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PERSPECTIVES IN RENAL MEDICINE

Thin basement membrane nephropathy

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Thin basement membrane nephropathy.

Thin basement membrane nephropathy (TBMN) is the most common cause of persistent glomerular bleeding in children and adults, and occurs in at least 1% of the population. Most affected individuals have, in addition to the hematuria, minimal proteinuria, normal renal function, a uniformly thinned glomerular basement membrane (GBM) and a family history of hematuria. Their clinical course is usually benign.

However, some adults with TBMN have proteinuria >500 mg/day or renal impairment. This is more likely in hospital-based series of biopsied patients than in the uninvestigated, but affected, family members. The cause of renal impairment in TBMN is usually not known, but may be due to secondary focal segmental glomerulosclerosis (FSGS) or immunoglobulin A (IgA) glomerulonephritis, to misdiagnosed IgA disease or X-linked Alport syndrome, or because of coincidental disease.

About 40% families with TBMN have hematuria that segregates with the *COL4A3/COL4A4* locus, and many *COL4A3* and *COL4A4* mutations have now been described. These genes are also affected in autosomal-recessive Alport syndrome, and at least some cases of TBMN represent the carrier state for this condition. Families with TBMN in whom hematuria does not segregate with the *COL4A3/COL4A4* locus can be explained by de novo mutations, incomplete penetrance of hematuria, coincidental hematuria in family members without *COL4A3* or *COL4A4* mutations, and by a novel gene locus for TBMN.

A renal biopsy is warranted in TBMN only if there are atypical features, or if IgA disease or X-linked Alport syndrome cannot be excluded clinically. In IgA disease, there is usually no family history of hematuria. X-linked Alport syndrome is much less common than TBMN and can often be identified in family members by its typical clinical features (including retinopathy), a lamellated GBM without the collagen α3(IV), α4(IV), and α5(IV) chains, and by gene linkage studies or the demonstration of a *COL4A5* mutation. Technical difficulties in the demonstration and interpretation of *COL4A3* and *COL4A4* mutations mean that mutation detection is not used routinely in the diagnosis of TBMN.

Key words: Alport syndrome, glomerular basement membrane, thin basement membrane nephropathy, type IV collagen.

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Most individuals with thin basement membrane nephropathy (TBMN) have persistent dysmorphic hematuria, minimal proteinuria (≤500 mg/day) and normal renal function [1–17]. On ultrastructural examination, their renal biopsies have a uniformly thinned glomerular basement membrane (GBM) without the long stretches of lamellation or thickening seen in Alport syndrome. In addition, there is often another family member with hematuria, but not with X-linked Alport syndrome or renal failure. The prognosis of TBMN is usually excellent.

TBMN is also known as "thin basement membrane disease," "benign familial hematuria," "benign persistent hematuria," and "benign essential hematuria." We have used the term "TBMN" because it reflects the underlying ultrastructural abnormality, and because TBMN is not necessarily a "disease" nor "benign" nor "familial."

"Benign persistent hematuria" was first reported nearly 80 years ago [1, 18]. This was described as the painless, microscopic, and often incidental hematuria that occurred in young adults, without the hypertension or edema seen in chronic nephritis, and with a good prognosis. It was another 50 years before the distinctively thinned GBM was noted [7].

EPIDEMIOLOGY OF TBMN

TBMN has been reported in Caucasians, Chinese, Indians, and Africans [19, 28]. The median age at presentation is 7 years in children [1–6], and 37 years in adults [7–17], and hematuria from TBMN has been reported in infants as young as 1 year, and in an 86-year-old [7]. The majority of studies (71%) suggest that TBMN is more common in females than males (median male: female ratio = 1.6) [1–5, 9–11, 13–16].

The prevalence of TBMN cannot be accurately estimated from population-based studies because many individuals are unaware they are affected. For example, we have found that even in families in whom TBMN had been diagnosed, only half the affected family members knew they had hematuria [19]. The prevalence of TBMN may, however, be inferred from the frequency of persistent dysmorphic hematuria in the community. Hematu-

Table 1. Clinical features in children and adults with biopsy-proven thin-basement membrane nephropathy (TBMN)

Median	Children with TBMN (total of 6 studies)	Adults with TBMN (total of 11 studies)
% Patients with loin pain (range)	Not commented on in any of the studies	14% (7–31%) (3 studies)
% Patients with macroscopic hematuria (range)	34% (5–65%) (5 studies)	7% (0–25%) (11 studies)
% Patients with any proteinuria (range)	6% (0–65%) (6 studies)	50% (0–71%) (10 studies)
% Patients with proteinuria >500 mg/day (range)	0% (0–0%) (4 studies)	16% (0–57%) (6 studies)
% Patients with hypertension (>140/90 mm Hg) (range)	0% (0–0%) (6 studies)	17% (0–37%) (8 studies)
% Patients with impaired renal function (creatinine >0.11 mmol/L)	0% (0–0%) (4 studies)	0% (0–29%) (7 studies)

