International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

ARTICLE TITLE	FROM BASEMENT MEMBRANE DEFECTS TO PRECISION MEDICINE: ADVANCES IN ALPORT SYNDROME
ARTICLE INFO	Karolina Krowiak, Anita Krowiak, Anita Warzocha, Piotr Pitrus, Karol Bednarz, Maria Jasiewicz, Gabriela Majka, Magdalena Kowalczyk, Wiktoria Hander, Aleksandra Karnas. (2025) From Basement Membrane Defects to Precision Medicine: Advances in Alport Syndrome. *International Journal of Innovative Technologies in Social Science*. 3(47). doi: 10.31435/ijitss.3(47).2025.3654
DOI	https://doi.org/10.31435/ijitss.3(47).2025.3654
RECEIVED	23 July 2025
ACCEPTED	02 September 2025
PUBLISHED	09 September 2025
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

FROM BASEMENT MEMBRANE DEFECTS TO PRECISION MEDICINE: ADVANCES IN ALPORT SYNDROME

Karolina Krowiak *(Corresponding Author, email: karolinakr.1996@gmail.com)*
Clinical Provincial Hospital No. 2 in Rzeszow, Lwowska 60, 35-301 Rzeszów, Poland
ORCID ID: 0009-0001-6704-0838

Anita Krowiak
Clinical Provincial Hospital No. 2 in Rzeszow, Lwowska 60, 35-301 Rzeszów, Poland
ORCID ID: 0009-0008-0077-0925

Anita Warzocha
University Clinical Hospital F.Chopinin Rzeszów, Fryderyka Szopena 2,35-055 Rzeszów, Poland
ORCID ID: 0009-0006-9845-4634

Piotr Pitrus
Clinical Provincial Hospital No. 2 in Rzeszow, Lwowska 60, 35-301 Rzeszów, Poland
ORCID ID: 0009-0006-2168-9187

Karol Bednarz
Clinical Provincial Hospital No. 2 in Rzeszow, Lwowska 60, 35-301 Rzeszów, Poland
ORCID ID: 0000-0001-9196-1621

Maria Jasiewicz
Medical Center in Łańcut ul. Paderewski 5, 37-100 Łańcut, Poland
ORCID ID: 0009-0008-0718-2528

Gabriela Majka
Rzeszów University, Rzeszów, Poland, Tadeusza Rejtana 16C, 35-310 Rzeszów, Poland
ORCID ID: 0009-0002-7100-5119

Magdalena Kowalczyk
Rzeszów University, Rzeszów, Poland, Tadeusza Rejtana 16C, 35-310 Rzeszów, Poland
ORCID ID: 0009-0000-6786-8232

Wiktoria Hander
Rzeszów University, Rzeszów, Poland, Tadeusza Rejtana 16C, 35-310 Rzeszów, Poland
ORCID ID: 0009-0002-3000-9703

Aleksandra Karnas
Rzeszów University, Rzeszów, Poland, Tadeusza Rejtana 16C, 35-310 Rzeszów, Poland
ORCID ID: 0009-0005-9708-3467

ABSTRACT

Alport syndrome is a hereditary disorder characterized by progressive renal dysfunction, sensorineural hearing loss, and ocular abnormalities, resulting from mutations in COL4A3, COL4A4, COL4A5. The clinical phenotype ranges from isolated hematuria to early-onset end-stage renal disease, with variability determined by inheritance patterns and specific genotypes. Diagnosis relies on combination of clinical assessment, renal biopsy with electron microscopy, and targeted genetic testing, enabling precise characterization of disease severity and informing management strategies. Current therapeutic approaches focus on renoprotective interventions, primarily angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, with emerging evidence supporting adjunctive use of sodium-glucose cotransporter 2 inhibitors. Novel experimental therapies, including endothelin receptor antagonists, glucagon-like peptide-1 receptor agonists, microRNA-targeted treatments, and gene or stem cell-based strategies, aim to address underlying molecular mechanism, though long-term safety and efficacy require further investigation. Advances in understanding genotype-phenotype correlations, combined with improvements in diagnostic workflows and therapeutic modalities, provide opportunities to slow disease progression, optimize clinical outcomes, and improve quality of life. This review summarizes current knowledge of AS, emphasizing clinical heterogeneity, diagnostic approaches, and evolving treatment paradigms.

Methods: A comprehensive literature review was performed, using peer-reviewed sources, supplemented with data from recent clinical trials and preclinical studies. The review focused on recent advances in genetics, pathophysiology, clinical phenotypes, inheritance patterns, genotype-phenotype correlations, diagnostic workflows, and therapeutic developments in Alport syndrome.

Conclusion: Advances in genetic diagnostics have enabled earlier detection and improved prognostication in AS. While current therapies focus on slowing renal decline, novel targeted interventions my transform disease management in the future. Ongoing clinical trials will determine their long-term efficacy and safety.

