factor or integrins, may later be proven important in human eye and kidney development. A variety of human congenital syndromes affecting both organs have been described. An interesting pathophysiological classification scheme on kidney diseases has been very recently reported by Pohl et al (1). We propose a clinical diagnostic approach of oculorenal syndromes with their genetic’s links.

Renal Dysgenesis and Eye Abnormalities
Pax and WT1 Gene Families

Pax genes are a family of developmental control genes that encode nuclear transcription factors. They are characterized by the presence of the paired domain, a conserved amino acid motif with DNA-binding activity. Originally, paired-box-containing genes were detected in Drosophila melanogaster, where they exert multiple functions during embryogenesis. In vertebrates, Pax genes are also involved in embryogenesis. Mutations in four out nine characterized Pax genes have been associated with either congenital human diseases such as Waardenburg syndrome (Pax3), Aniridia (Pax6), Peter’s anomaly (Pax6), renal coloboma syndrome (Pax2), or spontaneous mouse mutants, which all show defects in development. Recently, analysis of spontaneous and transgenic mouse mutants has revealed that vertebrate Pax genes are key regulators during organogenesis of kidney, eye, ear, nose, limb muscles, vertebral column, and brain (2).

The expression pattern of Wilms’ tumor suppressor 1 (WT1) during embryogenesis is highly complex. WT1 has at least two functions during the first stage of kidney development. First, it may be required for the inductive signal that induces the outgrowth of the ureter from the mesonephros. Second, it seems to be involved in either survival or reception of the survival signal from the ureteric bud (3). In addition to its role in genitourinary formation, WT1 is required for the differentiation of ganglion cells in the developing retina (4).

Wilms’ tumor gene was originally identified on the basis of its mutational inactivation in 10 to 15% of all Wilms’ tumors. A preliminary report on the expression of WT1 in the developing eye is remarkable because it points toward a possible role for WT1 in ocular development (5). Severe abnormalities were also found in the WT1−/− retinas at later stages of development. Consistent with the expression of WT1 in the inner portion of the WT1+/+ retina, a significant fraction of cells was lost apoptosis in the developing retinal ganglion cells of mutant E18 embryos. Defects in the remaining ganglion cells in the WT1−/− retinas are indicated by failure of these cells to give rise to normally growing optic nerve fiber bundles. This phenotype of the WT1−/− retinas is reminiscent of the abnormalities seen in mice, which lack the POU-domain transcription factor Pou4f2 (also known as Brn-3b) (6).

Coloboma. Typical isolated ocular coloboma is a congenital abnormality caused by defective closure of the embryonic fissure of the optic cup (Figure 1). The defect is typically located in the lower part of the iris. The association of a coloboma to urinary anomalies may evoke a papillorenal syndrome. However, among some patients with a ‘renal-coloboma’ syndrome, Pax2 mutation was not found. A clinical analysis can nevertheless help the diagnostic orientation as shown in Figure 2.

Renal-Coloboma Syndrome (OMIM 120330). The predominant abnormalities associated with renal-coloboma syndrome are bilateral optic nerve colobomas and renal hypoplasia, with or without renal failure. A significant degree of clinical variation is observed between family members who share the same mutation (7). Moreover, patients with renal-coloboma syndrome and Pax2 mutations may have additional congenital anomalies that occur with variable penetrance. These anomalies include vesico-ureteral reflux (VUR), auditory anomalies, CNS anomalies, and skin and joint anomalies (8).
Patients with mutations in Pax2 have colobomatous eye defects. Developmental abnormalities of the optic fissure during optic cup and stalk development result in a group of defects, including orbital cysts, microphthalmia, optic disc dysplasia, and colobomas of the optic nerve and (9) All patients identified to have mutations in Pax2 have been observed to have colobomatous defects at the posterior pole of the globe (8). Iris colobomas have not been observed in patients with mutations in Pax2. Sometimes the optic nerve colobomas in patients with renal-coloboma syndrome are described as morning glory syndrome (10).

Patients with Pax2 mutations often exhibit small kidneys with reduction in size of both the renal pelvis and renal cortex. The renal disease in patients with Pax2 mutations is usually...
progressive and frequently necessitates renal transplantation after chronic renal failure (7,8), although patients with very minimal renal involvement have also been identified (3). Renal cortical biopsies have demonstrated mesangial fibrosis and glomerulosclerosis, involving glomeruli, hyalinization of glomeruli, atrophic tubules, and hyperplastic gomerali with an overall decreased number of glomeruli (7,8,11). Pathologic examination of kidneys revealed cortical thinning, hypoplastic papillae with low numbers of gomerali, and collecting ducts in the cortex and the papilla, respectively, consistent with renal hypoplasia (8).

VUR is an important factor when considering determinants of renal function loss in patients with renal-coloboma syndrome (12). It arises during development of the ureter in embryogenesis, and there is evidence that VUR can begin in utero. VUR can cause both renal failure and scarring. It has been observed in 5 of 19 patients with Pax2 mutations, although the frequency may be higher because VUR has a tendency to resolve with age (8,13). However, the more common, nonsyndromic form of VUR maps to 1p13 and is not linked to the PAX2 locus (14). The renal histology description associated with renal-coloboma syndrome includes interstitial fibrosis, glomerulosclerosis, and tubular atrophy and is similar to those observed in patients with VUR (12). In addition, later stages of reflux nephrophy in patients with VUR are associated with proteinurin and end-stage renal failure, which also occur in patients with renal-coloboma syndrome.

The exact incidence of renal-coloboma syndrome (or of Pax2 mutations) in the population is unknown. During embryonic development, Pax2 expression (which gene localizes to human chromosome band 10q24.3-q25.1 [15]) occurs in the developing urogenital system (kidney, ureter, and genital tract), as well as the developing eye, ear, and central nervous system (CNS) (16). In the kidney, Pax2 expression occurs in the early stages of mesenchymal to epithelial differentiation, preceding formation of the glomerulus. Pax2 expression is also found in the ureteric bud and at low levels in epithelia such as collecting duct, renal pelvis, and ureter (16). In the developing eye, Pax2 expression starts in the optic placode and then continues in the optic vesicle. As the optic vesicle folds and becomes a bilayer optic cup, Pax2 expression is restricted to the optic fissure and along the length of the optic stalk (17).

