Retinal Abnormalities Characteristic of Inherited Renal Disease

Judy Savige, Sujiva Ratnaike, and Deb Colville

Department of Medicine, Northern Health, The University of Melbourne, Epping, Victoria, Australia

ABSTRACT

Many inherited renal diseases have retinal features that are helpful diagnostically. These include coloboma, drusen, atrophy and pigmentation (retinitis pigmentosa), hamartoma, vascular anomalies, and crystals. Retinal abnormalities occur because the kidney and retina share developmental pathways and structural features including basement membrane collagen IV protomer composition and their vascularity, and because both the kidney and retina are functionally dependent on ciliated cells. Diagnosis of inherited renal disease is important because of the risks of further renal and systemic complications, the implications for other family members, the predictability of the clinical course, and the possibility of treatment. Furthermore, retinal abnormalities may help explain the pathogenesis of the renal disease, and can sometimes be used to monitor its course.

Inherited disease accounts for half of all children and 1 in 5 adults with end-stage renal failure (Table 1).1 The prevalence of individual diseases varies from 1 in 5 to 10,000 for Alport syndrome and membranoproliferative glomerulonephritis type 2, to 1 in 50,000 for the rarer conditions such as Fabry disease.2 The challenge is to identify inherited renal disease when the phenotype is mild or atypical, or when there is no family history, which occurs with de novo mutations, recessive inheritance, and dominant disease with variable expression or penetrance.

Inherited renal disease is suspected when there is a family history of similar features, or when abnormalities affect multiple systems without another obvious explanation.3 Databases such as ORPHANET (http://www.orpha.net) and OMIM (http://www.ncbi.nlm.nih.gov/omim) suggest patterns of organ involvement. Many inherited renal diseases have hearing loss (Table 2), and ocular, especially retinal, abnormalities. Notable exceptions, based on current knowledge, are the autosomal dominant and recessive forms of polycystic kidney disease, medullary cystic kidney disease, and thin basement membrane nephropathy.

WHY THE KIDNEY AND RETINA SHARE INVOLVEMENT IN INHERITED DISEASES

Inherited renal disease often also involves the retina because the kidney and retina develop at the same embryonic stage and share developmental pathways;4 the glomerular filtration barrier and retinochoroidal junction are structurally similar;5 the glomerulus and chorioretina are both large capillary beds, and the renal epithelial (podocyte) and retinal pigment epithelial (RPE) cells are critically dependent on cilia to function.

The Kidney and Eye Share Developmental Pathways

Both the PAX and WT1 pathways are important in the embryogenesis of the kidney and retina.4 The PAX genes encode nuclear transcription factors that control development of the kidney, eye, ear, brain, vertebral column and limb muscles.6 PAX2 is required for development of the urogenital tract, eye, ear, and brain. The WT1 gene is necessary for ureteric bud formation and retinal ganglion cell differentiation.7,8 Mutations in PAX2 result in the renal-coloboma syndrome with vesicoureteric reflux, and WT1 mutations produce Wilm’s tumor, and the WAGR, Frasier, and Denys-Drash syndromes.9–11

The Retinochoroidal Junction Resembles the Glomerular Filtration Barrier

RPE cells, Bruch’s membrane, and the fenestrated choriocapillaries of the retina resemble the podocytes, glomerular basement membrane (GBM), and fenestrated capillaries of the glomerular tuft, respectively. The epithelial cells have organ-specific functions, the basement membranes support the adjacent structures and form a barrier that prevents the

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Correspondence: Dr. Judy Savige, Department of Medicine, Northern Health, The University of Melbourne, The Northern Hospital, Epping, Victoria 3076, Australia. Phone: +61 3 8405 8823; Fax: +61 3 8405 8724; E-mail: jasavige@unimelb.edu.au

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Table 1. Inherited renal diseases that present in adults as well as children

| Autosomal recessive polycystic kidney disease |
| Alport syndrome |
| Membranoproliferative glomerulonephritis |
| Neophronphthisis |
| Bardet-Biedl syndrome |
| Alagille syndrome |
| MELAS syndrome |
| Kears-Sayre syndrome |
| LCAT deficiency |
| Cystinosis |
| Fabry disease |

Table 2. Inherited renal diseases associated with hearing loss

| Renal coloboma syndrome |
| CHARGE syndrome |
| Alport syndrome |
| MELAS syndrome |
| Kears-Sayre syndrome |
| Leber Amaurosis |
| Alstrom syndrome |
| Fabry disease |
| Charcot-Marie-Tooth disease |
| Bartter syndrome |
| Wolfram syndrome |
| Hurler syndrome |
| Nephronophthisis |
| Bardet-Biedl syndrome |

Retinal abnormalities in inherited renal disease include coloboma, drusen, atrophy and pigmentation (retinitis pigmentosa), hamartoma, vascular anomalies, and crystals (Table 3; Figure 1). These changes may also be accompanied by the retinal associations of renal failure such as hemorrhage, arteriolar narrowing, exudates, infarcts, calcification, and macular degeneration.

