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Genetic testing and glomerular hematuria—A nephrologist's perspective

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Abstract

Alport syndrome is an inherited disorder of the kidneys that results from variants in three collagen IV genes—*COL4A3*, *COL4A4*, and *COL4A5*. Early diagnosis and pharmacologic intervention can delay the progression of chronic kidney disease and the onset of kidney failure in patients with Alport syndrome. This article describes the evolution of approaches to the diagnosis and early treatment of Alport syndrome.

KEYWORDS
Alport syndrome, basement membranes, collagen IV, genetic kidney disease

Hematuria is a common reason for referral to nephrologists and urologists. While hematuria can originate anywhere in the urinary tract, in children and adolescents hematuria usually arises from lesions of glomerular capillary walls that allow the escape of erythrocytes into the urinary space. The causes of these lesions can be broadly divided into two categories, acute and chronic inflammatory processes (glomerulonephritis), which are typically but not always acquired, and genetically mediated abnormalities of the glomerular basement membrane collagen IV$^{\alpha 345}$ network.

The kidney phenotypes associated with genetic variants of the collagen IV$^{\alpha 345}$ network constitute a spectrum from isolated microscopic hematuria with sustained good kidney function at one extreme and progressive chronic kidney disease culminating in kidney failure at the other extreme (Quinlan & Rheault, 2021). Many affected individuals have extrarenal manifestations, most commonly sensorineural hearing loss and distinctive ocular anomalies arising from defective collagen IV$^{\alpha 345}$ networks in the cochlea and eye, while in many others, the phenotypic abnormalities are limited to the kidneys. Collagen IV$^{\alpha 345}$ disease is genetically heterogeneous due to the involvement of three genes, two of which are autosomal—*COL4A* and *COL4A4*, while the third—*COL4A5*—resides on the X chromosome. An affected person's phenotype may evolve with aging and may be influenced by chromosomal sex. Due to this genetic and phenotypic heterogeneity, the naming of the conditions associated with genetic variants of the collagen IV$^{\alpha 345}$ network has been the subject of debate. As argued elsewhere, my preference is to collectively describe these conditions as Alport syndrome (Kashtan, 2021; Kashtan et al., 2018), the eponymic term classically used to denote people with hematuria and progressive kidney disease associated with sensorineural hearing loss; this is the approach I will take in the discussion to follow (Table 1).

The condition we know as Alport syndrome was first described in the 1920s (Alport, 1927), and up until the early 21st century Alport syndrome was considered an untreatable disorder, with dialysis and kidney transplantation being the only therapeutic options available to patients with kidney failure. Then, in 2003, a study published by Gross et al. (2003) demonstrated that early treatment with ramipril suppressed kidney disease and doubled the duration of survival in transgenic Alport mice. This study's results, along with the growing off-label use of angiotensin-converting enzyme (ACE) inhibitors to delay the progression of kidney disease, led to the treatment of many Alport patients with these agents. Off-label therapy enabled retrospective studies, in European and Japanese Alport cohorts, that demonstrated dramatic increases in age at the onset of kidney failure in patients treated with ACE inhibitors, compared to untreated patients (Gross et al., 2012, Yamamura et al., 2020). Both the animal and human studies showed that initiation of ACE inhibitor therapy before kidney function begins to decline has the greatest positive impact on kidney outcomes in Alport patients. A recent prospective trial of children

TABLE 1 Genetics of Alport syndrome

Inheritance	Affected gene(s)	Genetic state	Frequency[a]
X-linked	*COL4A5*	Hemizygous (male)	~60%
		Heterozygous (female)	
Autosomal	*COL4A3* or *COL4A4*	Recessive (homozygous or compound heterozygous)	~15%
		Dominant (heterozygous)	~25%
Digenic	*COL4A3*, *COL4A4*, and *COL4A5*		Rare
	COL4A3/COL4A4 in *trans*	Simulates autosomal recessive transmission	
	COL4A3/COL4A4 in *cis*	Simulates autosomal dominant transmission	
	Variants in *COL4A5* and in *COL4A3* or *COL4A4*	Non-Mendelian transmission pattern	

[a]Compiled from Fallerini et al. (2014), Morinière et al. (2014), Yamamura et al. (2019), Mencarelli et al. (2015).

with Alport syndrome showed that ramipril therapy delayed the onset of proteinuria, the earliest sign of progressive kidney disease in Alport patients (Gross et al., 2020). These studies led to the promulgation of clinical practice recommendations for the treatment of Alport syndrome using ACE inhibitors or angiotensin receptor blockers (Kashtan et al., 2013; Kashtan & Gross, 2021).