Renal-Coloboma Like Syndrome. Pax2 mutation was not found in some patients with renal-coloboma syndrome or a renal-coloboma-like syndrome (13). Other syndromes that involve renal and ocular anomalies and have similarities to renal-coloboma syndrome include Senior-Loken syndrome (SLS), CHARGE syndrome (colobomas, heart anomalies, choanal atresia, retardation, genitourinary anomalies, and ear anomalies), COACH syndrome (cerebellar vermis hypo/aplasia, oligophrenia, congenital ataxia, coloboma, hepatic fibrosis), Joubert syndrome, acrorenoocular syndrome, and bilateral macular coloboma with hypercalciuria syndrome.

Senior-Loken Syndrome (OMIM 266900). SLS is an autosomal recessive disorder defined by the association of nephronophthisis and tapetoretinal degeneration. It occurs in approximately 18% of all cases of nephronophthisis (18). Nephronophthisis can also be associated with conditions affecting extrarenal organs, such as retinitis pigmentosa (SLS) and ocular motor apraxia (Cogan syndrome). Except for the ocular involvement, the pathologic and clinical features of SLS are virtually identical to those of isolated nephronophthisis, including course of renal disease. Affected individuals invariably progress to end-stage renal failure, usually before the age of 20 yr (18,19). They present a long-standing history of polyuria-polydipsia, nocturia, mild proteinuria, unremarkable urine sediment, and symmetrically reduced-size kidneys containing multiple small cysts.

For nephronophthisis (NPHP), the primary genetic cause of chronic renal failure in young adults, three loci have been mapped, with forms on chromosomes 2q13 (NPHP1, juvenile form), 9q22 (NPHP2, infantile form), and 3q21-q22 (NPHP3, adolescent form). Localization of a SLS locus to the region of NPHP3 opens the possibilities of both diseases arising by mutations within the same pleiotropic gene or two adjacent genes (20). Recently, a second locus associated with the juvenile form of the disease, NPHP4, was mapped to chromosome 1p36 and constitutes a new locus for SLS associated with retinitis pigmentosa (21–23).

CHARGE Syndrome (OMIM 302905). CHARGE syndrome is named from its six major clinical features: Coloboma of the eye, Heart defects, choanal Atresia, Retarded growth and development including CNS anomalies, Genital hypoplasia and/or urinary tract anomalies, and Ear anomalies and/or hearing loss (24).

Ocular abnormalities were found in 44 of 50 patients diagnosed with CHARGE syndrome. The majority had retinochoroidal colobomata with optic nerve involvement, but only 13 patients had an iris defect. Two patients had typical iris colobomata with normal fundi. Additional features were microphthalmos in 21 patients, optic nerve hypoplasia in 4, nystagmus in 12, and a vertical disorder of eye movement in 4 of the 22 cases with facial palsy (25). Of the 24 patients who underwent renal ultrasound, 10 (42%) were diagnosed with urinary tract anomalies, including a solitary kidney, hydronephrosis, renal hypoplasia and duplex kidneys. Further evaluation revealed vesicoureteral reflux, neurogenic bladder secondary to spinal dysraphism, nephrolithiasis, ureteropelvic junction obstruction, and a nonfunctioning upper pole in both duplex kidneys (26).

COACH Syndrome (OMIM 216360). COACH syndrome is characterized by hypoplasia of cerebellar vermis, oligophrenia, congenital ataxia, coloboma, and hepatic fibrosis. The occurrence of multiple cases in single sibships suggests an autosomal recessive inheritance. Progressive renal insufficiency with fibrocystic changes on renal biopsy is found as a common manifestation of COACH syndrome (27). Nephronophthisis, fibrocystic renal disease, oligophrenia, and small medullary cysts have also been described.

Aniridia. Aniridia is a severe eye disease characterized by iris hypoplasia. Both sporadic and familial cases with autosomal dominant inheritance have been reported. Mutations in the Pax6 gene have been shown to be the genetic cause of the disease (OMIM 106210). Other ocular findings include de-
creased vision, cataract, glaucom, Peter’s anomaly (congenital anomaly of the anterior segment), and corneal clouding. Some of the sporadic cases are caused by large chromosomal deletions, some of which also include the Wilms tumor gene (WAGR syndrome), resulting in an increased risk of developing Wilms tumor (28). A variety of WT1 mutations induces renal development defects such as the dominant Wilms tumor/aniridia/genital anomaly/mental retardation syndrome (WAGR syndrome; OMIM 194072), Denys-Drash syndrome (DDS; OMIM 194080), and Frasier syndrome (FS; OMIM 136680).

Wilms tumor (nephroblastoma) is a childhood tumor of the kidney (1/10,000 live births) originating from the metanephric blastema. Patients with Wilms tumor are at an increased risk for developing ocular disorders, including aniridia and, less frequently, optic nerve hypoplasia resulting from inactivation of the aniridia gene Pax6, which lies telomeric of WT1 on chromosome 11p13 (29). Unlike the genetic mechanism leading to the development of retinoblastoma, an embryonal tumor of childhood affecting the retina, which only requires the inactivation of one single gene, the biological pathways leading to the development of Wilms tumor are complex and likely involve several genetic loci (30).

Denys-Drash Syndrome. On 100 reports of intragenic WT1 mutations, the accompanying clinical phenotypes revealed 5% of sporadic Wilms tumours and >90% of patients with the DDS (renal nephropathy, severe hypertension, a steroid-resistant nephrotic syndrome that rapidly progresses to end-stage renal disease before the age of 5 yr, male pseudohermaphrodisism, predisposition to Wilms tumor [31]). Renal biopsy showed diffuse mesangial sclerosis and focal segmental sclerosis. Podocytes exhibit decreased or absent WT1 expression but persistent Pax2 expression. It is proposed that patients with early onset, rapidly progressive nephrotic syndrome and diffuse mesangial or focal segmental sclerosis should be tested for WT1 mutations to identify those at risk for developing Wilms tumor (32).

Frasier Syndrome. FS includes a slowly progressing nephrotic syndrome attributable to minimal glomerular changes or focal segmental glomerulosclerosis and complete male or female gender reversal in 46 XY patients but no signs of Wilms tumor. In contrast to DDS, end-stage renal disease develops more slowly and at a later stage in life (3).