In all series, TBMN was confirmed by biopsy in the patient or a family member, and patients were not further identified by a single clinical entity such as 'isolated hematuria,' or known to have a hearing loss or family history of Alport syndrome. Some series of adults included occasional children. The number of studies in which individual clinical features were noted are provided in parentheses (1–17).

ria on a single occasion is very common, but hematuria that persists occurs in only 1% to 2% of children [20, 21] and about 2.5% of adults [22]. Persistent hematuria in children is usually "dysmorphic" or "glomerular" on phase-contrast urinary microscopy [23], and although a glomerular origin has not been confirmed in the majority of adults, most have no urologic cause demonstrated [22, 24]. Thus, persistent hematuria in both children and adults appears to originate from the glomerulus more often than from elsewhere in the urinary tract. Furthermore, many series of children [25–27] and adults [13, 28–30] with persistent hematuria have demonstrated that TBMN is the most common histologic diagnosis despite nephrologists' reluctance to biopsy patients with normal renal function.

The frequency of TBMN has also been measured directly. A thinned GBM was found in 5.2% of a series of 76 renal transplant biopsies where the definition of thinning did not overlap with the normal range [31].

Thus, both direct and indirect approaches suggest that TBMN occurs in more than 1% of the population, which makes it one of the most common conditions affecting the kidney after infections, hypertension, and stones.

CLINICAL FEATURES

TBMN is characterized clinically by persistent hematuria, minimal proteinuria, normal renal function, another family member with hematuria, and a benign course. We reviewed the clinical features in six pediatric and 11 adult studies (Table 1) [1–17] where TBMN was confirmed by biopsy in the patient or a family member, and where patients were not identified by a single clinical entity such as "isolated hematuria," and were not known to have a hearing loss or family history of Alport syndrome.

Children in the pediatric studies had the clinical features typical of TBMN, and none had proteinuria >500 mg/day, hypertension, or renal impairment. Proteinuria of any degree was uncommon, occurring in a median of 6% children (range, 0% to 65%).

In contrast, a median of 50% adults with TBMN had some degree of proteinuria (range, 0% to 71%), while 16% had proteinuria >500 mg/day (range, 0% to 57%), and 17% had hypertension (range, 0% to 37%). Most adults had normal renal function, but 29% in one report had renal impairment.

What could explain the atypical features in these adults with TBMN? We compared the clinical features in 71 of our adults with biopsy-proven TBMN and 45 of their family members who had not been investigated previously but who we showed had hematuria and hence considered affected (Table 2). We found that adults with TBMN who had undergone renal biopsy were more likely to have proteinuria >500 mg/day than their unbiopsied but affected family members ($P < 0.02$); and while 7% biopsied patients had some degree of renal impairment, none of their uninvestigated affected relatives did. These observations suggest that adults with suspected TBMN who undergo renal biopsy have more severe clinical features than other affected individuals.

Hematuria is characteristic of TBMN. It is usually "asymptomatic" and may be demonstrated incidentally during a clinic visit for another complaint, or as part of a medical examination for insurance or employment purposes [28]. The hematuria is also described as "isolated" because proteinuria is usually absent or minimal. The urinary red blood cells are dysmorphic, with an irregular size and shape, and variable hemoglobin content typical of glomerular bleeding [32]. These red cells have escaped through transient 2.25 μm wide gaps in the glomerular endothelium and basement membranes into the urinary space [33]. Urinary red blood cell counts on phase-contrast microscopy are often about 150,000/mL urine, which correspond to 100 to 150 red blood cells passing through the membranes of each glomerulus daily. Red blood cell casts are reported less often than with other glomerular lesions that result in similar levels of hematuria [28, 29], and unusual hyaline "string casts" with red blood cell columns have been described [29]. Hematuria does not occur in all patients with TBMN and, in one report, 8% of patients with biopsy-proven disease had no glomerular bleeding [11].

Table 2. Proteinuria and renal impairment in patients with biopsy-proven thin-basement membrane nephropathy (TBMN) and affected family members

	Hospital-based biopsied patients ($N = 71$)	Affected family members of biopsied patients ($N = 45$)	P value
Gender	11M, 60F	13M, 32F	NS
Age *years* (median, range)	34 (10–68)	36 (4–71)	NS
Proteinuria >500 mg/day	15 (21%)	2 (4%)	<0.02
Impaired renal function (serum creatinine >0.11 mmol/L)	5 (7%)	0 (0%)	NS

Affected family members were from 18 families of hospital-based biopsied patients and were identified as affected because they had hematuria [30].