As these developments in the treatment of Alport syndrome were taking place, there were concurrent advances in the methodologies used to detect variants in the *COL4A3*, *COL4A4*, and *COL4A5* genes. In 1990, following the mapping of the major Alport locus to the X chromosome (Hostikka et al., 1990), Barker et al. (1990) described the cloning of the *COL4A5* gene and the first *COL4A5* variants in Alport families. Soon after, researchers at the Hospital Necker reported the cloning of the *COL4A3* and *COL4A4* genes, their localization to chromosome 2, and the first variants in patients with autosomal Alport syndrome (Boye et al., 1998; Heidet et al., 2001). A steady stream of reports of new *COL4A3*, *COL4A4*, and *COL4A5* variants flowed from research laboratories, but the clinical utility of genetic testing to diagnose Alport syndrome was limited by the laborious and expensive nature of Sanger sequencing and the limited number of research laboratories with the interest and capability to perform these analyses. The introduction of next-generation sequencing methods (Fallerini et al., 2014; Morinière et al., 2014), allowing the simultaneous analysis of the *COL4A3*, *COL4A4*, and *COL4A5* genes, and the entrance of commercial and in-house hospital laboratories into the genetic testing arena, have dramatically improved the ease and reduced the expense of genetic testing for Alport syndrome, although spotty insurance coverage, at least in the United States, still impedes molecular diagnosis for some patients.

Due to these advances in treatment and in diagnosis, we have arrived at the point where we can make an early diagnosis of Alport syndrome and initiate effective, and relatively safe, therapy in those patients with a high risk of progressive kidney disease. Alport syndrome can be reliably diagnosed in many patients using methods that predate widespread genetic testing—careful clinical evaluation including audiologic and ophthalmologic examinations, meticulous pedigree analysis, and kidney biopsy employing electron microscopy and immunostaining for collagen IV α chains, or in some cases immunostaining of skin biopsy specimens for the α5(IV) chain (Van der Loop et al., 1999)—but the results of such evaluation may be ambiguous because of the phenotypic and genotypic heterogeneity associated with variants in the *COL4A3*, *COL4A4*, and *COL4A5* genes. Collagen IV genotype is prognostically important, particular for males with X-linked Alport syndrome and for patients with autosomal recessive Alport syndrome (Bekheirnia et al., 2010; Jais et al., 2000; Zhang et al., 2021). Precise information about the collagen IV genotype enables cascade testing of at-risk relatives of index cases, improves reproductive counseling, and enhances the evaluation of potential living-related donors for Alport patients requiring kidney transplantation.

So which patients with hematuria should undergo genetic testing for *COL4A3*, *COL4A4*, and *COL4A5* variants? Hematuria is most often asymptomatic and microscopic, but may be macroscopic and associated with other signs and symptoms. The first step for the nephrologist, or in many cases the urologist, is to attempt to localize the source of the hematuria. This is typically (although not always) straightforward in the pediatric population, in which hematuria most often arises from glomeruli, and more distal causes can usually be identified by non-invasive imaging (Yap & Lau, 2008). Cystoscopy is rarely indicated in pediatric patients with hematuria, in contrast to adults in whom urinary tract cancer is a relatively frequent cause of hematuria (Linder, Bass, Mostafid, & Boorjian, 2018). There are certain signs and symptoms that strongly suggest a glomerular origin of hematuria, including tea- or cola-like discoloration of the urine, macroscopic hematuria associated with upper respiratory infection, absence of dysuria, lack of clots, and the presence of red blood cell casts. In patients with glomerular hematuria, examination of a urine sample using phase microscopy reveals dysmorphic erythrocytes, as opposed to the isomorphic erythrocytes observed in the urine of patients with non-glomerular hematuria.