Eya1 Gene

The Drosophila eyes absent gene (eya) is involved in the formation of compound eyes. Flies with loss-of-function mutations of this gene develop no eyes and form the ectopic eye in the antennae and the ventral zone of the head on target expression. A highly conserved homologous gene in various invertebrates and vertebrates has been shown to function in the formation of the eye. In contrast, a human homologue, EYA1, has been identified by positional cloning as a candidate gene for branchio-oto-renal (BOR) syndrome (OMIM 113650), in which phenotypic manifestations are restricted to the areas of branchial arch, ear, and kidney, with usually no anomalies in the eye. The EYA1 gene is expressed very early, between the 4th and 6th weeks of human development. Deafness relates to abnormalities in the three ossicles of the middle ear derived from the first and second branchial arches, whereas the branchial fistulae relates to abnormalities of the second, third, and fourth arches. In the embryonic human kidney, the EYA1 gene is expressed strongly; in the BOR syndrome, there is an inductive fault between the ureteric bud and the metanephric mesenchymal mass as the ureteric bud branches into the renal parenchyma (33). Mutations in human EYA1 gene are mapping on chromosome 8q13.3.

The BOR syndrome is an autosomal dominant disease characterized by hearing loss of early onset, preauricular pits, branchial clefts, and early progressive chronic renal failure in up to 40% of family affected members (33). Azuma et al. (34) identified three novel missense mutations in patients who had congenital cataracts and ocular anterior segment anomalies. One of the patients had clinical features of BOR syndrome as well. The most important renal abnormalities that lead to end-stage renal disease include unilateral renal agenesis with controlateral hypoplasia characterized by decreased renal volume and size, loss of ultrasound normal corticomедullary differentiation, and hyperechogenicity of the renal cortex. Histologically there is glomerular hyalinization, mesangial proliferation, and basement membrane splitting. Bilateral renal agenesis is the extreme, leading to miscarriage or immediate neonatal death. Other renal abnormalities include bifid kidneys with double ureters, cystic dysplasia, vesico-ureteric reflux, and pelviureteric stenoses (33). The BOR syndrome should be included in the differential diagnosis of deafness and chronic renal failure in childhood and adolescence.

BMP7 Mutation (OMIM 600779)

The bone morphogenetic proteins are members of the TGF-β superfamily purified by Ozkaynak et al. (35). Hahn et al. (36) mapped the BMP7 gene to human chromosome 20 by study of human-rodent somatic cell hybrid lines with cDNA probes. Marker et al. (37) suggested that the human BMP7 gene may be on 20q13.1–q13.3, extrapolating from the fact that the BMP7 gene in the mouse is between Ada (localized to 20q12–q13.11) and Pck1 (localized to 20q13.2–q13.31).

BMP-7 and Kidney Development. During vertebrate development, the metanephric mesenchyme undergoes an epithelial transformation to form the glomerulus and the tubules of the nephrons. This nephrogenic process begins at 11.5 days post conception (dpc) with mesenchymal condensation and is initiated by signals coming from the ureteric bud such as growth factors. Observations reported suggest that BMP-7 is an early inducer of nephrogenesis. Moreover, deletion of BMP-7 in mice results in failure of the metanephric mesenchyme and leads to loss of mesenchymal cell condensation around the ureteric bud and eventually to glomerular and tubular agenesis and severely hypoplastic kidneys. In addition to its role as a renal morphogen, BMP-7 probably is a critical renal tubular differentiation factor determining epithelial cell phenotype. In the absence of BMP-7, only incomplete mesenchymal condensations are identified in the kidney at 12.5 dpc and the metanephric mesenchymal cells died before 14.5 dpc, a phenome-
<table>
<thead>
<tr>
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<th>Kidney</th>
<th>Clinical Syndrome</th>
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<tr>
<td><strong>Before nephrogenesis</strong></td>
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<tr>
<td><em>Pax2</em> 10q24.3–q25.1</td>
<td>Orbital cysts, microphthalmia, coloboma (optic nerve, retina)</td>
<td>Renal agenesis, duplication, vesico-ureteral reflux, hydronephrosis</td>
<td>Renal-coloboma syndrome</td>
</tr>
<tr>
<td><em>Pax6</em>, <em>WT1</em> 11p13</td>
<td>Aniridia, decreased vision, cataract, glaucoma, Peter’s anomaly, corneal clouding</td>
<td>Nephroblastoma, renal failure</td>
<td>WAGR contiguous deletion syndrome</td>
</tr>
<tr>
<td><em>JAG</em> (NOTCH 1) 20q121</td>
<td>Proteinia embryotoxon, keratoconus, strabismus, myopia, retinitis pigmentosa</td>
<td>Renal dysplasia, mesangiolipidosis, tubulointerstitial nephritis, tubuloacidosis, renal failure, medullary cystic disease</td>
<td>Alagille syndrome</td>
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<td><strong>During nephrogenesis</strong></td>
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<td><strong>ureteric duct induction</strong></td>
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<tr>
<td><em>Pax2</em> 10q24.3–q25.1</td>
<td>Orbital cysts, microphthalmia, coloboma (optic nerve, retina)</td>
<td>Renal agenesis, duplication, vesico-ureteral reflux, hydronephrosis</td>
<td>Renal-coloboma syndrome, morning glory syndrome</td>
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<td><em>EYA1</em> 8q13.3</td>
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<td><strong>collecting system development</strong></td>
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<td><em>EGF</em>, <em>EYA1</em>, <em>Pax2</em></td>
<td>Orbital cysts, microphthalmia, coloboma (optic nerve, retina)</td>
<td>Renal agenesis, duplication, vesico-ureteral reflux, hydronephrosis</td>
<td>WAGR syndrome</td>
</tr>
<tr>
<td><em>WT1</em></td>
<td>Aniridia</td>
<td>Nephroblastoma, renal failure</td>
<td>Oligomeganephronia, BOR syndrome, Renal-coloboma syndrome</td>
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<td><strong>mesenchymal-epithelial transition</strong></td>
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<td><strong>glomerulogenesis filtration barrier</strong></td>
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<tr>
<td><em>BMP7</em> chr20</td>
<td>Absence of lens formation (in mice)</td>
<td>Renal hypo/dysplasia, tubular agenesis</td>
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<td><em>Integrin α8</em></td>
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<td><em>LMX1b</em> 9q34.1</td>
<td>Strabismus cataract, micro-cornea, microphthalmia, nystagmus, glaucoma, keratoconus, heterochromia</td>
<td>Normal renal architecture, proteinuria, microscopic hematuria, glomerulonephritis, nephrotic syndrome, renal failure</td>
<td>Nail-patella syndrome</td>
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<td><strong>mesangial</strong></td>
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<td><strong>PDGF-β and PDGF-β receptors</strong></td>
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<td><em>WT1</em></td>
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<td><strong>After nephrogenesis</strong></td>
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<tr>
<td>collecting system, mesenchyme-derived tubules</td>
<td>Blepharochalasis</td>
<td>Cyst formation</td>
<td>ADPKD</td>
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<tr>
<td><em>PKD1</em>, <em>PKD2</em> (16p/4q)</td>
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<td><em>vHL</em> 3p26–p25</td>
<td>Retinal hemangioma, retinal detachment</td>
<td>Cyst formation, renal hemangioblastoma, renal cell carcinoma, renal cysts</td>
<td>von Hippel Lindeau disease</td>
</tr>
</tbody>
</table>
Table 1. Oculorenal syndromes\(^{a}\) (cont’d)