Coloboma result from defective closure of the embryonic fissure of the optic cup. These defects are typically located in the lower part of the iris, chorioretina, or optic disc. Optic disc coloboma occur in vesicoureteric reflux and other structural urinary tract disease. Optic disc and chorioretinal and iris coloboma are found in the CHARGE and COACH syndromes, and possibly in nephropathias and tuberous sclerosis. Coloboma are identified by careful ophthalmoscopic examination and photography of both fundi of the presenting individual and their family members. Coloboma are typically asymmetrical, with, for example, a normal eye or mild defect in one eye, and a severe central abnormality in the other. Likewise, the severity of the defect varies in individual members of a family. There is no treatment and they may be complicated by glaucoma, retinal detachment, and central serous retinopathy.

Renal-Coloboma Syndrome (Papillorenal Syndrome, OMIM 120330)

Coloboma are found in <5% of patients with reflux nephropathy or other renal structural defects but many are probably unrecognized. Inheritance is autosomal dominant, but only 50% of patients with the renal-coloboma syndrome have PAX2 mutations. The other genes are not known. PAX2 mutations are different in each family and have their effect through interfering with the vascular supply of the urinary tract and eye. Some mutations cause reflux only without coloboma but none causes isolated coloboma. The renal abnormalities in renal-coloboma syndrome include vesicoureteric reflux, renal hypoplasia, multicystic or dysplastic kidneys, and renal failure. The age at presentation and rate of progression to renal failure vary even within families. Ocular features vary from optic disc pits to large chorioretinal coloboma, and abnormalities are usually asymmetrical. Pits are subtle and may be overlooked on ophthalmoscopy. In more severe disease the retinal vessels emerge from the periphery of the optic disc. The surrounding retina appears atrophic. Vision varies from normal to severely impaired. Fewer than 20% of patients have associated sensorineural hearing loss, seizures, Arnold-Chiari malformations, or skin and joint laxity. Patients with papillorenal syndrome should be monitored for ophthalmologic complications and other family members screened carefully for optic disc defects. PAX2 mutations do not occur in the CHARGE or COACH syndromes and do not cause iris coloboma.

CHARGE Syndrome (OMIM 214800)

This comprises Coloboma of the iris, Heart anomalies, Atresia of the nasal choanae, Retardation of growth and/or development, Genital and/or urinary abnormalities (hypogonadism), and Ear abnormalities with deafness. This condition affects 1 in 10,000 individuals and demonstrates autosomal dominant inheritance. Sixty percent of patients have a mutation in the CHD7 gene which codes for a DNA-binding protein involved in early embryonic development. Ninety percent of chil-
Children have coloboma of the optic disc, chorioretina or iris, 20% to 40% have a structural urinary tract anomaly including solitary kidney, renal hypoplasia, duplex kidney, or vesicoureteric reflux, and 60% have heart defects (often Fallot’s tetralogy). Kidney problems are often associated with ipsilateral facial palsy.

**WAGR Syndrome (OMIM 194072)**

This is a rare genetic syndrome with Wilms’ tumor, Aniridia, Genitourinary anomalies including gonadal tumors, mental Retardation, and obesity. It results from a deletion involving the contiguous genes, PAX6 and WT1, on chromosome 11. PAX6 regulates neuronal migration in the cerebral cortex. Loss of these genes produces ocular and genitourinary anomalies, respectively. The iris is deficient, and the optic nerve and fovea are hypoplastic. These abnormalities may be complicated by a fragile cornea, glaucoma, and retinal detachment. Fifty percent of patients develop renal cancer.

**COACH Syndrome (OMIM 216360)**

This condition is characterized by Cerebellar vermis hypo/aplasia, Oligophrenia, congenital Ataxia, ocular Coloboma, and Hepatic fibrosis. This affects 1 in 200,000 individuals and inheritance is autosomal recessive. It probably represents a subtype of Joubert syndrome with liver disease. Mutations affect one of the MKS3, CC2D2A, or RPGRIP1L genes. MSK3 mutations account for nearly 60% of cases. Patients may have the molar tooth sign, a midbrain-hindbrain malformation also seen in Joubert syndrome and congenital hepatic fibrosis. Although they have medullary renal cysts, they do not necessarily develop renal failure. Optic nerve coloboma, mental retardation, nystagmus, and congenital ataxia occur.

