Pathogenic Variants in the Genes Affected in Alport Syndrome (COL4A3–COL4A5) and Their Association With Other Kidney Conditions: A Review

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Massively parallel sequencing identifies pathogenic variants in the genes affected in Alport syndrome (COL4A3–COL4A5) in as many as 30% of individuals with focal and segmental glomerulosclerosis (FSGS), 10% of those with kidney failure of unknown cause, and 20% with familial immunoglobulin A (IgA) glomerulonephritis. FSGS associated with COL4A3–COL4A5 variants is usually present by the onset of kidney failure and may develop because the abnormal glomerular membranes result in podocyte loss and secondary hyperfiltration. The association of COL4A3–COL4A5 variants with kidney failure or IgA glomerulonephritis may be coincidental. However, pathogenic variants in these conditions occur more often than they should by chance, which suggests that the variants are disease-causing. COL4A3–COL4A5 variants are also found in cystic kidney diseases after autosomal dominant polycystic kidney disease has been excluded. COL4A3–COL4A5 variants should be suspected in individuals with FSGS, kidney failure of unknown cause, or familial IgA glomerulonephritis, especially where there is persistent hematuria and a family history of hematuria or kidney failure.

Introduction

The widespread use of massively parallel sequencing has identified pathogenic variants in the genes affected in Alport syndrome in cohorts with other kidney phenotypes, including focal and segmental glomerulosclerosis (FSGS), kidney failure of unknown cause, familial immunoglobulin A (IgA) glomerulonephritis, and possibly cystic kidney disease. These genes, COL4A3, COL4A4, and COL4A5, encode the α3, α4, and α5 chains, respectively, of collagen IV. This review examines how often these associations occur; the evidence for the associations with COL4A3–COL4A5 variants being coincidental, causative, or modifying; and the potential pathogenetic mechanisms and clinical significance of identifying underlying COL4A3–COL4A5 variants.

Alport Syndrome

Alport syndrome (Online Mendelian Inheritance in Man 303630, 120070, 120131) is an inherited kidney disease characterized by hematuria, progressive kidney failure, hearing loss, and ocular abnormalities.1,2 It is the second most common cause of inherited kidney failure after autosomal dominant polycystic kidney disease, and affects at least 1 in 5,000, and probably more like 1 in 2,000 of the population.3,4 Eighty-five percent of Alport syndrome is X-linked5 and caused by pathogenic variants in COL4A5,6 and the remaining 15% is autosomal recessive and results from the combination of 2 variants in either COL4A3 or COL4A4 on opposite chromosomes.7 The risks of Alport syndrome are high. Kidney failure requiring replacement therapy develops by the age of 40 years in 90% of men with a COL4A5 variant, and 15%-30% of women with a COL4A5 variant develop kidney failure by age 60 years.8 Most men and women with recessive Alport syndrome have kidney failure by the end of their second decade of life.8

Individuals with a heterozygous COL4A3 or COL4A4 variant are carriers of recessive Alport syndrome and are sometimes said to have thin basement membrane nephropathy (TBMN)9 or, alternatively, autosomal dominant Alport syndrome.10 These heterozygotes typically have hematuria and normal levels of proteinuria, blood pressure, and kidney function, with no hearing loss or ocular defects,10 but up to 10% have kidney failure by 60 years of age.11,12 Approximately 1% of the population has a heterozygous COL4A3 or COL4A4 variant, a prevalence demonstrated by the number of thinned glomerular membranes in normal transplant donor kidney biopsies,13 but also consistent with the frequency of autosomal recessive Alport syndrome.8 Heterozygous COL4A3 and COL4A4 variants are at least 20 times as common as COL4A5 variants in the population.

The diagnosis of Alport syndrome is suspected when there is persistent hematuria and kidney failure or hearing loss, often in the presence of a family history of hematuria or kidney failure.5 Lenticulon, fleck retinopathy, and kidney biopsy with a lamellated or uniformly thinned glomerular basement membrane (GBM) are pathognomonic for Alport syndrome.2,8 COL4A3 and COL4A4 heterozygotes may be detected by screening strategies for hematuria at school, for employment or insurance purposes, or at antenatal visits, but many individuals with a pathogenic variant in COL4A3–COL4A5 are unrecognized. This is especially true for men with COL4A5 variants associated with mild disease, women with a COL4A5 variant, and men and women with a heterozygous COL4A3 or COL4A4 variant.

