REVIEW

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Alport syndrome and Alport kidney diseases – elucidating the disease spectrum

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Purpose of review
With the latest classification, variants in three collagen IV genes, *COL4A3*, *COL4A4*, and *COL4A5*, represent the most prevalent genetic kidney disease in humans, exhibiting diverse, complex, and inconsistent clinical manifestations. This review breaks down the disease spectrum and genotype–phenotype correlations of kidney diseases linked to genetic variants in these genes and distinguishes classic Alport syndrome (AS) from the less severe nonsyndromic genetically related nephropathies that we suggest be called Alport kidney diseases.

Recent findings
Several research studies have focused on the genotype–phenotype correlation under the latest classification scheme of AS. The historic diagnoses of benign familial hematuria and thin basement membrane nephropathy linked to heterozygous variants in *COL4A3* or *COL4A4* are suggested to be obsolete, but instead classified as autosomal AS by recent expert consensus due to a significant risk of disease progression.

Summary
The concept of Alport kidney disease extends beyond classic AS. Patients carrying pathogenic variants in any one of the *COL4A3/A4/A5* genes can have variable phenotypes ranging from completely normal/clinically unrecognizable, hematuria without or with proteinuria, or progression to chronic kidney disease and kidney failure, depending on sex, genotype, and interplays of other genetic as well as environmental factors.

Keywords
Alport syndrome, collagen IV, glomerular basement membrane, hematuria, podocyte

INTRODUCTION

Collagen IV is a class of extracellular matrix protein found ubiquitously in basement membranes of various organs, including kidneys [1]. Six collagen IV α chains, α1(IV) to α6(IV), encoded by *COL4A1* to *COL4A6* genes, respectively, assemble into three different heterotrimers: collagen α1α1α2(IV), α3α4α5(IV), and α5α5α6(IV). Collagen α3α4α5(IV) is the major component of the mature glomerular basement membrane (GBM), though there is a thin layer of collagen α1α1α2(IV) at the GBM's endothelial aspect (Fig. 1a, b). Pathogenic variants in *COL4A3*, *COL4A4*, or *COL4A5* leading to absence or disruption of the GBM collagen α3α4α5(IV) network (Figs. 1 and 2) cause Alport syndrome (AS) [2,3]; thus, these will be referred to as Alport genes in this article.

The "classic" AS presentation is characterized by childhood-onset hematuria, later onset proteinuria, progressive decline in kidney function, and kidney failure (KF) in adolescence or young adulthood, along with sensorineural hearing loss, and eye abnormalities [4,5]. Because *COL4A5* is X-linked, male patients with X-linked Alport syndrome (XLAS) typically exhibit more severe symptoms than females with XLAS. In contrast, *COL4A3* and *COL4A4* are on chromosome 2, and variants cause the more rare autosomal recessive Alport syndrome (ARAS), which affects males and females equally [1].

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KEY POINTS

- We suggest the term Alport kidney diseases to represent the broadened spectrum of nonsyndromic clinical presentations associated with pathogenic variants in *COL4A3/A4/A5* genes (Alport genes) that are less severe than classic Alport syndrome (AS).
- Four groups of kidney diseases caused by variants in Alport genes are presented: classic severe AS, mild to moderate AS, proteinuric/nephrotic Alport kidney disease with focal segmental glomerulosclerosis lesions, and hematuric Alport kidney disease.
- More data from large cohorts provide a better understanding of genotype–phenotype correlations in each subgroup of patients with Alport kidney diseases and suggest that combining genetic status with clinical presentation to classify patients may be advantageous.

Heterozygous *COL4A3* and *COL4A4* variants have been linked to thin basement membrane nephropathy (TBMN), also called benign familial hematuria (BFH) [6]. However, these are now considered disfavored terms for less severe kidney diseases within the Alport spectrum, and in some cases have been classified as autosomal forms of AS [7]. Moreover, a variable degree of GBM thinning is in some cases the only early pathologic finding in diseases within the Alport spectrum and is quite common, making "thinning of GBM" a nonspecific finding (Table 1). Therefore, it has been suggested that "thin basement membrane lesion" be used as a term to describe the pathology rather than to justify a diagnosis of TBMN as a specific disease entity [7].

