SEMINARS IN
NEPHROLOGY

The Genetics of Thin Basement Membrane Nephropathy

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The diagnosis of thin basement membrane nephropathy (TBMN) usually is made on the basis of the clinical features or the glomerular membrane ultrastructural appearance. Only now are we beginning to understand the genetics of TBMN and the role of diagnostic genetic testing. The similarity of clinical and glomerular membrane features first suggested TBMN might represent the carrier state for autosomal-recessive Alport syndrome. This was confirmed subsequently by the demonstration that 40% of families with TBMN have hematuria that segregates with the corresponding locus (*COL4A3/COL4A4*), and identical mutations occur in both conditions. To date, about 20 *COL4A3* and *COL4A4* mutations have been shown in TBMN, and these mainly are single nucleotide substitutions that are different in each family. The families in whom hematuria does not appear to segregate with the *COL4A3/COL4A4* locus cannot all be explained by de novo mutations, and nonpenetrant or coincidental hematuria. This suggests a further TBMN locus. In patients with persistent hematuria, testing for *COL4A3* and *COL4A4* mutations to diagnose TBMN is problematic because of the huge size of these genes, their frequent polymorphisms, and the likelihood of a further gene locus. It is far more practicable to perform genetic testing to exclude or confirm X-linked Alport syndrome because this condition is the major differential diagnosis of TBMN and has a very different prognosis.
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Thin basement membrane nephropathy (TBMN), or *benign familial hematuria*, usually is diagnosed clinically or on renal biopsy examination. The diagnosis is made clinically when there is persistent glomerular hematuria, minimal proteinuria (<500 mg/d), normal renal function, and no other obvious cause.[1] Two thirds of individuals with TBMN have a family history of hematuria,[2,3] but not of X-linked Alport syndrome or renal failure. TBMN most often has to be distinguished from immunoglobulin (Ig)A glomerulonephritis and from X-linked Alport syndrome, from X-linked syndrome especially in young males and carrier females, because of the possibility of treatment in IgA disease[4] and the very different prognoses for these conditions. The distinction often is obvious clinically because patients with IgA disease and Alport syndrome are more likely to have proteinuria or renal impairment but overlap can occur and up to 40% of patients with biopsy examination–proven TBMN in some series have proteinuria greater than 300 mg/d and 7% have some degree of renal impairment.[1]

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A renal biopsy examination is performed in patients suspected clinically of having TBMN when there are atypical clinical features and when IgA disease, X-linked Alport syndrome, and a coincidental or superimposed glomerular or tubulointerstitial lesion cannot be excluded. The light microscopic appearance in TBMN usually is nearly normal with only a mild increase in mesangial cells and matrix. The characteristic and diagnostic feature, however, is the uniform glomerular basement membrane (GBM) thinning evident on ultrastructural examination.[5,6] The GBM width in TBMN is less than the normal range established within individual laboratories and varies from 200 to 262 nm depending on fixation techniques, patient age, and patient sex. In TBMN, most glomerular capillaries show thinning, at least 50% of the GBM in each capillary is affected, only isolated regions of lamellation or thickening occur,[7] and the affected GBM does not thicken or split with time. The thinning seen in TBMN must be distinguished from that present in normal children, the focal attenuation that occurs with IgA disease and other forms of glomerulonephritis, and the diffuse thinning, usually accompanied by lamellation, in boys and carrier females with X-linked Alport syndrome.[8]

If the distinction between TBMN, IgA glomerulonephritis, and X-linked Alport syndrome is not obvious clinically, then it usually will be apparent on immunohistochemical and ultra-

