Alport Syndrome and Other Collagen Disorders

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Contents

Abstract

Type IV collagen is a ubiquitous component of basement membranes along with laminin, entactin/nidogen, and heparan sulfate proteoglycans. Six type IV collagen genes (*COL4A1–COL4A6*) encode six unique alpha chains of type IV collagen [α1(IV)–α6(IV)]. Mutations in several of the type IV collagen genes can cause a number of progressive and

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nonprogressive glomerular disorders. Mutations in *COL4A3*, *COL4A4*, and *COL4A5* may cause Alport syndrome (AS), an inherited kidney disease that classically leads to ESKD, sensorineural hearing loss, and eye abnormalities in affected individuals. Mutations in *COL4A6* along with *COL4A5* are associated with AS accompanied by leiomyomatosis. Heterozygous mutations in *COL4A3* and *COL4A4* are associated with thin basement membrane nephropathy (TBMN), a generally nonprogressive kidney disorder presenting with isolated microscopic hematuria. Finally, mutations in *COL4A1* cause hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC) syndrome. This chapter will review the genetics, clinical manifestations, pathology, diagnosis, and treatment of each of these type IV collagen disorders.

Keywords
Glomerular basement membrane · Type IV collagen · End-stage kidney disease · Hematuria · Proteinuria · Sensorineural hearing loss · Alport syndrome · Familial nephritis

Normal GBM Structure

Glomerular basement membranes (GBMs) are vital for normal functioning of the glomerular filtration barrier and are composed of type IV collagen, laminin, entactin/nidogen, and agrin, a heparan sulfate proteoglycan (Miner 2012). Laminin forms a network within the GBM based on heterotrimeric association of α, β, and γ isoforms. Laminin-521 is the form found in mature GBM and has the composition α5β2γ1 (Miner 2012). Mutations in *LAMB2* encoding laminin β2 cause massive failure of the glomerular filtration barrier with clinical symptoms of congenital nephrotic syndrome and eye abnormalities (Zenker et al. 2004). Laminin and type IV collagen networks closely interact and are bridged by entactin/nidogen and agrin molecules.

There are six isoforms of type IV collagen designated α1(IV)–α6(IV) encoded by one of six distinct genes, *COL4A1–COL4A6*. *COL4A1* and *COL4A2* are present on chromosome 1 and encode α1(IV) and α2(IV). The α3(IV) and α4(IV) chains are encoded by the *COL4A3* and *COL4A4* genes on chromosome 2, while the α5(IV) and α6(IV) genes are encoded by the *COL4A5* and *COL4A6* genes on the X chromosome. Each pair of genes is situated in a 5′-5′ head-to-head orientation, with intervening promoter and transcriptional regulatory sites (Poschl et al. 1988; Segal et al. 2001). All type IV collagen isoforms share several common structural features: a collagenous domain of ∼1,400 amino acids containing the repetitive triplet sequence glycine-X-Y (Gly-X-Y, with X and Y representing other amino acids), a noncollagenous carboxy-terminal (NC1) domain of ∼230 amino acids that includes 12 conserved cysteine residues, and a noncollagenous amino-terminal sequence of 15–20 residues (7S domain). Individual type IV collagen isoforms associate to form trimers determined by specific interactions regulated by sequences in the NC1 domain. Despite the large potential number of trimer conformations, only three major trimeric species have been found in mammalian species: α1α1α2(IV), α3α4α5(IV), and α5α5α6(IV) (Khoshnoodi et al. 2006; Hudson 2004). In contrast to type I collagens that lose their NC1 domains after trimerization and form fibrillar networks, type IV collagen trimers form open, nonfibrillar networks through NC1-NC1 and amino-terminal interactions between trimers.

α1α1α2(IV) networks are ubiquitously present in basement membranes including the developing GBM. The α3α4α5(IV) network is restricted to mature GBM, Bowman's capsule, and distal tubule in the kidney and is also found in alveolar basement membranes and basement membranes of the testis, eye, and ear (Khoshnoodi et al. 2008). The α5α5α6(IV) network is restricted in the kidney to Bowman's capsule and distal tubular

and collecting duct basement membranes and is also found in epidermal basement membranes, the eye, bronchial epithelium, and smooth muscle (Peissel et al. 1995; Yoshioka et al. 1994).

Alport Syndrome

Epidemiology

Familial nephritis was first reported in the medical literature in the early 1900s (Guthrie 1902). In 1927, Cecil Alport published a description of a large family affected by kidney disease and deafness with a male predominance, and this entity thereafter took on his name (Alport 1927). It was not until 1972, after the widespread application of electron microscopy to kidney biopsies, that AS was recognized as a disorder of GBMs (Hinglais et al. 1972). In the 1980s, histochemical investigations determined that type IV collagen chains were missing in the GBM of individuals with AS (Kashtan et al. 1986; Olson et al. 1980). In 1990, mutations in *COL4A5* were identified as causative of X-linked AS (Barker et al. 1990). Shortly thereafter, mutations in *COL4A3* and *COL4A4* were identified in patients with autosomal recessive and autosomal dominant AS (Mochizuki et al. 1994; Jefferson et al. 1997). AS is a rare disease, affecting approximately 1:50,000 people and is seen in all ethnicities and races (Levy and Feingold 2000). AS accounts for approximately 0.5% of adults and 1.7% of children with end-stage kidney disease (ESKD) in the United States (Saran et al. 2016).

Genetics and Pathogenesis

AS can be inherited as an X-linked condition due to mutations in *COL4A5* on the X chromosome (Barker et al. 1990). Affected males are hemizygotes and have only one copy of a mutated *COL4A5* allele, whereas affected females are heterozygotes with one normal *COL4A5* allele and one mutated *COL4A5* allele. Due to X-inactivation, this leads to a mosaic expression pattern for α5(IV) in basement membranes in females. Autosomal recessive inheritance can also be observed due to homozygous or compound heterozygous mutations in *COL4A3* or *COL4A4* (Mochizuki et al. 1994). Digenic inheritance was also recently described (Mencarelli et al. 2015). Finally, autosomal dominant AS is caused by heterozygous mutations in *COL4A3* or *COL4A4* (Jefferson et al. 1997). Individuals with heterozygous mutations in *COL4A3* or *COL4A4* may exhibit classic AS or TBMN with non-progressive isolated microscopic hematuria. Classically, approximately 80% of AS was thought to be inherited in an X-linked manner, with 15% autosomal recessive and 5% autosomal dominant inheritance patterns observed. With the advent of next-generation sequencing, it is clear that autosomal dominant AS is more common than previously recognized, accounting for approximately 19–31% of affected families (Fallerini et al. 2013; Moriniere et al. 2014).