Once the source of the hematuria is localized to the glomerulus, additional studies can narrow the range of diagnostic possibilities and guide the selection of confirmatory testing. Basic laboratory evaluation of patients with glomerular hematuria typically includes the estimation of kidney function using serum creatinine and cystatin C, based on age-specific formulas (Inker et al., 2021; Pierce et al., 2021); determination of the serum complement components C3 and C4; and measurement of urine protein levels (urine albumin-creatinine and/or protein-creatinine ratio). Low serum complement levels are indicative

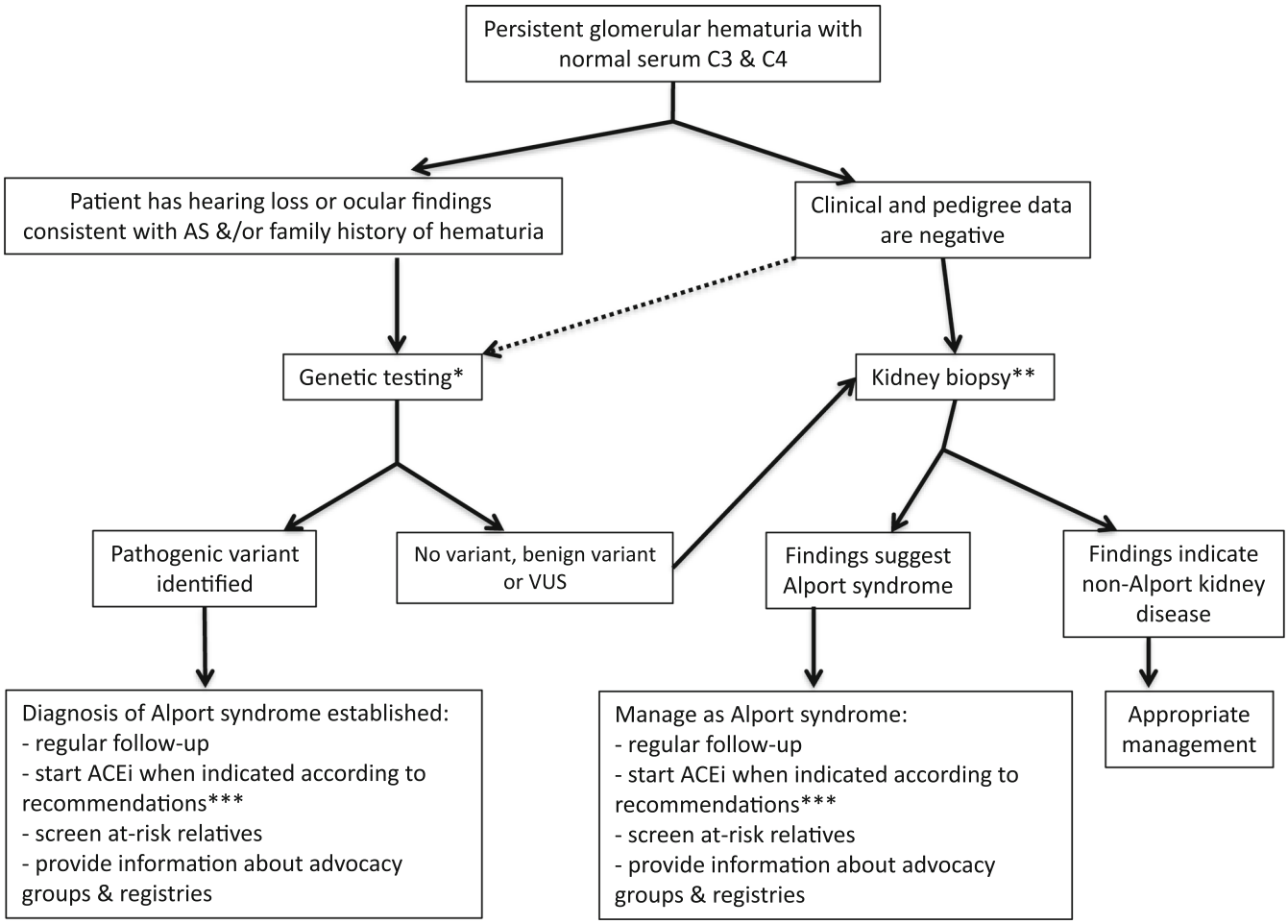

FIGURE 1 An approach to diagnosis of individuals with persistent glomerular hematuria using genetic testing and/or kidney biopsy (adapted from Kashtan, 2021). This algorithm presents a possible approach to diagnosis of individuals with persistent glomerular hematuria using genetic testing and/or kidney biopsy. Genetic testing is suggested when clinical findings and/or family history suggest a diagnosis of Alport syndrome. When other clinical findings suggestive of Alport syndrome are absent and family history is negative, but kidney function and urine protein excretion are normal, genetic testing prior to kidney biopsy would be a reasonable choice (dotted arrow). However, when a patient who has no clinical findings or family history suggestive of Alport syndrome but has proteinuria and/or abnormal kidney function, kidney biopsy may provide a more rapid approach to obtaining diagnostic information. If kidney biopsy shows findings suggestive of Alport syndrome, genetic testing can be undertaken to confirm the diagnosis. *The genetic testing approach may vary based on the level of suspicion of a diagnosis of Alport syndrome. When suspicion is high, next-generation sequencing (NGS) of *COL4A3*, *COL4A4*, and *COL4A5* is indicated. When suspicion of a diagnosis of Alport syndrome is moderate or low, a broad NGS panel including loci for focal segmental glomerulosclerosis, complement regulatory disorders and polycystic kidney disease, or whole-exome sequencing, should be considered. **Kidney biopsy