With the increased utilization of molecular genetic testing in clinical practice, pathogenic variants in Alport genes have been increasingly reported in patients with diverse clinical presentations, including a more proteinuria-predominant phenotype (nephrotic-range proteinuria or steroid-resistant nephrotic syndrome) [8,9], kidney failure of unknown etiology [10], familial immunoglobulin A (IgA) nephropathy with thin basement membrane [11], and renal cysts in whom polycystic kidney disease has been ruled out [12,13]. Several studies also consistently reported that pathogenic Alport gene variants are the most frequently found genetic abnormalities in adult-onset familial nephrosis with focal segmental glomerulosclerosis (FSGS) lesions [8,9].

Detection of Alport gene variants among patients with diverse clinical presentations challenges the traditional classification of AS/TBMN/BFH/ADAS, and newer terms such as "spectrum of Alport syndrome", "Alport-related nephropathy", "collagen IV related renal disease", and "collagen IV associated nephropathy" have been used in the literature to denote the kidney disease states linked to pathogenic variants in *COL4A3/A4/A5*. This review aims to summarize the different clinical manifestations in this disease spectrum and the challenges in categorizing patients due to overlapping and inconsistent presentations and the complex genetics involved. We also put forth the term "Alport kidney disease" to describe nonsyndromic kidney disease resulting from pathogenic variants in the Alport genes. Importantly, retention of "Alport" distinguishes *COL4A3/A4/A5* nephropathies from the much rarer ones caused by variants in *COL4A1* and *COL4A2* (Gould syndrome) [14]. We hope this term will be considered for adoption by relevant stakeholders, including patients, clinicians, geneticists, and scientists.

CLINICAL SPECTRUM OF KIDNEY DISEASES ASSOCIATED WITH ALPORT GENE VARIANTS

Based on the diverse kidney phenotypes described above, we propose that the spectrum of kidney diseases associated with pathogenic Alport gene variants be categorized into four groups: classic severe AS (male hemizygous XLAS and ARAS of either sex); mild to moderate AS (female heterozygous XLAS, ADAS, and digenic AS); Alport kidney disease with predominant proteinuria, steroid-resistant nephrotic syndrome, and FSGS lesions (AD); and hematuric Alport kidney disease, a mild condition that portrays the clinical picture of thin basement membrane lesions with very minimal risk of KF (AD) (Table 1). We note that not every patient with a pathogenic variant in an Alport gene will fit perfectly in a specific group, as many factors can impact disease manifestation. Moreover, disease classification can be dynamic, as patients initially placed into a less severe group may develop severe/high-risk features, emphasizing the importance of follow-up for patients in all groups, as previously suggested [7].

GROUP 1: CLASSIC SEVERE ALPORT SYNDROME

This category encompasses hemizygous males with XLAS and males or females with ARAS. Rare females with biallelic pathogenic *COL4A5* variants would also fit in this category [15]. These patients generally exhibit a 100% penetrance of hematuria since infancy. Albuminuria develops later and is an indicator of kidney disease progression; KF is inevitable. In males with XLAS, 70% reach kidney failure by the