**Drusen**

Drusen are yellowish-white deposits of cellular and inflammatory debris

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### Table 3. Inherited renal diseases associated with retinal abnormalities

<table>
<thead>
<tr>
<th>Retinal Abnormality</th>
<th>Disease</th>
<th>Retinal Features</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coloboma or cavitary abnormality of the optic disc</td>
<td>PAX2 mutations (&quot;papillorenal syndrome&quot;)</td>
<td>Includes optic pits, optic disc coloboma, the morning glory anomaly, and the papillorenal syndrome</td>
<td>Normal to severe impairment depending on the defect</td>
</tr>
<tr>
<td></td>
<td>COACH syndrome</td>
<td>Optic disc, chorioretinal and iris coloboma</td>
<td>No treatment available</td>
</tr>
<tr>
<td></td>
<td>CHARGE syndrome Nephronophthisis (uncommonly) Tuberous sclerosis (uncommonly)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drusen</td>
<td>Alport syndrome</td>
<td>Perimacular dots and flecks and peripheral coalescing flecks; these are not technically drusen</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Membranoproliferative glomerulonephritis type II</td>
<td>Macular drusen, eventually retinal atrophy and hemorrhage</td>
<td>Needs regular review; may deteriorate</td>
</tr>
<tr>
<td>Retinal pigmentation/atrophy</td>
<td>MELAS syndrome Nephronophthisis LCAT deficiency</td>
<td>Retinal atrophy, Atrophy, pigmentation, Usually normal, sometimes macular degeneration and hemorrhage</td>
<td>Normal to severe impairment, Night blindness to severe impairment, May become severe</td>
</tr>
<tr>
<td></td>
<td>Alstrom syndrome Alagille syndrome</td>
<td>Retinal atrophy, optic disc drusen</td>
<td>May become severe, May become severe</td>
</tr>
<tr>
<td>Phakomatoses</td>
<td>Tuberous sclerosis Neurofibromatosis</td>
<td>Hamartoma, useful diagnostically Hamartoma, optic nerve glioma</td>
<td>Normal</td>
</tr>
<tr>
<td>Vascular abnormalities</td>
<td>HANAC Fabry disease Von Hippel Lindau syndrome</td>
<td>Tortuous retinal vessels Tortuous retinal vessels Haemangioblastoma, tortuous vessels</td>
<td>Normal</td>
</tr>
<tr>
<td>Amyloidosis Sturge-Weber syndrome Ehlers Danlos syndrome</td>
<td>Plaques around blood vessels, hemorrhage, infarcts Tortuous retinal vessels Angioid streaks</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Crystals</td>
<td>Oxalosis Cystinosis</td>
<td>Highly refractile crystals Highly refractile crystals</td>
<td>Normal</td>
</tr>
<tr>
<td>Bartter/Gitelman syndromes</td>
<td>Yellow-white calcium deposits in the mid-periphery</td>
<td></td>
<td>Normal</td>
</tr>
</tbody>
</table>
located beneath the RPE. They are obvious on fundus ophthalmoscopy and photographs especially red-free images. Occasional drusen occur normally with aging and increased numbers are found with some forms of glomerulonephritis.\textsuperscript{45} The \textit{dots and flecks} in Alport syndrome are not technically drusen because they affect the internal limiting membrane rather than the RPE.\textsuperscript{46} They are smaller than the drusen in membranoproliferative glomerulonephritis (dense deposit disease). These are identical to the drusen in macular degeneration but are present from early adulthood. (H) Late form of dense deposit disease with extensive retinal drusen, hemorrhage, and atrophy. These individuals should be assessed and monitored by an ophthalmologist because of the risk of complications and the possibility of treatment. (I) Retinal drusen and atrophy in Jeune syndrome, a form of nephronophthisis. (J) Red-free images of Jeune syndrome in which the abnormalities are more obvious. (K) Retinal atrophy in Joubert syndrome, another form of nephronophthisis, demonstrated by optical coherence tomography. The black line indicates peripapillary thickness is 1% normal. (L) Retinal atrophy in MELAS syndrome. The patient initially had poor vision that progressed. (M) Chorio-retinal atrophy in Kearns Sayre syndrome. The retina is thinned and depigmented. Vision was affected. (N) Hamartoma in tuberous sclerosis. A white tuber with fine linear hemorrhage was present unilaterally. This abnormality is found in the majority of patients with tuberous sclerosis and must be distinguished from retinal infarcts due to hypertension, diabetes, or lupus. (O) Corkscrew vessels in Fabry syndrome. These are asymptomatic but sudden visual loss may occur with central artery occlusion. These must be distinguished from the changes in hypertension. (P) Von Hippel Lindau syndrome. Tortuous vessels are seen leading to a hemangioblastoma just outside the field. The obvious macular lipid exudates are due to leakage from abnormal vessels. Vision was impaired.