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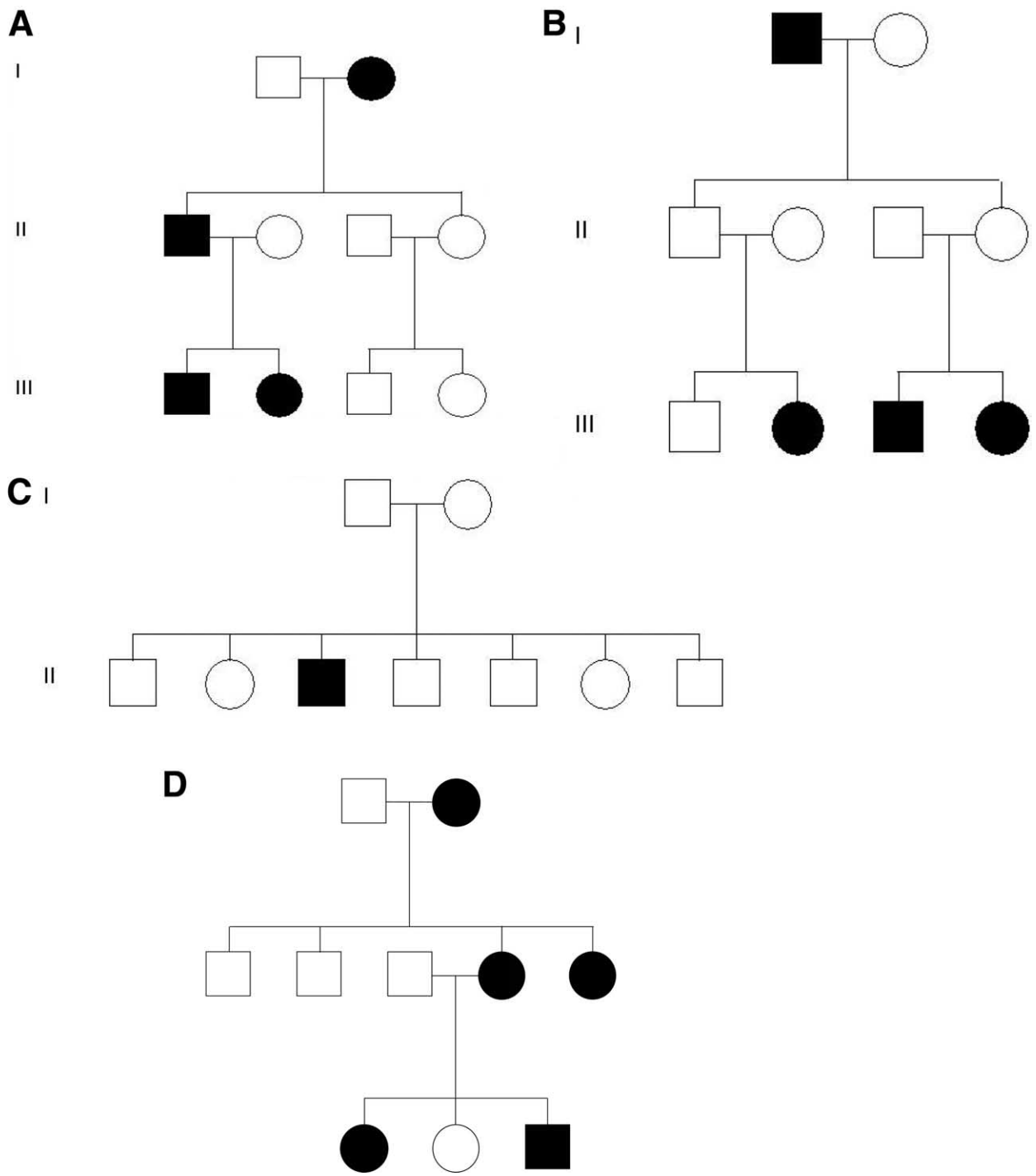

Figure 1 (A) Inheritance of TBMN with complete penetrance of hematuria. This shows hematuria in each generation and males and females affected equally often. Hematuria in both a father and son is characteristic of autosomal-dominant inheritance and will not occur in X-linked Alport syndrome. (Colored symbols in all figures indicate hematuria.) (B) Inheritance of TBMN with nonpenetrance of hematuria. In this family, hematuria does not occur in the middle generation although both the son and the daughter must have the mutant gene. (C) Inheritance of TBMN with de novo mutation. Only 1 family member has hematuria despite a large number being tested. This occurs with both de novo mutations and nonpenetrance of hematuria. (D) Inheritance of hematuria consistent with both TBMN and X-linked Alport syndrome. The absence of an adult male with hematuria and renal impairment makes it difficult to distinguish between these conditions.