Over 1,200 pathogenic mutations have been identified in the *COL4A5* gene in patients with XLAS (Crockett et al. 2010; Hertz et al. 2012). There are no hot spots within the gene and mutations have been found in all 51 exons. *COL4A5* is a large gene and about 10–15% of mutations occur as spontaneous events; therefore a family history is not required to consider a diagnosis of AS. A variety of mutation types have been described: large rearrangements (~20%), small deletions and insertions (~20%), missense mutations altering a glycine residue (Gly-X-Y repeat region) in the collagenous domain of α5(IV) (30%), other missense mutations (~8%), nonsense mutations (~5%), and splice site mutations (~15%) (Jais et al. 2000). Genotype has a strong correlation with kidney disease progression in males with XLAS (Jais et al. 2000; Gross et al. 2002). In males with a large deletion, nonsense mutation, or a small mutation changing the mRNA reading frame, the risk of developing ESKD before age 30 is 90%. In contrast, splice site mutations and missense mutations have a less severe renal phenotype with 70% and 50%

reaching ESKD by age 30 years, respectively (Jais et al. 2000). In addition, the position of a glycine substitution within the gene may also impact the rate of disease progression as those with 5′ glycine missense mutations demonstrate a more severe phenotype than those with 3′ glycine mutations (Gross et al. 2002). In contrast to males with XLAS, there is no genotype-phenotype correlation in females with XLAS (Jais et al. 2003). In patients with autosomal recessive AS, the presence of at least one mutation leading to a premature stop codon was associated with earlier onset renal failure; however a genotype-phenotype correlation was not confirmed in other small studies (Storey et al. 2013; Oka et al. 2014). There does not appear to be a genotype-phenotype correlation in patients with autosomal dominant AS (Marcocci et al. 2009; Kamiyoshi et al. 2016). It is unclear why some individuals with one *COL4A3* or *COL4A4* mutation develop progressive kidney disease while others have a more benign clinical course (Lemmink et al. 1996).

Mutations in any of the *COL4A3*, *COL4A4*, or *COL4A5* genes may alter the composition of affected basement membranes. In the setting of severe mutations in *COL4A5* or severe homozygous or compound heterozygous mutations in *COL4A3* or *COL4A4* (deletions, frameshift mutations, premature stop codons leading to the absence of protein expression), the other collagen chains normally present in the type IV collagen trimer are degraded, and no α3α4α5(IV) trimers are deposited in basement membranes (Gunwar et al. 1998). In the absence of the α3α4α5(IV) network, the embryonal α1α1α2(IV) network persists. Missense mutations may produce misfolded proteins that are retained within the endoplasmic reticulum of the cell and degraded (Bateman et al. 2009). Alternately, missense mutations that affect the glycine residues involved in triple helix formation may lead to the formation of abnormally folded trimers that can be deposited into the basement membrane. In this case, an abnormal type IV collagen network is formed. The α3α4α5(IV) is not necessary for development of the GBM; however it is required for normal maintenance of the GBM structure and function due to its increased strength and stability compared to the α1α1α2(IV) network. This may be in part due to the greater number of disulfide bonds in the α3α4α5(IV) network making it more highly cross-linked and thus more resistant to proteases than the α1α1α2(IV) network (Gunwar et al. 1998; Zeisberg et al. 2006). The glomerular capillary walls of AS patients are mechanically weak and provoke pathologic stretch-related responses in glomerular cells (Meehan et al. 2009).

Clinical Features

Individuals with AS may have progressive chronic kidney disease (CKD), sensorineural hearing loss, and ocular abnormalities. The frequency of each finding depends on genotype, gender, and age. In general, patients with autosomal dominant AS and females with XLAS have less severe kidney disease and are less likely to have extrarenal manifestations (Marcocci et al. 2009; Savige et al. 2016).

Renal Findings

Males with XLAS and males and females with autosomal recessive AS have a similar clinical course. Kidney disease in AS progresses predictably through a series of clinical phases (Gross et al. 2012a) [Table 1, Fig. 1]. Phase 0 typically lasts from birth until late childhood or early adolescence and is characterized by isolated microscopic hematuria, with the absence of proteinuria and normal kidney function. Episodes of gross hematuria are common in up to 60% of affected individuals, particularly in association with infection, which may lead to diagnostic confusion with IgA nephropathy (Jais et al. 2000; Gubler et al. 1981).

Table 1 Clinical stages of Alport syndrome

Stage	Definition
0	Isolated microscopic hematuria +/− gross hematuria
I	Hematuria + microalbuminuria (30–300 mg albumin/g creatinine)
II	Hematuria + overt proteinuria (>300 mg albumin/g creatinine)
III	Decline of glomerular filtration rate by >25%
IV	End-stage renal disease

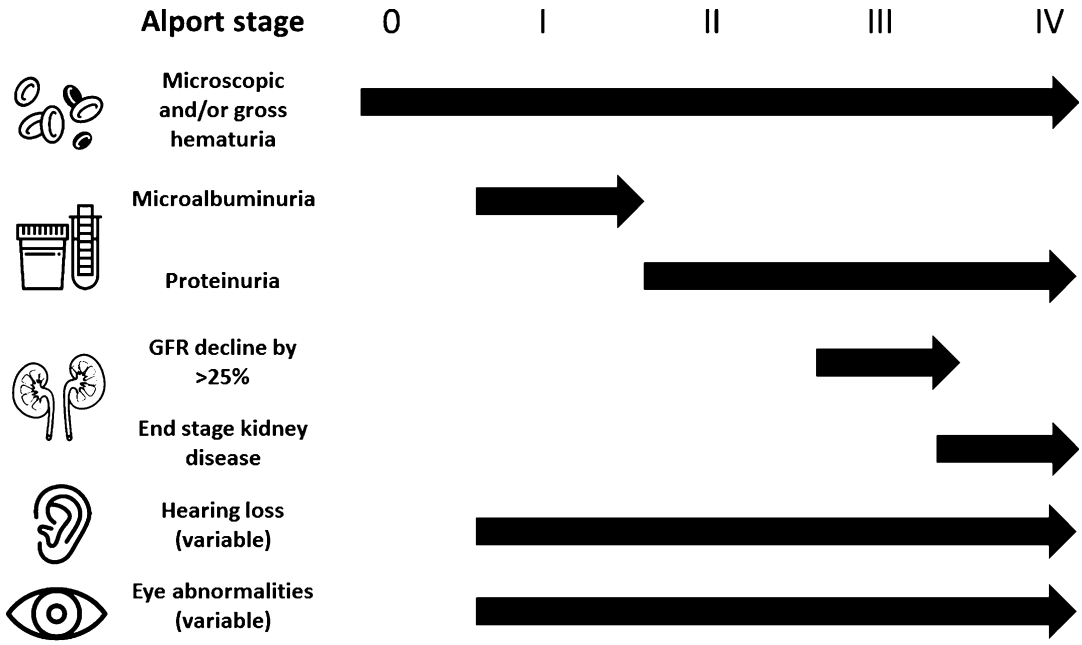

Fig. 1 Clinical stages of Alport renal disease and extra-renal manifestations over time. Alport renal disease follows a distinct progression from hematuria alone to microalbuminuria to proteinuria to GFR decline and ESKD. Onset of hearing loss and eye abnormalities is variable, but is rare prior to the onset of microalbuminuria

Persistent gross hematuria for months or years is also observed. In phase I, microalbuminuria (30–300 mg albumin/g creatinine) develops, but renal function remains normal (Kashtan et al. 2013; Gubler et al. 1981). Overt proteinuria (>300 mg albumin/g creatinine) signals the start of phase II and the beginning of a decline of renal function (Kim et al. 1995). Hypertension may be present in this phase, whereas blood pressures are generally normal prior to this. In phase III, individuals have a progressive decline of renal function with >25% reduction in GFR. The rate of passage through these phases is primarily a function of the causative mutation and gender. Progression from one phase to the next is utilized as an outcome measure in clinical trials of AS (Gross et al. 2012a). Females with XLAS and males and females with autosomal dominant AS demonstrate a similar progression through each phase; however the course may be slow enough that they do not require renal replacement therapy in their lifetime (Jais et al. 2003; Kamiyoshi et al. 2016).