Figure 1. Retinal abnormalities in inherited renal disease. (A) Optic pit. This is a mild form of the optic disc coloboma that occurs with reflux nephropathy due to \textit{PAX2} mutations. It may also be found in the CHARGE and COACH syndromes. Vision was normal in this eye but coloboma are typically asymmetrical. (B) Morning glory anomaly. Vision was impaired. (C) Normal central retina. The central retina was also normal in the fellow eye. This individual had a child with an iris coloboma and single kidney. (D) This is the peripheral retina of the individual whose fundus is shown in (C). Retinal coloboma were present in the periphery bilaterally. (E) Dot and fleck retinopathy in Alport syndrome. The retinopathy spares the macula and is bilateral. Vision was not affected; (F) Peripheral retinopathy in Alport syndrome. This is more common than the central retinopathy and comprises confluent dots and flecks \textgreater 2 disc diameters from the foveola. Again vision was not affected. (G) Widespread large soft macular drusen in membranoproliferative glomerulonephritis (dense deposit disease). These are identical to the drusen in macular degeneration but are present from early adulthood. (H) Late form of dense deposit disease with extensive retinal drusen, hemorrhage, and atrophy. These individuals should be assessed and monitored by an ophthalmologist because of the risk of complications and the possibility of treatment. (I) Retinal drusen and atrophy in Jeune syndrome, a form of nephronophthisis. (J) Red-free images of Jeune syndrome in which the abnormalities are more obvious. (K) Retinal atrophy in Joubert syndrome, another form of nephronophthisis, demonstrated by optical coherence tomography. The black line indicates peripapillary thickness is 1% normal. (L) Retinal atrophy in MELAS syndrome. The patient initially had poor vision that progressed. (M) Chorio-retinal atrophy in Kearns Sayre syndrome. The retina is thinned and depigmented. Vision was affected. (N) Hamartoma in tuberous sclerosis. A white tuber with fine linear hemorrhage was present unilaterally. This abnormality is found in the majority of patients with tuberous sclerosis and must be distinguished from retinal infarcts due to hypertension, diabetes, or lupus. (O) Corkscrew vessels in Fabry syndrome. These are asymptomatic but sudden visual loss may occur with central artery occlusion. These must be distinguished from the changes in hypertension. (P) Von Hippel Lindau syndrome. Tortuous vessels are seen leading to a hemangioblastoma just outside the field. The obvious macular lipid exudates are due to leakage from abnormal vessels. Vision was impaired.

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located at the macula. They resemble the drusen in macular degeneration but occur in early adulthood and are accompanied by renal manifestations.

Alport Syndrome (X-Linked OMIM 301050; Autosomal Recessive OMIM 203780)

Alport syndrome affects 1 in 10,000 individuals and accounts for 2% of adults with ESRD. At least 80% of patients have X-linked disease with COL4A5 mutations and the others have autosomal recessive or dominant inheritance with mutations in the COL4A3 or COL4A4 genes. These genes code for the chains that comprise the collagen IV $\alpha_3\alpha_4\alpha_5$ protomer which is found in the GBM, the stria vascularis of the cochlea, cornea, lens capsule, and internal limiting membrane, and Bruch’s membrane of the retina. Individuals with Alport syndrome have hematuria and develop kidney failure, hearing loss, corneal dystrophy, lenticonus, and retinopathy. Retinopathy is present in half the males and 1 in 5 females with X-linked disease, and probably the majority of those with recessive disease. Central perimacular dots and flecks and retinal thinning are typical and, rarely, a macular hole occurs especially in the temporal macula. In severe disease the flecks outline a perimacular lozenge. Peripheral flecks are more common than the perimacular retinopathy. Retinal abnormalities are best visualized using red-free photographs and the peripheral retinopathy requires multiple images. Vision is not affected. The central and peripheral retinopathies are diagnostic for Alport syndrome, but the diagnosis may also be confirmed with a positive family history, GBM lamellation, and absence of the $\alpha_3\alpha_4\alpha_5$ protomers from the kidney or skin, or genetic testing. Many mutations have been described in X-linked Alport syndrome, and they are generally different in each family. Certain variants, such as large deletions and rearrangements, nonsense mutations, and carboxy terminus missense mutations, result in early onset renal failure and retinopathy in males. Many fewer mutations have been described in recessive and the rare dominant forms, and their effect on phenotype is not clear.

Membranoproliferative Glomerulonephritis Type 2 (Dense Deposit Disease, or Mesangiocapillary Glomerulonephritis, Associated with Factor H Deficiency, OMIM 609814)

This accounts for 2% of all glomerular disease. Patients have hematuria and proteinuria and develop renal impairment by early adulthood. Facial and shoulder girdle lipodystrophy, and C3 nephritic factor, and low C3 levels may occur. At least some forms of this disease are inherited, and mutations and disease haplotypes have been identified in the complement Factor H (CFH) gene. The intramembranous GBM deposits and retinal drusen have an identical composition. Vision is affected, and patients should be assessed and reviewed regularly by an ophthalmologist because of the risk of retinal complications such as neovascular membranes.

RETINAL ATROPHY AND PIGMENTATION (RETINITIS PIGMENTOSA)

Individuals with renal disease and retinal atrophy first complain of poor night vision and even tunnel vision. Initially, the abnormality is only demonstrated with an electroretinogram but subsequently the retinal appearance is abnormal with pallor, pigmentation and mottling, attenuated arterioles and venules, and obvious chorioidal vessels.