structural examination of the renal biopsy specimen. If TBMN cannot be differentiated from X-linked Alport syndrome on electron microscopy, then the GBM should be examined for type IV collagen chains. The GBM in TBMN comprises all the α3(IV), α4(IV), and α5(IV) collagen chains,[9] but these are absent from the GBM of 80% of males with X-linked Alport syndrome and are patchily absent in female carriers.[10] The epidermal basement membrane in skin biopsy specimens shows

Table 1 Mutations in the *COL4A3* and *COL4A4* Genes in TBMN

Mutations	Nucleotide Change	Exon/intron	Study
COL4A3			
G464V	1391 G>T	22	Tazon Vega, et al.[20]
G532C	1594 G>T	25	Wang, et al.[22]
G584C	1750 G>T	25	Wang, et al.[22]
G596R	1786 G>C	26	Wang, et al.[22]
G695R	2083 G>A	28	Wang, et al.[22]
IVS29-11 C>T		Intron 29	Wang, et al.[22]
G985V	2953 G>T	35	Badenas, et al.[15]
IVS35+1 G>A		Intron 35	Wang, et al.[22]
G1015E	3044 G>A	36	Badenas, et al.[15]
IVS40-7 C>G		Intron 40	Wang, et al.[22]
COL4A4			
31del11		2	Badenas, et al.[15]
IVS23-1 G>C		Intron 23	Badenas, et al.[15]
IVS24 deletion	184-bp deletion	Intron 24 and exon 25	Gross, et al.[21]
1935del18	18-bp deletion	25	Gross, et al.[21]
2385delG	Frameshift at 795, stop at 803	29	Tazon Vega, et al.[20]
2583/86delG	Frameshift at 861/862, stop at 868	30	Buzza, et al.[18]
G957R	2869 G>C	32	Ozen, et al.[19]
G960R	2878 G>C	32	Badenas, et al.[15]
S969X	2907 C>G	32	Buzza, et al.[18]
3222insA		35	Badenas, et al.[15]
R1377X	4129 C>T	44	Buzza, et al.[16]

similar immunohistochemical abnormalities to those seen in Alport syndrome.[11]

Genetics of TBMN

About two thirds of individuals with TBMN have at least 1 other family member with hematuria.[12] The inheritance of hematuria in these families is autosomal dominant[3] and some individuals with apparently sporadic disease may be explained by de novo mutations and nonpenetrance of the hematuria in other family members (Fig 1 A-1C).

The similarity of the clinical features and the GBM appearance in TBMN and in carriers of autosomal-recessive Alport syndrome[13,14] first suggested these conditions were caused by mutations in the same genes (*COL4A3* or *COL4A4*), and our laboratory showed subsequently that about 40% of individuals with TBMN had hematuria that segregated with the *COL4A3*/*COL4A4* locus.[12]

We also described identical mutations in both autosomal-recessive Alport syndrome (R1377X and S969X in *COL4A4*)[16,17] and in TBMN where there was no family history of Alport syndrome. To date, 6 mutations have been described that are common to both conditions (G464V, G1015E in *COL4A3* and a 184-bp deletion in intron 24 and exon 25, and an 18-bp deletion in exon 25 in *COL4A4*) from about 40 known mutations in autosomal-recessive Alport syndrome and 21 in TBMN (Table 1, Figs 2 and 3).[15-22] These observations confirm that TBMN represents the carrier state for autosomal-recessive Alport syndrome at least in some families. The autosomal-dominant nature of inheritance of TBMN still is consistent with TBMN being the carrier state for autosomal-recessive Alport syndrome.