In untreated males with XLAS, the risk of ESKD is 50% by age 25 years, 80% by 40 years, and 100% by age 60 year (Jais et al. 2000). With the adoption of early treatment with angiotensin-converting enzyme (ACE) inhibitor therapy, the age at ESKD may be increasing in this population (Gross et al. 2012b). In patients with autosomal recessive AS, the risk of ESKD is 50% by age 21–22 years; however ESKD as young as 9 years has been reported (Storey et al. 2013; Oka et al. 2014). In patients with autosomal dominant AS, the lifetime risk of ESKD is lower and most often occurs after the age of 40 years (Kamiyoshi et al. 2016; Marcocci et al. 2009). In one retrospective study, the median renal survival in autosomal dominant AS was 70 years (Kamiyoshi et al. 2016).

Females who are heterozygous for *COL4A5* mutations are commonly referred to as "carriers" of AS; however this term is not entirely accurate because almost all have some manifestation of disease (Rheault 2012; Savige et al. 2016). Hematuria is reported in 95.5% of affected women and proteinuria in 75% (Jais et al. 2003). Proteinuria is a risk factor for adverse pregnancy outcomes in general, and there are reports of hypertension,

preeclampsia, and decline in renal function during pregnancy in women with XLAS (Yefet et al. 2016; Hladunewich et al. 2016; Alessi et al. 2014). Females with XLAS have a smaller, but not insignificant, risk of ESKD compared to affected males. There was a 12% risk of ESKD by age 40 years and 30% by age 60 years reported by the European Community Alport Syndrome Concerted Action group (Jais et al. 2003). A more recent European report similarly showed 15.4% prevalence of ESKD in women with XLAS (Temme et al. 2012b). The explanation for the wide variation in outcomes for females with XLAS is unclear, but likely multifactorial. Risk factors for ESKD in females with XLAS include proteinuria and sensorineural hearing loss (Grunfeld et al. 1985; Jais et al. 2003). There does not appear to be a genotype-phenotype to explain the severity of kidney disease (Jais et al. 2003). X-inactivation, the process by which one X chromosome in females is silenced to adjust for gene dosage differences between males and females, may play a role as well in CKD progression in women with XLAS (Guo et al. 1995; Iijima et al. 2010; Rheault et al. 2010). Further studies are necessary to determine how to accurately predict the risk of progressive kidney disease in women who are affected with XLAS.

Sensorineural Hearing Loss

Newborn hearing screening is always normal in AS, but bilateral loss of perception of high-frequency sounds often becomes detectable in late childhood or early adolescence. The hearing loss is progressive and extends into the range of conversational speech with advancing age, often requiring amplification with hearing aids or cochlear implants. Sensorineural hearing loss (SNHL) is present in 50% of males with XLAS by approximately age 15, 75% by age 25, and 90% by age 40 (Jais et al. 2000). Similar to renal disease, genotype can predict the risk of SNHL in affected individuals. Severe mutations such as splice site mutations, deletions, insertions, and nonsense mutations are associated with a 90% risk of SNHL before the age of 30 years; however missense mutations are associated with a lower risk of SNHL of 60% at age 30 years (Jais et al. 2000). SNHL is less common in females with XLAS. About 10% of XLAS females have SNHL by 40 years of age and about 20% by age 60 (Jais et al. 2003). SNHL is common in autosomal recessive AS as well with approximately 40–66% of individuals affected (Storey et al. 2013; Oka et al. 2014). The risk of SNHL in autosomal dominant AS is lower than other genetic forms of the disease, with only 2–13% of individuals affected depending on the series (Kamiyoshi et al. 2016; Marcocci et al. 2009).

The SNHL in AS is due to the absence of the α3α4α5(IV) network in the cochlea (Wester et al. 1995). In normal cochleae, the α3α4α5(IV) network is expressed in a number of basement membranes including the spiral limbus, the spiral ligament, and stria vascularis and in the basement membrane situated between the organ of Corti and the basilar membrane (Kleppel et al. 1989; Cosgrove et al. 1998; Harvey et al. 2001). However, this network is absent in animal models of AS and in men with XLAS (Cosgrove et al. 1998; Harvey et al. 2001; Zehnder et al. 2005). Cochleae from men with XLAS demonstrate separation between the organ of Corti, the structure that produces nerve impulses in response to sound vibrations, and the underlying basement membrane (Merchant et al. 2004). This separation may be responsible for the decreased acuity of hearing observed in patients with AS. An alternative hypothesis is that hearing is impaired by changes in potassium concentration in the scala media, or cochlear duct, induced by the absence of the α3α4α5(IV) network in the stria vascularis (Gratton et al. 2005). Further research is required to elucidate the exact cause of hearing loss in patients with AS.

Ocular Findings

Anomalies of the lens, retina, and cornea are common in patients with AS (Savige et al. 2015). The α3α4α5(IV) network is normally found in several basement membranes in the eye including the lens capsule, corneal basement membrane, Descemet's membrane, internal limiting membrane of the retina, and the retinal pigment epithelium basement membrane (Kleppel et al. 1989; Cheong et al. 1994; Ohkubo et al. 2003; Chen et al. 2003b).

Ocular anomalies are more common in males with XLAS and males and females with autosomal recessive AS, affecting 35–80% of affected individuals (Jais et al. 2000; Wang et al. 2014; Oka et al. 2014; Storey et al. 2013). Ocular findings are less common in women with XLAS (~15%) and are almost never observed in autosomal dominant AS (Jais et al. 2003; Marcocci et al. 2009; Kamiyoshi et al. 2016).