FSGS

FSGS is characterized histologically by mesangial sclerosis and clinically by proteinuria and progressive kidney failure.
that typically does not respond to treatment with steroids and alkylating agents nor recur in a kidney transplant.\textsuperscript{14,15}

Alport syndrome and TBMN are commonly also diagnosed when there is also a histologic finding of FSGS.\textsuperscript{10,12,16} The association of FSGS with pathogenic COL4A3–COL4A5 variants has been confirmed with massively parallel sequencing.\textsuperscript{17} Most men with a pathogenic COL4A5 variant and proteinuria have FSGS, as do nearly 40% of individuals with a heterozygous COL4A3 or COL4A4 variant and proteinuria.\textsuperscript{18}

Conversely, pathogenic COL4A3–COL4A5 variants represent the single most common genetic cause of FSGS and occur more often than any other gene affected in disease of pediatric (NPHS2, NPHS1, CD2AP, PLCE1, MYO1E) or adult (INRF, TRPC6, ACTN4, ANLN) onset.\textsuperscript{19-22} Pathogenic variants in COL4A5, COL4A3, or COL4A4 are found in FSGS,\textsuperscript{23} but COL4A5 variants are overrepresented considering that they are much less frequent in the general population.\textsuperscript{24} Many cohorts of FSGS also include unsuspected autosomal recessive Alport syndrome with 2 COL4A3 or COL4A4 variants. The development of FSGS with heterozygous COL4A3 or COL4A4 variants is more variable, and often only one affected member of a family has proteinuria and FSGS. This variability may relate to increased age, coincidental hypertension, diabetes, obesity, nephrotic medication use, or other factors. There is no evidence at present for an association of proteinuria with variant type in heterozygotes.\textsuperscript{24}

Overall, COL4A3–COL4A5 variants are found in 22%–38% of people with familial FSGS\textsuperscript{27,23} and 5%–10% of those with sporadic disease\textsuperscript{23,25,26} (Table 1). The demonstration of a COL4A3–COL4A5 variant is just as common in children with FSGS as adults.\textsuperscript{27} The finding of syndromic features such as hearing loss, lenticonus or fleck retinopathy, or a lamellated GBM makes the demonstration of a COL4A5 variant or 2 COL4A3 or COL4A4 variants more likely, but syndromic abnormalities do not increase the likelihood of finding a heterozygous COL4A3 or COL4A4 variant.\textsuperscript{8}

In FSGS, features suggesting an underlying pathogenic COL4A3–COL4A5 variant are the same as for individuals who do not have FSGS. These include persistent hematuria and a family history of hematuria or kidney failure.\textsuperscript{13} Hematuria with urinary red blood cell counts >50,000/mL occurs with nearly all pathogenic COL4A5 variants and with 2 COL4A3 or COL4A4 variants, and less often with a heterozygous COL4A3 or COL4A4 variant.\textsuperscript{10} Hematuria is uncommon with most other genetic causes of FSGS.

The finding of a lamellated GBM is pathognomonic for a pathogenic COL4A5 variant or 2 COL4A3 or COL4A4 variants. However, in individuals with FSGS, a lamellated or thinned GBM occurs less often because FSGS is often diagnosed on the basis of proteinuria without a kidney biopsy, or in cases in which a kidney biopsy is performed but the GBM is not examined.\textsuperscript{27}

FSGS increases the risk of kidney failure for all of the COL4A3–COL4A5 variants. Proteinuria and FSGS become more obvious with increasing age.\textsuperscript{12} FSGS occurs earlier with COL4A5 variants\textsuperscript{23} and progresses more rapidly than with heterozygous COL4A3 or COL4A4 variants. Although 1 study found that nearly 20% of 116 individuals with a heterozygous COL4A3 or COL4A4 variant had developed kidney failure 30 years after their diagnosis,\textsuperscript{12} this was a hospital-based cohort of patients who were more likely to have severe disease.