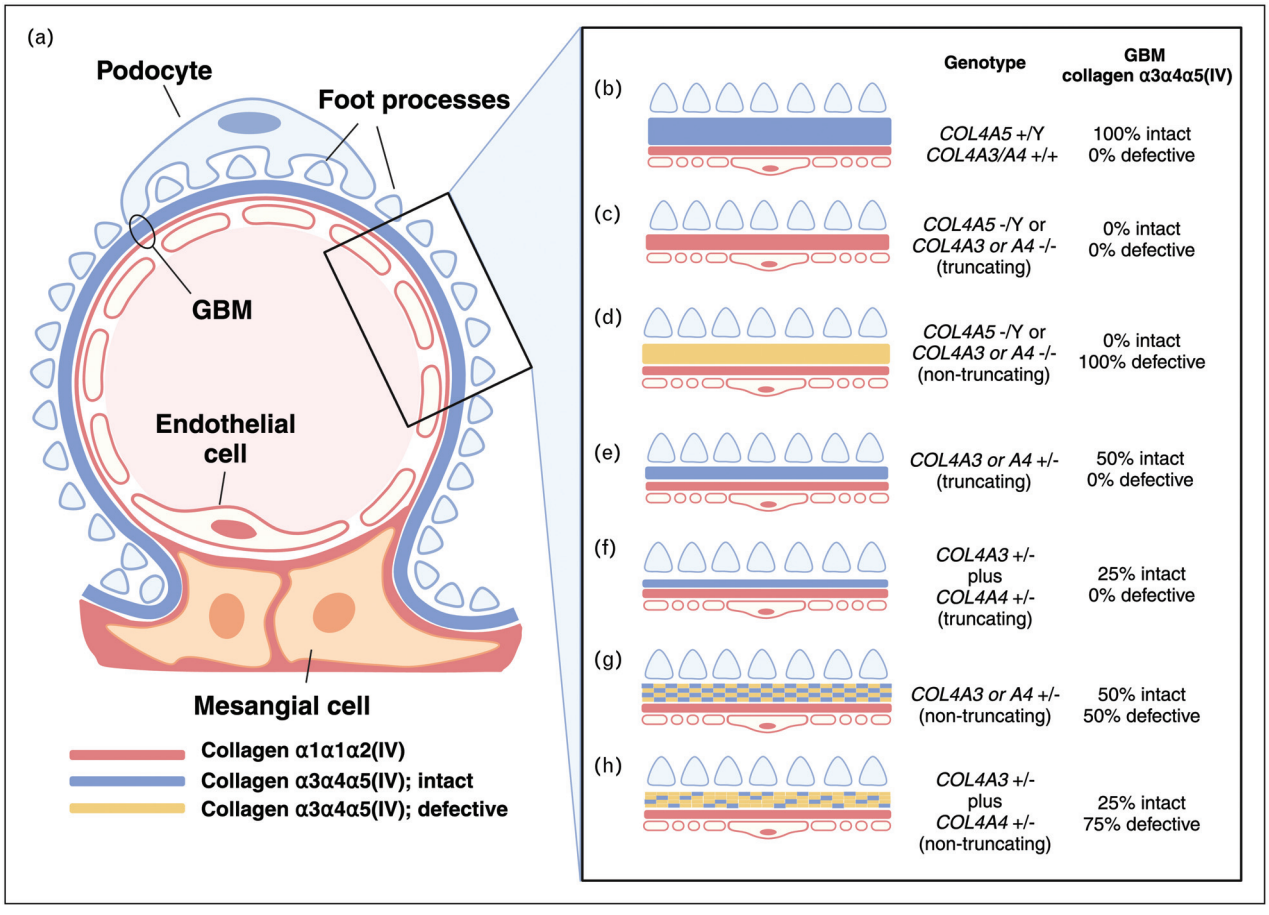

FIGURE 1. Schematic diagram of glomerular basement membrane (GBM) collagen IV in health and disease associated with different types of Alport gene variants. (a) The GBM is a network of extracellular matrix proteins flanked by endothelial cells and podocyte foot processes. (b) Normal GBM consists predominantly of a thick layer of collagen α3α4α5(IV) (blue) secreted by podocytes. Collagen α1α1α2(IV) (red), secreted by endothelial cells, appears as a thin layer at the endothelial aspect of the GBM. (c, d) In classic severe Alport syndrome (AS), (c) truncating variants result in no deposition of collagen α3α4α5(IV) in the GBM with a compensatory increase of collagen α1α1α2(IV), while (d) nontruncating variants result in deposition of defective collagen α3α4α5(IV) (yellow). (e, g) As for *COL4A3* or *A4* heterozygotes, (e) in cases of truncating variants, the wild-type allele contributes to expression of approximately 50% of intact collagen α3α4α5(IV) to the GBM, while (g) in cases of nontruncating variants, deposition of collagen α3α4α5(IV) derived from both alleles results in a mixture of 50% intact and 50% defective collagen α3α4α5(IV). (f) In digenic AS due to heterozygous variants in both *COL4A3* and *COL4A4*, truncating variants in both genes result in a decrease in GBM deposition of intact collagen α3α4α5(IV) to 25% of