Nephronophthisis

These diseases affect 1 in 50,000 individuals and account for 10% to 25% of all children with inherited renal failure. Inheritance is autosomal recessive. Mutations affect the NPHP1 through NPHP10 (nephrocystin) genes. Homozygous NPHP1 mutations account for 25% of patients, and mutations in the other genes, each for <3%. These genes code for proteins found in the primary cilia or centrosome, and result in defective signal-
genes. The kidneys are often cystic. Other clinical features include hepatic fibrosis, polydactyly, cerebellar ataxia (with cerebellar vermis hypoplasia and the molar tooth sign on MRI), and abnormal eye movements including rotary nystagmus, psychomotor retardation, and developmental delay. Retinal abnormalities include retinitis pigmentosa and possibly chorioretinal coloboma. As with the Senior Loken syndrome, the retinitis pigmentosa is often severe and the electoretinogram is abnormal early.

Cogan syndrome (oculomotor apraxia; OMIM 257550) is also due to NPHS mutations and may be a mild form of Joubert syndrome. Renal failure, poor hearing, and reduced muscle tone occur but there are no retinal abnormalities.

Meckel-Gruber syndrome (OMIM 249000) may be caused by mutations in the same genes as Joubert syndrome but is fatal in early life. It is characterized by cystic kidney dysplasia, liver fibrosis, occipital encephalocoele, and polydactyly.

Jeune syndrome (asphyxiating thoracic dystrophy; OMIM 208500) is characterized by cystic kidney disease, a long narrow thorax, short limb dwarfism, brachydactyly, and other skeletal defects. Respiratory distress may be severe. Retinal atrophy occurs, but is mild.

Alstrom disease (OMIM 203800) is due to mutations in the ALMS1 gene and clinically resembles the Bardet-Biedl syndrome. Affected individuals have renal failure with FSGS and tubulointerstitial fibrosis. They also have hearing loss, liver dysfunction, dilated cardiomyopathy, delayed puberty, obesity, and diabetes without mental retardation, polydactyly, or hypogonadism. Retinal atrophy occurs with large pigment clumps, vascular attenuation, and optic disc pallor. Vision is poor.

Nephronophthisis and its variants must be distinguished from Medullary cystic kidney disease (OMIM 191845), which presents in adulthood, and demonstrates autosomal dominant inheritance. It is often caused by mutations in the UMOD gene, which codes for uromodulin, or Tamm Horsfall protein. This disease typically results in renal failure in middle age, sometimes with a high serum urate, but there are no known retinal associations.

Alagille Syndrome (Arteriohepatic Dysplasia, OMIM 118450) This is very rare and <50 families have been described worldwide. Inheritance is autosomal dominant, and the diagnosis is usually made in children with cholestasis or their adult relatives, but sometimes in isolated adults. It results from mutations in the JAG1 gene, which encodes a ligand for Notch1. This stimulates a signaling pathway that determines cell fate in embryogenesis. Clinical features include renal arterial stenosis, hypertension, and renal failure but the kidneys may not be involved. There are reduced intrahepatic bile ducts and liver failure that typically presents with neonatal jaundice. In addition, peripheral pulmonary artery hypoplasia results in pulmonary hypertension, and various cardiac anomalies, vertebral arch defects, and a peculiar facies are present. The retina is commonly diffusely hypopigmented or speckled, and optic disc anomalies, especially drusen, are present in nearly all affected individuals.

MELAS (Myopathy, Encephalopathy, Lactic Acidosis, Stroke-like Episodes Syndrome, OMIM 540000) This condition affects 1 in 30,000 to 100,000 individuals and is due to an A3243G mutation in the mitochondrial DNA coding for tRNA (Leu). Inheritance is mitochondrial with transmission from mother to child. Presentation occurs from childhood through early adulthood. In addition to the classical features, patients usually have FSGS and steroid-resistant nephrotic syndrome that progresses to end-stage renal failure before middle age. Hearing loss, cardiomyopathy, and diabetes are also common but clinical features vary between families. Retinal atrophy occurs in at least half the patients but the electoretinogram is abnormal in 90%. The diagnosis is confirmed with a muscle biopsy demonstrating ragged-red fibers, or on mitochondrial DNA sequencing.

Kearns-Sayre Syndrome (OMIM 530000) Kearns-Sayre is a rare mitochondrial disease affecting 1 in 30,000 to 100,000 individuals. It typically results from a 4.9-kb deletion in mitochondrial DNA. Many cases occur de novo. The onset is usually before the age of 20 but sometimes later. Kearns-Sayre syndrome is associated with a Bartter-like tubular defect, together with chronic progressive external ophthalmoplegia, ptosis, hearing loss, cardiac conduction abnormalities, cerebellar ataxia, and diabetes. Despite retinal atrophy and pigmentation, visual loss is usually mild. Again the diagnosis is confirmed with ragged-red fibers on muscle biopsy, or with mitochondrial DNA sequencing.

