

Molecular genetics, clinical spectrum, and management of Alport syndrome: A narrative review

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Abstract

Alport syndrome is a genetically heterogeneous disorder with X-linked, autosomal dominant, autosomal recessive, and digenic inheritance patterns. The X-linked form, most commonly due to COL4A5 mutations, is the most prevalent and typically results in more severe disease in males, while heterozygous females are usually less severely affected. Autosomal recessive Alport syndrome arises from biallelic mutations in COL4A3 or COL4A4 and often mirrors the severity seen in X-linked males. Autosomal dominant Alport syndrome, involving a single pathogenic allele in COL4A3 or COL4A4, generally leads to later-onset and milder renal involvement. Digenic inheritance—pathogenic variants in two of COL4A3, COL4A4, or COL4A5—produces variable clinical phenotypes. Accurate delineation of these inheritance patterns is crucial for predicting disease severity and informing prognosis and genetic counseling. Advances in next-generation sequencing have improved diagnostic precision, enabling detection of mosaicism, complex rearrangements, and variants with atypical or milder presentations. Research into modifier genes and epigenetic influences may further refine individualized management strategies.

Keywords: Alport syndrome, COL4A3, COL4A4, COL4A5, X-linked inheritance, Autosomal dominant, Autosomal recessive, Digenic inheritance, Hematuria, Proteinuria, End-stage renal disease, Sensorineural hearing loss, Anterior lenticonus, Ocular abnormalities, Genotype-phenotype correlation, Next-generation sequencing, Genetic counseling, Renal pathology, Family history, Mutation analysis, Molecular diagnosis, Collagen IV, Basement membrane, Kidney biopsy, Clinical diagnosis, Genetic testing, Inheritance patterns

Introduction

Alport syndrome is a rare hereditary nephropathy, with an estimated prevalence of 1 in 5,000 to 10,000 individuals; however, this figure may be underestimated due to evolving diagnostic criteria and recent advances in genetic testing. Pathogenic variants in COL4A3, COL4A4, and COL4A5 are more frequent than previously recognized. First described by Arthur Cecil Alport in 1927, the syndrome is primarily characterized by persistent hematuria, sensorineural hearing loss, and a familial inheritance pattern, with males typically exhibiting more severe clinical manifestations (**Table 1**). Mutations in any of the COL4A3, COL4A4, or COL4A5 genes disrupt the collagen IV $\alpha 345$ network, which is essential for the structural integrity of basement membranes in the kidney, ear, and eye. Key features of Alport syndrome are summarized in **Table 2**. The disorder is also referred to by several other terms, including congenital hereditary hematuria, hematuric hereditary nephritis, hereditary familial congenital hemorrhagic nephritis, hereditary hematuria syndrome, and hereditary interstitial pyelonephritis. Collectively, these terms describe genetic conditions present from birth that cause persistent or recurrent hematuria.

Mutations in Alport Syndrome

About 80–85% of Alport syndrome cases are inherited through X-linked mutations in the COL4A5 gene. Nearly 80% of males with X-linked Alport syndrome (XLAS) experience hearing loss by adolescence. Alport syndrome results from mutations in the genes encoding the alpha-3,

alpha-4, and alpha-5 chains of type IV collagen. Three main genetic forms exist: X-linked Alport syndrome (XLAS), caused by mutations in the COL4A5 gene and accounting for about 80–85% of cases. Autosomal recessive Alport syndrome (ARAS): Results from mutations in the COL4A3 or COL4A4 genes and represents about 10–15% of cases. Autosomal dominant Alport syndrome (ADAS):

Caused by mutations in the COL4A3 or COL4A4 genes; this form is rare. Researchers have identified more than 300 mutations in the COL4A5 gene in families with XLAS. Most are minor changes, including single nucleotide substitutions, small deletions of fewer than ten base pairs, and mutations affecting gene transcription.

Table 1. Frequency of selected features of Alport syndrome.

Feature	XLAS (Males)	XLAS (Females)	ARAS	ADAS
Hematuria	100%	>90%	100%	>50%
Proteinuria	100%	70%	100%	No data
ESKD	~80% (by age 40 yrs)	~20% (by age 60 yrs)	~80% (by age 30 yrs)	No data
SNHL (sensorineural hearing loss)	~50%-60%	Rare	~50%-60%	Rare
Anterior lenticonus	50%	<5%	75%	Rare
Central or perimacular fleck retinopathy	70%	20%	75%	No data

Table 2. Landmark features of Alport syndrome.