KEYWORDS

Alport Syndrome, COL4A3, COL4A4, COL4A5, Genetic Diagnosis, Renoprotective Therapy, Emerging Treatments

CITATION

Karolina Krowiak, Anita Krowiak, Anita Warzocha, Piotr Pitrus, Karol Bednarz, Maria Jasiewicz, Gabriela Majka, Magdalena Kowalczyk, Wiktoria Hander, Aleksandra Karnas. (2025) From Basement Membrane Defects to Precision Medicine: Advances in Alport Syndrome. *International Journal of Innovative Technologies in Social Science*. 3(47). doi: 10.31435/ijitss.3(47).2025.3654

1. Introduction

1.1 Alport Syndrome

Alport syndrome (AS) is a rare inherited genetic disorder caused by mutations in genes encoding type IV collagen, a key structural component of basement membranes. [1] Type IV collagen is present in many tissues, particularly in the kidneys, inner ear, and eyes. Therefore, AS affects multiple organ systems, manifesting as progressive kidney failure, hearing loss, and ocular abnormalities. [2] The estimated prevalence is approximately 1 in 50, 000, with disease expression varying according to sex and mode of inheritance. AS is transmitted in three primary patterns: X-linked, autosomal dominant, and autosomal recessive, with the X-linked form being the most common, predominantly affecting males. Damage to type IV collagen results in characteristic alterations in basement membrane architecture, leading to significant clinical consequences, including progressive renal failure, hearing impairment, and visual loss. [3]

The clinical presentation of AS is heterogeneous, with symptom onset renging from childhood to adulthood. Microscopic hematuria is often the earlies manifestation, progressing to proteinuria and chronic kidney disease (CKD) over time. Hearing impairment may be congenital or, more frequently, progressive, while ocular abnormalities, such as anterior lenticonus, corneal opacification, and retinopathy, are also common clinical features of the disease. [4]

Despite advances in diagnostic methods, AS remains both a diagnostic and therapeutic challenge. Early identification, facilitated by modern techniques such as DNA sequencing, is essential for implementing targeted

therapeutic strategies that can delay the disease progression. Growing research interest is focused on novel treatment, including gene therapy, which may offer the potential for disease-modifying interventions. [5]

The purpose of this review is to present the current state of knowledge regarding molecular mechanisms, diagnosis, and treatment of AS. It also discusses recent advances in understanding disease pathogenesis and explores both established and experimental therapies that may, in the future, improve the quality of life for patients affected by this rare condition.

2. Molecular Genetics and Pathophysiology

AS is a hereditary nephropathy characterized by progressive renal failure, sensorineural hearing loss, and ocular abnormalities. The disorder results from mutations in genes encoding type IV collagen, an essential structural component of basement membranes in the kidney, cochlea and eye. Specifically, pathogenic variants in COL4A3, COL4A4, and COL4A5 disrupt the formation of the α3α4α5 collagen IV network, leading to basement membrane dysfunction and the characteristic clinical manifestations of the syndrome. [6]

2.1. Genetic Basis

Approximately 80-85% of AS cases are inherited in an X-linked manner due to pathogenic variants in the COL4A5 gene. These mutations predominantly affect males, who typically experience more severe and rapidly progressive disease, whereas heterozygous females may present with milder symptoms. Autosomal recessive AS, resulting from mutations in both alleles of COL4A3 or COL4A4, accounts for approximately 15% of cases and affects both sexes equally. [7] Around 20% of patients inherit the disorder in an autosomal dominant manner, caused by mutations in the COL4A3 or COL4A4 genes. This form generally presents with similar clinical and pathological features to the X-linked type but demonstrates slower progression of renal impairment and less frequent auditory or ocular involvement.[8]

Recent studies have also identifies digenic inheritance patterns, in which mutations in two different collagen genes contribute synergistically to the disease phenotype. This genetic complexity underscores the importance of comprehensive molecular testing in all suspected cases of AS. [9, 10]

Genotype-phenotype correlations play a pivotal in understanding the natural history of AS and in providing accurate prognosis information and genetic counselling. The severity of clinical manifestation, including the age at onset and rate of progression of renal failure, hearing loss, and extrarenal features, varies according to the specific pathogenic variant in COL4A3, COL4A4 and COL4A5.

