SAGE Open Medical Case Reports
Volume 12: 1–4

DOI: 10.1177/2050313X241275794
journals.sagepub.com/home/sco
Sage

A variant of unknown significance in the COL4A5 gene-related renal disease: A novel case report

Teresa Trinka[1] and Mohammed Faizan[2]

Abstract

In this case report, we report our findings of a variant of uncertain significance in the COL4A5 gene in four family members. Patient 0 is a 16-year-old female with no prior medical history referred to Pediatric Nephrology for the evaluation of microscopic hematuria. Upon further investigation, she was found to have a family history of both microscopic hematuria and kidney disease, prompting genetic testing and intimation of a possible cause and inheritance pattern for kidney disease and hematuria in the COL4A5 gene.

Keywords

Pediatrics, nephrology, case report, Alport syndrome, genetic testing

Date received: 27 March 2024; accepted: 19 July 2024

Introduction

Alport syndrome is an inherited disease caused by pathogenic variants in the COL4A3/A4/A5 genes that encode collagen IV components.[1] It is characterized by structural abnormalities and dysfunction of the glomerular basement membrane (GBM) and the basement membrane of other tissues as well. There are wide variations in Alport syndrome presentation, ranging from isolated hematuria with non-progressive renal disease to progressive renal disease with extrarenal abnormalities, such as hearing loss and ocular changes.[2] Given these variations in the presentation, genetic testing has become particularly useful for the diagnosis and management of Alport syndrome, particularly within families with a history of kidney disease. Here, we report our findings of a variant of uncertain significance (VUS) in the COL4A5 gene in four family members.

Case presentation

Patient 0 is a 16-year-old female with no medical history, referred to pediatric nephrology for evaluation of microscopic hematuria. The patient had a marginally elevated urine protein to creatinine ratio. Upon further evaluation, she had an unremarkable physical exam with blood pressure and serum creatinine levels within normal ranges. However, family history revealed a history of microscopic hematuria in the patient's mother and maternal aunt. The patient's mother reported that maternal grandfather had lifelong kidney disease, for which he received a kidney transplant at the age of 50. The patient's fraternal twin has no renal presentation at this time. All four patients underwent genetic testing with a next-generation sequencing-based panel consisting of 385 genes associated with kidney disease (the Renasight™ test; Natera, Inc., Austin, TX, USA). Variants were interpreted based on the ACMG/AMP guidelines for the interpretation of DNA variants.[3] No positive genetic findings were reported in the patients. However, a suspicious VUS in *COL4A5* (NM_000495.5:c.276+2dup) was identified in all four members. This variant is predicted to disrupt the canonical splice site of exon 4; it has not been observed in the population databases (gnomAD v4),[4] and functional studies would be required to determine the effect of this variant on RNA processing. Given these findings, a more complete family history was gathered to better understand the extent of kidney disease throughout the extended family. This revealed four other members of the family with kidney disease, included in Figure 1 below. Genetic

[1]Warren Alpert Medical School of Brown University, Providence, RI, USA
[2]Department of Pediatrics, Hasbro Children's Hospital, Providence, RI, USA

Corresponding Author:
Teresa Trinka, Warren Alpert Medical School of Brown University, 222 Richmond Street, Providence, RI 02903, USA.
Email: Teresa_trinka@brown.edu