Feature	X-Linked Alport Syndrome (XLAS)	Autosomal Recessive Alport Syndrome (ARAS)	Autosomal Dominant Alport Syndrome (ADAS)
Inheritance Category	X-linked (accounts for ~80–85% of cases).	Autosomal Recessive (accounts for ~10–15% of cases).	Autosomal Dominant (accounts for ~5–20% of cases).
Relevant Gene(s)	COL4A5.	COL4A3 or COL4A4.	COL4A3 or COL4A4.
Usual Genotype	Hemizygous (males); Heterozygous (females).	Homozygous or compound heterozygous.	Heterozygous.
Affected Sex Distribution	Males significantly more severely affected than females.	Equal severity and distribution between males and females.	Equal severity and distribution between males and females.
Typical Renal Severity	- Males: Severe; 100% progress to end-stage kidney disease (ESKD), often by early adulthood. - Females: Highly variable; usually milder, slower progression, but up to 25% risk of ESKD by age 60.	Severe: 100% progress to early-onset ESKD (often by adolescence or young adulthood) in both sexes.	Milder and slowly progressive; ESKD occurs later in life (often after age 40) and only in a minority of patients.
Key Extrarenal Manifestations	- High-frequency sensorineural hearing loss (SNHL). - Ocular features (anterior lenticonus, maculopathy). - Rarely, diffuse leiomyomatosis (ASDL).	- High-frequency sensorineural hearing loss (SNHL). - Ocular features (anterior lenticonus, maculopathy).	- SNHL can occur but is typically late-onset and less common. - Ocular abnormalities are very rare.
Expected Transmission Risk	- Affected males: 0% risk to sons; 100% of daughters will inherit the variant. - Affected females: 50% chance of passing the variant to any child.	- If both parents are carriers: 25% risk per pregnancy of an affected child; 50% risk of a carrier child. - Affected individual: 100% pass one variant (child will be a carrier unless partner also holds a variant).	An affected parent has a 50% chance of passing the variant to each biological child.
Variability & Genotype–Phenotype Correlation	- Strong correlation in males: Truncating mutations (nonsense, frameshift) cause early ESKD and severe extrarenal signs; missense mutations cause a later onset of ESKD. - Females: Highly variable due to random X-chromosome inactivation (lyonization).	Strong correlation: protein-truncating mutations lead to severe, classic Alport presentation with absent collagen chains, whereas missense variants may result in a more protracted, moderate course.	High intra- and inter-familial variability. The phenotype spans from isolated, lifelong benign hematuria (thin basement membrane nephropathy) to progressive renal failure. Influenced by genetic modifiers and environmental factors.

Approximately 20% of COL4A5 mutations are medium to large deletions. A deletion involving both COL4A5 and COL4A6 results in a combined phenotype of XLAS and leiomyomatosis, which affects the esophagus, female reproductive organs, and airways. Two genes in the COL4A4 gene have been identified in patients with ARAS. These include frameshift mutations, amino acid substitutions, single-nucleotide changes, splice-site mutations, and small in-frame deletions. Details of these mutations are illustrated in **Table 3**.

Clinical Impact & Disease Severity

In males with X-linked Alport syndrome (XLAS) and individuals with autosomal recessive Alport syndrome (ARAS), truncating variants are strongly associated with early-onset end-stage renal disease (ESRD), frequently manifesting before the age of 30. In contrast, patients harboring missense mutations generally exhibit a more indolent clinical course, with prolonged preservation of renal function [2–4]. Carriers of truncating mutations have a significantly increased risk of extrarenal manifestations, including sensorineural hearing loss and ocular abnormalities such as anterior lenticonus and macular flecks, with reported odds two to four times higher than in non-carriers [2,3]. Immunofluorescence analysis of the glomerular basement membrane (GBM) in patients with pathogenic truncating mutations typically reveals a complete absence of the $\alpha3$ – $\alpha4$ – $\alpha5$ (IV) collagen network. As a result, the GBM relies predominantly on the embryonic $\alpha1$ – $\alpha1$ – $\alpha2$ collagen network, which cannot sustain long-term filtration function [2,3]. Recent genomic studies have demonstrated that truncating variants in COL4A5 are associated with a markedly increased prevalence of secondary structural abnormalities, including renal cysts in male patients [4]. Pathogenic variants in COL4A3, COL4A4, or COL4A5 impair deposition of collagen IV $\alpha3\alpha4\alpha5$ protomers within the basement membranes of the renal glomerulus, cochlea, cornea, lens capsule, and retina. The extensive diversity of pathogenic variants in these genes—regardless of inheritance pattern (X-linked, autosomal recessive, autosomal dominant, or digenic) or the presence of syndromic features—has led to the conceptualization of the “Alport spectrum disorder,” now recognized as the most common cause of genetic kidney disease and the second most prevalent cause of genetic kidney failure [5].