The pathogenesis of FSGS secondary to disease-causing COL4A3–COL4A5 variants is incompletely understood. However, COL4A3–COL4A5 variants result in reduced expression of the corresponding collagen IV α3α4α5 network, an abnormal GBM, and loss of the overlying podocytes,\textsuperscript{28} which is likely to produce hyperfiltration and FSGS as a secondary lesion. Pathogenic variants in the LMX1B transcription factor are associated with reduced expression of the collagen IV α3 and α4 chains in glomerular membranes,\textsuperscript{29} as well as podocyte loss and FSGS.\textsuperscript{30} In addition to the abnormal corneal\textsuperscript{31} and retinal\textsuperscript{32} basement membranes seen with COL4A5 variants, individuals with LMX1B variants also have fewer podocytes, suggesting a shared pathogenesis for epithelial cell loss.

Interestingly, mouse models incompletely replicate the clinical features of human COL4A3–COL4A5-associated disease.\textsuperscript{33} However, glomerulosclerosis is found more consistently than hematuria and GBM abnormalities in 2 of the 3 COL4A3, 3 of the 4 COL4A4, and 2 of the 5 COL4A5 mouse knockout models. Thus, increasing evidence suggests that pathogenic COL4A3–COL4A5 variants contribute to the development of FSGS. One pathogenic COL4A5 variant or 2 COL4A3 or COL4A4 variants are much more likely to cause disease than simply having a modifying effect. Pathogenic heterozygous COL4A3 and COL4A4 variants are also likely to result in FSGS, but are also so common that they may occur by chance when there is already another cause for proteinuria.

### Kidney Failure

Pathogenic COL4A5 and COL4A3 or COL4A4 variants are found in up to 10% of individuals with kidney failure in which the cause has not been known previously.\textsuperscript{34} COL4A5 variants are relatively more common than COL4A3 and

### Table 1. Likelihood of Identifying a Pathogenic Variant in an Alport Gene (COL4A5, COL4A3, COL4A4) Based on Whether the Disease Appears Familial or Sporadic

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Likelihood, %</th>
<th>Familial</th>
<th>Sporadic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal and segmental glomerulosclerosis</td>
<td>10-30\textsuperscript{23}</td>
<td>5-10\textsuperscript{23,25,26}</td>
<td></td>
</tr>
<tr>
<td>Kidney failure with no obvious cause</td>
<td>10\textsuperscript{34}</td>
<td>10\textsuperscript{34}</td>
<td></td>
</tr>
<tr>
<td>IgA glomerulonephritis</td>
<td>10-20\textsuperscript{49,50}</td>
<td>&lt;&lt;10</td>
<td></td>
</tr>
<tr>
<td>Cystic renal disease aged &lt;50 y (not ADPKD)</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td></td>
</tr>
</tbody>
</table>

Ig, immunoglobulin; ADPKD, autosomal dominant polycystic kidney disease.
COL4A4 variants in cohorts with kidney failure considering that they are much less common in the population.26,34–38

Most men with pathogenic COL4A4 variants, and individuals with 2 COL4A3 or COL4A4 variants, have often already been diagnosed based on their characteristic clinical features by the time kidney failure develops, but men with hypomorphic variants with a milder phenotype, women with a heterozygous COL4A4 variant,39 and individuals with a heterozygous COL4A3/COL4A4 variant are often unrecognized, and their disease may progress to kidney failure undetected. A family history of hematuria or kidney failure may have been overlooked, hearing loss may have been attributed to other causes (eg, middle ear infections, kidney failure, dialysis40), or these individuals may have presented too late for a kidney biopsy to have diagnostic features.

COL4A5 variants are more likely to cause proteinuria, FSGS, and kidney failure. Proteinuria, FSGS, and kidney failure occur in nearly all men with a hemizygous COL4A5 variant but only in some women with a heterozygous COL4A5 variant. In addition, men with a COL4A5 variant generally develop proteinuria at a younger age than women. In contrast, fewer heterozygous COL4A3 and COL4A4 variants are associated with proteinuria, FSGS, and kidney failure. However, COL4A3 and COL4A4 variants are so common that they may be coincidental or have a mainly modifying effect in individuals with kidney failure from another cause. Thus, the finding of a COL4A3 or COL4A4 variant in a person with kidney failure (and, to a much lesser extent, the finding of a COL4A5 variant) does not exclude another underlying cause such as membranous glomerulopathy. Additional risk factors for kidney failure associated with COL4A3–COL4A5 variants include a superimposed IgA glomerulonephritis41–46 and cystic kidney disease.11,18,47