<table>
<thead>
<tr>
<th>Genes, Genes Products, and Chromosomes</th>
<th>Lesions</th>
<th>Clinical Syndrome</th>
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<tbody>
<tr>
<td><strong>collecting system</strong></td>
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<tr>
<td>TSC(_1) (9q34)</td>
<td>Retinal astrocytic hamartoma, microphthalmia, exophthalmos, optic nerve atrophy</td>
<td>Cyst formation, angiomyolipoma, renal cell carcinoma</td>
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<tr>
<td>TSC(_2) (Tuberin) (16p13.3)</td>
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<tr>
<td>X-linked Xq22</td>
<td>Cornea verticilata, cataract, conjunctival varicosity, retinal vessel tortuosity, retinal artery occlusion</td>
<td>Renal failure, isosthenuria, tubular dysfunction, irrefrangible lipid globules in urine, fom vacuole cells</td>
</tr>
<tr>
<td>Nephrocystin 2q13</td>
<td>Retinitis pigmentosa, retinal aplasia/hypoplasia, retinal dystrophy</td>
<td>Medullary cystic disease, renal failure, isosthenuria, hypokalemia, excess urinary sodium and potassium loss, interstitial fibrosis, tubular atrophy, relatively spared glomeruli</td>
</tr>
<tr>
<td>PEX 7p11.23</td>
<td>Corneal dystrophy, microphthalmia, retinal degeneration, cataract</td>
<td>Cyst formation, proteinuria, aminoaciduria, cortical dysplasia</td>
</tr>
<tr>
<td>Elastin 7q11.2</td>
<td>Stellate pattern of iris</td>
<td>Small, or solitary kidney pelvic kidney, nephrocalcinosis, renal insufficiency, renal artery stenosis, vesicoureteral reflex</td>
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<tr>
<td>P-type ATPase l3q14.3</td>
<td>Kayser-Fleischer corneal ring, cataract</td>
<td>Proximal renal tubular dysfunction, renal calculi</td>
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<td>Col(_4)A(_4) (2q35–q37)</td>
<td>Progressive anterior lenticonus, pigment epitheliopathy, cataract fundus punctatus, optic nerve drusen</td>
<td>Microscopic hematuria, nephritis, renal failure, nephrotic syndrome</td>
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<tr>
<td>Col(_4)A(_5) (xq11–q22)</td>
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<tr>
<td>Fibrillin 1 (FBN1) 15q21.1</td>
<td>Lens ectopia retina detachment, corneal flatness, hydromyogia, iris hypoplasia, early glaucoma</td>
<td>Focal segmental and/or mesangial glomerulonephritis, renal artery stenosis</td>
</tr>
<tr>
<td>JAG(_1) (NOTCH 1) 20q12</td>
<td>Protenia embryotoxon, keratoconus, strabismus, myopia, retinitis pigmentosa</td>
<td>Renal dysplasia, mesangiolipidosis, tubulointerstitial nephritis, tubulocystic disease, renal failure, medullary cystic disease</td>
</tr>
<tr>
<td>LCAT 16q22.1</td>
<td>Corneal dystrophy, corneal lipid deposits, corneal opacities, vascular retinopathy, arcus juvenitis, angiod streaks, papilledema, aniridia, megalocornea</td>
<td>Renal failure before 50 yr, Glomerular lacunes with dense bodies</td>
</tr>
</tbody>
</table>

\(^{a}\) EGF, epithelial growth factor; BMP7, bone morphogenetic protein7; PDGF, platelet degradation growth factor; ADPKD, autosomal dominant polycystic disease; \(v\)HL, von Hippel Lindau; TSC, tuberous sclerosis complex; PEX, peroxysome; LCAT, Lecithin:cholesterol acyltransferase.
non that is also observed when the metanephric mesenchyme is cultured in the absence of proper inductive tissues (38).

**BMP-7 and Eye Development.** Lens formation is the result of reciprocal inductive interaction between the optic vesicle and the surface ectoderm. Genetic evidence has demonstrated that the optic vesicle is required for lens formation in mice (39). This reciprocal interaction leads to the formation of the lens vesicle from the surface ectoderm at ~10.5 dpc (40). In about 35% of BMP-7m1/BMP-7m1 embryos, interaction between the optic vesicle and the surface ectoderm did not occur properly, resulting in the unilateral or bilateral absence of lens formation in these animals. The expression of BMP-7 during eye development suggests that it is involved directly in lens formation. The importance of BMP-7 during eye development has also been suggested by in vitro culture experiments showing that anti-BMP-7 antibodies can block lens formation in cultured rat embryos. However, 86% of the BMP-7m1 embryos did develop lens (or lenses), indicating that genes segregating in the F2 animals can suppress this aspect of the BMP-7-deficient phenotype.