normal, while (h) nontruncating variants in both genes result in a GBM network of 25% intact and 75% defective collagen α3α4α5(IV). Note that these percentages are only accurate if all nontruncated defective collagen IV trimers are secreted into the GBM, which is not always the case.

age of 30 years, and 90% at 40 years [16,17]. Electron microscopy of kidney biopsies usually shows diffusely thinned GBMs at early stages, and GBM lamellation and characteristic basket-weave at later stages [18]. Extrarenal features due to lack or dysfunction of collagen α3α4α5(IV) in cochlea and lens/retina/cornea basement membranes are common but not always present. Some hearing loss occurs in 90% of patients before the age of 40 [16]. Fleck retinopathy is common and can aid in the diagnosis of AS [19,20]. Peripheral fleck retinopathy is present in most cases of XLAS and ARAS, whereas central fleck retinopathy is present in 50–60% of patients with XLAS and ARAS. Both central fleck retinopathy and anterior lenticonus are associated with an increased risk of early-onset kidney failure [20].

Genotype–phenotype correlations in this category of patients are relatively straightforward. According to the Leiden Open Variation Database (LOVD; https://www.lovd.nl), the mean age at kidney failure was 25.1 ± 10.6 years overall in males with XLAS, 20.4 ± 5.0 years in those with nonsense