PHAKOMATOSES (NEUROCUTANEOUS SYNDROMES) These disorders include neurofibromatosis, tuberous sclerosis, von Hippel Lindau disease, and Sturge-Weber syndrome. Von Hippel Lindau and Sturge-Weber syndromes also cause vascular anomalies and are considered later.

Neurofibromatosis (NF) Types I and 2 (OMIM 162200 and 101000) Neurofibromatosis 1 and 2 affect 1 in 3000 and 1 in 100,000 live births and are due to mutations in the NF1 or NF2 genes, which code for neurofibromin, a GTP-ase-activating enzyme, or merlin, a cytoskeletal protein, respectively. Inheritance is autosomal dominant but about half of all mutations occur de novo. NF1 and NF2 mutations are characterized by pigmented skin lesions, neurofibromas, and acoustic neuroma (NF2). Hypertension occurs because of proximal renal artery stenosis, coarctation of the aorta, or phaeochromocytoma. Retinal abnormalities include ischemia, hamartoma including Combined Hamartoma of the Retina and Retinal Pigment Epithelium,
may not be obvious if glucose control and diabetes, which are usually major differential diagnoses are hypermoscopy and in retinal photographs. The wool spots with hemorrhages and infarcts (CHRRPE, both \( NF1 \) and \( NF2^{86} \)), optic glioma (\( NF1 \)), and optic atrophy secondary to pressure on the optic nerve.

**Tuberous Sclerosis (TSC) Types 1 and 2 (OMIM 191100 and 191092)**
TSC affects 1 in 10,000 individuals, and inheritance is autosomal dominant. Mutations occur in the \( TSC1 \) gene or more commonly the \( TSC2 \) gene, which code for hamartin and tuberin, respectively.\(^8^7\) Twenty percent of patients have no mutation identified. Both \( TSC1 \) and \( TSC2 \) are tumor suppressor genes that require a second hit before tumors develop. TSC mutations are highly penetrant but have variable expression. \( TSC2 \) is contiguous with the \( PKD1 \) gene for polycystic kidney disease, and patients with large deletions have both TSC and renal cysts.\(^8^8\) Sixty to 80% of patients with TSC have multiple bilateral angiomyolipoma in the kidney.\(^8^9\) These result in hematuria, and sometimes cancer. Thirty percent of patients have renal cysts. Facial adenoma sebaceum, cardiac rhabdomyoma, and pulmonary cysts are common. Ocular coloboma and eyelid tumors are rare. Most patients have at least one retinal or optic nerve hamartoma.\(^9^0\) These are highly vascular and eventually calcify, and must be differentiated from hypertensive infarcts. Vision remains normal. Retinal hamartoma are helpful diagnostically, but the diagnosis of TSC is also confirmed with genetic testing.

**VASCULAR ABNORMALITIES**

Some inherited renal diseases are associated with tortuous retinal vessels with hemorrhages and infarcts (\( cotton \ wooll spots \)). These are evident on ophthalmoscopy and in retinal photographs. The major differential diagnoses are hypertension and diabetes, which are usually obvious on history. However, retinal abnormalities can persist for months after a single episode of severe hypertension, and the diagnosis of diabetes may not be obvious if glucose control improves as renal function deteriorates.

**HANAC (Hereditary Angiopathy with Retinal Tortuositios, Nephropathy (Manifesting as Hematuria or Cysts), Aneurysms, and Muscular Cramps Syndrome, OMIM 611773)**
To date, only a few families have been described with this disease.\(^9^1–9^3\) It results from mutations in the \( COL4A1 \) gene. Affected individuals have hematuria, renal cysts, and GBM defects. Small and large arteries are tortuous. Other features include headache, muscle cramps with elevated levels of creatine kinase, supraventricular cardiac arrhythmia, Raynaud’s phenomenon, and leukoencephalopathy. The retina has tortuous vessels, and repeated retinal hemorrhage results in transient visual impairment that resolves spontaneously.

**Fabry Disease (OMIM 301500)**
This lysosomal storage disorder affects at least 1 in 50,000 males but milder forms are probably more common.\(^9^4\) Inheritance is X-linked and disease results from mutations in the \( GLA \) gene encoding \( \alpha \)-galactosidase. Mutations result in the accumulation of the glycolipid, ceramide, in blood vessels and other tissues.\(^9^5\) Mutations are different in each family but missense variants are most common (76%). Mutation type correlates with age at onset of renal failure. Symptoms appear in childhood but become particularly troublesome in the fourth decade. Fifty percent of patients have proteinuria by 35 years of age, and renal failure by 42.\(^9^6\) The renal biopsy demonstrates FSGS with lamellated zebra bodies. Other features include angiokeratoma on the lower abdomen and thighs, cardiomyopathy, mitral valve prolapse, painful peripheral neuropathy, hearing loss, stroke, and lack of sweating. Patients with atypical disease (cardiac or visceral features without angiokeratoma, renal disease, or corneal keratopathy) are recognized increasingly.\(^9^7,9^8\) Features in females vary from asymptomatic to severe.\(^9^9\) Fabry disease is also found in a series of patients with renal failure on dialysis, with cardiomyopathy, and in young patients with stroke.\(^1^0^0–1^0^2\) The retinal vessels are tortuous. Other ocular abnormalities include corneal verticillata or horse tails, and tortuous conjunctival vessels. Vision is normal. The diagnosis is confirmed on renal biopsy, with low enzyme levels (which may be normal in affected symptomatic females), or with genetic testing.