**Renal Cyst and Ocular Abnormalities**

**Alagille Syndrome (AGS; OMIM 118450).** In addition to neonatal jaundice, features of this syndrome include posterior embryotoxon and retinal pigmentary changes and:

- In the heart: pulmonic valvular stenosis as well as peripheral arterial stenosis
- In the bones: abnormal vertebrae (butterfly vertebrae) and decrease in interpediculate distance in the lumbar spine
- In the nervous system: absent deep tendon reflexes and poor school performance
- In the facies: broad forehead, pointed mandible, and bulbous tip of the nose
- In the fingers: varying degrees of foreshortening (41,42)
- The syndrome has an autosomal dominant inheritance, and the gene is located at 20p12 (43). Most often, AGS leads to chronic liver disease in childhood with severe morbidity and a mortality of 10 to 20%. LaBrecque et al. (44) described 15 affected persons in four generations. They all presented with renal dyslasia and renal artery stenosis associated in some cases with hypertension. Simple ophthalmic examination of children with neonatal cholestatic jaundice and their parents should allow early diagnosis of AGS, eliminating the need for extensive and invasive investigations. The most common ocular abnormalities in patients were posterior embryotoxon (95%), iris abnormalities (45%), diffuse fundus hypopigmentation (57%), speckling of the retinal pigment epithelium (33%), and optic disc anomalies (76%). Microcornea was not associated with large refractive errors, and visual acuity was not significantly affected by these ocular changes. Martin et al. (45) described three children with Alagille syndrome, in two of whom a unilateral multicystic dysplastic kidney was detected by prenatal ultrasound. In the third child, a solitary cortical cyst was detected later in childhood. All had normal renal function, growth, and liver synthetic function but continued to have clinical and biochemical signs of cholestasis. Thus the authors concluded that AGS should be included in the differential diagnosis of cystic kidney disorders associated with cholestatic liver disease. A mesangiopathic glomerulopathy with fibrillar deposits and foam cells and medullary cysts have been described (46). Other renal lesions include membranous nephropathy and lamellated glomerular basement membrane (47). Cystic renal disease with or without renal dysplasia, tubulointerstitial nephritis, renal tubular acidosis, renal artery stenosis, renovascular hypertension, horseshoe kidney, and vesicoureteric reflux have also been reported in association with AGS.

- Woolfenden et al. (48) described two children with sporadic AGS associated with moyo-moya. They interpreted this finding as indicating that AGS is a vasculopathy. Li et al. (49) demonstrated that AGS is caused by mutations in the human homolog of Jagged-1 (Jag1), which encodes a ligand for Notch1. They concluded that AGS is caused by haplosufficiency of Jag1. They mapped the human Jag1 gene (OMIM 601920) to the AGS critical region within 20p12. Giannakidis et al. (50) detected parental mosaicism for a Jag1 mutation in 4 of 51 families in which mutations had been identified in the AGS patients and where parental DNA was available. The co-localization and genetic interaction of Jag1 and Notch2 (OMIM 600275) imply that this ligand and this receptor physically interact, forming part of the signal transduction pathway required for glomerular differentiation and patterning. Notch2(del1)/Notch2(del11) homozygotes also display myocardial hypoplasia, edema, and hyperplasia of cells associated with the hyaloid vasculature of the eye. These data identify novel developmental roles for Notch2 in kidney, heart, and eye development (51).

**Zellweger Syndrome (OMIM 214100).** Zellweger syndrome is a fatal recessively inherited disease with disturbed function of many organs. The disease is caused by a defect of peroxisomes, subcellular organelles, which are absent in these patients. Several genes are necessary for the formation and function of the peroxisomes. The clinical picture of Zellweger syndrome can be caused by defects in a number of genes. Ophthalmologic manifestations include corneal opacification, cataract, glaucoma, pigmentary retinopathy, tapetoretinal degeneration, and optic atrophy (52). Polycystic kidneys with adequate functional renal parenchyma and cortical renal cysts were described. The Zellweger gene is on chromosome 7q11.13.

**Autosomal Dominant Polycystic Kidney Disease (OMIM 601313, 173910).** Autosomal dominant polycystic kidney disease (ADPKD) is a frequent genetic disorder affecting 1 out of 1000 individuals. The predicted protein has been named polycystin. Cell-matrix interactions have been suggested to be important for kidney development (53), and there is some evidence that laminin-1 and its receptors could be involved (54).

It has been determined that the embryogenetic stages of eye and kidney development occur rather simultaneously (55). From the 7th to the 10th week, the development of the ocular
architecture progresses in parallel with the differentiation of the kidney tubules (56). It is conceivable that the unknown factor leading to the development of renal tubular cysts in utero might simultaneously affect the eye and the kidney. Meyrier et al. (57) reported a strong association between ADPKD and blepharochalasis. Other ocular abnormalities including severe myopia, cataracts, papilledema, and peripheral retinal pigmentation have also been described in association with ADPKD (58).

Mutant mice that develop severe kidney phenotypes as adults include the Bcl-2 mutant mice with polycystic kidneys (59), the s-laminin/laminin β2 mutant mice, which develop massive proteinuria (60), the epidermal growth factor receptor mutant mice with cystic dilations of the collecting ducts (61), the tensin mutant mice, which develop progressive kidney degeneration (62), and the cyclooxygenase 2 mutant mice, which die from chronic renal failure most likely as a result of reduced nephron mass (63).

Digenic inheritance have been reported for polycystic kidney disease, where it was hypothesized that cyst formation results from the inheritance of one germline mutation in one of two PKD1 or PKD2 genes, and the occurrence of a second-hit, somatic mutation in the other interacting gene, thereby generating a trans-heterozygous situation in the affected cystic cell (64).

**von Hippel Lindau Disease (OMIM 193300).** The von Hippel-Lindau (vHL) syndrome is transmitted as an autosomal dominant trait with variable penetrance. Its clinical manifestations include cerebellar and retinal hemangioblastomas, pancreatic cysts, carcinoma, renal cell carcinoma, and pheochromocytoma (65). The vHL gene is on chromosome 3 (3p25-26) (66) and functions normally as a tumor suppressor by inhibiting transcription elongation (67).

The classic ophthalmologic finding is hemangiosioblastoma, a round, red tumor of the retina with a pair of feeding vessels showing an increase in diameter and tortuosity. Angiomatosis retinae may cause severe impairment of vision as a result of retinal detachment. Blindness or near-blindness typically happens without preceding symptoms and without pain. Capillary hemangioma of the retina may occur as either an isolated retinal vascular abnormality or as one of the many systemic abnormalities of vHL disease. Progressive intraretinal and sub-retinal exudation occurs as the angioma develops. If it remains untreated, either exudative or tractional retinal detachment or retinoschisis may result (68). Retinal telangiectasia associated with facioscapulohumeral muscular dystrophy (69) and Alport syndrome may also cause massive outpouring of exudate into the outer retinal layers and may result in exudative retinal detachment.