Earlier estimates classified most Alport syndrome cases as X-linked, autosomal recessive, or autosomal dominant. Recent genetic studies have shown that autosomal dominant cases are more prevalent than

previously recognized, with implications for genetic counseling and prognosis. Autosomal dominant Alport syndrome generally exhibits a slower progression and fewer extrarenal manifestations compared to the X-linked form [6].

Genotype–phenotype correlations in X-linked Alport syndrome are well established, explaining why X-linked and autosomal dominant cases differ clinically. Immunohistochemical studies can assess collagen IV $\alpha3$, $\alpha4$, and $\alpha5$ expression in renal and skin biopsies [7]. Mutations in COL4A5 that allow some $\alpha345$ network expression (such as certain missense or in-frame changes) are linked to slower kidney decline. In contrast, those that eliminate network expression (such as large rearrangements or nonsense mutations) cause more rapid progression. Similarly, most heterozygous COL4A3 or COL4A4 mutations lead to milder, slower disease [2,8].

Hematuria is usually the first sign of $\alpha345$ network deficiency in Alport syndrome, due to GBM thinning and resulting leakage of blood cells. In males, the lens capsule is thin and fragile (anterior lenticonus). The $\alpha345$ network is absent in cochlear basement membranes; while animal and human studies suggest multiple mechanisms for hearing loss, the exact pathogenesis remains unclear [9].

In Alport GBM, the $\alpha345$ network is supplanted by the $\alpha112$ collagen network, which expands from its customary subendothelial localization to occupy the entire GBM. This alteration is accompanied by aberrant deposition of laminin-2, collagen V, and collagen VI, potentially mediated by mesangial filopodia invasion. Compared with normal GBM, the matrix in Alport syndrome is less cross-linked and more susceptible to proteolytic injury. Altered signaling through collagen and laminin receptors elicits complex cellular responses.

Alport syndrome is a genetic disease that affects the kidneys and often causes hearing and eye problems. Mutations in COL4A3, COL4A4, and COL4A5 disrupt type IV collagen, leading to progressive kidney damage that begins with hematuria and can advance to proteinuria, hypertension, and ESRD. Glomerular disease results from a compromised filtration barrier, proteinuria, and progressive kidney failure. Tubulointerstitial fibrosis and atrophy, affecting both the glomerulus and the tubulointerstitium, drive kidney failure through fibrosis, atrophy, albuminuria, inflammation, and scarring.

Table 3. Different mutations of Alport syndrome.

Mutation Type	Description	Affected Genes	Clinical Impact / Notes
Missense Mutation	Changes to a single nucleotide, altering one amino acid in the collagen chain.	COL4A3, COL4A4, COL4A5	Often replaces critical glycine residues; severity varies depending on location and affected chain.
Nonsense Mutation	Introduces a premature stop codon, truncating the protein.	COL4A3, COL4A4, COL4A5	Associated with severe phenotypes and earlier onset of end-stage renal disease.
Frameshift Mutation	Insertion or deletion of nucleotides not divisible by three, disrupting the reading frame.	COL4A3, COL4A4, COL4A5	Results in a nonfunctional or absent collagen chain, typically leading to severe disease.
Splicing Mutation	Alters intron/exon boundary sequences, causing improper mRNA processing.	COL4A3, COL4A4, COL4A5	Disrupts normal trimer assembly and basement membrane scaffolding.
Major Rearrangements	Large deletions, insertions, or complex structural genomic changes.	COL4A5 (e.g., contiguous gene deletions)	Can lead to severe X-linked Alport syndrome combined with extrarenal features like diffuse leiomyomatosis.