**Von Hippel Lindau Disease (OMIM 193300)**
This condition affects 1 in 36,000 individuals. It results from mutations in the \( VHL \) gene, which codes for the protein that regulates hypoxia-inducible factor activity.\(^1^0^3\) Mutations result in upregulation of vascular endothelial growth factor and increased endothelial cell growth and migration.\(^1^0^4\) Inheritance is autosomal dominant, but 20% of mutations occur \textit{de novo}. However, two mutations are required for disease, one germline and one somatic. Germline mutations are different in each family. Nonsense mutations and deletions result in more severe disease.\(^1^0^5\) The timing of the somatic mutation probably determines the age at onset of disease, the organs affected, and severity. Thus, phenotypes vary even within families but penetrance is nearly 100% by age 60. Affected individuals develop renal cysts, and sometimes clear cell renal cancer. They also have \textit{cafe au lait} spots, nervous system hemangioblastomas, and sometimes, phemochromocytoma and pancreatic islet cell tumors. Fifty percent of patients have renal hemangioblastoma.\(^1^0^6\) These are usually multiple, vary in size, and are located in the central and mid-peripheral retina. They have a globular reddish appearance (\textit{sugar-coated raspberries}) and adjoining vessels are tortuous. They may be asymptomatic for years and regress spontaneously. However, they may be complicated by retinal hemorrhage, retinal tears, and detachment. Even small asymptomatic lesions should be treated. Early detection and treatment helps preserve vision,\(^1^0^7\) and in the fu-
ture, antiangiogenic factors may prove helpful. The diagnosis of von Hippel Lindau syndrome is usually made clinically, but may be confirmed also with genetic testing.

**Sturge-Weber Syndrome (OMIM 185300)**

One in 50,000 individuals are affected and many cases are sporadic. No mutant gene has been identified. The condition is characterized by facial nevi, cerebral hemangioma, and intracranial calcification. Vascular malformations occur in the kidney, within the renal pelvis, papilla, or urinary bladder. These are typically solitary and result in hematuria. They can be treated with laser. Vascular malformations of the retina and choroid may be complicated by retinal detachment or optic neuropathy.

**Amyloidosis**

Amyloid deposits are rigid, linear nonbranching aggregated fibrils with an antiparallel β-pleated sheet configuration. The inherited forms (AA) include those due to transthyretin mutations, familial amyloidotic polyneuropathy, and familial Mediterranean fever. Inheritance is autosomal recessive or dominant depending on the type. Inherited amyloidosis affects many tissues including the kidney and eye. It commonly results in kidney failure, but other features include dyslipidemia and xanthelasma, corneal opacities, and stomatocytes with increased membrane phospholipid, resulting in hemolytic anemia. Retinal manifestations include macular degeneration and hemorrhage from involvement and rupture of Bruch’s membrane. LCAT deficiency is diagnosed when LCAT levels are negligible, unesterified cholesterol and cholesterol ester levels are low, and LDL and triglyceride levels are increased. The diagnosis is also made with genetic testing.

**RETINAL CRYSTALS**

Retinal crystals are small and highly refractile, often with associated pigmentary changes (cystinosis, oxalosis) or large and dull (ectopic calcium deposits in chronic renal failure, Bartter and Gitelman syndrome). Vascular deposits may result in ischemia. The crystals must be distinguished from the normal youthful retinal sheen. Other causes of crystals are usually obvious on history (cholesterol emboli, tamoxifen, talc in intravenous drug users, and calcified drusen).

**Oxalosis (OMIM 260000)**

Oxalosis affects 1 in 100,000 individuals. Inheritance is autosomal recessive and due to mutations in the alanine glyoxylate aminotransferase (AGT) or the glyoxylate reductase/hydroxypyruvate reductase (GRHPR) genes. AGT deficiency is more common and causes more serious disease. Mutations result in increased synthesis of oxalate and subsequent urinary excretion and deposition of insoluble calcium oxalate in the kidney. As renal function deteriorates with progressive involvement, oxalate accumulates in other organs. Oxalosis results in nephrolithiasis, nephrocalcinosis, and renal failure. Renal failure occurs from infancy through to the sixth decade. The characteristic retinal findings are highly refractile crystals often in the arterioles, producing a flecked retinopathy, and crystals in the RPE layer, producing a hyperpigmented center surrounded by hypopigmentation (ringlets). Optic atrophy occurs with severe disease. Vision is usually normal, but may be impaired. The diagnosis of oxalosis is suspected in patients with stones or nephrocalcinosis in childhood, recurrent calcium oxalate stones in adulthood, or renal insufficiency associated with stones or nephrocalcinosis. The diagnosis is confirmed with urinary oxalate levels and genetic testing.