IgA Glomerulonephritis

Individuals with IgA glomerulonephritis and concomitant TBMN or X-linked Alport syndrome are not uncommon.11,46 As many as 20% of families with IgA glomerulonephritis have a pathogenic COL4A3 or COL4A4, or, less often, COL4A5 variant.48–50 IgA glomerulonephritis appears to occur independently of COL4A variant type, such as truncating or missense change.

Interestingly, often only 1 member of a family with a heterozygous COL4A3 or COL4A4 variant is identified with IgA glomerulonephritis. Such individuals may be diagnosed because they have undergone a kidney biopsy for proteinuria or decreased kidney function.46 Their families are often distinguished by most affected members having persistent hematuria without proteinuria and with normal kidney function, typical of a pathogenic COL4A3 or COL4A4 variant, rather than IgA glomerulonephritis, in which urinary red blood cell counts vary and proteinuria is common. Individuals with a COL4A3–COL4A5 variant with superimposed IgA glomerulonephritis usually have features more consistent with IgA glomerulonephritis alone, with higher urinary red blood cell counts and increased proteinuria.44

It is unclear whether the association of IgA glomerulonephritis and COL4A3–COL4A5 variants is coincidental or GBM thinning predisposes to mesangial IgA deposition. How often both diseases occur together is unknown because few individuals with IgA glomerulonephritis routinely undergo electron microscopy for GBM thinning or testing for genetic variants. Heterozygous COL4A3 and COL4A4 variants and IgA disease each affect approximately 1% of the population, so the conditions might coexist by chance in 0.01%. The argument for heterozygous COL4A3 or COL4A4 variants predisposing to IgA glomerulonephritis is that the associated GBM thinning may facilitate the egress of IgA molecules from the glomerular capillaries and their subsequent deposition in the mesangium (Fig 1).

Retinal drusen have been described in isolated case reports of IgA glomerulonephritis,11,51,52 dense deposit disease,53 and some other forms of glomerulonephritis.54–56 Drusen are white-yellow deposits characteristic of age-related macular degeneration. Their composition resembles that of the glomerular immune deposits,56 and their genetics and pathogenesis are well understood, with COL4A3 being one of the genes implicated.57,58 The mechanisms underlying retinal drusen formation may be shared with mesangial immune complex deposition, in which case COL4A3 and COL4A4 variants may also contribute to the development of IgA glomerulonephritis.11,49

Cystic Kidney Disease

Autosomal dominant polycystic kidney disease due to pathogenic PKD1 and PKD2 variants is the most common cause of cystic kidney disease, affecting as many as 1 in 1,000 individuals in the population,59 but occasional cysts are also found in approximately 30% of the unaffected population aged more than 70 years.60 In addition, occasional cysts are found in younger people, some of whom appear to have pathogenic COL4A5, COL4A3, or COL4A4 variants.11,18,47 How often cysts occur in individuals with pathogenic COL4A3–COL4A5 variants and whether these predispose to the occasional cysts found in older individuals are not known.

Cysts appear to be more common with heterozygous pathogenic COL4A4 variants than with COL4A5 variants,18 probably because COL4A4 variants are more common. Although there are no published reports of cysts associated with pathogenic heterozygous COL4A3 variants, individual laboratories have described these. Again, there appears to be no correlation between the variant type such as null or missense variants and the likelihood of cysts developing.

With COL4A3–COL4A5 variants, the kidney cysts may be unilateral or bilateral and vary in number and size up to 7 cm in diameter, but do not increase the kidney volume significantly.18 The cysts associated with these variants
are sometimes present from childhood but are more common after the age of 40 years. They may be found when kidney function is normal but are more common when proteinuria and decreased kidney function are also present. They often coexist with FSGS, which suggests that they are due to a more severe basement membrane defect. There is no association with hypertension, and liver cysts have not been reported.