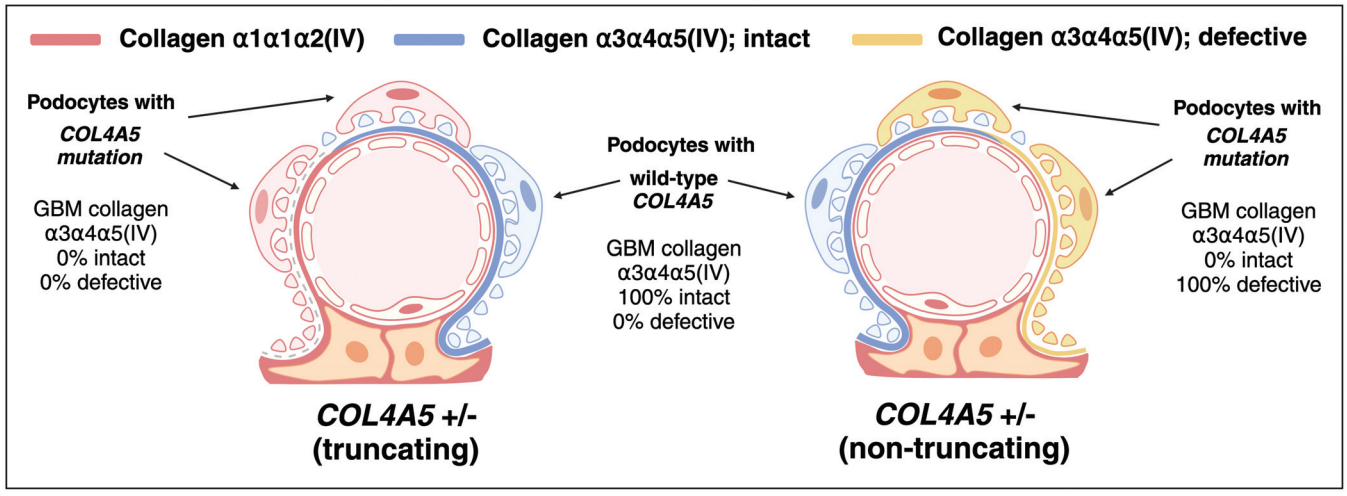

FIGURE 2. Schematic diagram of glomerular basement membrane (GBM) collagen IV in females with heterozygous X-linked Alport syndrome (AS). Unlike autosomal variants, heterozygous X-linked *COL4A5* variants cause mosaic deposition of collagen α3α4α5(IV) in the GBM depending on which allele (wild-type or mutant) is active in the overlying podocytes after X inactivation. For truncating variants, the affected region of the GBM (covered by red podocytes) completely loses collagen α3α4α5(IV) with a compensatory increase of collagen α1α1α2(IV). For nontruncating variants, the affected region of the GBM (covered by yellow podocytes) can deposit only defective collagen α3α4α5(IV). The unaffected regions covered by podocytes with wild-type alleles show normal GBM collagen α3α4α5(IV). Transition zones are depicted where podocytes expressing the wild-type *COL4A5* allele interdigitate with podocytes expressing a mutant allele.

variants, 21.1 ± 6.8 years in those with deletions, 25.2 ± 10.7 years in those with canonical splice site variants, 28.45 ± 12.4 years in those with collagenous-domain Gly substitutions, and 40.7 ± 17.6 years in those with non-Gly substitutions [21▪].

The molecular defect that best explains the most severe AS phenotypes is the lack of the collagen α3α4α5(IV) network in the GBM. Males with hemizygous truncating *COL4A5* variants or patients with homozygous/compound heterozygous truncating *COL4A3* or *COL4A4* variants cannot produce collagen α3α4α5(IV) heterotrimers, resulting in their complete absence from the GBM (Fig. 1c) and the most severe presentations. In contrast, patients with positive collagen α3α4α5(IV) staining by immunohistochemistry (Fig. 1d), most of whom should have missense variants (often glycine substitutions), show a lower degree of albuminuria and older age at KF [22,23]. This strongly suggests a correlation between genotype and the presence or absence of collagen α3α4α5(IV) in the GBM, even if the collagen IV is abnormal.

GROUP 2: MILD-TO-MODERATE ALPORT SYNDROME

This category includes a group of genetically heterogeneous patients, but they all share milder and more slowly progressive AS phenotypes, usually reaching KF after age 40. Extra-renal features are less common than in severe classic AS or are absent. Patients that fall into this category are females with heterozygous *COL4A5* variants, patients with heterozygous *COL4A3* or *COL4A4* variants who show symptoms of AS (ADAS), and patients with digenic AS.

Females with heterozygous X-linked Alport syndrome

In females, cells undergo X-chromosome inactivation during development to equalize the expression of X-linked genes with males. For *COL4A5*$^{+/-}$ females, this process creates a mosaic state in which segments of the GBM have either normal or absent/aberrant collagen α3α4α5(IV), depending on the nature of the variant (Fig. 2). GBM mosaicism underlies the variable and usually milder phenotypes, and such females were once considered "just carriers" of XLAS. However, they are now included in the AS spectrum because many develop classic AS phenotypes, though with a slower rate of kidney function loss; KF is not inevitable [24▪▪,25].