In the pediatric and adult studies reviewed here, macroscopic hematuria occurred in 34% children (median, range, 5% to 65%, in five studies) and 7% adults (median, range, 0% to 25%, in 11 studies) usually after exercise or with infections (Table 1). Loin pain was recorded in 14% adults (median, range, 7% to 31%, in three studies), but was not noted in any of the pediatric reports. The hypothesis that TBMN causes some cases of "loin pain-hematuria syndrome" [34] has not been examined further.

Six percent of children (median, range, 0% to 65%, in six studies) and 50% of adults (median, range, 0% to 71%, in 10 studies) with TBMN had proteinuria but typically ≤500 mg/day (Table 1). Nephrotic range proteinuria and urinary fat are rare. Marked proteinuria is sometimes due to secondary glomerulosclerosis [17, 35] or to other superimposed glomerular lesions [36]. The amount of proteinuria does not correlate with the degree of GBM thinning [13], and it has been unclear how gaps in the GBM allow red blood cells, but not protein, to escape. Some of the leaked protein may, however, be resorbed by the renal tubules.

Hypertension did not occur in any of pediatric studies but was present in 17% of adults with TBMN (median, range, 0% to 37%, in eight studies) (Table 1). This may be coincidental.

Most individuals with TBMN have normal renal function, but renal impairment is sometimes present in adults (median, 0%, range, 0% to 29%, in seven studies). The cause of renal impairment is often unknown, and proteinuria and hypertension are the only known risk factors. Renal impairment also occurs because of a secondary glomerulonephritis [17, 35–40], misdiagnosed X-linked Alport syndrome or immunoglobulin A (IgA) disease, or coincidental disease [41]. IgA glomerulonephritis occurs in 2% to 39% of different series of patients with TBMN [36–39], probably more often than by chance alone. Patients with both TBMN and IgA disease have the persistent hematuria seen with TBMN, but are not more likely to have proteinuria, hypertension or renal impairment than patients with uncomplicated IgA disease [39]. Focal segmental glomerulosclerosis (FSGS) occurs in at least 5% of patients with TBMN [17]. Systemic lupus erythematosus (SLE), membranous nephritis, diabetes, and mesangiocapillary glomerulonephritis have all been described in patients with TBMN [36], but TBMN is so common that these associations may be by chance. In contrast, the thinned GBM sometimes described in minimal change glomerulonephritis is probably artifactual [42].

TBMN appears to have no extrarenal manifestations and, in particular, the high-tone sensorineural hearing loss, anterior lenticonus, and dot-and-fleck retinopathy seen in Alport syndrome, another inherited disease affecting the GBM, do not occur [43]. Hypercalciuria, hyperuricosuria, and nephrolithiasis have been described in TBMN [44] but not confirmed [5, 6].

RENAL BIOPSY FEATURES

The light microsopic appearance of the renal biopsy in TBMN is nearly normal with only mild mesangial cell proliferation and slight matrix expansion [29, 45]. Premature glomerular sclerosis [17] and tubulointerstitial fibrosis may occur. Small mesangial deposits of IgM, C3, and C1q are seen sometimes but are nonspecific [29].

The GBM width is thinner in children than in adults, and in adult females compared with males. The diagnosis of TBMN is made when the GBM width on electron micrographs is less than the normal range established for individual laboratories [46, 47] (Fig. 1). The criteria for TBMN in children vary from <200 to 250 nm depending on age [48], and in adults from <200 nm [36], <250 nm [12] (World Health Organization criteria) to <264 nm [29] partly because of technical differences in tissue processing. In TBMN, the GBM is thinned in the majority of capillary loops, and at least 50% of the GBM is thinned in individual capillaries. There are only isolated regions of lamellation or thickening, and there is no progressive thickening or splitting over time.

TBMN has to be distinguished from the GBM thinning seen in normal children [49], and in IgA [50], minimal change, mesangiocapillary, and some forms of lupus glomerulonephritis [45]. While the GBM thinning in children is diffuse, the thinning in most of these glomerular diseases is focal.