Anterior lenticonus, a conical protrusion of the lens anteriorly through the capsule, is diagnostic for AS and is present in 13% of males with XLAS (Jais et al. 2003). Some reports suggest a higher incidence of anterior lenticonus in autosomal recessive AS with up to 80% affected in one series (Wang et al. 2014). Lenticonus generally presents in middle age, after the development of CKD. Due to the abnormal shape of the lens, vision may be affected. The absence of the α3α4α5(IV) network in the lens capsule leads to abnormal splits in the capsule that may rupture, allowing protrusion of the lens. The lens capsules of Alport patients with anterior lenticonus are thin with focal areas of dehiscence, suggesting that the lens capsule lacks the mechanical strength to maintain normal lens shape (Ohkubo et al. 2003; Sonarkhan et al. 2014; Kato et al. 1998). Increased distensibility in the lens capsule has been demonstrated in experimental models of AS and correlates with the observed clinical findings (Gyoneva et al. 2013). Healing of lens capsule ruptures may lead to cataract formation (Sonarkhan et al. 2014). Anterior lenticonus and cataracts can successfully be treated with lens replacement and do not recur (Liu et al. 2008).

Retinal anomalies are also common in AS including central or peripheral fleck retinopathy. Central fleck retinopathy appears as whitish-yellow perimacular dots and flecks that are present from early adolescence and is more common in patients with more severe kidney disease. It is present in 50–60% of men with XLAS and men and women with autosomal recessive AS and in ~15% of women with XLAS (Wang et al. 2014). Peripheral retinopathy appears as asymmetric patches of confluent flecks and is the most common ocular finding in patients with AS. With either type of retinopathy, visual acuity is normal and no treatment is required.

Corneal erosions can be observed in <10% of patients with AS due to abnormal α3α4α5(IV) network in the corneal subepithelium (Rhys et al. 1997; Burke et al. 1991). Posterior polymorphous corneal dystrophy is a more serious corneal issue that is visualized as vesicular lesions, linear bands, or irregular diffuse opacities of the posterior corneal surface involving Descemet's membrane by slit lamp exam (Teekhasaenee et al. 1991). Affected patients may be asymptomatic or have recurrent episodes of eye watering, foreign body sensation, and photophobia. Treatment may require corneal transplant.

Other Clinical Associations

The association of XLAS with smooth muscle tumors (leiomyomas) of the respiratory, gastrointestinal, and female reproductive tracts has been described in some families (Zhou et al. 1993; Antignac and Heidet 1996; Heidet et al. 1997). Symptoms such as difficulty swallowing, vomiting, epigastric or retrosternal pain, recurrent bronchitis, shortness of breath, cough, and stridor may appear in late childhood or adolescence. This syndrome arises from a contiguous gene deletion on the X chromosome involving exon 1 of *COL4A5*, the common promoter region that regulates gene expression of *COL4A5* and *COL4A6*, and the first two exons of the adjacent *COL4A6* gene (Zhou et al. 1993). The genotype-phenotype relationship in this disorder was put into question recently by a report that showed that deletions in this region may not always lead to leiomyomas and conversely that some families with XLAS and leiomyomas do not have deletions involving the common promoter region and *COL4A6* (Sa et al. 2013).

Deletions that extend downstream of the 3′ end of the *COL4A5* gene are associated with mental retardation, midface hypoplasia, and elliptocytosis in a small number of XLAS males (Jonsson et al. 1998; Vitelli et al. 1999). Abnormalities in arterial vessels have been described in males with XLAS including aortic root dilatation and aneurysms of the thoracic and abdominal aorta, possibly due to abnormalities of the α5α5α6(IV) network normally present in arterial smooth muscle basement membranes (Kashtan et al. 2010).

Renal Histopathology

Children with AS may have normal findings by light microscopy before about 5 years of age. In older patients, mesangial hypercellularity and matrix expansion may be observed. By age 10 years, focal segmental glomerulosclerosis (FSGS), tubular atrophy, and interstitial fibrosis become the predominant light microscopic abnormalities (Kashtan et al. 1998). Although some patients exhibit increased numbers of immature glomeruli or interstitial foam cells, these changes are not specific for AS.

Electron microscopy of kidney biopsy specimens is frequently diagnostic (Fig. 2). In early childhood, the predominant ultrastructural lesion in males is diffuse thinning of the GBM (Fig. 2b). This may be identical in appearance to patients with thin basement membrane nephropathy (TBMN), and differentiation between these two entities can be difficult in young children. The classic ultrastructural lesion in AS is diffuse thickening of the glomerular capillary wall, accompanied by "basket-weave" transformation of the lamina densa and intramembranous vesicles, scalloping of the epithelial surface of the GBM,