The primary goal of Alport syndrome treatment is to slow the progression of renal damage. Early initiation of renin-angiotensin system inhibitors, such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, is the most effective strategy. These agents reduce blood pressure and proteinuria, and both animal studies and clinical evidence support their role in delaying progression to end-stage renal disease (ESRD). Early intervention, particularly before significant renal function decline, yields the greatest benefit. Alport syndrome is inherited via X-linked, autosomal recessive, or, less commonly, autosomal dominant patterns. The X-linked form is most common and typically causes more severe manifestations in males, while females generally have milder symptoms because they have two X chromosomes. Advances in genetic testing have enabled precise diagnosis and identification of at-risk family members. Early recognition of Alport syndrome is essential for optimal symptom management, disease monitoring, and genetic counseling.

Modes of Inheritance

X-Linked Alport syndrome

After diagnosing Alport syndrome, determining the mode of inheritance is essential for assessing familial risk. X-linked inheritance is most common and typically identified by a family history of hematuria, as only 15% of mutations are de novo and penetrance is high. X-linked conditions may skip generations, with affected females often showing only hematuria due to X inactivation. At the same time, males present with a broader range of symptoms, including early-onset ESRD and extrarenal manifestations. Autosomal recessive traits generally affect both sexes equally within a generation. Genetic testing is the primary method for confirming inheritance patterns, as glomerular basement membrane (GBM) collagen IV analysis is less commonly used and can be difficult to interpret, particularly in female carriers. Skin biopsy offers a less invasive diagnostic alternative to renal biopsy [10].

In males, early-onset ESRD with extrarenal symptoms is common, whereas later onset may present primarily with hearing loss. By age forty, 70% of affected males have high-frequency hearing loss, 30% develop lenticonus, and many display retinopathy. Females exhibit a variable range of symptoms depending on X inactivation. GBM changes in males progress from thinning to lamellation, with loss of the $\alpha3\alpha4\alpha5$ network, and skin biopsy can assist in diagnosis [10].

Digenic Alport syndrome

Digenic Alport syndrome results from co-inheritance of pathogenic variants in COL4A5 and either COL4A3 or COL4A4, with clinical severity influenced by the combination and mode of inheritance. In males, an additional COL4A3 or COL4A4 variant may not worsen disease, while in females, digenic inheritance increases the risk of proteinuria. When both COL4A3 and COL4A4 variants are present, inheritance is autosomal dominant if variants are in cis and autosomal recessive if in trans. Digenic cases typically show intermediate proteinuria and kidney failure onset. Guidelines emphasize identifying all pathogenic digenic variants and managing affected family members, including counseling against kidney donation. Determining whether variants are in cis or trans is essential for predicting inheritance and clinical outcome [11].

Genetic testing in Alport syndrome

Genetic testing is recommended when Alport syndrome is

suspected but not confirmed, to distinguish it from thin basement membrane nephropathy (TBMN) and to rule out X-linked inheritance. Strong evidence supports early testing, including in pediatric patients, because timely intervention can delay kidney failure, confirm the diagnosis, and differentiate Alport syndrome from TBMN [12,13]. DNA sequencing and multiplex ligation-dependent probe amplification detect over 90% of X-linked Alport syndrome cases. Mutation detection is most effective in patients with early kidney failure and extrarenal symptoms. Researchers have identified more than 700 COL4A5 variants, most of which are unique to individual families. About 50% are nonsense mutations, and 40% are missense variants. Severe, early-onset disease is typically linked to large deletions, nonsense mutations, or missense mutations in the carboxyl-terminal region of the protein. In contrast, missense mutations in the amino-terminal region usually cause milder, later-onset symptoms. A thorough family history is essential for risk assessment. Linkage analysis is rarely needed, except when mutations are not detected or for prenatal or preimplantation genetic diagnosis. If no COL4A5 mutation is found, consider alternative genetic variants, autosomal recessive Alport syndrome, or other hereditary kidney disorders.

Screening of family members

Accurate assessment of hereditary risk in X-linked Alport syndrome requires identifying all affected family members, including female carriers. Offspring of affected females have a 50% risk of inheriting the pathogenic variant. Affected males transmit the mutation to all daughters and none of their sons. Hematuria in family members may indicate involvement, but consider other causes. Once the familial mutation is identified, genetic testing can confirm carrier or affected status [13].