Kidney disorders have been found in up to 60% of vHL subjects at autopsy. The mean age at detection of renal lesions is approximately 35 yr (65). Loin pain or complaints of an abdominal mass and, infrequently, gross hematuria have been reported, mainly in patients with large tumors. Hypertension, renal function deterioration, and proteinuria have rarely been observed in vHL patients with renal lesions. Cysts as numerous as in polycystic kidney disease are very seldom too (65). Renal cysts and angiomas develop in approximately two thirds of cases (70) and include benign cysts and renal cell carcinoma. In addition, renal adenomas, hemangiomas, and adrenal cell carcinoma occur but are rare. Simple cysts are most frequent and are observed in about 75% of patients. Renal cell carcinoma tends to occur in younger patients, has an equal gender distribution, and is usually bilateral and multicentric. The clear cell type of renal cell carcinoma is the most common type of cancer in vHL. Carcinomas occur in about one fourth of cases, metastasize in about half of those, and cause death in about one third (71). It is estimated that renal carcinoma will develop in approximately 70% of patients who survive to age 60 yr (70). Computer tomography scanning, which is more sensitive, should be performed every 3 yr or more frequently in patients with multiple cysts (70). The renal lesions, depending on the size and the number of the angioma, could generate enlargement of the kidney and may cause renal failure. Pheochromocytoma, which is often asymptomatic, may occur with equal frequency. Pheochromocytoma occurs in 10 to 19% of vHL patients. There is usually bilateral involvement. The median age is 28 yr. Polycythemia, due to the ectopic production of erythropoietin by the hemangioblastoma or carcinoma, is occasionally present and may disappear after the excision of the tumor (72).

**Sturge-Weber-Krabbe Syndrome (Phacomatosis Pigmentovascularis; OMIM 185300).** Sturge-Weber syndrome (SWS) or encephalotrigeminal syndrome is a dermato-oculo-neural syndrome involving cutaneous facial nevus flammeus in the area of the first and/or second division of the trigeminal nerve, ipsilateral glaucoma, ipsilateral diffuse cavernous hemangioma of the choroid, and ipsilateral leptomeningeal hemangioma (73). The classical cutaneous feature of SWS is facial nevus flammeus, which is usually unilateral and may be associated with hypertrophy of the involved skin of the face.

One of the oculan manifestations of SWS is diffuse choroidal hemangioma (74), usually on the same side as facial nevus flammeus. The ocular component manifests as glaucoma and vascular malformations of the conjunctiva, episclera, choroid, and retina. Glaucoma is present in approximately half of the cases on hemangioma’s facialis side. Patients in whom the lesion affects the upper eyelid are at increased risk of glaucoma (70). The Nevus of Ota is a melanocytic pigmentary disorder, most commonly involving the area innervated by the trigeminal nerve. Elevated intraocular pressure, with or without glaucomatous damage, is observed in 10% of the cases (75). Episcleral venous telangiectasia vessels were prominent features. Other ocular manifestations (retinal vascular tortuosity, iris heterochromia, choroidal hemangioma, buphthalmos, retinal detachment, and strabismus) also occurred (70–76). Optic neuropathy has not been reported as a component of this syndrome (77).

The involvement of the kidneys or urinary tract occurs usually by hemangiomas. Vascular manifestations occur within the renal pelvis, papilla, and urinary bladder. They are generally solitary, causing varying degrees of hematuria. Occasionally, the hemangioma may present as a mass with perirenal hematoma associated with other abnormalities, such as dupli-
cation of the inferior vena cava or abnormalities of the renal venous system (78).

**Tuberous Sclerosis Complex (OMIM 191100).** Tuberous sclerosis complex (TSC, synonym: Bourneville-Pringle disease) (79) an autosomal dominant disease with variable penetrance, is a multisystem disorder characterized by the formation of angiomylipomas or tubers affecting predominantly the brain, the skin (called adenoma sebaceum), the kidneys, the eyes, and the heart (80). Two different genetic loci have been identified: one on chromosome 9 (TSC1) and one on chromosome 16p (TSC2) that is immediately adjacent to the gene for the most common form of autosomal dominant polycystic kidney disease (PKD1) (81).

The most suggestive eye finding of TSC is the retinal astrocytic hamartoma found in 50 to 85% of patients (82). Other internal eye findings may include atypical colobomas, microphthalmia, exophthalmos, hypomelanic maculs, and optic nerve atrophy.

The main renal manifestations of TSC are angiomylipomas, cysts, and renal cell carcinomas. Hematuria is not a common feature, possibly because of the expansive rather than infiltrative growth. On rare occasions, patients may have a catastrophic presentation of sudden flank pain associated with a palpable abdominal mass and symptoms of anemia. This complex syndrome is referred to as the Wunderlich triad and is caused by spontaneous rupture of the tumor into the retroperitoneal space (83). Less than 40% of the patients with renal angiomylipoma have significant proteinuria. Massive proteinuria are rare. There is a high incidence of hypertension in TSC, even when the renal function is normal (84). Many patients with tuberous sclerosis have no symptoms referable to the kidney. Renin-dependent hypertension, due to focal areas or ischemia around the cyst, and chronic renal failure also can occur. Rarely, hypertension may result from renal artery atherosclerosis (85). The development of end-stage renal disease is unusual and appears to result primarily from the replacement and compression of the renal parenchyma by angiomylipoma and cysts. The angiomylipoma is found in 50 to 80% of the patients and bilateral localisation has also been reported. The main manifestations of the renal angiomylipomas relate to their potential for hemorrhage (hematuria, intratumoral, or retroperitoneal hemorrhage) and mass effects (abdominal or flank mass and tenderness, hypertension, renal insufficiency) (86). Angiomylipomas can also cause fever of unknown origin (87). Cystic disease is the second most common renal manifestation of TSC (88). Renal cysts in TSC are predominately bilateral, multiple and vary in size from microscopic “hamartial gers” to that of a “grapefruit,” often similar to the adult type of polycystic kidney disease. The major clinical problem associated with severe cystic changes in TSC is the development of nephrolithiasis, hypertension, and renal failure. The majority of the patients with TSC that present with polycystic-like kidneys at an early age have a contiguous gene syndrome with deletions affecting both the TSC-2 and the PKD1 genes (89). Renal cell carcinoma in TSC has also been reported (90). Other associations rarely recognized include renal interstitial disease (91), focal segmental glomerulosclerosis, glomerular microharmartomas (92), renal artery stenosis (93), ureteropelvic junction stenosis, and horseshoe kidney.