Nearly all females with XLAS have persistent microscopic hematuria from infancy, and the presence of albuminuria indicates risk of progression to KF [26], albeit at a much slower rate than males with XLAS. From the large European cohort of 506 female XLAS patients from 195 families and another cohort of 275 female patients from 179 families in Japan,

Table 1. Clinical groups and the associated Alport gene variants

Groups	Alport gene status	Clinical features	Biopsy findings	Kidney outcomes
1. Classic severe AS (males with XLAS, ARAS)	*COL4A5* -/Y *COL4A5* -/- (very rare) *COL4A3* or *A4* −/−	• Hematuria in infancy • Proteinuria in childhood • SNHL 90% by 40 y • Ocular defects >50%	• Thin GBM (early) • Splitting, lamellation, basket-weave (late)	KF 100% 70% by 30 y 90% by 40 y median age at KF 25 y
2. Mild to moderate AS				
2.1 Females with heterozygous XLAS	*COL4A5* +/−	• Hematuria in infancy • Proteinuria variable • SNHL 5.5–28% • Fleck retinopathy 25–30%,	• Thin GBM (variably) with segmental lamellation, basket-weave	KF not 100% 12–15% by 40 y 30–40% by 60 y median age at KF ≥50 y
2.2 ADAS	*COL4A3* or *COL4A4* +/−	• Intermittent hematuria • Proteinuria at >30 y • SNHL 8–16%, • Fleck retinopathy 1–3%	• Thin GBM • Splitting, lamellation, basket-weave (rare)	KF not 100% median age at KF ≥50 y
2.3 Digenic AS[a]	*COL4A3* +/− plus *COL4A4* +/−	• Hematuria • Proteinuria uncommon, median age at onset 43 y • SNHL rare • Ocular defects rare	• Thin GBM (early) • Splitting, lamellation • Basket-weave (uncommon)	KF not 100% Median age at KF 54 y
	COL4A3 or *A4* +/− plus *COL4A5* +/−	• Hematuria in infancy • Proteinuria at younger age than females with XLAS • SNHL 15% • Ocular defects 7%	• Thin GBM (early) • Splitting, lamellation • Basket-weave common	KF at 40, 44 y (2 patients)
3. Alport kidney disease with predominant proteinuria, steroid resistant nephrotic syndrome, and FSGS lesions	*COL4A3* or *COL4A4* +/−	• Proteinuria to nephrotic syndrome after 18 y • Hematuria not always present • Hearing loss rare • Ocular defects rare	• FSGS lesions with thin GBM • Splitting, lamellation can be present • Basket-weave rare	KF not 100% KF at 35–82 y
4. Hematuric Alport kidney disease	*COL4A3* or *COL4A4* +/−	• Intermittent or persistent microscopic hematuria without proteinuria • No SNHL • No ocular defects	• Diffusely thin GBM • No basket-weave	Minimal risk of KF

[a]Digenic AS in males with *COL4A5* −/Y plus *COL4A3* or *COL4A4* +/− have classic severe phenotypes similar to males with XLAS. Addition of pathogenic COL4A3 or A4 variants does not worsen the phenotypes.
ADAS, autosomal dominant Alport syndrome; ARAS, autosomal recessive Alport syndrome; AS, Alport syndrome; KF, kidney failure; SNHL, sensorineural hearing loss; XLAS, X-linked Alport syndrome; y, years.

only 12–15% developed KF before the age of 40 years, and 30–40% before the age of 60 years [16,27]. A more recent study of 86 female patients with XLAS from Korea estimated the median age at KF to be 50.2 (39.0–61.5) years [28▪]. Hearing loss occurred in 5.5–28%, usually developing by middle age. The presence of fleck retinopathy, although only observed in ~25–30% of patients, is helpful for diagnosis; anterior lenticonus has not been reported in females with XLAS [20,25]. Kidney biopsy is performed less in females because of equivocal diagnostic yield and procedural risks. The GBM may show thinning with or without lamellation. Finally, recent data indicate that there are genotype–phenotype correlations in females with XLAS [28▪,29] that are consistent with findings described above for the patients in Group 1.