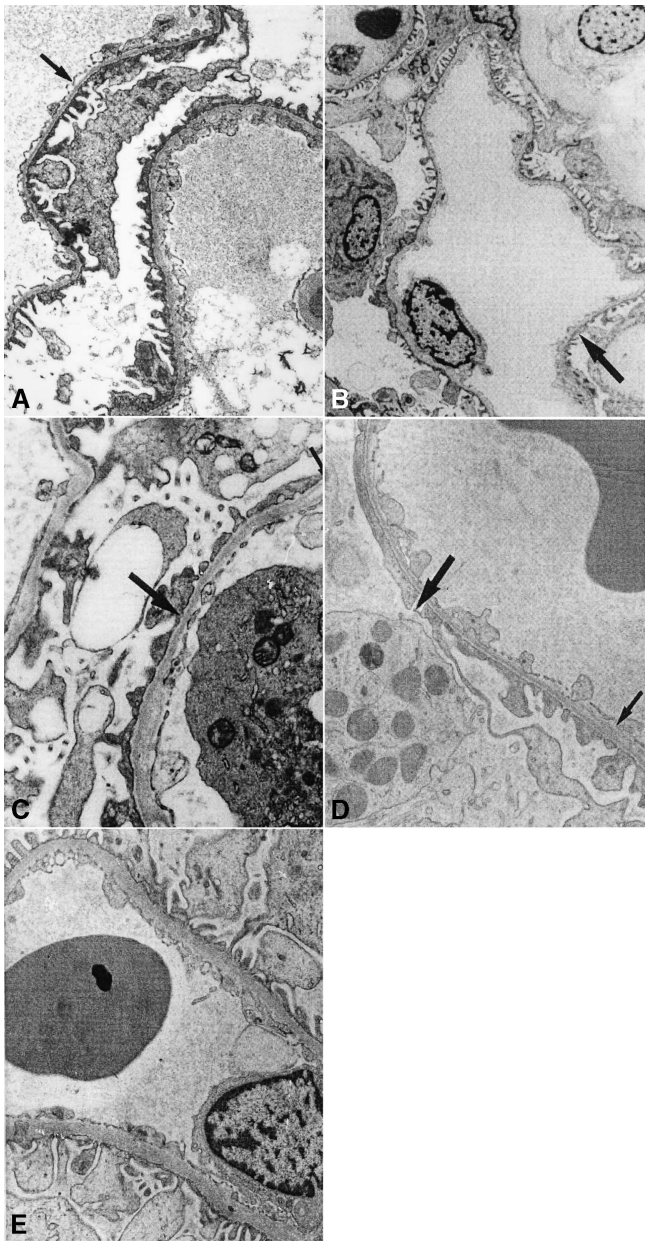

Fig. 1. Ultrastructural appearance of glomerular basement membrane (GBM). (*A*) Individual with thin basement membrane nephropathy (TBMN) showing uniform thinning (×6300). (*B*) Carrier of autosomal-recessive Alport syndrome showing uniform thinning (×550). (*C*) A 9-year-old boy with X-linked Alport syndrome showing thinning (arrow) and lamellation (×6000). (*D*) Female carrier with X-linked Alport syndrome showing thinning (arrow) and lamellation (small arrow) (×9000). (*E*) Normal individual (×6300).

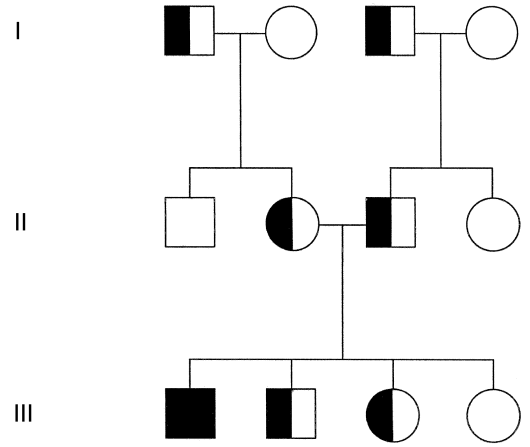

Fig. 2. Pedigree showing the inheritance of hematuria in two intermarried families with thin basement membrane nephropathy (TBMN). Half-shaded symbols indicate hematuria and heterozygosity for the causative mutation inherited from a parent; fully shaded symbols indicate the compound heterozygous state with mutations from both hematuric parents. The hematuria occurs in each generation, and males and females are affected equally often, suggesting autosomal-dominant inheritance. This is confirmed by the demonstration of a father and son who both have hematuria (but not renal failure). In generation III, the offspring of two parents with hematuria are compound heterozygous (with diseased genes from their father and mother) or heterozygous for mutations (from either their father or mother) or have normal genes, in a ratio of 1:2:1. Although TBMN may represent the carrier state for autosomal-recessive Alport syndrome, it is not clear that one in four of all offspring of two parents with TBMN necessarily develops Alport syndrome with renal failure, deafness, lenticonus, and retinopathy.