**Bardet-Biedl Syndrome (OMIM 209900).** Bardet-Biedl syndrome (BBS) is a genetically heterogeneous disorder with the primary features of obesity, pigmentary retinopathy, polydactyly, renal malformations, mental retardation, and hypogonadism. BBS is considered an autosomal recessive disorder, with increased risk for diabetes mellitus, hypertension, and congenital heart disease. The incidence of BBS is approximately 1/100,000 with a predicted heterozygote frequency of 1/160, and it has been suggested that heterozygotes are at increased risk of obesity and hypertension. What was once thought to be a homogeneous autosomal recessive disorder is now known to map to at least six loci: 11q13 (BBS1), 16q21 (BBS2), 3p13 p12 (BBS3), 15q22.3 q23 (BBS4), 2q31 (BBS5), and 20p12 (BBS6). There has been considerable interest in identifying the genes that underlie BBS, because some components of the phenotype are common. Cases of BBS mapping to BBS6 are caused by mutations in MKKS; mutations in this gene also cause McKusick-Kaufman syndrome (hydrometrocolpos, post-axial polydactyly and congenital heart defects). The BBS6 protein has similarity to a Thermoplasma acidophilum chaperonin, whereas BBS2 and BBS4 have no significant similarity to chaperonins. It has recently been suggested that three mutated alleles (two at one locus, and a third at a second locus) may be required for manifestation of BBS (trialectic inheritance). The identification of the gene BBS1 is a frequent cause of BBS and is not involved in triallelic inheritance (94).

Ocular abnormalities include rod-cone dystrophy, onset be end of second decade (major), retinitis pigmentosa, strabismus, and cataracts Renal abnormalities have been described in up to 100% of BBS patients, and renal failure occurring in 30 to 60% of patients is the major cause of morbidity and early mortality in BBS. Hypertension has been noted in 50 to 66% of cases. Dysplasia, chronic glomerulonephritis, cystic tubular disease, calycal and lower urinary tract malformations, defects of tubular concentrating ability, nephrogenic diabetes insipidus, and microaneurysms and occlusions in renal arterioles have all been reported (95).

**Glomerulopathies and Eye Abnormalities**

**Alport Syndrome.** The classic phenotype as described by Alport (96) is nephritis, often progressing to renal failure, and sensorineural hearing loss affecting both genders in successive generations. The renal disease becomes evident as recurrent microscopic or gross hematuria as early as childhood, earlier in males than in females. Progression to renal failure is gradual and usually occurs in males by the fifth decade. Nephrotic syndrome is unusual but has been reported. The renal histology is nonspecific; both glomerular and interstitial abnormalities, including foam cells, occur. Immunofluorescence studies have provided little evidence for an immunologic basis for renal damage. Hearing loss, which is sensorineural and primarily affects high tones, occurs in 30 to 50% of relatives with renal disease. In about 85% of AS pedigrees, the disease is X-linked (Xq22) (OMIM 301050), and mutations identified so far are in the α5 (IV) collagen chain gene (COL4A5) (97). In the vast
majority of the remaining families, the transmission is autosomal recessive with mutations detected in the genes coding α3 (IV) and α4 (IV) collagen chains (chromosome 2) (98). The gene frequency of AS is about 1 in 5000, and the disease accounts for about 0.6% of all patients who start renal replacement therapy in Europe. Diffuse leiomymatosis and megathrombocytopenia have also been described in AS.

The ocular manifestations (15 to 30%) of AS mainly involve the lens. Bilateral anterior lenticonus is the most specific abnormality (97–99). When present, the lenticonus is bilateral in about 75% of patients. It is far more common in affected males but may occur in females. Lens opacities may be seen in conjunction with lenticonus, occasionally resulting from rupture of the anterior lens capsule. Anterior lenticonus has been confused with anterior pyramidal opacities, which may be associated with microcornea and anterior chamber cleavage anomalies. Macular flecks are a second characteristic feature of AS. Govan (100) concluded that the diagnosis of AS may be made on the presence of characteristic features. Nontraumatic recurrent corneal erosion (101) and an association with a macular lesion similar to the cone dystrophy have only infrequently been reported. Pigmentary changes in the perimacular region, consisting of whitish or yellowish granulations surrounding the foveal area and corneal endothelial vesicles, have also been reported. Cataract, spherophakia, and cone dystrophy were also described in AS.

Persistent microscopic hematuria is a constant feature in male patients with AS. Many also have episodic gross hematuria, precipitated by upper respiratory infections, during the first two decades of life. Proteinuria is usually absent during the first few years of life but develops eventually in males with X-linked AS and proteinuria increases progressively with age and may culminate in the nephrotic syndrome. Hypertension also increases in incidence and severity with age. The rate of progression to renal failure is fairly constant among affected males within a particular family, although significant intrakindred variability in the rate of progression to renal failure has occasionally been reported.

Anti-GBM disease appears in 5 to 10% of Alport patients who received a kidney transplant after the development of renal failure. These antisera do not bind to Alport glomerular basement membrane and were found to be reactive to the α3(IV) chain. Kalluri et al. (102) found that posttransplant anti-GBM alloantibodies harvested from an X-linked Alport patient with complete COL4A5 gene deletion that were specifically targeted to the α3(IV) chain. In further studies, Kalluri et al. demonstrated posttransplant anti-α3(IV) collagen alloantibodies in a patient with autosomal recessive AS caused by deletion of the last 198 amino acids of the α3(IV) chain. Milliner et al. (103) estimated that approximately 1 to 5% of Alport patients who received renal transplants develop a specific anti-GBM nephritis, subsequently leading to loss of the renal graft. These data suggested that Alport syndrome patients with a type IV collagen mutation resulting in absence of the NC domain have an increased risk of developing anti-GBM nephritis after renal transplantation.