X-linked Alport syndrome

Females with X-linked Alport syndrome most frequently present with microscopic hematuria. A subset progresses to proteinuria, end-stage renal disease, sensorineural hearing loss, or peripheral retinopathy. Ocular manifestations, including lenticonus and central retinal changes, are uncommon. The distinction between “affected” and “carrier” status in females is debated, but “affected” is now preferred because it emphasizes the need for monitoring and early intervention. Most mothers of affected males are heterozygous for the pathogenic variant, often asymptomatic, and typically identified through cascade genetic screening after a proband’s diagnosis. Histological findings include glomerular basement membrane irregularities and mosaic expression of collagen IV $\alpha3\alpha4\alpha5$ due to random X-chromosome inactivation. Pharmacologic inhibition of the renin-angiotensin system is recommended for females with hypertension, proteinuria, or other renal risk factors. Early ACE inhibitor use may provide renal protection, though strong prospective evidence is limited. Poor prognosis is associated with early-onset macroscopic hematuria and persistent proteinuria. Renal biopsy is usually reserved for cases with significant proteinuria or declining renal function, as histological changes can be focal. Renal transplantation may be necessary for some patients, but post-transplant anti-GBM disease is rare in this population [14].

Risks associated with kidney donation and pregnancy

Females with pathogenic COL4A5 variants linked to X-linked Alport syndrome face increased long-term risk of kidney dysfunction if they donate a kidney. Consider donation only if no

alternative donors are available. Comprehensive genetic and clinical screening of all potential maternal donors, including apparent non-carriers, is necessary to rule out subclinical X-linked Alport syndrome before donation. Post-transplant patients require lifelong immunosuppressive medications, such as Cyclosporine, which can cause adverse effects like gingival hyperplasia. For immunosuppressed individuals, strict oral hygiene is critical, as pathogens such as *Treponema denticola* may cause severe gum infections and worsen tissue damage [15]. Pregnancy in women with pre-existing hypertension, proteinuria, or renal impairment carries a significantly increased risk of adverse maternal and fetal outcomes. These factors highlight the need for comprehensive preconception counseling and a multidisciplinary management strategy [16,17].

Autosomal recessive Alport syndrome presents similarly to the X-linked form in males. Diagnosis is confirmed by identifying biallelic mutations in COL4A3 or COL4A4, or by detecting the absence of specific collagen IV chains in the glomerular basement membrane (GBM). While genetic testing provides a definitive diagnosis, variant heterogeneity complicates interpretation; therefore, parental testing is recommended. Siblings have a 25% risk of being affected. Heterozygous carriers usually develop thin basement membrane nephropathy, which rarely progresses to renal failure. Treatment with renin-angiotensin system inhibitors may delay the onset of renal failure [18].

Thin basement membrane nephropathy (TBMN) affects about 1% of the general population. It is marked by persistent microscopic hematuria, mild proteinuria, preserved renal function, and diffuse thinning of the glomerular basement membrane (GBM). TBMN is most often associated with heterozygous pathogenic mutations in COL4A3 or COL4A4, as confirmed by modern genetic sequencing techniques [16–20]. Alport syndrome is commonly linked to hearing loss and ocular abnormalities. Autosomal dominant tubulointerstitial kidney disease caused by UMOD mutations (ADTKD-UMOD) is frequently associated with hyperuricemia and gout, which may also occur in Alport syndrome; therefore, both conditions are evaluated using the same gene panel [19]. Although TBMN is generally indolent, recent multicenter cohort studies have identified a significant subset of patients who progress to chronic kidney disease (CKD) and end-stage renal disease (ESRD), especially when comorbidities or a family history are present [21,22]. Current diagnostic protocols prioritize next-generation sequencing for molecular diagnosis and reserve renal biopsy for ambiguous or atypical cases [17,23,24].

Individuals with heterozygous variants in COL4A3, COL4A4, or COL4A5 are increasingly recognized as affected, reflecting their elevated lifetime risk of renal complications and underscoring the need for regular nephrological monitoring and early intervention [16]. This evolving understanding has led to the adoption of genotype-based classification systems that better reflect disease mechanisms and prognosis [16,17]. For proteinuria, renin-angiotensin system blockade remains a cornerstone of therapy, with evidence supporting earlier initiation in genetically at-risk individuals [16,25]. Investigational therapies, including targeted molecular and gene therapies, are under development, though their clinical application is currently limited by accessibility and cost [26–28]. Mutations in COL4A3, COL4A4, or COL4A5 disrupt the synthesis of the $\alpha 3$, $\alpha 4$, and $\alpha 5$ chains of type IV collagen, which are essential for the structural integrity of the GBM, cochlea, and ocular