Pathogenic COL4A3–COL4A5 variants are suspected in cystic kidney disease when there is no family history of polycystic kidney disease, the cysts are noted first before the age of 50 years, they are few in number and enlarge slowly, kidney volume is normal, and the liver is not affected.

One explanation for the association of pathogenic COL4A4 and COL4A5 variants with kidney cysts is that the cysts result from distension of basement membranes weakened by disruption of the collagen IV α3α4α5 network. The cysts must then originate from the glomeruli or distal tubules because the collagen IV α3, α4, and α5 chains are expressed only in these membranes. Dilated tubules are also found in mouse models with pathogenic variants in COL4A4 or COL4A5, but not COL4A3. Interestingly, kidney cysts occur with pathogenic COL4A1 variants and HANAC (hereditary angiopathy, nephropathy, aneurysms, and muscle cramps). COL4A1 encodes the collagen IV α1 chain, which forms the α1α1α2 network in the kidney proximal and distal tubules but not the adult GBM. Kidney cysts also occur in bull terrier and Dalmatian dogs with autosomal dominant Alport syndrome. Variants in many other genes encoding membrane or extracellular matrix proteins have been reported, even if rarely, with cyst formation or glomerular or tubular “dilatation” in human disease and mouse models (Table 2). Sometimes variants in these genes, such as COL4A1, are associated with cysts in the brain and tissues other than the kidney. Alternatively, cysts may arise from pathogenic variants affecting membrane genes that coincidentally interfere with embryogenesis.

The kidney cysts found with pathogenic COL4A3–COL4A5 variants are asymptomatic and typically not large or numerous enough to affect kidney function, and, according to our current understanding, do not require treatment. However, they may still represent markers for disease progression and an increased risk of kidney failure in individuals with a pathogenic COL4A3–COL4A5 variant. At the very least, the finding of cysts in an individual suspected of having a COL4A variant should not dissuade the clinician from requesting genetic testing.

**Other Potential Associations of COL4A3–COL4A4 Variants**

COL4A3 variants that result in GBM thinning potentially also affect the likelihood of diabetic nephropathy. Thus, a COL4A3 variant found in 20% of the normal population appears to protect against diabetic nephropathy. A genome-wide association study of 19,406 individuals with type 1 diabetes examined why some with good
Glycemic control developed diabetic nephropathy whereas others with poor control did not. This phenomenon was strongly linked to the rs55703767 variant of \( \text{COL4A3} \), corresponding to a predicted aspartate-to-tyrosine substitution at amino acid 326 (p.[Asp326Tyr]), an apparently benign variant that protected against diabetic nephropathy based on albuminuria and kidney failure (odds ratio of 0.77; \( P = 5.30 \times 10^{-9} \)). However, this variant resulted in GBM thinning, which is normally considered pathogenic. The allele’s protective effect was explained by the thinned GBM (by a mean of 19.7 ± 8.2 [standard error] nm; \( P = 0.02 \)). In diabetes, exposure of the collagen IV \( \alpha \)-chains to advanced glycation end-products from hyperglycemia thickens the GBM.66 The thinned GBM found with this \( \text{COL4A3} \) variant may tolerate more prolonged and pronounced hyperglycemia before the thickening seen in the next stage of diabetic nephropathy. Analogous studies of the collagen I molecule after similar periods of hyperglycemia exposure have found a damaged, less flexible molecule with abnormal binding to cells, integrins, and other membrane proteins.67-69

### Table 2. Pathogenic Variants in Genes Affecting a Basement Membrane or Extracellular Matrix Molecule and Any Reported Cystic Kidney Changes in the Corresponding Human Disease or Mouse Model