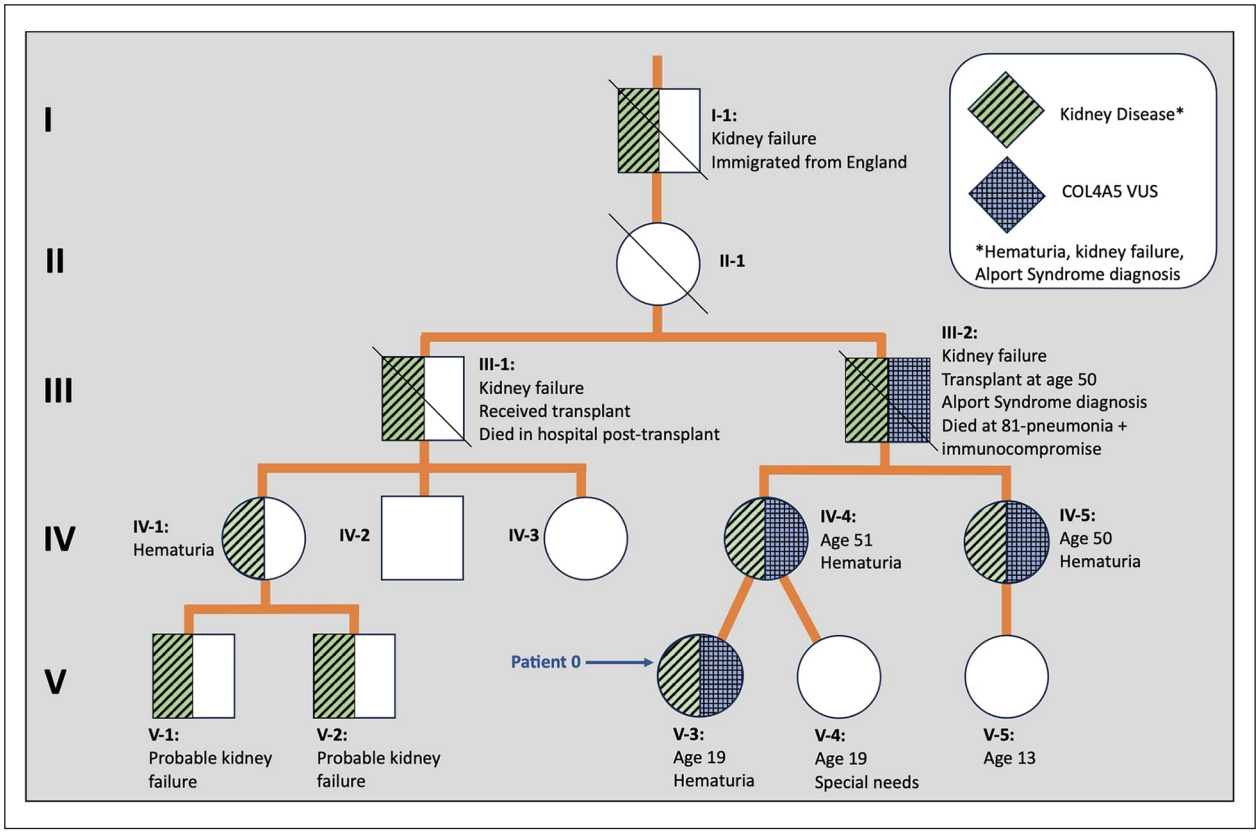

Figure 1. Pedigree of Patient 0 family, depicting relevant family medical and genetic history.

testing of spouses was not performed. The family reports no consanguinity of the marriages.

Patient 0 has been monitored closely for progression of symptoms, such as proteinuria or hearing loss. After 2 years of follow-up, patient's urine protein to creatinine ratio increased, along with an ambulatory blood pressure monitoring that revealed hypertension. Patient was started on lisinopril for disease progression. She has remained clinically asymptomatic without any episodes of gross hematuria or swelling and continues to be followed by Pediatric Nephrology.

Discussion

Alport syndrome is one of the most common inherited kidney disease[5] and is classified by mode of inheritance: X-linked Alport syndrome (XLAS) is caused by mutations in the COL4A5 gene, while autosomal recessive Alport syndrome and autosomal dominant Alport syndrome are caused by abnormalities in either COL4A3 or COL4A4 genes. The COL4A3, COL4A4, and COL4A5 genes encode for 3, 4, and 5 polypeptide chains of type IV collagen, respectively, which assembles into heterotrimers of type IV collagen in the GBM.[2] XLAS often includes a family history of hematuria or renal failure, although approximately 15% of cases are de novo variants with no family history.[6] Microscopic hematuria is observed in all male cases and approximately 98% of female cases.[7] It is reported that 90% of male patients develop end-stage renal disease (ESRD) by age 40, while in females, 12% of cases have developed ESRD by age 40.[8,9]

Genetic testing is an emerging tool for patient management in the field of nephrology. The identification of monogenic causes of chronic kidney disease (CKD) is important as it can inform clinical decision-making as well as prognosis.[10] Patients diagnosed with Alport syndrome benefit from effective and inexpensive treatment with renin-angiotensin-aldosterone system blockade, which has been shown to delay the development and progression of kidney failure in these patients.[11] Numerous studies highlight the benefits of using broad, unbiased genetic panels and their advantages over smaller, target panels due to the often complex and variable presentation of many renal disorders.[12,13] One such study is the Renasight Clincial Application, Review, and Evaluation (RenaCARE) study, which demonstrated that genetic testing with a 385 gene panel for CKD improved diagnostic accuracy, thereby changing clinical management of patients with both positive and negative findings.[14] Several genes, including COL4A5, have been identified as key players in the development of early-onset kidney disease. According to Domingo-Gallego et al.,[15] understanding the genetic diversity of early-onset kidney disease highlights the clinical utility of genetic testing for diagnosing and managing such

conditions. COL4A5 is implicated in Alport syndrome and underscores the genetic heterogeneity observed in kidney diseases presenting in childhood. Understanding the genetic landscape, particularly of COL4A5, guides clinicians in early detection and personalized treatment strategies, thereby enhancing our ability to intervene effectively in the progression of kidney diseases.