GENETICS OF TBMN

Two thirds of individuals with TBMN have at least one other hematuric family member when five relatives are tested [19], and the inheritance of hematuria in such families is autosomal dominant [28] (Fig. 2). The converse of this observation is, however, that one third of individuals with TBMN have no family members with hematuria. This apparent lack of affected family members can still be explained by a genetic disorder if mutations occur de novo or hematuria is incompletely penetrant.

The genetic nature of TBMN was unclear for many years, and immunohistochemical examination of the thinned GBM showed only that it comprised all α1(IV) to α5(IV) type IV collagen chains (including the Goodpasture epitope) [51, 52]. It was the demonstration of uniform GBM thinning in carriers of autosomal-recessive Alport syndrome [53] that first suggested TBMN represented the carrier state for autosomal-recessive disease or at least affected the same genes [19, 54–56] (Fig. 1) (A thinned GBM also occurs in young males and female carriers with X-linked Alport syndrome but this condition must be distinguished from TBMN because of its very different prognosis). We and others have now shown that at least 40% of individuals with biopsy-proven TBMN are from families where hematuria segregates with *COL4A3/COL4A4* locus for autosomal-recessive Alport syndrome, despite there being no family members with this condition [19, 57]. Our laboratory subsequently demonstrated the R1377X and S969X *COL4A4* mutations in both TBMN and autosomal-recessive Alport syndrome [58, 59], thereby confirming that TBMN may represent the carrier state for autosomal-recessive Alport syndrome.

The observation that TBMN sometimes represents the carrier state for autosomal-recessive Alport syndrome means that the offspring of two parents with TBMN may be at risk of developing autosomal-recessive Alport syndrome with kidney failure, hearing loss, lenticonus, and retinopathy. On average, one in four offspring will be compound heterozygotes for the causative mutations and are at risk. It is not clear, however, that compound heterozygotes necessarily develop Alport syndrome or whether they simply have hematuria.

The autosomal-dominant nature of inheritance of TBMN is still consistent with inheritance of the carrier state for autosomal-recessive Alport syndrome (Fig. 2). It is also consistent with the apparent increased prevalence of TBMN in females, despite males and females inheriting the causative mutations equally often. The increased prevalence in females can be explained by mutations resulting in further attenuation of their normally thinner GBM and thus higher urinary red blood cell counts and an increased likelihood of detection.

Many *COL4A3* and *COL4A4* mutations have now been reported in TBMN [57, 60–62]. As in other diseases affecting the *COL4* genes, mutations are usually different in each family and there is no "hotspot." In addition many mutations result in the substitution of glycine with larger, more highly charged residues that disrupt the collagen triple helix. Few studies have correlated mutations and clinical features in TBMN, but preliminary evidence suggests that mutations that result in glycine substitutions or stop codons do not necessarily affect the penetrance of hematuria or the development of proteinuria [62]. The only mutation described to date that has been associated with incompletely penetrant hematuria is P1132L in *COL4A4* [62].

The mutation detection rate in TBMN is low even when both *COL4A3* and *COL4A4* genes are examined. This is partly because of the relatively insensitive screening methods used and because the commonly used primer sets do not detect all splice-site mutations. Mutation detection is further complicated by frequent *COL4A3* and *COL4A4* polymorphisms and the difficulty in distinguishing mutations from rare sequence variants in nonhematuric controls who have not had TBMN excluded by biopsy. Mutation detection is not used currently in the routine diagnosis of TBMN.

Heterozygous *COL4A3* and *COL4A4* mutations also cause autosomal-dominant Alport syndrome [63, 64], which results in renal failure, hearing loss, and a lamellated GBM. Few mutations have been described in this form of Alport syndrome and it is not obvious how they differ from the heterozygous *COL4A3* and *COL4A4* mutations that cause the milder TBMN phenotype.

We and others have shown many families with TBMN have hematuria that does not segregate with the *COL4A3/COL4A4* locus [65, 66], but these families may still have mutations in the *COL4A3* and *COL4A4* genes if de novo mutations occur, hematuria is incompletely penetrant in some family members, or family members without the mutations have coincidental hematuria. These explanations may account for the majority of families with TBMN where hematuria does not segregate with the *COL4A3/COL4A4* locus because: the de novo mutation rate in *COL4A3* and *COL4A4* is 30% if mutations in both genes occur at the same rate (15%) as in the *COL4A5* gene in X-linked Alport syndrome [67]; the incomplete penetrance rate of hematuria at the *COL4A3/COL4A4* locus is about 20% in heterozygous carriers of autosomal-recessive Alport syndrome [59]; and 14% family members without the TBMN disease haplotypes have coincidental hematuria [19].