<table>
<thead>
<tr>
<th>Gene</th>
<th>Corresponding Protein</th>
<th>Amount, nsc(^a)</th>
<th>Corresponding Human Disease</th>
<th>Cysts in Human Disease(^b)</th>
<th>Mouse Model With Kidney Cysts(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{COL4A3} )</td>
<td>Collagen IV ( \alpha_3 ) chain</td>
<td>8.2</td>
<td>Thin basement membrane nephropathy</td>
<td>Yes(^{11})</td>
<td>NR</td>
</tr>
<tr>
<td>( \text{COL4A4} )</td>
<td>Collagen IV ( \alpha_4 ) chain</td>
<td>9.0</td>
<td>Thin basement membrane nephropathy</td>
<td>Yes(^{57})</td>
<td>Dilated renal tubules</td>
</tr>
<tr>
<td>( \text{COL4A5} )</td>
<td>Collagen IV ( \alpha_5 ) chain</td>
<td>3.8</td>
<td>X-linked Alport syndrome</td>
<td>Yes(^{57})</td>
<td>Dilated renal tubules</td>
</tr>
<tr>
<td>( \text{COL4A1} )</td>
<td>Collagen IV ( \alpha_1 ) chain</td>
<td>12.5</td>
<td>HANAC</td>
<td>Yes(^{92})</td>
<td>Glomerular cysts; dilated capsules, proximal tubules and collecting ducts</td>
</tr>
<tr>
<td>( \text{COL4A2} )</td>
<td>Collagen IV ( \alpha_2 ) chain</td>
<td>17.7</td>
<td>Brain vessel small disease (porencephaly)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>( \text{COL4A6} )</td>
<td>Collagen IV ( \alpha_6 ) chain</td>
<td>0.6</td>
<td>Leiomyomatosis–X-linked Alport syndrome</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>( \text{KCTD1} )</td>
<td>Potassium channel tetramerization domain containing 1</td>
<td>–</td>
<td>Scalp-ear-nipple syndrome</td>
<td>Yes(^d)</td>
<td>NR</td>
</tr>
<tr>
<td>( \text{LMX1B} )</td>
<td>LIM homeobox 1( \beta )</td>
<td>–</td>
<td>Nail patella syndrome</td>
<td>NR</td>
<td>Dilated tubules</td>
</tr>
<tr>
<td>( \text{BMP4} )</td>
<td>Bone morphogenetic protein 4</td>
<td>–</td>
<td>Microphthalmia, orofacial cleft</td>
<td>Yes(^{56})</td>
<td>Kidney cysts</td>
</tr>
<tr>
<td>( \text{LAMA5} )</td>
<td>Laminin subunit ( \alpha_5 )</td>
<td>9.5</td>
<td>Connective tissue abnormalities</td>
<td>Yes(^{77}) (with ( \text{COL4A5} ) variant)</td>
<td>Kidney cysts(^{38})</td>
</tr>
<tr>
<td>( \text{LAMB2} )</td>
<td>Laminin subunit ( \beta_2 )</td>
<td>14.7</td>
<td>Pierson syndrome</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>( \text{LMAC1} )</td>
<td>Laminin subunit ( \gamma_1 )</td>
<td>8.8</td>
<td>Dandy Walker syndrome</td>
<td>Yes</td>
<td>Kidney cysts(^{39})</td>
</tr>
<tr>
<td>( \text{LAMA2} )</td>
<td>Laminin subunit ( \alpha_2 )</td>
<td>0.04</td>
<td>Muscular dystrophy</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>( \text{LAMB1} )</td>
<td>Laminin subunit ( \beta_1 )</td>
<td>0.98</td>
<td>Lissencephaly</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>( \text{COL1A1} )</td>
<td>Collagen I ( \alpha_1 ) chain</td>
<td>0.25</td>
<td>Osteogenesis imperfecta</td>
<td>Yes(^{80})</td>
<td>NR</td>
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<tr>
<td>( \text{COL1A2} )</td>
<td>Collagen I ( \alpha_2 ) chain</td>
<td>0.59</td>
<td>Osteogenesis imperfecta</td>
<td>Yes(^{80})</td>
<td>NR</td>
</tr>
<tr>
<td>( \text{COL3A1} )</td>
<td>Collagen III ( \alpha_1 ) chain</td>
<td>–</td>
<td>Ehlers-Danlos syndrome</td>
<td>Yes(^{81})</td>
<td>NR</td>
</tr>
<tr>
<td>( \text{DCN} )</td>
<td>Decorin</td>
<td>0.07</td>
<td>Corneal dystrophy</td>
<td>NR</td>
<td>Dilated capsules, tubules</td>
</tr>
<tr>
<td>( \text{FBN1} )</td>
<td>Fibrillin 1</td>
<td>1.4</td>
<td>Marfan syndrome</td>
<td>Yes(^{82})</td>
<td>NR</td>
</tr>
<tr>
<td>( \text{TNX1B} )</td>
<td>Tenascin</td>
<td>–</td>
<td>Ehlers-Danlos syndrome</td>
<td>NR</td>
<td>Kidney cysts(^{93})</td>
</tr>
<tr>
<td>( \text{CD151} )</td>
<td>Tetraspanin</td>
<td>–</td>
<td>Nephropathy with pretibial epidermolysis bullosa and deafness</td>
<td>NR</td>
<td>Dilated tubules(^{84})</td>
</tr>
<tr>
<td>( \text{FRAS1} )</td>
<td>Fraser extracellular matrix complex subunit 1</td>
<td>0.04</td>
<td>Fraser syndrome</td>
<td>Yes(^{85})</td>
<td>Kidney cysts</td>
</tr>
<tr>
<td>( \text{FREM1} )</td>
<td>Fraser extracellular matrix protein 1</td>
<td>–</td>
<td>Fraser syndrome</td>
<td>Yes(^{85})</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: HANAC, hereditary angiopathy with nephropathy, aneurysms, and muscle cramps; NR, not reported; nsc, normalized spectral count.