Table 2 Mutations in the *COL4A3* and *COL4A4* Genes in Autosomal-Dominant Alport Syndrome

Mutation	Nucleotide Change	Exon	Study
COL4A3			
40del24		1	Longo, et al.[28]
Exon 21 deletion		Intron 20	Van der Loop, et al.[26]
G1045V	3134 G>T	37	Pescucci, et al.[29]
G1198S	3592 G>A	42	Longo, et al.[28]
G1219C	3655 G>T		Pescucci, et al.[29]
COL4A4			
K325N	975 G>T	16	Ciccarese, et al.[27]
G448S	1344 G>A	20	Longo, et al.[28]
G957R	2869 G>C	32	Pescucci, et al.[29]
C1634S	4980 T>A	48	Pescucci, et al.[29]

Table 3 Polymorphisms in the *COL4A3* and *COL4A4* Genes

Polymorphism	Nucleotide Change	Exon	Study
COL4A3			
3′UTR	3′UTR-10 C>T		Tazon Vega, et al.[20]
G43R	127 G>C	2	Heidet, et al.[23]
IVS2+12C>A		Intron 2	Badenas, et al.[15]
P74P	222 G>T	3	Tazon Vega, et al.[20]
P116T	346 C>A	6	Wang, et al.[22]
P141L	422 C>T	7	Longo, et al.[28]
A158D	473 C>T	9	Badenas, et al.[15]
E162G	485 A>G	9	Heidet, et al.[23]
P293R	878C>G	15	Badenas, et al.[15]
D326Y	976 G>T	17	Heidet, et al.[23]
L399L	1195 T>C	21	Longo, et al.[28]
R408H	1223 G>A	21	Heidet, et al.[23]
H451R	1352 A>G	22	Heidet, et al.[23]
G484G	1452 G>A	23	Badenas, et al.[15]
P574L	1721 C>T	25	Heidet, et al.[23]
P690P	2070 T>A	27	Wang, et al.[22]
K834R	2501 A>G	32	Tazon Vega, et al.[20]
G895G	2685 A>C	33	Wang, et al.[22]
A899A	2697 C>A	33	Wang, et al.[22]
P1109S	3325 C>T	38	Longo, et al.[28]
IVS39+18delA		Intron 39	Badenas, et al.[15]
D1269E	3806 C>A	43	Heidet, et al.[23]
L1474P	4421 T>C	48	Lemmink, et al.[13]
Q1495R	4484 A>G	49	Longo, et al.[28]
COL4A4			
IVS1-2C>T		Intron 1	Badenas, et al.[15]
16T	17 C>T	2	Badenas, et al.[15]
G65G	195 T>C	5	Tazon Vega, et al.[20]
G116E	347 G>A	6 Buzza	
IVS17+71A>G		Intron 17	Longo, et al.[28]
IVS17+36A>C		Intron 17	Longo, et al.[28]
L365L	1095 T>C	18	Longo, et al.[28]
P482S	1444 C>T	21	Badenas, et al.[15]
G545A	1634 G>C	23	Boye, et al.[24]
G611G	1833 >C	25	Tazon Vega, et al.[20]
IVS28-5C>T		Intron 28	Badenas, et al.[15]
R877Q	2630 G>A	30	Longo, et al.[28]
G999E	2996 G>A	33	Buzza, et al.[18]
L1004P	3011 T>C	33	Boye, et al.[24]
G1198G	3594 G>A	39	Badenas, et al.[15]
K1228K	3684 G>A	39	Badenas, et al.[15]
M1327V	3979 A>G	42	Boye, et al.[24]
P1360P	4080 A>G	42	Badenas, et al.[15]
P1403S	4207 C>T	44	Boye, et al.[24]
IVS45-15C>T		Intron 45	Tazon Vega, et al.[20]
IVS46-8T>C		Intron 46	Boye, et al.[24]
V1516V	4548 A>G	47	Badenas, et al.[15]
F1644F	4932 C>T	48	Badenas, et al.[15]

It remains unclear whether individuals with TBMN are always carriers for autosomal-recessive Alport syndrome and the offspring of 2 affected parents are at risk for renal failure from Alport syndrome, or whether some offspring with complex heterozygous mutations simply have the TBMN phenotype. In this respect, TBMN and autosomal-recessive Alport syndrome are analogous to β-thalassemia minor and major. In both cases, the carrier states are very common, have a mild phenotype, and often are undetected, but the offspring of 2 carriers are at risk for a life-threatening disease. Although the β-thalassemia trait confers an evolutionary advantage against malaria, any advantage of TBMN is not known.