On the other hand, TBMN that does not segregate with the *COL4A3/COL4A4* locus could be explained by mutations in a novel gene. The *MYH9* gene on 22q represented a further possible locus for TBMN, because *MYH9* mutations result in an autosomal-dominant Alport-like syndrome [68], because the autosomal-recessive and dominant forms of a disease often affect the same gene, and because TBMN is sometimes the carrier state for autosomal-recessive Alport syndrome. However, our laboratory has been unable to demonstrate linkage to this locus in any of eight families with TBMN that did not segregate with *COL4A3/COL4A4* previously. It remains unclear whether there is a further genetic locus for TBMN and, if there is, what this might be.

RISKS OF TBMN

The commonly used alternative name "benign familial hematuria," as well as numerous reports, attest to the generally excellent prognosis of TBMN. No specific therapy is available but hypertension, proteinuria, and renal impairment may need treatment.

The most common hazards of TBMN are the misunderstanding and anxiety associated with this diagnosis, and the risks and wastefulness of unnecessary investigations. Nevertheless, some patients with TBMN develop renal impairment and the reasons for this, apart from hypertension and proteinuria being predisposing factors, are unknown.

There are also genetic implications of making the diagnosis of TBMN. On average, half the offspring of any affected individual will have the causative mutation and about half will have hematuria, depending on its level of penetrance. It is not, however, known how often the offspring of two parents with TBMN will develop autosomal-recessive Alport syndrome.

Can individuals with TBMN be kidney donors? Many nephrologists currently use kidneys from donors with TBMN, and there are many anecdotal instances where there have been no apparent adverse outcomes. The real risks of donation and the outcome for the recipients are, however, unknown.

Table 3. Clinical features in hospital-based patients with biopsy-proven thin-basement membrane nephropathy (TBMN) or immunoglobin A (IgA) glomerulonephritis

	TBMN ($N = 71$)	IgA glomerulonephritis ($N = 32$)	P value
Gender	11M, 60F	22M, 10F	<0.001
Age *years* (median, range)	34 (10–68)	31 (5–61)	NS
Reported macroscopic hematuria	13 (18%)	10 (31%)	NS
Any proteinuria	33 (46%)	21 (66%)	NS
Proteinuria >500 mg/day	15 (21%)	21 (66%)	<0.001
Hypertension	14 (20%)	10 (31%)	NS
Renal impairment	5 (7%)	7 (22%)	<0.05

This study [30] suggested a family history of hematuria was infrequent in both TBMN and IgA disease. However, other reports have found two thirds of individuals with TBMN have another family member with hematuria, while only 5% to 10% patients with IgA disease have hematuria.

DIFFERENTIAL DIAGNOSIS

The two most important conditions that TBMN must be distinguished from are IgA glomerulonephritis and X-linked Alport syndrome. IgA disease is common and may resemble TBMN clinically. However, it occurs more often in males and typically has fluctuating urinary red blood cell counts (hematuria is macroscopic during infections and microscopic between these episodes), and often proteinuria >500 mg/day, and progressive renal impairment (Table 3). Fewer than 10% individuals with IgA disease have another family member with hematuria [28, 30] and this may be coincidental rather than indicating inherited disease.

TBMN must also be distinguished from other common glomerular diseases that cause hematuria. These are poststreptococcal, mesangiocapillary, proliferative lupus, and crescentic glomerulonephritis. In all these conditions, the symptoms are usually of recent and sudden onset, and macroscopic hematuria, proteinuria, hypertension, and renal impairment as well as systemic features may be present. There is no family history of hematuria.

It is not usually difficult to differentiate TBMN from other less common inherited diseases that result in glomerular bleeding. These include familial FSGS (in which proteinuria predominates but low levels of hematuria may occur), sickle cell nephropathy (which occurs in heterozygotes as well as homozygotes), and mesangiocapillary glomerulonephritis type II (in which there is usually distinctive lipodystrophy and retinopathy).

DISTINCTION FROM X-LINKED ALPORT SYNDROME

It is important to distinguish TBMN from X-linked Alport syndrome, especially in young males and in females because of the very different prognoses for these conditions.

X-linked Alport syndrome is uncommon, occurring in 1 in 50,000 live births [69], and young males often have proteinuria >500 mg/day and renal impairment, in addition to the hematuria, while children with TBMN do not [1–6] (Table 4). In addition, the demonstration of a bilateral hightone sensorineural hearing loss is specific for Alport syndrome and is often present in childhood. While anterior lenticonus and the dot-and-fleck retinopathy are also diagnostic of Alport syndrome [70], they are often not evident until the third decade (Fig. 3).