2.2 Pathophysiological Mechanisms

Type IV collagen is essential for the structural integrity of basement membranes. In AS, mutations in COL4A3, COL4A4 or COL4A5 disrupt the assembly of the α3α4α5 collagen IV network. This defect results in thinning, splitting, and lamellation of the glomerular basement membrane (GBM), compromising its filtration function. [10] Consequently, a damaged GBM allows blood cells and protein to leak into the urine, causing hematuria and proteinuria, and eventually leading to CKD and end-stage renal failure (ESRD). [11]

Most AS cases are caused by X-linked mutations in COL4A5, which are associated with early-onset ESRD and hearing loss, particularly in males. Large deletions and nonsense mutations are correlated with severe phenotypes, leading to rapid progression to ESRD, often before the age of 30. In contrast, missense mutations lead to milder phenotypes with delayed onset of renal failure, typically after the third decade of life. [13]

Additionally hearing impairment in AS usually develops gradually rather than being present congenital, most commonly emerging during adolescence between 12 and 18 years of age. In the cochlea, sensory hair cells within the organ of Corti are anchored to the basement membrane. Mutations affecting type IV collagen disrupt this membrane, impairing the structural and functional integrity of the hair cells, which results in progressive sensorineural hearing loss (SNHL). Ocular manifestations also develop progressively. A characteristic change involves the lens, in which the middle part protrude into the anterior chamber due to compromised lens capsule integrity. These extrarenal features are hallmark manifestation of AS and are useful in clinical diagnosis. [6, 12, 14]

3. Clinical Manifestation

3.1 Classic Severe AS (XLAS males and ARAS patients)

The most severe clinical phenotype of AS occurs in hemizygous males with X-linked COL4A5 mutations and in patients with autosomal recessive COL4A3 or COL4A4 mutations. These individuals typically present with microscopic hematuria in infancy, followed by the onset proteinuria in early childhood.

SNHL develops in up to 90% of patients by the age of 40, while ocular abnormalities, most commonly anterior lenticonus or retinal flecks, are present in over half of cases. Kidney failure (KF) occurs in all affected individuals, with 70% reaching to ESRD by age 30 and 90% by age 40. The median age at KF is approximately 25 years. [15, 16]

3.2 Mild to moderate AS

This category includes heterozygous females with X-linked AS (XLAS), autosomal dominant AS (ADAS), and digenic forms of the disease. The clinical course is generally milder, and kidney failure is not inevitable. [15]

3.2.1 Females with heterozygous XLAS

Affected females frequently presents with microscopic hematuria from infancy, with variable onset and severity of proteinuria over time. SNHL occurs in approximately 5-28% of cases, while fleck retinopathy is observed in 25-30%. KF develops in 12-15% of women by the age of 40 and in 30-40% by the age of 60, with a median onset occurring after of 50 years. [5, 15]

3.2.2 ADAS

ADAS typically presents with intermittent microscopic hematuria, with proteinuria developing after the age of 30. SNHL is reported in 8-16% of cases, while ocular changes are rare (1-3%). Progression to KF is variable, with a median after the age of 50. [15, 16]

3.3 Digenic AS

3.3.1 COL4A3 +/- and COL4A4 +/-

Patients with heterozygous pathogenic variants in both COL4A3 and COL4A4 typically presents with microscopic hematuria and develop proteinuria after the age of 40. KF is not inevitable, with a median reported onset of approximately 54 years. [5, 15]

3.3.2 COL4A3 or COL4A4 +/- plus COL4A5 +/-

This form of digenic AS manifestes with hematuria in infancy and earlier onset of proteinuria compared with heterozygous XLAS females. SNHL occurs in approximately 15% of cases, and ocular defects are observed in around 7%. Reported ages at onset of KF in documented cases are 40 and 44 years. [5, 15]

4. Diagnosis

Early and accurate diagnosis of AS is essential for initiate appropriate therapeutic interventions, maximize their efficacy in slowing disease progression, and delay the onset of ESRD. Clinical suspicion should be raised in patients presenting persistent hematuria or proteinuria on urinalysis, a documented family history of CKD, characteristic auditory or ocular abnormalities, or renal biopsy findings demonstrating pathological alterations of the GBM. The presence of any single diagnostic feature strongly correlates with positive genetic test. [17, 18]

Histopathological examination of renal biopsy reveals characteristic alterations that vary according to the disease stage and genetic subtype. In the early stages, the GBM typically shows diffuse thinning, while advanced disease is characterized by splitting, irregular lamellation and the classical”basket-weave” appearance on electron microscopy. In heterozygous XLAS females, GBM changes are variable, often demonstrating focal lamellation and a basket-weave pattern. [16] In ADAS, GBM thinning predominates, with splitting, lamellation and basket-weave changes occurring infrequently. In digenic AS, early GBM thinning is commonly accompanied by splitting and lamellation, while the basket-weave change being is less common. Patients with COL4A3 or COL4A4 variants in combination with COL4A5 mutation often exhibit similar the histological findings, although the basket-weave pattern is more frequently observed. [16]

Genetic analyses have demonstrated that pathogenic variants in COL4A3, COL4A4, or COL4A5 are present in over 30% of cases of adult-onset familial focal segmental glomeruloscerosis (FSGS). [18, 19, 20] Additionally, AS and thin basement membrane nephropathy frequently coexist with IgA nephropathy but may remain undiagnosed if renal biopsy specimens are not evaluated for GBM lamellation or thinning using electron microscopy. [18, 21]