tissues [16,17]. Collagen defects compromise basement membrane architecture, resulting in progressive renal impairment, sensorineural hearing loss, and ocular abnormalities [25]. The X-linked form, due to COL4A5 mutations, is generally more severe in males because of hemizygoty, while heterozygous females may exhibit a spectrum of symptoms [22]. Inheritance patterns influence disease transmission: affected fathers cannot transmit the X-linked form to sons, whereas heterozygous mothers have a 50% risk of passing the mutation to each child. Autosomal dominant Alport syndrome arises from a single pathogenic COL4A3 or COL4A4 allele, while autosomal recessive cases require mutations in both alleles [16,25]. Both autosomal forms affect males and females equally and often present early with hematuria, proteinuria, hypertension, edema, and extrarenal manifestations. Diagnosis requires an integrated approach that combines clinical, genetic, and histopathological data, with next-generation sequencing increasingly supplanting invasive tissue diagnostics [16,17]. Early use of renin-angiotensin system inhibitors can slow disease progression, while advanced cases may require renal replacement therapy [25]. Although advances in diagnostics and gene therapies are improving outcomes, early detection and management remain challenging [16,27]. Current recommendations for Alport syndrome management include regular monitoring of blood pressure and albuminuria, early initiation of renin-angiotensin system blockade, renal function surveillance, hearing and ophthalmologic assessments, genetic counseling, and transplant planning. Sodium-glucose cotransporter-2 inhibitors are also suggested. Emerging strategies such as endothelin pathway modulation, antifibrotic therapies, RNA-based treatments, gene delivery, and gene editing represent important future modalities. The latest ERKNet, ERA, and ESPN guidelines should serve as key references for diagnostic, surveillance, therapeutic, reproductive, and kidney donor recommendations.

Genetic counseling

Thin basement membrane nephropathy (TBMN) is an inherited disorder, most often caused by heterozygous pathogenic variants in COL4A3 or COL4A4. It is characterized by persistent hematuria, mild proteinuria, and generally preserved renal function. About 70% of affected individuals present with hematuria, though the clinical spectrum varies. Approximately half of the offspring of affected individuals inherit the pathogenic variant. When both parents carry a COL4A3 or COL4A4 mutation, their children have a 25% risk of developing autosomal recessive Alport syndrome (ARAS), which is more severe. Alport syndrome is genetically heterogeneous and results from mutations in COL4A3, COL4A4, or COL4A5, with over 1,000 unique mutations identified. Molecular diagnosis relies on gene sequencing, which has evolved from Sanger sequencing to next-generation sequencing (NGS). NGS enables comprehensive analysis and improved diagnostic accuracy, especially in cases with unclear inheritance patterns or phenotypes, and can detect variants missed by previous technologies [28,29].

A recent multicenter study evaluated pregnancy outcomes in women with COL4A3-5-related Alport syndrome (AS), analyzing 192 pregnancies across 17 international centers. Most participants had preserved renal function before conception, and pregnancy outcomes were generally favorable, with all resulting in live births. The median gestational age was 39 weeks, and the mean birth weight was 3135 grams. Rates of gestational hypertension and preeclampsia were slightly higher than in the general chronic kidney

disease (CKD) population, but most women maintained stable renal function after delivery. Women with ARAS had a higher incidence of preterm delivery and lower birth weights compared to those with less severe genetic subtypes. These findings underscore the need for individualized pre-pregnancy counseling that considers genotype, traditional risk factors, and current evidence to optimize reproductive outcomes in women with Alport spectrum disorders [29].