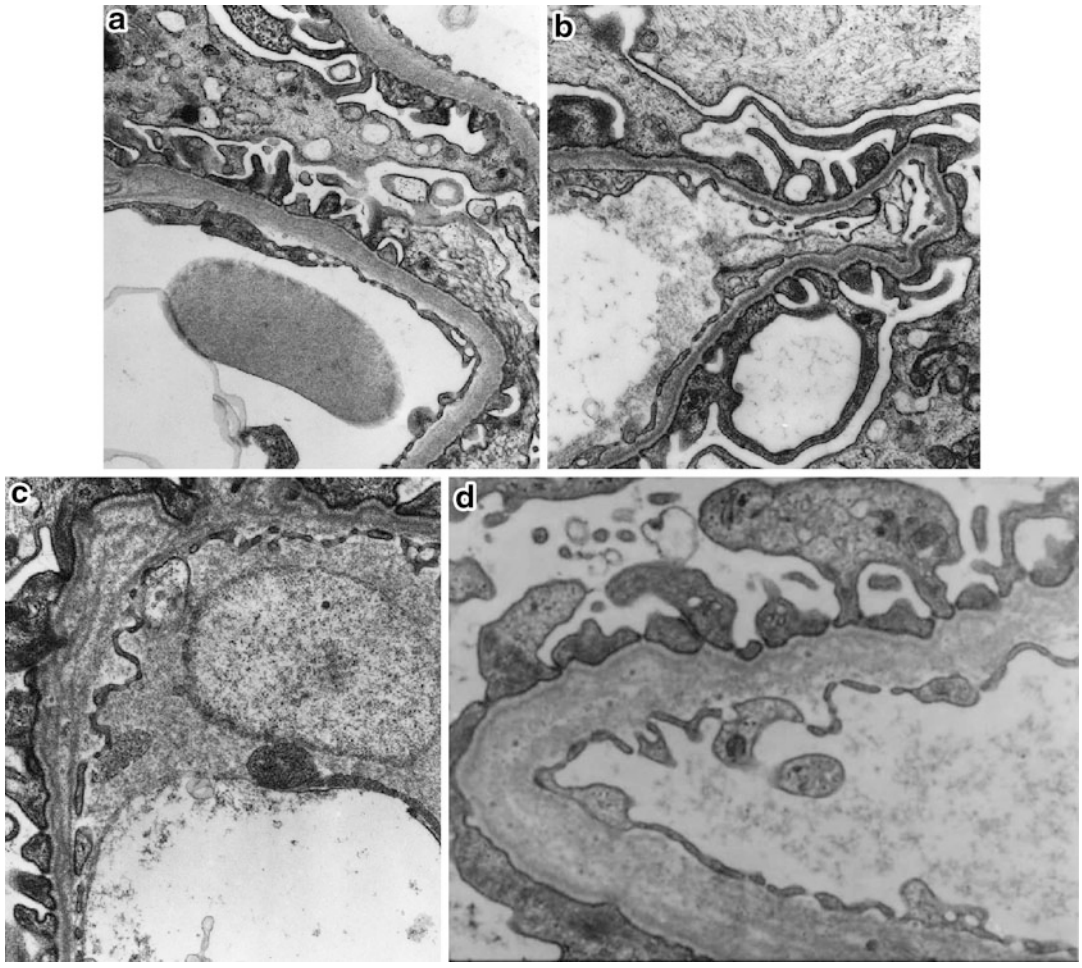

Fig. 2 Electron micrographs from patients with hematuria. Magnifications are similar, but not identical. (**a**) Normal GBM. (**b**) Attenuated GBM in a patient with TBMN. (**c**) This female with a heterozygous *COL4A5* mutation exhibits both thin and split, lamellated GBM. (**d**) This male with XLAS shows diffuse thickening and lamellation of GBM (Reprinted from Kashtan (2002), with permission from Elsevier)

and effacement of overlying podocyte foot processes (Fig. 2c, d). These changes are more prevalent in males with XLAS and males and females with autosomal recessive AS, and the percentage of GBM displaying this lesion increases progressively with age (Rumpelt 1980). Affected females with XLAS can display a spectrum of lesions, demonstrating either predominantly normal-appearing GBM, focal GBM thinning, diffuse GBM thinning, thickening/basket weaving, or diffuse basket weaving. The classic GBM lesion is not found in all kindreds with AS. Recently, a number of families with primary FSGS with or without the classic AS basement membrane lesion have been found to have mutations in *COL4A3* or *COL4A4* (Deltas and Pierides 2015; Malone et al. 2014). These findings expand the spectrum of histopathology phenotype associated with type IV collagen mutations (Miner 2014).

Routine immunofluorescence microscopy is normal or shows nonspecific deposition of immunoglobulins. In contrast, specific immunostaining for type IV collagen α chains is frequently diagnostic and can distinguish between the X-linked and autosomal recessive forms of the disease (Fig. 3). In approximately 80% of XLAS males, immunostaining of kidney biopsy specimens for α3(IV), α4(IV), and α5(IV) chains is completely negative (Kashtan et al. 1996). About 60–70% of XLAS females exhibit mosaic expression of these chains, while in the remainder of females, immunostaining for these chains is normal. It is important to note that normal immunostaining for type IV collagen does not exclude a diagnosis of AS in males or females. Mutations in *COL4A3* and *COL4A4* in patients with autosomal recessive AS may prevent expression of α3α4α5(IV) trimers but will have no effect on expression of α5α5α6(IV) trimers. Therefore, in kidney biopsy specimens from patients with autosomal recessive AS, immunostaining for α3(IV), α4(IV), and α5(IV) chains is negative in

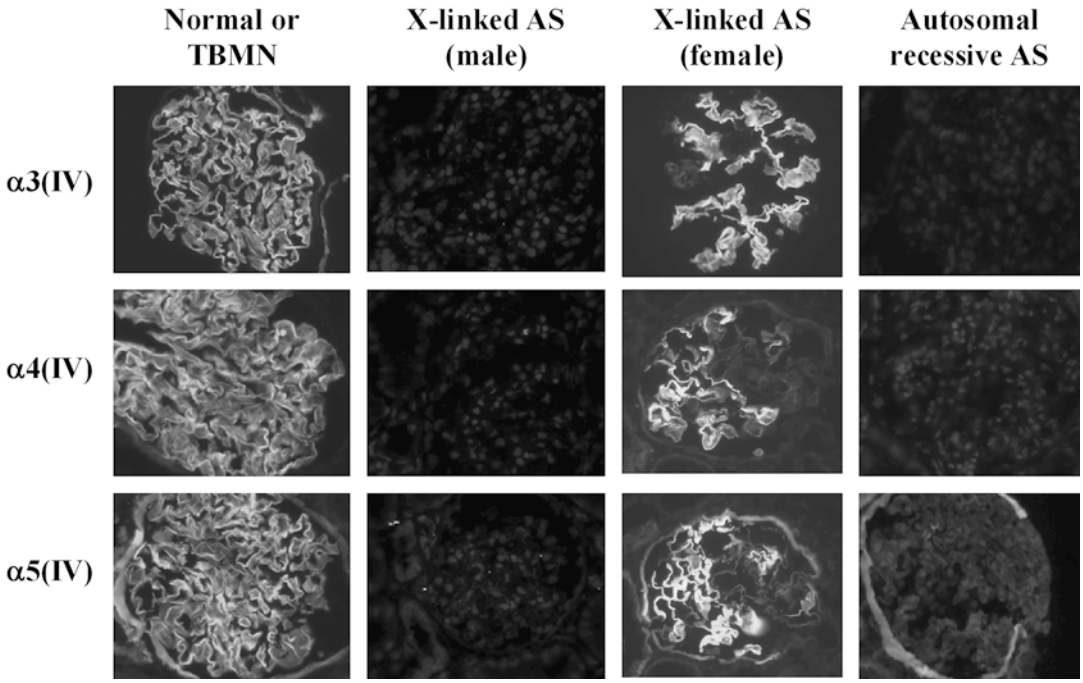

Fig. 3 Glomerular immunofluorescence microscopy in XLAS and ARAS. α3(IV), α4(IV), and α5(IV) chains are expressed in the GBM in patients with normal glomeruli and TBMN. All three chains are missing in affected males with XLAS. A mosaic pattern is present for heterozygous females with XLAS due to X-inactivation. In ARAS, α3(IV), α4(IV), and α5(IV) chains are absent from the glomerulus; however α5(IV) is visible in Bowman's capsule as part of the α5α5α6 network (Reprinted from Kashtan (2005), with permission from Elsevier)

the GBM. However, expression of α5(IV) in Bowman's capsule, distal tubular basement membranes, and collecting duct basement membranes remains positive for α5(IV), due to the normal expression of α5α5α6(IV) trimers. Immunostaining in autosomal dominant AS is normal.

Skin Histopathology

In some situations, a skin biopsy can be considered as an initial diagnostic step. Normal epidermal basement membranes contain the α5α5α6(IV) trimer. Consequently, about 80% of males with XLAS can be diagnosed by skin biopsy on the basis of the absence of α5(IV) expression in EBM. In 60–70% of XLAS females, there is a mosaic, discontinuous expression pattern for α5(IV) by immunostaining. Epidermal basement membrane expression of α5(IV) is normal in patients with autosomal recessive or autosomal dominant AS.

Diagnosis and Differential Diagnosis

Accurate, early diagnosis of AS is important in order to initiate potentially beneficial therapy when appropriate and to identify other family members who may be at risk of kidney disease. Differentiation between AS and other causes of glomerular hematuria can be performed based on careful clinical evaluation, examination of pedigree data, selective application of invasive diagnostic tests such as skin or kidney biopsy, hearing assessment, and genetic testing (Table 2).