should, if possible, always include routine transmission electron microscopy (TEM). When TEM shows glomerular basement membrane changes suggestive of Alport syndrome, or when TEM is not available, studies of collagen IV alpha-chain expression can provide useful diagnostic and prognostic information. ***See Kashtan and Gross, 2021 for clinical practice recommendations. ACEi, angiotensin-converting enzyme inhibitor; VUS, variant of uncertain significance

of an acquired or inherited hypocomplementemic glomerulonephritis and should lead to further testing to distinguish among several possible diagnoses, including post-infectious glomerulonephritis, lupus nephritis, or an inherited abnormality of complement regulation (Smith et al., 2019). Normal serum complement levels suggest that the glomerular hematuria is more likely to be caused by IgA nephropathy or by a genetic abnormality of the collagen $IV^{\alpha 345}$ network. While confirmation of a suspected diagnosis of IgA nephropathy requires kidney biopsy, a suspected diagnosis of Alport syndrome can usually be confirmed by genetic testing.

The approach the nephrologist takes to distinguish IgA nephropathy from Alport syndrome will depend on individual patient factors. A family history of hematuria, kidney disease or kidney failure, or clinical features suggestive of Alport syndrome such as sensorineural deafness and characteristic ocular changes (lenticonus, maculopathy) will point the nephrologist in the direction of genetic testing. It is important to note that a negative family history or the absence of extrarenal manifestations does not exclude a diagnosis of Alport syndrome, so genetic testing when a patient has isolated glomerular hematuria, followed by kidney biopsy if genetic testing is not diagnostic, is a

reasonable choice. When a patient with glomerular hematuria has additional signs suggesting advanced kidney disease, such as hypertension, proteinuria, or impaired kidney function, the nephrologist will often opt for kidney biopsy, especially if there are no other findings suggestive of Alport syndrome, in order to establish a diagnosis and a treatment plan more quickly (Figure 1).