**Cystinosis (OMIM 219800)**

This condition also affects about 1 in 100,000 individuals and accounts for 5% of children with renal failure. Inheritance is autosomal recessive, and mutations occur in the CTNS gene for cystinosin. Many Caucasians have the same mutation consistent with a founder effect. Compound heterozygotes have milder, usually adult-onset, disease and carriers are asymptomatic. Affected children typically present in infancy with polyuria and dehydration from damaged proximal tubular cells. Untreated, they develop renal failure before the teenage years. However, retinal (and corneal and iris) crystals occur even without systemic features. Affected individuals complain of gritty eyes and, if severely affected, have poor night and color vision and reduced visual acuity. They also have retinal crystals with hypopigmentation, and pigmentary stippling. Adult-onset disease was formerly considered primarily ocular but probably all patients have at least some renal involvement. The diagnosis is based on clinical features, increased leukocyte cystine levels, and genetic testing.

**Tubular Defects (Bartter Syndrome, OMIM 607364 and Gitelman Syndrome, OMIM 263800)**

These each affect about 1 in 50,000 individuals and inheritance is autosomal recessive. Bartter syndrome is due to mutations in genes coding for proteins found in the thick ascending limb of the loop of Henle and is characterized by hy-
pokalemia, alkalosis, and normal or low blood pressure. Patients present in utero or before school age. They typically have polyuria, polydipsia, and a tendency for dehydration, features also seen with loop diuretics such as furosemide. Mutations affect the NKCC2, ROMK, CLCNKB, BSN, and CASR genes. Patients also often have a magnesium deficiency and develop widespread calcium deposits. Gitelman syndrome results from mutations in the SLC12A3 gene, which codes for the thiazide-sensitive Na-Cl cotransporter in the distal convoluted tubule. This disease is mild and patients present in adolescence or later. They are asymptomatic or have fatigue, muscle cramps, and rarely seizures or cardiac arrhythmias. Symptoms are due mainly to hypokalemia. BP is normal. Carriers may have mild features. Patients with either condition sometimes have large dullish yellow-white deposits in the retinal midperiphery, sometimes with pigment deposition. Visual fields and acuity are normal.

INCIDENTAL RETINAL FINDINGS

Nail Patella Syndrome (Hereditary Osteo-onychodysplasia, OMIM 161200)

This affects about 1 in 50,000 individuals and inheritance is autosomal dominant. It is due to mutations in the LMX1B gene, which encodes the transcription factor that regulates expression of collagen IV, and determines dorsal limb and eye development in the embryo. However, LMX1B is also expressed after birth in the glomerular podocyte, suggesting it has a regulatory role in that cell. Mutations affect a critical region of the gene (the LIM or homeodomain) and result in haploinsufficiency. Most patients have thumb nail hypoplasia, absent patellae, radial head dislocation, and iliac horns. The presence of renal disease (hematuria and proteinuria in 40% to 60%) depends on the underlying mutation and 15% of patients develop renal failure by middle age. The renal biopsy demonstrates variable amounts of glomerulosclerosis, with GBM thickening, rarefaction, and collagen III fibrils.

About one third of patients develop primary open-angle glaucoma by the age of 40, and sometimes optic atrophy. Other ocular associations are ptosis, epicanthal folds, microcornea, keratoconus, cataracts, and possibly cloverleaf iris pigmentation. Individuals with the nail and bone manifestations of the nail-patella syndrome should be screened for hematuria and proteinuria, and reviewed annually for increased intraocular pressure and glaucoma.

CONCLUSIONS

Many inherited renal diseases are diagnosed with expensive and labor-intensive laboratory techniques. However, retinal abnormalities in inherited renal disease are sufficiently common and characteristic to help with the diagnosis. Most of these features are obvious on ophthalmoscopy or in retinal photographs. Some are easier to identify with red-free images or peripheral retinal views. Retinal abnormalities may affect vision, and most patients with inherited renal disease require an ophthalmological assessment and sometimes further testing, monitoring, and treatment. The diagnosis of inherited renal disease is important because of the risk of complications, the implications for family members, and the possibility of treatment. Retinal abnormalities may also assist with assessing disease progression and the response to treatment, and in explaining the pathogenesis of the renal lesions. Inherited forms of renal disease where, currently, there are no known retinal associations, warrant further ophthalmic investigation.

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DISCLOSURES

None.

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