In suspected AS, genetic testing should include analysis COL4A3, COL4A4, and COL4A5, as inheritance patterns cannot be reliably determined clinically. [18, 22] In high-suspicion cases, targeted next-

generation sequencing (NGS) of these genes is recommended. In lower-suspicion cases, broader gene panels or whole-exome sequencing should be considered. [22] Renal biopsy, ideally including transmission electron microscopy (TEM), remains valuable for detecting characteristic GBM changes, and collagen IV α-chain immunofluorescence can aid diagnosis when TEM in unavailable. [22] NGS detects approximately 95% of all missense and nonsense variants, insertions and deletions, and most splicing variants near intron-exon boundaries, where approximately 5-10% of all pathogenic variants in Alport syndrome are duplications, insertions, and deletions, but sequencing is less sensitive in detecting them, which may require the use of additional analytical methods. [18, 23, 24]

5. Current and Emerging Therapies

Alport nephropathy typically follows a characteristic progression, beginning with isolated hematuria, followed by moderate albuminuria, overt proteinuria, and ultimately a decline in glomerular filtration rate (GFR). The interval between these stages is variable and is predominantly determined by patient sex and the underlying COL4A genotype. The rate of disease progression spans a wide spectrum, from rapidly progressive forms necessitating kidney replacement therapy in adolescence or early adulthood, to indolent courses in which individuals may reach advanced age with preserved renal function. [5]

5.1 Current Standard of Care

Management of AS involves both symptomatic treatment and genetic counselling for patients and their family. Optimal blood pressure control remains a cornerstone of therapy, most commonly achieved through the administration of angiotensin converting enzyme (ACE) inhibitors or angiotensin I/II receptor blockers (ARB). ACE inhibitor therapy has demonstrated efficacy in patients with proteinuria and preserved renal function, significantly delaying progression to ESRD. [14, 25] In male patients with X-linked AS and individuals with ARAS, initiation of ACE inhibitor therapy is recommended at the time of diagnosis, and in the latter group, preferably after the age of 12-24 months. In females with X-linked AS, ACE inhibitor therapy should be initiated upon the onset of microalbuminuria, comfirmed on repeated measurements. Similatly, in patients with heterozygous variants in COL4A3 or COL4A4, treatment with an ACE inhibitor is indicated following confirmation of persistent microalbuminuria on serial assessments. [26]

Emerging evidence suggests that sodium-glucose cotransporter 2 inhibitors (SGLT2i), such as dapagliflozin, are well tolerated and may confer renoprotective benefits in patients with AS. Preliminary clinical data, including small pediatric case series, indicate a significant reduction in proteinuria when SGLT2i are administered either as monotherapy or in combination with renin-angiotensin system inhibitors (RASi). [27] These agents are currently available in most European countries for individuals with stage 3 chronic kidney disease and proteinuria exceeding 0, 2 g/g creatinine, supporting their potential applicability in AS. Although short-term studies demonstrate reductions in albuminuria, large-scale randomized controlled trial – such as the ongoing DOUBLE PRO-TECT Alport study- are warranted to determine whether these effects translate into delayed progression to KF. [28]

5.2. Novel and Experimental Therapies

Several novel therapeutic strategies targeting diverse pathophysiological mechanism in AS have demonstrated potential renoprotective effects in preclinical and early studies, although their long-term efficacy and safety require further confirmation in large-scale clinical trials. [28, 29]

5.2.1 Barboxolone methyl

Barboxolone methyl is an activator of the Keap1-Nrf2 pathway with anti-inflammatory antioxidant properties, investigated in the treatment of AS. In the phase 3 CARDINAL trial, bardoxolone demonstrated short-term attenuation of eGFR decline. [29, 30] However, therapy was associated with reversible worsening of albuminuria, increased blood pressure and transient elevation of liver transaminases. The U.S Food and Drug Administration (FDA) concluded that current evidence is insufficient to support its long-term efficacy and safety, raising concerns about potentially deleterious increases in intraglomerular hemodynamics, as well as the lack of robust data from animal model and other CKD studies. [29, 30, 31]

5.2.2. Endothelin Type Receptor (ETAR) and Angiotensin II Type 1 Receptor (AT1R) Inhibitors

ETAR and AT1R inhibitors – activation of ETAR contributes to both renal and auditory pathology in AS. Sparsentan, a dual ETAR/AT1R antagonist, has demonstrated superiority over selective ETAR or AT1R blockade in AS murine models, reducing proteinuria, prolonging survival, and attenuating both structural and functional auditory impairment. Atrasentan, a selective ETAR inhibitor, has been shown to reduce albuminuria and the risk of renal events in diabetic CKD, although its use is associated with increased incidence of oedema and anemia. [28, 29, 32]