Future Directions

Alport syndrome is an inherited disorder of type IV collagen that leads to progressive kidney disease, hearing loss, and ocular complications. As the condition advances, many patients develop end-stage kidney disease, for which transplantation is the preferred treatment and offers favorable long-term outcomes. Unlike most recurrent glomerular diseases, Alport syndrome rarely recurs after transplantation because donor kidneys have normal glomerular basement membrane collagen. Advances in genetic diagnosis, risk stratification, and targeted therapies are expected to improve management and transplant success further. However, treatment options remain limited, underscoring the need for innovative approaches. Gene therapy, aiming to correct mutations and restore protein function, shows significant promise. Recombinant adeno-associated virus (rAAV) vectors have advanced renal gene therapy, with some agents already in clinical use, though renal targeting remains challenging. Developments in gene-editing technologies, such as CRISPR/Cas9, may allow direct correction of pathogenic mutations. Research into antifibrotic and anti-inflammatory agents may also provide new options to slow disease progression. Large-scale longitudinal studies and international registries are expected to enhance understanding of genotype-phenotype correlations, refine patient stratification, and support personalized medicine. Early diagnosis through expanded genetic screening and multidisciplinary care teams will be crucial for optimizing outcomes. Future research should focus on identifying novel biomarkers for earlier detection and disease monitoring, as well as developing small-molecule therapies that target specific pathways. Enhanced patient education and advocacy can support earlier intervention and improve access to emerging therapies. Collaboration among research institutions, patient organizations, and industry partners will be essential to accelerate clinical trials and translate discoveries into practice.

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References

- Ben Moshe Y, Bekheirnia N, Smith RJH, Hicks J, Braun MC, Bekheirnia MR. Genetic diagnosis and renal biopsy findings in the setting of a renal genetics clinic. *Am J Med Genet C Semin Med Genet*. 2022 Sep;190(3):302–8.
- Savige J, Weinstock BA. What patients want to know about genetic testing for kidney disease. *Front Med (Lausanne)*. 2023 Jun 5;10:1201712.
- Kashtan CE, Gross O. Clinical practice recommendations for the diagnosis and management of Alport syndrome in children, adolescents, and young adults—an update for 2020. *Pediatr Nephrol*. 2021 Mar;36(3):711–9.
- Yamamura T, Horinouchi T, Nagano C, Omori T, Sakakibara N, Aoto Y, et al. Genotype-phenotype correlations influence the response to angiotensin-targeting drugs in Japanese patients with male X-linked Alport syndrome. *Kidney Int*. 2020 Dec;98(6):1605–14.
- Chavez E, Goncalves S, Rheault MN, Fornoni A. Alport Syndrome. *Adv Kidney Dis Health*. 2024 May;31(3):170–9.
- Beicht S, Strobl-Wildemann G, Rath S, Wachter O, Alberer M, Kaminsky E, et al. Next generation sequencing as a useful tool in the diagnostics of mosaicism in Alport syndrome. *Gene*. 2013 Sep 10;526(2):474–7.
- Kagawa M, Kishiro Y, Naito I, Nemoto T, Nakanishi H, Ninomiya Y, et al. Epitope-defined monoclonal antibodies against type-IV collagen for diagnosis of Alport's syndrome. *Nephrol Dial Transplant*. 1997 Jun;12(6):1238–41.
- Savige J, Lipska-Zietkiewicz BS, Watson E, Hertz JM, Deltas C, Mari F, et al. Guidelines for Genetic Testing and Management of Alport Syndrome. *Clin J Am Soc Nephrol*. 2022 Jan;17(1):143–54.
- Gregorio V, Caparali EB, Shojaei A, Ricardo S, Barua M. Alport Syndrome: Clinical Spectrum and Therapeutic Advances. *Kidney Med*. 2023 Mar 21;5(5):100631.
- Chavez E, Goncalves S, Rheault MN, Fornoni A. Alport Syndrome. *Adv Kidney Dis Health*. 2024 May;31(3):170–9.
- Savige J, Renieri A, Ars E, Daga S, Pinto AM, Rothe H, et al. Digenic Alport Syndrome. *Clin J Am Soc Nephrol*. 2022 Nov;17(11):1697–706.
- Christodoulaki V, Kosma K, Marinakis NM, Tilemis FN, Stergiou N, Kampouraki A, et al. Alport Syndrome: Clinical Utility of Early Genetic Diagnosis in Children. *Genes (Basel)*. 2024 Aug 2;15(8):1016.
- Liu N, Wen X, Ou Z, Fang X, Du J, Lin X. Case report: Preimplantation genetic testing for X-linked alport syndrome caused by variation in the *COL4A5* gene. *Front Pediatr*. 2023 Aug 10;11:1177019.
- Koyun M, Aksoy GK, Çomak E, Akman S. Outcome of females with Alport syndrome. *Pediatr Nephrol*. 2022 Aug;37(8):1937.
- Kamarajan P, Timm JC, Goetting-Minesky MP, Malone ET, Ganther S, Radaic A, et al. Purification of Native Dentilisin Complex from *Treponema denticola* by Preparative Continuous Polyacrylamide Gel Electrophoresis and Functional Analysis by Gelatin Zymography. *Bio Protoc*. 2024 Apr 5;14(7):e4970.
- Miner JH. Pathology vs. molecular genetics: (re)defining the spectrum of Alport syndrome. *Kidney Int*. 2014 Dec;86(6):1081–3.
- Savige J, Storey H, Watson E, Hertz JM, Deltas C, Renieri A, et al. Consensus statement on standards and guidelines for the molecular diagnostics of Alport syndrome: refining the ACMG criteria. *Eur J Hum Genet*. 2021 Aug;29(8):1186–97.
- Boeckhaus J, Gale DP, Simon J, Ding J, Zhang Y, Bergmann C, et al. SGLT2-Inhibition in Patients With Alport Syndrome. *Kidney Int Rep*. 2024 Sep 24;9(12):3490–500.
- Bollée G, Dahan K, Flamant M, Morinière V, Pawtowski A, Heidet L, et al. Phenotype and outcome in hereditary tubulointerstitial nephritis secondary to UMOD mutations. *Clin J Am Soc Nephrol*. 2011 Oct;6(10):2429–38.
- Li Y, Wang J, Liu G. Re: Zaffalon et al.: Anterior segment and macular OCT in Alport syndrome (*Ophthalmology*. 2023;130:515). *Ophthalmology*. 2024 Apr;131(4):e15.
- Torra R, Lipska-Zietkiewicz B, Acke F, Antignac C, Becker JU, Cornec-Le Gall E, et al; ERKNet, ERA Genes&Kidney and ESPN Inherited renal disorders working group. Diagnosis, management and treatment