In children with familial glomerular hematuria, alternate potential diagnoses include the autosomal dominant *MYH9* disorders (Epstein and Fechtner syndromes, in which thrombocytopenia and large platelets are a constant feature, familial IgA nephropathy, X-linked membranoproliferative glomerulonephritis, and familial hemolytic uremic syndrome) (Bostrom and Freedman 2010; Kiryluk and Novak 2014; Redahan et al. 2014). The presence of autosomal dominant microscopic hematuria in a family with no history of ESKD or hearing loss is suggestive of TBMN (see below), but AS cannot be definitively excluded. In children with no family history of hematuria, AS is still possible since 10–15% of cases are due to spontaneous mutations. Alternately the differential diagnosis may include IgA nephropathy, C3 glomerulopathy, lupus nephritis, active or resolving postinfectious glomerulonephritis, Henoch-Schönlein nephritis, and TBMN. Some of these entities may be diagnosed or suspected based on clinical and laboratory findings; however others can only be confirmed by kidney biopsy.

In a child at risk for AS based on family history, the presence of persistent hematuria is diagnostic. Biopsy or genetic studies are required when clinical and pedigree information cannot rule out AS in a patient with hematuria (Savige et al. 2013). Several options are available for confirming a diagnosis of AS including skin biopsy, kidney biopsy, and genetic testing. Skin biopsy may be utilized as the initial invasive diagnostic procedure in patients suspected of having XLAS because it is less invasive and less expensive than a kidney biopsy. Unfortunately, not all centers offer this procedure and this may limit its utility as a diagnostic test. On skin biopsy, the majority of subjects with XLAS will display abnormal expression of the α5(IV) chain in epidermal basement membranes, as described above. Skin biopsy is normal in individuals with autosomal recessive and autosomal dominant AS and should not be utilized if this diagnosis is suspected. If skin biopsy is not diagnostic, kidney biopsy with type IV collagen immunostaining and careful examination of GBM ultrastructure by electron microscopy can be performed.

Mutation analysis using conventional Sanger sequencing is capable of identifying *COL4A5* mutations in 80%–90% of males with XLAS (Martin et al. 1998). Next-generation sequencing has supplanted Sanger sequencing in recent years and allows for simultaneous evaluation of *COL4A3, COL4A4*, and *COL4A5* mutations (Moriniere et al. 2014; Kovacs et al. 2016). Identification of a specific mutation can provide some prognostic information about the risk of kidney disease progression and risk of associated symptoms such as hearing loss and eye findings in a patient (Jais et al. 2000). Once a new diagnosis of

Table 2 Type IV collagen disorders.

	Gene	Protein	Risk of ESKD	Kidney pathology: IF	Kidney pathology: EM	Extrarenal manifestations
Alport syndrome						
X-linked males	*COL4A5*	α5(IV)	100%	Absent α3α4α5(IV) in GBM in 80%	GBM thinning (early) GBM lamellation (late)	Hearing loss Lenticonus Retinopathy
X-linked females	*COL4A5*	α5(IV)	30% by age 60 years	Mosaic α3α4α5(IV) in GBM in 60–70%	GBM thinning (early) GBM lamellation (late)	Hearing loss Retinopathy
Autosomal recessive	*COL4A3* or *COL4A4* (biallelic)	α3(IV) α4(IV)	100%	Absent α3α4α5(IV) in GBM in majority	GBM thinning (early) GBM lamellation (late)	Hearing loss Lenticonus Retinopathy
Autosomal dominant	*COL4A3* or *COL4A4* (heterozygous)	α3(IV) α4(IV)	50% by 50–70 years	Normal α3α4α5(IV) GBM	GBM thinning (early) GBM lamellation (late)	Hearing loss Retinopathy
Thin basement membrane nephropathy						
Autosomal dominant	*COL4A3* or *COL4A4* (heterozygous)	α3(IV) α4(IV)	0	Normal α3α4α5(IV) GBM	GBM thinning	None
HANAC syndrome						
Autosomal dominant	*COL4A1*	α1(IV)	Not reported	Normal α3α4α5(IV) GBM	Normal GBM thickening and splitting of BM in tubules, Bowman's capsule, and interstitial capillaries	Arterial aneurysms muscle cramps

BM basement membrane, *EM* electron microscopy, *ESKD* end-stage renal disease, *GBM* glomerular basement membrane, *HANAC* hereditary angiopathy with nephropathy, aneurysms, and cramps, *IF* immunofluorescence microscopy

AS is made in a family, all potentially affected family members including females should be screened with a urinalysis to identify those at risk of progressive kidney disease (Savige et al. 2013).

Treatment

The goal of treatment in children and adults with AS is to slow the progression of CKD and to delay the need for dialysis or kidney transplantation. There are no currently approved therapies for AS. Recommendations for treatment are derived from expert consensus, uncontrolled studies, retrospective registry studies, and data from treatment in animal models.

Treatment of mice and dogs with AS with angiotensin-converting enzyme (ACE) inhibition leads to significantly prolonged renal survival (Grodecki et al. 1997; Gross et al. 2003). Uncontrolled studies in pediatric and adult patients with AS have shown that angiotensin blockade can transiently reduce proteinuria (Cohen and Lemann 1996; Proesmans and Van Dyck 2004). In a large multicenter, randomized, double-blind study comparing losartan with placebo or amlodipine in proteinuric children, evaluation of the subpopulation with AS demonstrated a significant reduction in proteinuria in the losartan-treated group over 12 weeks of therapy (Webb et al. 2011). A 3-year extension of this study showed comparable efficacy of either

enalapril or losartan in reducing proteinuria in children with AS (Webb et al. 2013). A retrospective review of Chinese children with AS showed a decline in proteinuria with ACE inhibition over the first 2 years of therapy that was sustained over 5 years of follow-up (Zhang et al. 2016). A report from the European Alport Registry, which included 283 patients followed over 20 years, compared renal outcomes in AS patients initiated on therapy with ACE inhibitors at various timing: microalbuminuria, proteinuria, or in CKD (CKD) stage III–IV (Gross et al. 2012b). Findings from this retrospective review suggested that earlier treatment with ACE inhibitors is more beneficial. They demonstrated a delay in renal replacement therapy by 3 years in the treated CKD group and by 18 years in the treated proteinuric group (Gross et al. 2012b). Similar benefits of ACE inhibition were found in women with XLAS or individuals heterozygous for *COL4A3* or *COL4A4* mutations (Temme et al. 2012b). Side effects of ACE inhibition are rarely reported but include hyperkalemia, cough, and hypotension. Based on these promising retrospective findings, a prospective, double-blind, randomized, placebo-controlled trial is underway in Germany to compare outcomes in children with AS treated with the ACE inhibitor ramipril vs. placebo at an early disease time point (microalbuminuria or isolated hematuria) (Gross et al. 2012a). Prospective trials in AS are challenging due to the rare nature of the disease and slow progression to hard end points such as doubling of serum creatinine or ESKD.