5.2.3 Glucagon – like peptide – 1 receptor agonists (GLP-1 RAs)

GLP-1 RAs have demonstrated significant cardioprotective and renoprotective effects in patients with type 2 diabetes mellitus and CKD. Large randomized controlled trials have shown that GLP-1 RAs reduce major adverse cardiovascular events and attenuate CKD progression, primarily through reductions in albuminuria. Proposed renoprotective mechanisms include anti-inflammatory, antifibrotic and antioxidative actions, which are of particular relevance to AS, in which chronic inflammation and progressive fibrosis are central to disease pathogenesis. [33]

5.2.4 Paricalcitol

Paricalcitol, a selective vitamin D receptor activator, downregulates renin expression and may exert synergistic nephroprotective effects when combined with ACE inhibitors in AS. In COL4A3 knockout mice, paricalcitol – but not calcitriol- enhanced the renoprotective effect of early ACE inhibition, delaying progression to renal failure more effectively than monotherapy. Despite promising preclinical data, clinical evidence in AS patients remains insufficient to recommended routine use. [34, 35]

5.2.5 MicroRNA-21 Inhibition (miR-21)

miR-21 has been implicated in the fibrogenic processes central to AS pathogenesis. Preclinical studies in AS mouse models demonstrated that targeted inhibition with anti-miR-21 oligonucleotides improved renal histology, reduces microalbuminuria, and extended median survival by over 40%, likely via modulation of metabolic pathways. A phase 2 clinical trial (HERA, NCT02855268) evaluating anti-miR-21 therapy in AS patients was discontinued, with ongoing considerations for trial redesign under new sponsorship. [34]

5.2.6 Stem cell – based therapies

In AS aim to replace defective podocytes and restore functional GBM architecture. Preclinical studies using induced pluripotent stem cell (iPSCs) and other stem cell sources have demonstrated partial restoration of collagen IV networks, delayed renal pathology, and lifespan extension in selected murine models. However, results have been inconsistent, with some models showing no survival benefit. Bone marrow transplantation has shown limited efficacy and carrier substantial procedural risk, precluding clinical application. At present, stem cell-based strategies remain experimental, with no evidence supporting their use in humans. [34, 36, 37]

5.2.7 Gene therapy

Represents a promising but still experimental approach in AS. Preclinical studies have demonstrated restoration of collagen IV expression in the GBM using inducible transgene system in murine models. CRISPR/Cas9-mediated correction of COL4A3 and COL4A5 mutations in patient-derived podocytes has achieved high editing efficiencies, although technical challenges and the need for early intervention remain major limitations. Additionally, X-chromosome reactivation strategies offer a potential future therapeutic avenue for females with X-linked AS by restoring expression of the functional COL4A5 allele. To date, these approaches remain in preclinical development without translation to human therapy. [28, 39, 40]

6. Conclusions

Alport syndrome is a complex, multisystem disorder with significant variability in presentation and prognosis, determined by of inheritance and the specific underlying genetic mutations. Early and accurate diagnosis, supported by advances in molecular testing, allows timely initiation of renoprotective therapy, which is essential for delaying the onset of ESRD. Current management primarily relies on ACE inhibitors and ARBs, with growing evidence supporting adjunctive use of SGLT2 inhibitors. Novel therapeutic approaches targeting defined molecular pathways, as well as experimental strategies such as gene and stem cell therapies, hold considerable potential but require rigorous validation in well-designed clinical trials. The successful translation of these advances into clinical practice has potential to markedly improve long-term outcomes and quality of life for patients with AS.

Funding Statement: The article did not receive any funding.
Institutional Review and Board Statement: Not applicable
Informed Consent Statement: Not applicable
Data Availability Statement: Not applicable
Conflict of Interest Statement: No conflicts of interest to declare.
Acknowledgements: None.