Autosomal dominant Alport syndrome

The features of ADAS, caused by heterozygous variants in *COL4A3* or *COL4A4*, are similar to those of XLAS and ARAS, but extrarenal manifestations are less prevalent, and KF is delayed and is not

inevitable. A recent systematic review of 777 patients with ADAS reported in 48 publications showed hearing loss and eye abnormalities in 16% and 3% of patients, respectively [30]. A subsequent study of 240 individuals from 78 families reported hearing loss and ocular abnormalities in only 8% and 1%, respectively [31]. Collectively, these frequencies are far less than in classic severe AS. These two studies reported that 24–29% of patients developed KF, at a median age of 53–67 years [30,31].

It is important to note here that for individuals carrying a heterozygous pathogenic *COL4A3* or *COL4A4* variant, which is estimated to be ~1% of the population [32], very few will develop symptoms consistent with an AS diagnosis. This is discussed in detail below under Group 4. But of relevance here, two independent studies of patients with heterozygous pathogenic variants in *COL4A3* [33▪▪] or in either *COL4A3* or *COL4A4* [34▪▪] found that non-truncating variants (mainly Gly substitution missense variants) caused more severe symptoms, such as higher degree and/or earlier hematuria and proteinuria, lower GFR, and higher rates of KF vs. truncating or in-frame deletion variants. This suggests a dominant negative effect in which defective collagen IV chains disrupt the integrity of the intact ones (Fig. 1g). This is opposite to the situation for XLAS and ARAS, in which truncating variants cause the more severe disease.

Digenic Alport syndrome

Variants in more than one Alport gene have been found in a very small number of patients with a clinical diagnosis within the spectrum of AS. The possible combinations include patients carrying *COL4A3* plus *COL4A4* variants, and either a *COL4A3* or a *COL4A4* variant plus a *COL4A5* variant. The three patterns differ in modes of inheritance and clinical courses depending on the involvement of *COL4A5*, the nature of the pathogenic variants, and other factors [35].

The presence of an additional variant may or may not affect phenotypes depending on whether the collagen α3α4α5(IV) network can be worsened further. In the case of severe AS (Group 1) with collagen α3α4α5(IV) completely absent from the GBM, an additional Alport gene variant cannot worsen the phenotype. However, for patients who have a heterozygous *COL4A3* or *COL4A4* variant and thus can still deposit normal collagen α3α4α5 (IV) into the GBM, an additional variant in another *COL4A* gene will increase the percentage of defective collagen α3α4α5(IV) to 75% from 50% and worsen the phenotype (Fig. 1h). Digenic patients show phenotypes intermediate between ADAS and ARAS in terms of age at KF, and hearing loss was more frequent than in ADAS but less frequent than in ARAS [36▪].

GROUP 3: ALPORT KIDNEY DISEASE WITH PREDOMINANT PROTEINURIA, STEROID-RESISTANT NEPHROTIC SYNDROME, AND FOCAL SEGMENTAL GLOMERULOSCLEROSIS LESIONS

Deltas *et al.* were the first to demonstrate a link between proteinuria with FSGS lesions and heterozygous variants in *COL4A3* or *COL4A4* [37,38], and they have studied additional families that support this link [39–41]. Several other independent sequencing initiatives have shown that about 10% of patients with FSGS lesions and heavy proteinuria have variants in Alport genes, primarily heterozygous variants in *COL4A3* and *COL4A4* [8–10,42,43]. These patients do not have ocular abnormalities and only rarely experience hearing loss, usually later in life, making it difficult for physicians to order genetic testing for Alport gene variants. Nevertheless, they carry a high risk of kidney disease progression, reaching KF at 40–65 years, later than classic severe AS [8,9].

In most of these patients, electron microscopy only showed segmental thinning or splitting of GBM [9,42], which is not characteristic of AS; though FSGS lesions are expected to develop late in the course of classic AS, they are associated with GBM basket-weave thickening and tubulointerstitial scarring. This suggests the possibility that some Alport gene variants may cause the proteinuria-predominant phenotype associated with FSGS lesions [44]. Secreted solely by podocytes, the production of aberrant collagen α3α4α5(IV) may affect podocyte homeostasis, resulting in podocyte damage, proteinuria, and development of FSGS lesions [45]. Knockin of a human *COL4A3* variant that expresses misfolded collagen α3(IV) chains into mice increased the unfolded protein response pathway, which can be linked to podocyte endoplasmic reticulum stress [46]. This may explain why heterozygous substitution variants are associated with more severe proteinuria than heterozygous truncating variants [33▪▪] and why not all patients harboring heterozygous *COL4A3* or *COL4A4* variants have proteinuria-predominant phenotypes.