About 95% female carriers of X-linked Alport syndrome have hematuria [71, 72], but they cannot be distinguished from individuals with TBMN on the basis of proteinuria >500 mg/day or renal impairment (Table 4). While the typical hearing loss, lenticonus, and retinopathy are again diagnostic for Alport syndrome, they are found in fewer than 10% female carriers in adulthood [71, 72].

In both young males and female carriers with hematuria, a family history of renal failure often helps distinguish between TBMN and X-linked Alport syndrome, and patients should be encouraged to actively seek out the medical details of distant relatives. Where the nature of the renal failure in the distant family member is not known, it is often useful to examine that person for the characteristic hearing loss, lenticonus, or retinopathy (retinal photography is particularly helpful). It must be emphasized that the bilateral high tone sensorineural hearing loss is highly suggestive of Alport syndrome, and the lenticonus and distinctive retinopathy do not occur in any other condition. The absence of these features does not, of course, exclude Alport syndrome since they are not present in 25% patients.

It remains difficult to diagnose X-linked Alport syndrome clinically in families where there are few males, no males are affected, the males are too young to demonstrate the clinical phenotype, or the phenotype is atypical, for example, renal failure develops in later life or hearing is normal. X-linked Alport syndrome is also difficult to diagnose in families where the mutation has occurred in the present generation and there are no other affected family members. Although most X-linked Alport carriers have hematuria, and it should be possible to confirm the X-linked nature of the inheritance of hematuria and renal failure within their families, this is

Table 4. Clinical features in patients with thin-basement membrane nephropathy (TBMN), and young males and female carriers with X-linked Alport syndrome

	TBMN (N = 71)	Young males with X-linked Alport syndrome (N = 8)	Female carriers with X-linked Alport syndrome (N = 42)
Prevalence	Common	Uncommon	Uncommon
Gender	11M, 60F	8 M	42 F
Age *years* (median plus range)	34 (10–68)	11 (5–26)	35 (6–85)
Proteinuria >500 mg/day	15 (21%)	3 (38%) (P NS)[a]	5 (11%) (NS)
Renal impairment	5 (7%)	5 (63%) (<0.001)	2 (5%) (NS)
Hearing loss clinically detectable	2 (3%)	4 (50%) (<0.001)	2 (5%) (NS)
Known family history of renal failure	3/71 (4%)	6/8 (75%) (<0.0001)	35/42 (83%) (<0.0001)

The diagnosis of Alport syndrome was demonstrated in all cases by renal biopsy, and X-linked inheritance was confirmed by linkage to the *COL4A5* locus. The eight males with X-linked Alport syndrome were from eight families and the 42 female carriers were from 18 families. Clinical features were compared with the chi-square test with Yates' correction for small numbers.

[a]Children with TBMN do not have proteinuria >500 mg/day (1–6), and if patients with TBMN were age-matched with the young males with X-linked Alport syndrome, proteinuria disinguishes between the two groups ($P < 0.001$)

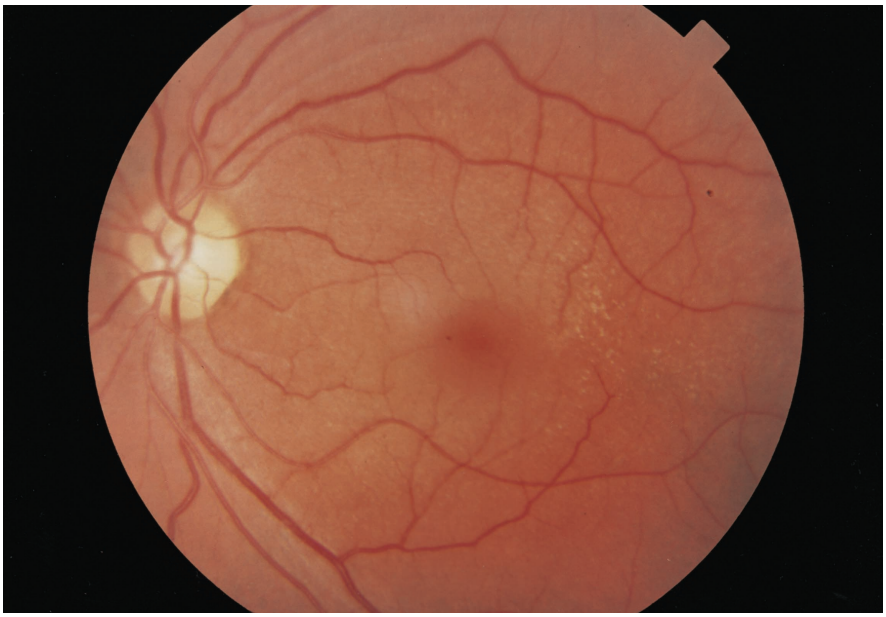

Fig. 3. Retinal photograph showing perimacular white dot-and-fleck retinopathy that is pathognomonic for Alport syndrome. This is present in about 70% males with X-linked Alport syndrome by the age of 20 years and about 10% female carriers. It is also found in autosomal-recessive Alport syndrome but not in carriers or individuals with thin basement membrane nephropathy (TBMN). The retinopathy is not associated with any visual loss, and although often evident on ophthalmoscopy, it is most easily demonstrated with retinal photographs.