Routine mutation detection in TBMN is complicated by the huge size of the *COL4A3* and *COL4A4* genes with 52 and 48 exons, respectively.[23,24] Mutations usually are different in each family, and affect both genes equally often and without apparent

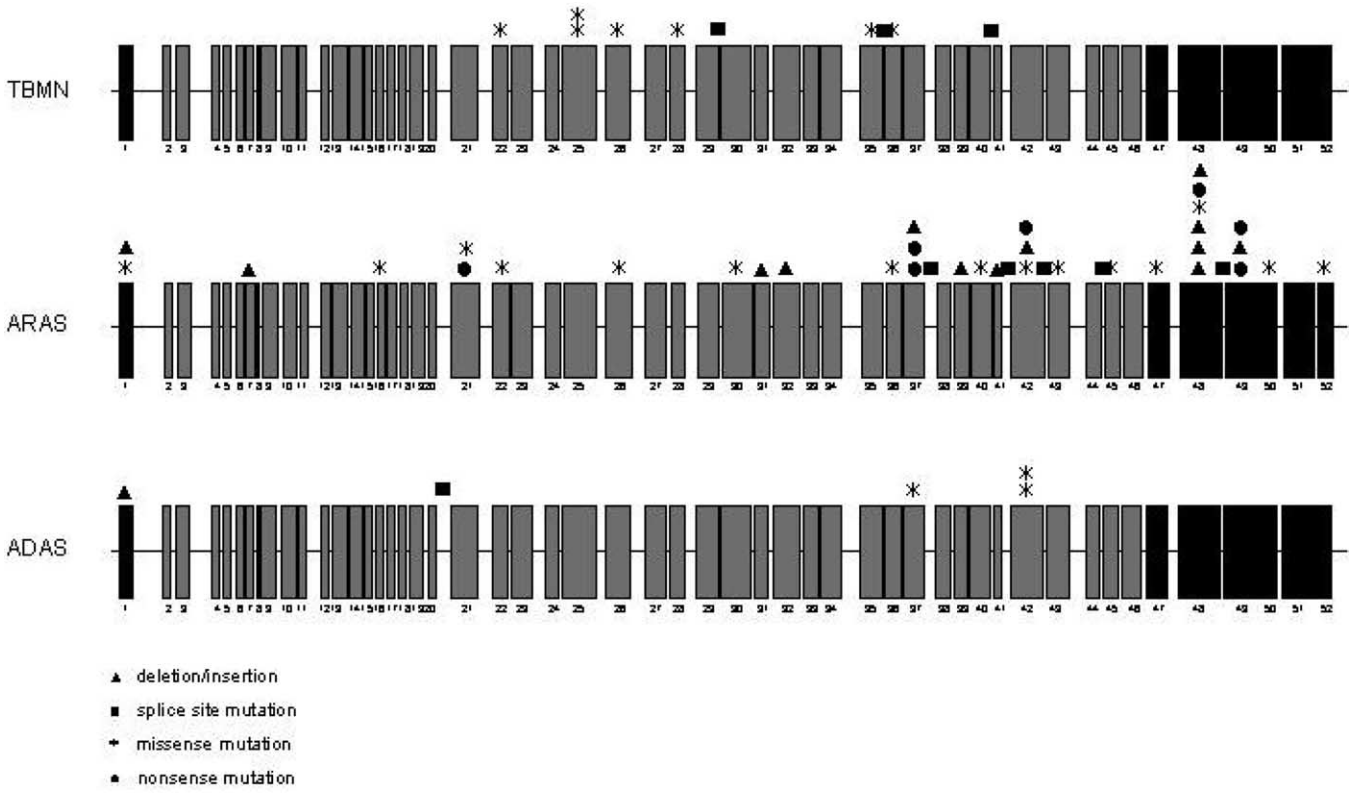

Figure 2 Mutations in the *COL4A3* gene in TBMN, autosomal-recessive Alport syndrome, and autosomal-dominant Alport syndrome.