In nephrology, the association of renal failure and deafness immediately brings to mind the AS with which every nephrologist is well acquainted; this is not always correct. Moreover, there are various inherited conditions in which sensorineural deafness is associated with renal disease, including Alport’s variants, Muckle-Wells syndrome, Refsum disease, Cockayne syndrome, renal tubular acidosis, ichthyosis and prolinuria, Charcot-Marie-Tooth syndrome, Alström’s syndrome, ataxia, hyperuricemia, photomyoclonus, familial spastic paraplegia with intellectual retardation, mitochondrial disorders, and hypo and hyperparathyroidism (104).

**Nail Patella Syndrome (NPS, Onychoosteedysplasia)** (OMIM 161200). Hereditary osteo-onychodysplasia (HOOD) or nail-patella syndrome (NPS) is a rare, autosomal dominant disorder. Dysplasia of the nails and absent or hypoplastic patellae are the cardinal features but others are iliac horns, abnormality of the elbows interfering with pronation and supination, and in some cases nephropathy. Renal involvement is an inconstant finding as the presence of fibrillar collagen within the GBM. The gene is closely linked to those coding for ABO blood groups and for adenyate kinase. The three genes are located at the distal end of the long arm of chromosome 9 (9q34) (105).

Ocular manifestations include a dark pigmentation at inner margin of iris, Strabismus, lens opacities, Lester sign, microcornea, microphthalmia, keratoconus, cataracts, heterochromia, anisocoria, and nystagmus have also been reported (106). Anterior segment anomalies can lead to impaired vision and glaucoma (107).

Clinical renal involvement seems to occur in about 30 to 40% of cases (108). Proteinuria, sometimes associated with microscopic haematuria, is the most frequent presenting feature. Nephrotic syndrome was observed in 3 of 122 patients reviewed by Meyrier et al. (109). Progression to end-stage renal failure occurs in about 30% of patients with renal symptoms. Cases of rapid evolution to renal failure have been observed in the pediatric population. Various types of superimposed nephritis, Goodpasture syndrome (110), membranous nephropathy (111), necrotizing angiitis (112), and IgA nephropathy (109) have been observed in HOOD patients. As demonstrated by electron microscopy by Morita et al. (113) among others, many collagen fibrils are present in the thickened basement membranes and in mesangial matrix of otherwise normal glomeruli. Abnormalities of collagen at this site have also been demonstrated in AS. Both of these conditions may be special forms of heritable disorders of connective tissue.

The Goodpasture antigen, an autoantibody, is directed against type IV collagen of basement membrane or some element closely associated with it. The occurrence of Goodpasture syndrome in a patient with NPS (110) may be more than a coincidence. Taguchi et al. (114) demonstrated that characteristic ultrastructural changes in the glomerulus can be present, even in patients without apparent clinical renal involvement. From study of a large family with 30 patients with NPS (which the authors referred to as HOOD), Looij et al. (115) concluded that a person with NPS has a risk of about 1 in 4 of having a child with NPS nephropathy and a risk of about 1 in 10 of having a child in whom renal failure will develop. The nail-patella locus and the ABO blood group locus are
linked. The recombination fraction is about 10%, but it is higher in females than in males (116). The LIM-homeodomain protein Lmx1b plays a central role in dorsal/ventral patterning of the vertebrate limb. Targeted disruption of Lmx1b results in skeletal defects, including hypoplastic nails, absent patellae, and a unique form of renal dysplasia (117). Dreyer et al. (118) showed that the Lmx1B gene maps to 9q in the same region than the NPS locus by fluorescence in situ hybridization. Most NPS families only inquire about prenatal diagnosis in the hope that severity can be predicted. It is in this regard that ultrasound may be of use in detecting early signs of severe renal damage, because there is no correlation between the Lmx1b mutation and the presence of kidney disease or overall NPS severity.

**LCAT Deficiency (OMIM 245900).** Familial lecithin: cholesterol acyltransferase (LCAT) deficiency syndrome is inherited as an autosomal recessive disorder and is characterized by disturbances in lipid metabolism. The gene for LCAT is found on the long arm of chromosome 16 in the region 16q22 (119) and appears to be linked to the serum α-haptoglobin locus (120). Clinically this enzymatic defect is characterized by diffuse corneal opacities: “arcus lipoides juvenilis”, target cell hemolytic anemia, lipid accumulation, and “sea-blue” histiococytes on bone marrow, spleen, and arterial walls, and decreased cone plasma esterified cholesterol and kidney defects.

Corneal opacities are found in all patients. They consist of numerous minute, grayish dots in the entire corneal stroma giving the cornea a cloudy to misty appearance. Arcus juvenilis may be seen in younger patients with blue sclera, megacornea, or aniridia. Fundus changes, as aneurysmatic vein dilatations angiod streaks, papilledema, retina arterial occlusion, and disc protrusion have been occasionally described.

Renal impairment with proteinuria before the age of 50 yr is a common feature that is the major cause of morbidity and mortality. Typical histologic findings are lacunae containing characteristic dense bodies in the glomerular and tubule membranes and the interstitium.

The gene encoding LCAT on chromosome 16 is the site of the mutation in both Norum disease and fish-eye disease. According to Norum et al. (121), there is apparently no increased risk of premature atherosclerotic cardiovascular disease in either form of LCAT deficiency.

**Ocular Abnormalities Associated with Proximal Renal Tubular Acidosis**

The human Na⁺-HCO₃⁻-cotransporter (NBC1) gene encodes two electrogenic sodium-bicarbonate cotransport proteins, pancreatic type (pNBC1) and kidney type (kNBC1), which are candidate proteins for mediating electrogenic sodium-bicarbonate cotransport in ocular cells. Both kidney type (kNBC1-1) and pancreatic type (pNBC1-1) transporters are present in the corneal endothelium, trabecular meshwork, ciliary epithelium, and lens epithelium. In the human lens epithelial (HLE) cells, RT-PCR detected mRNAs of both kNBC1-1 and pNBC1-1. Although a Na⁺-HCO₃⁻ cotransport activity has not been detected in mammalian lens epithelia, the normal transport activity of NBC1-1 is indispensable not only for the maintenance of corneal and lenticular transparency but also for the regulation of aqueous humor outflow. Mutations in the coding region of the human NBC1 gene in exons common to both pNBC1 and kNBC1 result in a syndrome with a severe ocular and renal phenotype (blindness, band keratopathy, glaucoma, cataracts, and proximal renal tubular acidosis) (122).

**References**