often not practicable. It is, however, sometimes possible to exclude X-linked Alport syndrome from examination of the pedigree. For example, the presence of adult males with hematuria but without renal failure or deafness usually (but not always) excludes X-linked Alport syndrome [72]; and the demonstration of a father and son with hematuria but with normal renal function indicates autosomal-dominant inheritance and is not compatible with X-linked disease.

A renal biopsy should be performed to exclude X-linked Alport syndrome if this is not possible by other means (Fig. 1) (Table 5). In boys and female carriers with X-linked disease, the GBM is thinned but there are also regions of splitting and thickening that worsen progressively with time and that distinguish the GBM from that seen in TBMN [73, 74]. In affected adult males with X-linked Alport syndrome, the GBM is lamellated and thickened with subepithelial frilling. In 80% of affected males, the GBM, distal tubular basement membrane, and Bowman's capsule lack the α3(IV), α4(IV) and α5(IV) chains of type IV collagen, but in female carriers these molecules are normally or segmentally present because of lyonization [75, 76]. Immunohistochemical studies may be technically difficult and normal type IV collagen chain composition does not exclude Alport syndrome in males or female carriers. Examination of the type IV collagen composition of epidermal basement membrane from skin biopsies sometimes help distinguish between X-linked Alport syndrome (where the α5(IV) chain is absent in many patients) and TBMN [77, 78].

Genetic studies are used infrequently in the routine diagnosis of X-linked Alport syndrome. They can, however, confirm that hematuria within a family segregates

Table 5. Ultrastructural, immunohistochemical, and genetic characteristics in patients with thin-basement membrane nephropathy (TBMN), and young male and female carriers with X-linked Alport syndrome

	TBMN	Young males with XLAS	Female carriers with XLAS
GBM	Thinned	Thinned with regions of lamellation; becomes thickened and more lamellated with time	Thinned with regions of lamellation; may thicken and become more lamellated with time
Type IV collagen chains in GBM	α3(IV)–α5(IV) chains all present	α3(IV)–α5(IV) chains absent from GBM, distal TBM and Bowman's capsule in 80% cases	Normal α3(IV)–α5(IV) chain distribution or patchy loss
Type IV collagen chains in epidermal basement membrane	α5(IV) chain present	α5(IV) chain missing	Normal α5(IV) chain distribution or patchy loss
Genes affected	*COL4A3/COL4A4* and possibly other loci	*COL4A5*	*COL4A5*

Abbreviations are: GBM, glomerular basement membrane; TBM, tubular basement membrane. The genes affected may be implicated by linkage studies or mutation detection.

with the *COL4A5* locus and they can demonstrate the causative *COL4A5* mutations [79]. Linkage studies are easier and more readily available than mutation detection but they require the cooperation and characterization of many family members. It is usually easier to exclude linkage than to confirm it, and it may be relatively easy to show that hematuria is not linked to the *COL4A5* gene. Mutation detection is laborious and relatively insensitive, and there is usually no advantage to knowing the mutations in individual families. There are, however, several large research centers in Europe that sequence the *COL4A5* gene and can detect more than 80% mutations.

MANAGEMENT OF TBMN

There are no evidence-based guidelines for the management of patients with TBMN. After this diagnosis has been made clinically or on renal biopsy, many physicians begin by monitoring adult patients for the development of hypertension, proteinuria, or renal impairment every 1 to 2 years. Family doctors may subsequently be involved. Patients at risk of renal impairment cannot be identified at presentation apart from those who have proteinuria or hypertension. Patients with proteinuria >500 mg/day, hypertension, or renal impairment should be treated, and reviewed regularly. In addition, family members of patients with TBMN should be offered the opportunity to be tested for hematuria.

CONCLUSION

TBMN is one of the most common conditions affecting the kidney, but we are only now coming to acknowledge its prevalence and to understand its genetic basis. We still do not know why renal function occasionally deteriorates, the relationship between a thinned GBM and secondary glomerular disease, whether mutations in the *COL4A3* and *COL4A4* genes account for all cases of TBMN, and the consequences, if any, of kidney donation for both the donor and recipient.

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