Clinical practice guidelines have been developed to guide treatment of children with AS (Kashtan et al. 2013) (Table 3). Treatment with ACE inhibitors or angiotensin receptor blockers should be offered to all affected individuals, male or female, with AS and overt proteinuria (Kashtan et al. 2013). ACE inhibition should be considered for affected individuals at the microalbuminuria stage if they have either a family history of ESKD at a young age (<30 years) or a known severe *COL4A5* mutation (deletion, splice site, or nonsense mutation). Women of childbearing age, including adolescents, should be carefully counseled about the risks of birth defects while taking ACE inhibitors and risks and benefits of treatment considered prior to initiation. Treatment of hypertension and other manifestations of CKD is similar to children with other etiologies of CKD.

In animal models of AS, several novel strategies have proven effective in prolonging renal survival including TGFβ-1 inhibition (Sayers et al. 1999), chemokine receptor 1 suppression (Ninichuk et al. 2005), administration of bone morphogenic protein-7 (Zeisberg et al. 2003), blockade of matrix metalloproteinases (Zeisberg et al. 2006), anti-microRNA-21 therapy (Gomez et al. 2015), treatment with mycophenolate mofetil (Petrova et al. 2014) or paricalcitol (Rubel et al. 2014), and bone marrow transplantation (Sugimoto et al. 2006; Gross et al. 2009a). Cyclosporine therapy slowed the progression of kidney disease in a dog model of AS; however human studies have demonstrated significant

Table 3 Recommendations for treatment based on urinary findings and anticipated disease course

	Family history of early ESKD (<30 years) or severe[a] COL4A5 mutation		Family history of late ESKD (>30 years) or less severe[b] COL4A5 mutation	
	Males	Females	Males	Females
Hematuria	Intervention prior to onset of microalbuminuria is not recommended at this time	No	No	No
Hematuria + microalbuminuria	Consider intervention	Consider intervention	No	No
Hematuria + proteinuria	Yes	Yes	Yes	Yes

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ESKD end stage renal disease
[a]Deletion, nonsense, or splice site mutation
[b]Missense mutation

nephrotoxicity and adverse effects, and this treatment is no longer recommended (Chen et al. 2003a; Charbit et al. 2007; Massella et al. 2010; Sugimoto et al. 2014). Gene therapy, the transfer of wild-type *COL4A5* genes into glomerular cells to restore the normal composition of the GBM, is an attractive potential therapy for Alport syndrome. Proof of concept studies in mice has demonstrated that restoration of the normal collagen α3α4α5(IV) network in Alport mice slows the progression of kidney disease and prolongs lifespan (Lin et al. 2014). However, application to humans with Alport syndrome is still in development and is limited by the ability to deliver genes to the glomerulus.

Kidney Transplantation

Outcomes following kidney transplantation in patients with AS are generally excellent with graft survival as good or better than other forms of glomerulonephritis (Yilmaz et al. 2015; Temme et al. 2012a). Clinicians involved in transplantation of AS patients must be aware of the two important aspects of the disease. First, the donor selection process must avoid accepting donors who may be at risk for CKD themselves. Second, post-transplant management should provide surveillance for post-transplant anti-GBM nephritis.

As discussed above, women with XLAS are at risk for progressive CKD (Rheault 2012). Nephrectomy in this population may lead to poor outcomes in the donor including hypertension, proteinuria, or more rapid progression of CKD. A report from Germany described five women with XLAS and one ARAS carrier who served as kidney donors (Gross et al. 2009b). One donor had proteinuria prior to transplant and all had microscopic hematuria. Three donors developed new-onset hypertension and two developed new proteinuria, while renal function declined by 25–60% over 2–14 years after donation in four of the donors, highlighting the increased donor risk in this population (Gross et al. 2009b). In addition, receipt of a kidney from a heterozygous carrier may not be optimal for the recipient. A donor kidney from a woman with XLAS may have shorter graft survival than would be expected from a graft with completely normal basement membranes; however this has not been studied.

In males with XLAS and a complete absence of α5(IV) in the GBM, autoantibodies may develop that then cause anti-GBM nephritis after transplant in about 3% of patients (Dehan et al. 1996; Brainwood et al. 1998; Kashtan 2006). Onset is typically in the first year after transplant and presents with hematuria or elevated creatinine. Kidney allograft biopsy with routine immunofluorescence should be performed early in the evaluation of AS patients after transplantation if anti-GBM disease is suspected. Anti-GBM nephritis often results in irreversible graft failure within weeks to months of diagnosis. Treatment with cytotoxic therapy and plasmapheresis have been attempted with little success (Kashtan 2006). The risk of recurrence in subsequent grafts is high. Females with XLAS are at little or no risk of developing anti-GBM nephritis after transplantation to the presence of at least some α5(IV) in the kidney due to X-inactivation. Both males and females with autosomal recessive AS can develop post-transplant anti-GBM nephritis due to antibodies directed against the α3(IV) chain (Brainwood et al. 1998; Kalluri et al. 1995).

Thin Basement Membrane Nephropathy

Epidemiology

The prevalence of thin basement membrane nephropathy (TBMN) is estimated at 1–2% of the general population, making it one of the most common causes of glomerular hematuria (Haas 2006). In children undergoing kidney biopsy for persistent microscopic hematuria without proteinuria, 15–50% are diagnosed with TBMN (Trachtman et al. 1984; Schroder et al. 1990; Piqueras et al. 1998). Classically, families with isolated microscopic hematuria transmitted in an autosomal dominant manner were described as having "benign familial hematuria" (Marks and Drummond 1969; McConville et al. 1966). Kidney biopsies in these individuals are usually

normal except for thin GBMs compared to age- and sex-matched controls (Haas 2006). Over time, it has become clear that these pathological findings are not only seen in benign conditions and can be observed in early AS or women with XLAS who have a risk of progressive CKD. The more descriptive term of "thin basement membrane nephropathy (TBMN)" has gradually supplanted the prior nomenclature to more accurately describe the associated findings and risks. While usually nonprogressive, careful evaluation and follow-up of individuals with TBMN are required to monitor for progressive kidney disease.

Genetics

In discussing the genetics of TBMN, it is important to recall that GBM thinning is a pathological description rather than a distinct, homogeneous entity. The first causative mutation for TBMN was identified in 1996 when Lemmink and colleagues reported a heterozygous *COL4A3* mutation in a family with autosomal dominant hematuria (Lemmink et al. 1996). Since then, a number of heterozygous mutations in *COL4A3* and *COL4A4* (the carrier state for autosomal recessive AS) have been found in association with TBMN (Rana et al. 2005; Nabais Sa et al. 2015). GBM thinning can also be seen in early kidney biopsies in individuals with hemizygous or heterozygous mutations in *COL4A5* (XLAS) or biallelic mutations in *COL4A3* or *COL4A4* (autosomal recessive AS). Approximately 40–50% of families with TBMN will have a mutation in *COL4A3* or *COL4A4* identified or demonstrate linkage to this region. Mutations at other unknown genetic loci may exist, but have not been identified. The factors that influence clinical outcome in individuals with heterozygous mutations in *COL4A3* or *COL4A4* are unknown, but may be related to genotype or the presence of modifier genes. Recently, co-inheritance of podocin variants with heterozygous mutations in *COL4A3* and *COL4A4* was found to be associated with worse renal outcomes (Stefanou et al. 2015).