REFERENCES

1. Quinlan, C., & Rheault, M. N. (2021). Genetic Basis of Type IV Collagen Disorders of the Kidney. *Clinical journal of the American Society of Nephrology : CJASN*, *16*(7), 1101–1109. https://doi.org/10.2215/CJN.19171220
2. Ostrowska-Spaleniak, A., Krix-Jachym, K., & Rękas, M. (2017). Ocular manifestation and surgical treatment outcomes in Alport syndrome – case series. Klinika Oczna / Acta Ophthalmologica Polonica, 119(2), 116-119. https://doi.org/10.5114/ko.2017.71782
3. Kang, E., Park, B. H., Lee, H., Kang, H. G., Kim, J. H., Kim, Y. N., Jung, Y., Rim, H., & Shin, H. S. (2025). A comprehensive review of Alport syndrome: definition, pathophysiology, clinical manifestations, and diagnostic considerations. *Kidney research and clinical practice*, *44*(4), 566–575. https://doi.org/10.23876/j.krcp.24.065
4. Moczulska, A., Walkosz, J., Zarębska, E., Mleczko, M., Zachwieja, K., Wierzchowska-Słowiaczek, E. ... Drożdż, D. (2017). Rozpoznanie zespołu Alporta i nefropatii cienkich błon podstawnych w wieku dziecięcym. Annales Academiae Medicae Silesiensis, 71, 73-81. https://doi.org/10.18794/aams/69243
5. Kashtan C. E. (2021). Alport Syndrome: Achieving Early Diagnosis and Treatment. *American journal of kidney diseases : the official journal of the National Kidney Foundation*, *77*(2), 272–279. https://doi.org/10.1053/j.ajkd.2020.03.026
6. Martínez-Pulleiro, R., García-Murias, M., Fidalgo-Díaz, M., & García-González, M. Á. (2021). Molecular Basis, Diagnostic Challenges and Therapeutic Approaches of Alport Syndrome: A Primer for Clinicians. *International journal of molecular sciences*, *22*(20), 11063. https://doi.org/10.3390/ijms222011063
7. Savige, J., & Harraka, P. (2021). Pathogenic Variants in the Genes Affected in Alport Syndrome (COL4A3-COL4A5) and Their Association With Other Kidney Conditions: A Review. *American journal of kidney diseases : the official journal of the National Kidney Foundation*, *78*(6), 857–864. https://doi.org/10.1053/j.ajkd.2021.04.017
8. Shang, S., Peng, F., Wang, T., Wu, X., Li, P., Li, Q., & Chen, X. M. (2019). Genotype-phenotype correlation and prognostic impact in Chinese patients with Alport Syndrome. *Molecular genetics & genomic medicine*, *7*(7), e00741. https://doi.org/10.1002/mgg3.741
9. Daga, S., Fallerini, C., Furini, S., Pecoraro, C., Scolari, F., Ariani, F., Bruttini, M., Mencarelli, M. A., Mari, F., Renieri, A., & Pinto, A. M. (2019). Non-collagen genes role in digenic Alport syndrome. *BMC nephrology*, *20*(1), 70. https://doi.org/10.1186/s12882-019-1258-5
10. Kashtan, C. E., Ding, J., Garosi, G., Heidet, L., Massella, L., Nakanishi, K., Nozu, K., Renieri, A., Rheault, M., Wang, F., & Gross, O. (2018). Alport syndrome: a unified classification of genetic disorders of collagen IV α345: a position paper of the Alport Syndrome Classification Working Group. *Kidney international*, *93*(5), 1045–1051. https://doi.org/10.1016/j.kint.2017.12.018
11. Cosgrove, D., & Liu, S. (2017). Collagen IV diseases: A focus on the glomerular basement membrane in Alport syndrome. *Matrix biology : journal of the International Society for Matrix Biology*, *57-58*, 45–54. https://doi.org/10.1016/j.matbio.2016.08.005
12. Ramakrishnan, R., Shenoy, A., & Meyer, D. (2022). Ocular Manifestations and Potential Treatments of Alport Syndrome: A Systematic Review. *Journal of ophthalmology*, *2022*, 9250367. https://doi.org/10.1155/2022/9250367
13. Savige, J., Huang, M., Croos Dabrera, M. S., Shukla, K., & Gibson, J. (2022). Genotype-Phenotype Correlations for Pathogenic *COL4A3-COL4A5* Variants in X-Linked, Autosomal Recessive, and Autosomal Dominant Alport Syndrome. *Frontiers in medicine*, *9*, 865034. https://doi.org/10.3389/fmed.2022.865034
14. Adone, A., & Anjankar, A. (2023). Alport Syndrome: A Comprehensive Review. *Cureus*, *15*(10), e47129. https://doi.org/10.7759/cureus.47129
15. Puapatanakul, P., & Miner, J. H. (2024). Alport syndrome and Alport kidney diseases - elucidating the disease spectrum. *Current opinion in nephrology and hypertension*, *33*(3), 283–290. https://doi.org/10.1097/MNH.0000000000000983
16. Gregorio, V., Caparali, E. B., Shojaei, A., Ricardo, S., & Barua, M. (2023). Alport Syndrome: Clinical Spectrum and Therapeutic Advances. *Kidney medicine*, *5*(5), 100631. https://doi.org/10.1016/j.xkme.2023.100631
17. Martínez-Pulleiro, R., García-Murias, M., Fidalgo-Díaz, M., & García-González, M. Á. (2021). Molecular Basis, Diagnostic Challenges and Therapeutic Approaches of Alport Syndrome: A Primer for Clinicians. *International journal of molecular sciences*, *22*(20), 11063. https://doi.org/10.3390/ijms222011063