hotspots (Table 1). Most mutations are single nucleotide substitutions that result in missense or nonsense mutations. Some of these replace glycine with larger, more highly charged residues that disrupt the collagen triple helix and some affect splice sites. Six are deletions or insertions. There are very few studies that have examined genotype-phenotype correlations, but those that do have shown that different family members with the same mutations commonly have different clinical features.[22]

Heterozygous *COL4A3* and *COL4A4* mutations also cause autosomal-dominant Alport syndrome (Table 2).[25-29] To date, 9 mutations that result in this form of Alport syndrome have been described but it is not clear why these produce a different phenotype (renal failure, hearing loss, and a lamellated GBM) from that seen with the heterozygous *COL4A3* and *COL4A4* mutations causing TBMN.

However, only 40% of our families with TBMN have hematuria that segregates with the *COL4A3/COL4A4* locus. This suggests another genetic locus for TBMN[5,30,31] and we have examined this possibility further. First, we reanalyzed our *COL4A3/COL4A4* linkage studies in 21 families with TBMN and found that de novo mutations, nonpenetrant hematuria, and coincidental hematuria in unaffected family members could not explain the lack of segregation in all the unlinked families. Second, we reviewed the results of screening for *COL4A3* and *COL4A4* mutations using single-stranded conformational polymorphism (SSCP) analysis in 24 individuals with biopsy examination–proven disease whose families already had been examined for linkage to *COL4A3/COL4A4*. Eleven (44%) had hematuria that segregated with *COL4A3/COL4A4*, and mutations were demonstrated in 9 of these (80% of expected). On the other hand, only 1 mutation was identified in the 13 families (8%) in whom hematuria did not segregate with *COL4A3/COL4A4*. These observations suggest that our mutation screening methods are sensitive and that another genetic locus for TBMN is likely.

Finally, we have examined other genes that are potential loci for TBMN. We studied 9 families with TBMN (6 confirmed on renal biopsy examination) and hematuria that did not segregate with *COL4A3/COL4A4*. We excluded linkage to *MYH9* (the locus for autosomal-dominant hereditary nephritis with hematologic abnormalities[32]), *LAMA5* (coding for the laminin α5 chain), and the genes for perlecan and fibronectin in all 9 families. We showed 3 families had hematuria that segregated with *LAMC1* (coding for laminin γ1) and 1 each for *LAMB2* (laminin β2 chain), nidogen, and agrin, but these families were too small for the results to be conclusive and segregation sometimes occurred at several loci simultaneously. Nevertheless, we went on to screen the *LAMC1* gene by SSCP in 15 unrelated individuals with TBMN and although we identified novel polymorphisms we found no mutations.

The major gene locus for TBMN is *COL4A3/COL4A4* because 40% of families have hematuria that segregates here. This locus also accounts for some other families with TBMN in whom