Clinical Findings

Children with TBMN typically present with persistent microscopic hematuria, although intermittent hematuria or even gross hematuria may be observed. The penetrance of hematuria is only approximately 70% (Savige et al. 2003). TBMN is the most common cause of persistent microscopic hematuria in children and adults and is common in the general population with an estimated prevalence of 1–2% (Tryggvason and Patrakka 2006; Haas 2006). A family history of dominantly inherited hematuria with a negative history of renal failure or hearing loss is typical. Adults with familial hematuria may not be aware that they are affected, and urinalyses on first degree family members may be useful to make the diagnosis in a child with isolated microscopic hematuria (Blumenthal et al. 1988).

Proteinuria is rare in childhood but can be observed in up to 30% of adult patients (Gregory 2005; van Paassen et al. 2004). CKD is observed in <5% of affected adults (Gregory 2005; Auwardt et al. 1999; Nieuwhof et al. 1997; van Paassen et al. 2004). Individuals with progressive CKD and a heterozygous mutation in *COL4A3* or *COL4A4* may be more accurately described as having autosomal dominant AS rather than TBMN. Extrarenal abnormalities, such as hearing loss or ocular defects, are rare and probably not related to the underlying type IV collagen mutation.

Renal Histopathology

Light and routine immunofluorescence microscopy typically is entirely normal. Adult patients with TBMN who have proteinuria, CKD, or hypertension may exhibit premature glomerular obsolescence (Nieuwhof et al. 1997). In contrast to patients with AS, type IV collagen immunostaining is normal (Kashtan et al. 1986; Pettersson et al. 1990). Electron microscopy is required for diagnosis and identifies the characteristic isolated thinning of the GBM with preservation of normal podocyte anatomy (Fig. 2b). Patients with TBMN typically exhibit diffuse thinning of the lamina densa. The

thickness of normal GBM is age and sex dependent (Haas 2006). Both the lamina densa and the GBM increase rapidly in thickness between birth and age 2 years, followed by gradual thickening throughout childhood and adolescence (Vogler et al. 1987). Normal GBM thickness of adult men is greater than that of adult women (Steffes et al. 1983). Because a variety of techniques can be used to measure GBM width, there is no standard definition of "thin" GBM, and local normative values should be taken into consideration. The cutoff value in adults ranges from 250 nm to 330 nm, depending upon the technique (Dische 1992; Tiebosch et al. 1989). For children, the normal range for GBM width is >200–250 nm (250 nm is within 2SD of the mean at age 11) (Schroder et al. 1990; Lang et al. 1990; Milanesi et al. 1984).

Diagnosis and Differential Diagnosis

In a child with persistent isolated microscopic hematuria of glomerular origin, a strong family history of hematuria inherited in an autosomal dominant manner, and a negative family history for renal failure or hearing loss, a presumptive clinical diagnosis of TBMN can be made without need for a kidney biopsy. Genetic testing is not required. If there are atypical findings (no family history of hematuria, presence of non-orthostatic proteinuria or microalbuminuria, elevated creatinine, recurrent gross hematuria, etc.), then a kidney biopsy may be required for diagnosis. IgA nephropathy and AS are alternate diagnoses that may be seen in this clinical scenario.

In the young child with GBM thinning by kidney biopsy and a negative or limited family history, the challenge for the physician is to distinguish nonprogressive TBMN from AS. Audiometry and ophthalmologic examination may be helpful if abnormal, but may not be useful given the usual absence of these abnormalities in young children. Immunostaining for type IV collagen α3(IV), α4(IV), and α5(IV) chains can be particularly helpful in these situations to identify individuals with AS who may be early in their clinical course or women with XLAS. Genetic testing for mutations in all three associated genes (*COL4A3-COL4A5*) is recommended in individuals with TBMN and proteinuria, renal impairment, or when AS cannot be excluded based on family history.

Monitoring and Treatment

Individuals with TBMN should be monitored every 1–2 years for progression of their disease including evaluation for proteinuria, hypertension, and renal impairment and to update the family history. Treatment for children and adults with TBMN is not recommended since the course is typically nonprogressive. The presence of proteinuria should prompt treatment with an ACE inhibitor, similar to patients with AS (Savige et al. 2013; Kashtan et al. 2013).

Hereditary Angiopathy with Nephropathy, Aneurysms, and Cramps (HANAC) Syndrome

Clinical Features and Histopathology

Hereditary angiopathy with nephropathy, aneurysms, and cramps (HANAC) syndrome is a very rare systemic disorder. Kidney involvement in HANAC syndrome is variable and may include isolated microscopic hematuria or cortical and/or medullary cysts (Plaisier et al. 2007; Gale et al. 2016). In reports of kidney biopsy findings in HANAC syndrome, light and immunofluorescence microscopy is normal (Plaisier et al. 2007). By electron microscopy, irregular thickening and splitting of the basement membranes of the tubules, Bowman's capsule, and interstitial capillaries are observed. Electron-lucent areas can also be present. Type IV collagen immunostaining is normal. Progressive CKD can be observed, but generally in individuals after the age of 40–50 years.

Patients with HANAC syndrome present with an angiopathy that affects both small and large vessels leading to retinal tortuosity and retinal hemorrhages, leukoencephalopathy, and intracranial aneurysms (Plaisier et al. 2007). They often have muscle cramps with persistent elevated creatine kinase levels.

Genetics

Mutations in *COL4A1* encode the α1 chain of type IV collagen HANAC syndrome in an autosomal dominant manner (Plaisier et al. 2007). α1(IV) is expressed in the GBM during development and appears to be important for normal podocyte differentiation (Chen et al. 2016). Mutations are localized in the region of the protein that encompasses the major integrin binding site, suggesting that abnormal interactions between cells and the basement membrane may underlie the systemic defects observed in this syndrome (Plaisier et al. 2010). The type of mutation influences the patient phenotype in individuals with *COL4A1* mutations (Chen et al. 2016).

Monitoring and Treatment

No specific treatment is available for individuals with HANAC syndrome, and supportive care is tailored to individual signs and symptoms. Blood pressure, urinalysis, and creatinine should be monitored routinely and hypertension promptly treated to reduce risk of stroke. Ophthalmologic evaluation is recommended at diagnosis and routinely thereafter to monitor for retinal involvement, glaucoma, and cataracts. Brain imaging to assess for asymptomatic cerebral aneurysms should be performed at diagnosis. Genetic counseling is recommended to review risk of disease in other family members and to review reproductive risk if applicable.

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