\(^a\)Protein amounts are provided where available as normalized spectral counts.41 These values indicate that cyst formation or tubular dilation did not appear to depend on whether the protein was more abundant in the tissue.

\(^b\)Information sought in Online Mendelian Inheritance in Man and online.

\(^c\)Information based on the Mouse Genome Informatics database.

\(^d\)Unpublished data (J.S.).
Clinical Significance of Identifying an Underlying COL4A3–COL4A5 Variant or Variants

For individuals with FSGS, kidney failure of unknown cause, familial IgA glomerulonephritis, or cystic kidney disease not caused by ADPKD who are demonstrated to have a pathogenic COL4A3–COL4A5 variant, published guidelines recommend management. Thus, individuals with a COL4A3–COL4A5 variant should be monitored for the development of proteinuria, hypertension, and decreased kidney function, and those with a COL4A5 variant or 2 COL4A3 or COL4A4 variants should be screened for hearing loss and the retinal complications affecting vision.

Men with X-linked Alport syndrome due to a COL4A5 variant and women with a COL4A5 variant and proteinuria, hypertension, or decreased kidney function should be treated with renin-angiotensin-aldosterone blockade to delay kidney failure. Individuals with autosomal recessive Alport syndrome due to 2 variants in COL4A3 or COL4A4 in trans should undergo treatment from the time of diagnosis. Individuals with a heterozygous COL4A3 or COL4A4 variant should be treated from the onset of proteinuria, hypertension, or decreased kidney function.

Affected individuals’ at-risk family members should also be screened for pathogenic variants in COL4A3–COL4A5. We suggest that first-degree family members of men and women with a COL4A5 variant, 2 COL4A3 or COL4A4 variants, or a heterozygous COL4A3 or COL4A4 variant should undergo genetic testing.

It has been suggested that the proteinuria due to FSGS associated with COL4A3–COL4A5 variants does not respond to treatment with steroids or alkylating agents, and that most types of FSGS associated with pathogenic COL4A3–COL4A5 variants do not recur post-kidney transplantation. Although this is generally true, COL4A3 and COL4A4 variants are so common that they may also occur coincidentally with steroid-responsive nephrotic syndrome or other causes of kidney failure.

Conclusions

Many individuals with possibly pathogenic COL4A3–COL4A5 variants are undiagnosed, and the demonstration of variants in these genes in individuals with FSGS, kidney failure of unknown cause, familial IgA glomerulonephritis, and, possibly, cystic kidney disease has extended the spectrum of COL4A3–COL4A5-associated disease. COL4A3–COL4A5 variants occur too often together with these phenotypes to always be coincidental. Nevertheless, identification of a COL4A3 or COL4A4 variant does not exclude that there is also another cause for the kidney disease. Identifying a COL4A3–COL4A5 variant regardless of the clinical presentation means that affected individuals should be treated on the basis of the expert guidelines for the diagnosis and management of Alport syndrome and TBMN, and that at-risk family members should also be identified and treated.

Article Information

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