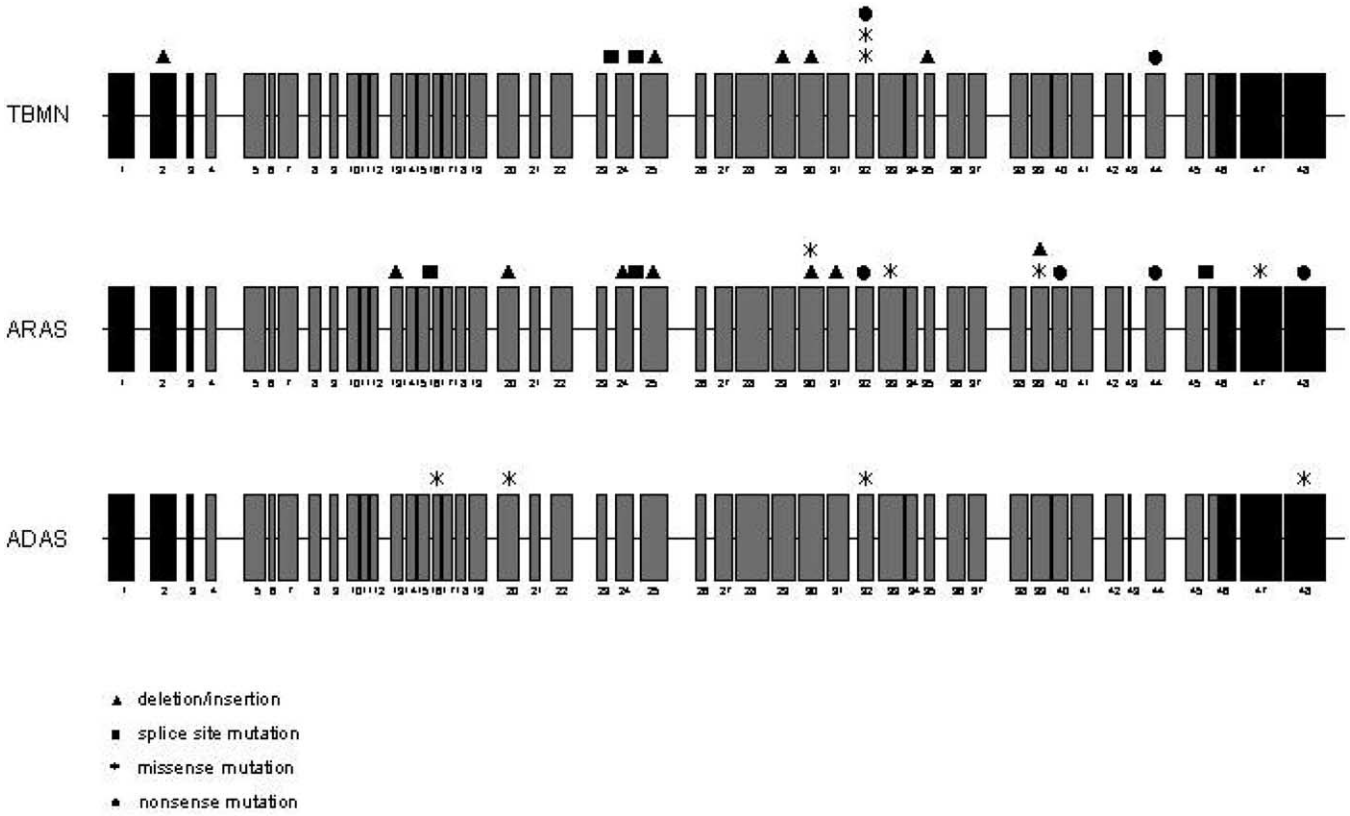

Figure 3 Mutations in the *COL4A4* gene in TBMN, autosomal-recessive Alport syndrome, and autosomal-dominant Alport syndrome.

segregation is not obvious because of the effects of de novo mutations, nonpenetrant hematuria, and coincidental hematuria. Although up to 20% of patients diagnosed with TBMN on renal biopsy examination actually have X-linked Alport syndrome[5] caused by *COL4A5* mutations, TBMN and X-linked Alport syndrome always must be distinguished because of their very different prognoses. The identity of a further gene locus for TBMN remains unknown.

Genetic Testing for TBMN

Genetic tests are rarely necessary for the diagnosis of TBMN and anyway are usually problematic. The techniques used most commonly are linkage analysis and mutation detection. Linkage studies theoretically require the cooperation of a large number of family members who must be characterized accurately as affected or unaffected on the basis of whether they have hematuria or not on phase-contrast microscopy.[33] DNA from family members then is examined by using at least 4 highly variable microsatellite markers, which enables the identification of haplotypes that segregate with hematuria within individual families. Linkage analysis has some advantages over mutation detection. First, very little DNA is required and sufficient amounts usually can be extracted from buccal brushings. Second, DNA from both affected and unaffected family members is equally helpful in the analysis and the total number of family members studied is more important than the number of affected individuals. Third, although it is quite difficult to prove linkage (ie, a large number of individuals from any single family must be tested), often only a few family members are needed to exclude linkage. Finally, linkage studies are quick and inexpensive. Nevertheless, they still have the major drawback that only 40% of families with TBMN have hematuria segregating with the *COL4A3/COL4A4 locus* and that linkage is complicated because of de novo mutations, and non-penetrant and coincidental hematuria as discussed above.