Recent studies have identified *COL4A3*, *COL4A4*, and *COL4A5* variants in patients in whom glomerular hematuria is not the presenting complaint. Variants of these genes have been found in patients with steroid-resistant nephrotic syndrome, patients classified as having focal segmental glomerulosclerosis on the basis of kidney biopsy, and in patients with chronic kidney disease or kidney failure of undetermined etiology (Gast et al., 2016; Groopman et al., 2019; Malone et al., 2014). Consequently, testing for *COL4A3*, *COL4A4*, and *COL4A5* variants should be included when genetic testing is performed in these patient groups.

When the clinician chooses genetic testing, either before or after kidney biopsy, a testing method must be selected. Genetic counselors who have training and experience in genetic kidney diseases can be extremely helpful to both clinicians and patients in assessing testing options and determining insurance coverage. The selected methodology should allow simultaneous sequencing of the *COL4A3*, *COL4A4*, and *COL4A5* genes (next-generation sequencing or whole-exome sequencing). Genetic counselors can assist nephrologists in the interpretation of testing results and in discussion of the results and their implications with patients and families. When a broad next-generation sequencing panel or whole-exome sequencing is used, genetic counselors can help with the follow-up of variants in genes that were not anticipated but may be clinically significant.

COL4A3, *COL4A4*, and *COL4A5* variants identified in patients with Alport syndrome can be generally characterized as truncating variants that prevent the synthesis of full-length α chains and abolish formation of collagen $IV^{\alpha345}$ networks, and non-truncating variants that allow synthesis of abnormal α chains and deposition of defective collagen $IV^{\alpha345}$ networks in basement membranes. Non-truncating variants include missense variants, most commonly single base-pair substitutions that replace a conserved glycine residue in the collagenous domain of the α chain by another amino acid, small in-frame deletions and insertions, and splicing variants that result in exon-skipping (Horinouchi et al., 2018; Savige et al., 2021). Truncating variants include nonsense variants, large deletions, duplications, and splicing variants that are incompatible with exon-skipping (Horinouchi et al., 2018, Savige et al., 2021). Truncating variants in the *COL4A5* gene are associated with earlier onset of kidney failure, hearing loss, and ocular changes in males with X-linked Alport syndrome, compared to non-truncating variants (Bekheirnia et al., 2010; Horinouchi et al., 2018; Jais et al., 2000). Among patients with autosomal recessive Alport syndrome, those with one or two missense variants in *COL4A3* or *COL4A4* appear to have later onset of kidney failure compared to patients who have other kinds of variants (Zhang et al., 2021).

Sequencing of the *COL4A3*, *COL4A4*, and *COL4A5* genes may reveal a variant of uncertain significance, or VUS, which, while not found in normal control populations, has not been previously described in a patient with Alport syndrome and is not clearly pathogenic based on predictive algorithms (Savige et al., 2021). Approaches that can be taken to assess a VUS in a patient suspected of having Alport syndrome include kidney biopsy, if not already performed, and testing of affected and unaffected family members to determine if the variant tracks with the abnormal phenotype. A variant initially categorized as a VUS may later be recognized as pathogenic as a result of reporting in unrelated patients or of functional studies (Savige et al., 2021).

In conclusion, early genetic diagnosis of Alport syndrome in patients with glomerular hematuria enables appropriate monitoring and pharmacologic intervention, with beneficial effects on kidney outcomes. Identification of a pathogenic variant in an index case facilitates the evaluation of at-risk family members and allows precise reproductive counseling and living related donor kidney evaluation.

CONFLICT OF INTEREST

Clifford E. Kashtan is the Executive Director of the Alport Syndrome Treatments and Outcomes Registry (ASTOR, ClinicalTrials.gov Identifier NCT00481130). He is a site investigator for the CARDINAL trial of bardoxolone methyl sponsored by Reata Pharmaceuticals and for the HERA trial sponsored by Sanofi-Genzyme. He has recent or current consulting relationships with Travere Therapeutics, ONO Pharmaceuticals, Daiichi-Sankyo, Boerhinger-Ingelheim, BridgeBio, and METiS Pharmaceuticals.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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