- of the Alport syndrome - 2024 guideline on behalf of ERKNet, ERA and ESPN. *Nephrol Dial Transplant.* 2025 May 30;40(6):1091–106.
22. Papazachariou L, Papagregoriou G, Hadjipanagi D, Demosthenous P, Voskarides K, Koutsofti C, et al. Frequent COL4 mutations in familial microhematuria accompanied by later-onset Alport nephropathy due to focal segmental glomerulosclerosis. *Clin Genet.* 2017 Nov;92(5):517–27.
23. Wojcik MH, Lemire G, Berger E, Zaki MS, Wissmann M, Win W, et al. Genome Sequencing for Diagnosing Rare Diseases. *N Engl J Med.* 2024 Jun 6;390(21):1985–97.
24. Groopman EE, Marasa M, Cameron-Christie S, Petrovski S, Aggarwal VS, Milo-Rasouly H, et al. Diagnostic Utility of Exome Sequencing for Kidney Disease. *N Engl J Med.* 2019 Jan 10;380(2):142–51.
25. Gross O, Tönshoff B, Weber LT, Pape L, Latta K, Fehrenbach H, et al. A multicenter, randomized, placebo-controlled, double-blind phase 3 trial with open-arm comparison indicates safety and efficacy of nephroprotective therapy with ramipril in children with Alport's syndrome. *Kidney Int.* 2020 Jun;97(6):1275–86.
26. Zhou L, Zhang Y, Tian C, Liao J, Yu H, Tang L. Corneal endothelial neovascularization and glaucoma in X-linked Alport syndrome. *Eur J Ophthalmol.* 2025 May;35(3):NP1–NP6.
27. Song ZR, Li Y, Liu ZY, Li MS, Chen YQ, Lv JC, et al. Multifactorial Predictors of Renal Outcomes in Alport Syndrome: Integrating Genetic, Clinical, and Cystic Phenotypes. *Kidney Med.* 2026 Jan 13;8(3):101264.
28. Okuda Y, Mikami N, Hamada R, Hataya H, Tanaka K, Terano C, et al. Investigation of clinical and genetic characteristics of Alport syndrome using a national registry in Japan (JP-ALPS). *Clin Exp Nephrol.* 2026 Jan;30(1):87–95.
29. Gosselink ME, Snoek R, Cerkauskaite-Kerpauskiene A, van Bakel SPJ, Vollenberg R, Groen H, et al. Reassuring pregnancy outcomes in women with mild COL4A3-5-related disease (Alport syndrome) and genetic type of disease can aid personalized counseling. *Kidney Int.* 2024 May;105(5):1088–99.