18. Savige, J., Ariani, F., Mari, F., Bruttini, M., Renieri, A., Gross, O., Deltas, C., Flinter, F., Ding, J., Gale, D. P., Nagel, M., Yau, M., Shagam, L., Torra, R., Ars, E., Hoefele, J., Garosi, G., & Storey, H. (2019). Expert consensus guidelines for the genetic diagnosis of Alport syndrome. *Pediatric nephrology (Berlin, Germany)*, *34*(7), 1175–1189. https://doi.org/10.1007/s00467-018-3985-4
19. Gast, C., Pengelly, R. J., Lyon, M., Bunyan, D. J., Seaby, E. G., Graham, N., Venkat-Raman, G., & Ennis, S. (2016). Collagen (COL4A) mutations are the most frequent mutations underlying adult focal segmental glomerulosclerosis. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*, *31*(6), 961–970. https://doi.org/10.1093/ndt/gfv325
20. Voskarides, K., Damianou, L., Neocleous, V., Zouvani, I., Christodoulidou, S., Hadjiconstantinou, V., Ioannou, K., Athanasiou, Y., Patsias, C., Alexopoulos, E., Pierides, A., Kyriacou, K., & Deltas, C. (2007). COL4A3/COL4A4 mutations producing focal segmental glomerulosclerosis and renal failure in thin basement membrane nephropathy. *Journal of the American Society of Nephrology : JASN*, *18*(11), 3004–3016. https://doi.org/10.1681/ASN.2007040444
21. Savige, J., Rana, K., Tonna, S., Buzza, M., Dagher, H., & Wang, Y. Y. (2003). Thin basement membrane nephropathy. *Kidney international*, *64*(4), 1169–1178. https://doi.org/10.1046/j.1523-1755.2003.00234.x
22. Kashtan, C. E., & Gross, O. (2021). Clinical practice recommendations for the diagnosis and management of Alport syndrome in children, adolescents, and young adults-an update for 2020. *Pediatric nephrology (Berlin, Germany)*, *36*(3), 711–719. https://doi.org/10.1007/s00467-020-04819-6
23. Fallerini, C., Dosa, L., Tita, R., Del Prete, D., Feriozzi, S., Gai, G., Clementi, M., La Manna, A., Miglietti, N., Mancini, R., Mandrile, G., Ghiggeri, G. M., Piaggio, G., Brancati, F., Diano, L., Frate, E., Pinciaroli, A. R., Giani, M., Castorina, P., Bresin, E., … Ariani, F. (2014). Unbiased next generation sequencing analysis confirms the existence of autosomal dominant Alport syndrome in a relevant fraction of cases. *Clinical genetics*, *86*(3), 252–257. https://doi.org/10.1111/cge.12258
24. Morinière, V., Dahan, K., Hilbert, P., Lison, M., Lebbah, S., Topa, A., Bole-Feysot, C., Pruvost, S., Nitschke, P., Plaisier, E., Knebelmann, B., Macher, M. A., Noel, L. H., Gubler, M. C., Antignac, C., & Heidet, L. (2014). Improving mutation screening in familial hematuric nephropathies through next generation sequencing. *Journal of the American Society of Nephrology : JASN*, *25*(12), 2740–2751. https://doi.org/10.1681/ASN.2013080912
25. Kashtan, C. E., Ding, J., Gregory, M., Gross, O., Heidet, L., Knebelmann, B., Rheault, M., Licht, C., & Alport Syndrome Research Collaborative (2013). Clinical practice recommendations for the treatment of Alport syndrome: a statement of the Alport Syndrome Research Collaborative. *Pediatric nephrology (Berlin, Germany)*, *28*(1), 5–11. https://doi.org/10.1007/s00467-012-2138-4
26. Huang, H. X., Tsai, I. J., & Greenbaum, L. A. (2025). Alport syndrome: Expanding diagnosis and treatment. *Pediatrics and neonatology*, *66 Suppl 1*, S13–S17. https://doi.org/10.1016/j.pedneo.2024.10.005
27. Boeckhaus, J., Gale, D. P., Simon, J., Ding, J., Zhang, Y., Bergmann, C., Turner, A. N., Hall, M., Sayer, J. A., Srivastava, S., Kang, H. G., Cerkauskaite-Kerpauskiene, A., Gillion, V., Claes, K. J., Krueger, B., de Fallois, J., Walden, U., Choi, M., Schueler, M., Mueller, R. U., … Gross, O. (2024). SGLT2-Inhibition in Patients With Alport Syndrome. *Kidney international reports*, *9*(12), 3490–3500. https://doi.org/10.1016/j.ekir.2024.09.014
28. Reiterová, J., & Tesař, V. (2023). Current and Future Therapeutical Options in Alport Syndrome. *International journal of molecular sciences*, *24*(6), 5522. https://doi.org/10.3390/ijms24065522
29. Chavez, E., Rodriguez, J., Drexler, Y., & Fornoni, A. (2022). Novel Therapies for Alport Syndrome. *Frontiers in medicine*, *9*, 848389. https://doi.org/10.3389/fmed.2022.848389
30. Chertow, G. M., Appel, G. B., Andreoli, S., Bangalore, S., Block, G. A., Chapman, A. B., Chin, M. P., Gibson, K. L., Goldsberry, A., Iijima, K., Inker, L. A., Knebelmann, B., Mariani, L. H., Meyer, C. J., Nozu, K., O'Grady, M., Silva, A. L., Stenvinkel, P., Torra, R., Warady, B. A., … Pergola, P. E. (2021). Study Design and Baseline Characteristics of the CARDINAL Trial: A Phase 3 Study of Bardoxolone Methyl in Patients with Alport Syndrome. *American journal of nephrology*, *52*(3), 180–189. https://doi.org/10.1159/000513777
31. Warady, B. A., Pergola, P. E., Agarwal, R., Andreoli, S., Appel, G. B., Bangalore, S., Block, G. A., Chapman, A. B., Chin, M. P., Gibson, K. L., Goldsberry, A., Iijima, K., Inker, L. A., Kashtan, C. E., Knebelmann, B., Mariani, L. H., Meyer, C. J., Nozu, K., O'Grady, M., Rheault, M. N., … Chertow, G. M. (2022). Effects of Bardoxolone Methyl in Alport Syndrome. *Clinical journal of the American Society of Nephrology : CJASN*, *17*(12), 1763–1774. https://doi.org/10.2215/CJN.02400222
32. Heerspink, H. J. L., Parving, H. H., Andress, D. L., Bakris, G., Correa-Rotter, R., Hou, F. F., Kitzman, D. W., Kohan, D., Makino, H., McMurray, J. J. V., Melnick, J. Z., Miller, M. G., Pergola, P. E., Perkovic, V., Tobe, S., Yi, T., Wigderson, M., de Zeeuw, D., & SONAR Committees and Investigators (2019). Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. *Lancet (London, England)*, *393*(10184), 1937–1947. https://doi.org/10.1016/S0140-6736(19)30772-X
33. Boeckhaus, J., Mabillard, H., & Sayer, J. A. (2025). GLP-1 receptor agonists-another promising therapy for Alport syndrome?. *Journal of rare diseases (Berlin, Germany)*, *4*(1), 5. https://doi.org/10.1007/s44162-024-00065-8