Some authorities suggest proteinuria and FSGS lesions that occur in this subgroup of patients are results of other genetic modifiers that could have been overlooked [47,48▪]. However, most cohorts reporting the link between Alport gene variants and FSGS lesions also examined other genes implicated in nephrotic syndrome but could not detect any variants [8,9].

GROUP 4: HEMATURIC ALPORT KIDNEY DISEASE

This last group covers a subgroup of individuals carrying heterozygous pathogenic variants in *COL4A3* or *COL4A4*, estimated to be around 1% of the population, ~70% of whom have hematuria [32]. This group encompasses the largest proportion of the whole disease spectrum. Unlike patients in groups 2 and 3, most individuals in this group have only isolated microscopic hematuria associated with thin GBM without any high-risk features (such as proteinuria), putting them at a slightly increased risk of developing KF late in life. These are the patients whom Kashtan *et al.* [7] previously suggested should be made cognizant of this risk and to be proactive about monitoring and treatment according to expert recommendations [49,50]. A subset of these individuals will be parents or siblings of patients with ARAS and will be aware of the importance of maintaining kidney health. Although this group of patients has a benign prognosis, as what was assumed for those with thin basement membrane lesions, it should be emphasized that their underlying Alport gene status may be similar to ADAS. The type of variant or other modifying factors such as hypertension, obesity, and other comorbidities could be what differentiate these patients from ADAS, but this remains uncertain. Moreover, polygenic risk factors can impact the chances that *COL4A3* or *COL4A4* heterozygous individuals develop severe phenotypes [51▪▪]. In any event, some individuals initially placed into Group 4 will develop symptoms over the course of decades and will need to be recategorized.

CONCLUSION

The genetic and clinical complexities of Alport syndrome and the related Alport kidney diseases make the classification of patients with less severe manifestations difficult and subjective. These patients are much more numerous than those with classic severe AS, so there is an urgency to ensure that they receive appropriate attention and care from nephrologists even if the risk of KF is low. This led the Alport Syndrome Classification Working Group to suggest the diagnosis of autosomal AS for any individuals with heterozygous *COL4A3* or *COL4A4* variants [7], including those with isolated thin basement membrane lesions who might never reach KF. Although the working group recommended classifying patients based on mode of inheritance, in this review we proposed a more detailed patient classification across the disease spectrum by severity of AS phenotypes, from the classic severe AS (XLAS in males and ARAS), in which there is no intact collagen α3α4α5(IV) in the GBM, to hematuric Alport kidney disease, the most favorable prognosis with only a slightly increased risk of KF over the general population. We also emphasized those patients with a proteinuria-predominant Alport kidney disease presentation (Group 3) who might be diagnosed as FSGS and given unnecessary immunosuppressive therapy. With the growing evidence for genotype–phenotype correlations, the phenotype-based classification somewhat follows the underlying genetic abnormalities. Establishing a solid link between GBM collagen IV defects (Figs. 1 and 2) and clinical presentation will lead to better patient classification, risk stratification, and improved patient care.

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Conflicts of interest

J.H.M. is a member of the Alport Syndrome Foundation's Scientific Advisory Research Network, has served as a consultant to Bayer AG and Eloxx Pharmaceuticals, and has received funding for research from Chinook Therapeutics, LTI Therapeutics, and Keros Therapeutics. P.P. has no conflict of interest to declare.

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- ▪ of special interest
- ▪▪ of outstanding interest

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