Screening for mutations in TBMN also has problems. The most commonly used screening methods are SSCP and denaturing high-performance liquid chromatography. SSCP often needs to be performed under different conditions to demonstrate all the mutations, the results may be nonspecific, and the mutation detection rate is only 80% at most. Denaturing high-performance liquid chromatography is more sensitive, but requires special equipment, optimization of testing conditions for individual amplicons, and it is expensive. Direct sequencing is the gold standard for mutation detection[34] but again this is expensive and labor-intensive, and may miss the heterozygous nucleotide changes found in TBMN. In X-linked Alport syndrome, screening messenger RNA/complementary DNA from skin or a hair follicle for *COL4A5* mutations is possible,[35] but the *COL4A3* and *COL4A4* genes are not expressed in the skin or

other easily accessible tissues. In TBMN, both the *COL4A3* and *COL4A4* genes must be tested for mutations, and testing is limited both by the size of the genes and the insensitivity of many detection methods. Commonly used mutation detection techniques may not demonstrate large deletions, and some splice site and deep intronic mutations depending on the amplification primers used. The frequent *COL4A3* and *COL4A4* polymorphisms also will interfere with test interpretation (Table 3). Mutations, unlike polymorphisms, usually change the amino acid sequence, occur in a highly conserved region that is often of structural or functional significance in the protein, and are not present in 100 alleles from nonhematuric normals.

The 2 major differential diagnoses of TBMN are IgA glomerulonephritis and X-linked Alport syndrome. Is it possible to exclude these diagnoses using genetic tests? Genetic testing is not useful in the diagnosis of IgA disease. Only 5% of patients have another family member with hematuria, and although 50% of families with IgA disease have hematuria linked to 6q, the affected gene has not been identified and there are at least 2 other loci.[36,37]

When the diagnosis of TBMN is not clear on clinical or renal biopsy specimen features, it is very useful to exclude X-linked Alport syndrome by *COL4A5* linkage studies or to confirm this diagnosis by demonstrating a *COL4A5* mutation.[38] The high penetrance of hematuria on phase-contrast microscopy in affected males and female carriers with X-linked Alport syndrome[39] means that individuals can be characterized accurately as affected or unaffected and that X-linked Alport syndrome can be excluded by *COL4A5* linkage studies using as few as 3 family members. Alternatively, an assay for *COL4A5* mutations now is available commercially, and although the *COL4A5* gene has 51 exons, the assay has a sensitivity of about 80% and is able to detect deep intronic and splice site mutations. Furthermore, interpretation of the results is easier than in TBMN because the *COL4A5* coding sequence contains very few polymorphisms. Nevertheless, these assays are expensive, and although we would not advocate screening for *COL4A3* and *COL4A4* mutations in individuals in whom TBMN is suspected, screening or directly sequencing the *COL4A5* gene for mutations is helpful in excluding X-linked Alport syndrome in selected cases.

Genetic Counselling in TBMN

The inheritance of TBMN is autosomal dominant, and mutations are transmitted equally often to males and females in successive generations. Thus, the advice given to individuals with TBMN is that, on average, half of their offspring will have the genetic mutation and many or all of those with the mutation will have hematuria depending on its level of penetrance. Likewise, a parent and grandparent also are likely to have the mutation (depending on the de novo mutation rate) and hematuria (again, depending on the mutation's penetrance). Nonpenetrance of hematuria may mean that TBMN appears to skip a generation. The inheritance pattern is complicated further by the suggestion from several studies that females in a family with TBMN are more likely to have hematuria.

The precise relationship of TBMN and autosomal-recessive Alport syndrome still is not clear, and the risk for the offspring of 2 affected parents having a child with autosomal-recessive Alport syndrome is not known.

Finally, the pattern of inheritance of hematuria in families with TBMN may be identical to that seen in families with X-linked Alport syndrome that comprise only females (Fig 1D). It is important to remain aware of this possibility.

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