34. Torra, R., & Furlano, M. (2019). New therapeutic options for Alport syndrome. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*, *34*(8), 1272–1279. https://doi.org/10.1093/ndt/gfz131
35. Rubel, D., Stock, J., Ciner, A., Hiller, H., Girgert, R., Müller, G. A., & Gross, O. (2014). Antifibrotic, nephroprotective effects of paricalcitol versus calcitriol on top of ACE-inhibitor therapy in the COL4A3 knockout mouse model for progressive renal fibrosis. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*, *29*(5), 1012–1019. https://doi.org/10.1093/ndt/gft434
36. Lin, X., Suh, J. H., Go, G., & Miner, J. H. (2014). Feasibility of repairing glomerular basement membrane defects in Alport syndrome. *Journal of the American Society of Nephrology : JASN*, *25*(4), 687–692. https://doi.org/10.1681/ASN.2013070798
37. Kuebler, B., Aran, B., Miquel-Serra, L., Muñoz, Y., Ars, E., Bullich, G., Furlano, M., Torra, R., Marti, M., Veiga, A., & Raya, A. (2017). Integration-free induced pluripotent stem cells derived from a patient with autosomal recessive Alport syndrome (ARAS). *Stem cell research*, *25*, 1–5. https://doi.org/10.1016/j.scr.2017.08.021
38. Kuebler, B., Aran, B., Miquel-Serra, L., Muñoz, Y., Ars, E., Bullich, G., Furlano, M., Torra, R., Marti, M., Veiga, A., & Raya, A. (2017). Generation of integration-free induced pluripotent stem cell lines derived from two patients with X-linked Alport syndrome (XLAS). *Stem cell research*, *25*, 291–295. https://doi.org/10.1016/j.scr.2017.08.019
39. Daga, S., Donati, F., Capitani, K., Croci, S., Tita, R., Giliberti, A., Valentino, F., Benetti, E., Fallerini, C., Niccheri, F., Baldassarri, M., Mencarelli, M. A., Frullanti, E., Furini, S., Conticello, S. G., Renieri, A., & Pinto, A. M. (2020). New frontiers to cure Alport syndrome: COL4A3 and COL4A5 gene editing in podocyte-lineage cells. *European journal of human genetics : EJHG*, *28*(4), 480–490. https://doi.org/10.1038/s41431-019-0537-8
40. Lin, X., Suh, J. H., Go, G., & Miner, J. H. (2014). Feasibility of repairing glomerular basement membrane defects in Alport syndrome. *Journal of the American Society of Nephrology : JASN*, *25*(4), 687–692. https://doi.org/10.1681/ASN.2013070798