Alport syndrome is an example of one such disease that can benefit from the introduction of genetic testing as its clinical presentation varies widely from case to case. Additionally, Alport syndrome can manifest as other diseases such as focal segmental glomerular sclerosis, for which genetic testing is necessary for reclassification of the clinical diagnosis.[1] Guidelines for genetic testing and management of Alport syndrome, released by the American Society of Nephrology, recommend genetic testing in patients with persistent dysmorphic hematuria for greater than 6 months without an identifiable cause.[16] Studies indicate that nearly 100% of men and 95% of women with a pathogenic COL4A5 variant will have hematuria.[17] Another issue discussed in the American Society of Nephrology guidelines for Alport syndrome is the increased identification of "hypomorphic variants" in the COL4A5 gene. These variants are usually associated with milder disease, including hematuria alone or late-onset kidney failure, but should be acted upon by clinicians, as they may eventually cause kidney failure.[18]

In the family presented here, genetic testing provided an intimation of a possible cause and inheritance pattern for kidney disease and hematuria. Genetic testing for patient 0 gave rise to cascade testing in three additional family members to date, with the potential for testing of other affected family members. The VUS identified is predicted to affect the highly conserved splice donor site for exon 4. Functional studies are necessary to determine the impact of this variant and to invoke stronger evidence for reclassification. To our knowledge, this variant has not been reported to be associated with Alport Syndrome (AS) and is absent from population databases. However, based on the clinical presentation of these patients and the lack of other positive genetic findings, this VUS is suspicious and warrants further investigation, which may help to guide management and treatment recommendations for members of this family, along with other patients testing positive for the c.276+2dup VUS in the *COL4A5* gene.

Conclusions

Case studies, such as the one presented here, demonstrate the cascade effect of genetic testing within families, offering crucial insights into disease inheritance and management. Despite challenges posed by VUSs, ongoing research and functional studies are essential for refining diagnostic criteria and enhancing treatment recommendations. As genetic testing continues to evolve, it has the potential to improve patient outcomes for patients with Alport syndrome and other genetic kidney diseases through early intervention and personalized care.

Authors' note

Portions of this manuscript were presented at the American Society of Nephrology Kidney Week, November 5, 2022.

Acknowledgements

None.

Author contributions

M.F. was responsible for conception of the project, data analysis, and critical review of the manuscript. T.T. was responsible for data collection and analysis, literature review, and writing of the manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

ORCID iD

Teresa Trinka https://orcid.org/0009-0008-0231-8836

References

1. Warady BA, Agarwal R, Bangalore S, et al. Alport syndrome classification and management. *Kidney Med* 2020; 2(5): 639–649.
2. Nozu K, Nakanishi K, Abe Y, et al. A review of clinical characteristics and genetic backgrounds in Alport syndrome. *Clin Exp Nephrol* 2019; 23(2): 158–168.
3. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015; 17(5): 405–424.
4. Chen S, Francioli LC, Goodrich JK, et al. A genomic mutational constraint map using variation in 76,156 human genomes. *Nature* 2024; 625(7993): 92–100.
5. Grunfeld JP. Hereditary renal diseases. *Saudi J Kidney Dis Transplant* 1997; 8(3): 227–234.
6. Rheault MN and Kashtan CE. Inherited glomerular diseases. In: Avner ED, Harmon WE, Niaudet P, et al. (eds.) *Pediatric nephrology*. Springer Berlin Heidelberg, 2016, pp.777–803.

7. Yamamura T, Nozu K, Fu XJ, et al. Natural history and genotype–phenotype correlation in female X-linked Alport syndrome. *Kidney Int Rep* 2017; 2(5): 850–855.
8. Jais JP, Knebelmann B, Giatras I, et al. X-linked Alport syndrome: natural history in 195 families and genotype- phenotype correlations in males. *J Am Soc Nephrol* 2000; 11(4): 649–657.
9. Jais JP, Knebelmann B, Giatras I, et al. X-linked Alport syndrome: natural history and genotype-phenotype correlations in girls and women belonging to 195 families: a "European community Alport syndrome concerted action" study. *J Am Soc Nephrol* 2003; 14(10): 2603–2610.
10. Bleyer AJ, Westemeyer M, Xie J, et al. Genetic etiologies for chronic kidney disease revealed through next-generation renal gene panel. *Am J Nephrol* 2022; 53(4): 297–306.
11. Gross O, Licht C, Anders HJ, et al. Early angiotensin-converting enzyme inhibition in Alport syndrome delays renal failure and improves life expectancy. *Kidney Int* 2012; 81(5): 494–501.
12. Mansilla MA, Sompallae RR, Nishimura CJ, et al. Targeted broad-based genetic testing by next-generation sequencing informs diagnosis and facilitates management in patients with kidney diseases. *Nephrol Dial Transplant* 2021; 36(2): 295–305.
13. Mallett AJ, McCarthy HJ, Ho G, et al. Massively parallel sequencing and targeted exomes in familial kidney disease can diagnose underlying genetic disorders. *Kidney Int* 2017; 92(6): 1493–1506.
14. Dahl NK, Bloom MS, Chebib FT, et al. The clinical utility of genetic testing in the diagnosis and management of adults with chronic kidney disease. *J Am Soc Nephrol* 2023; 34(12): 2039–2050.
15. Domingo-Gallego A, Pybus M, Bullich G, et al. Clinical utility of genetic testing in early-onset kidney disease: seven genes are the main players. *Nephrol Dial Transplant* 2022; 37(4): 687–696.
16. Savige J, Lipska-Zietkiewicz BS, Watson E, et al. Guidelines for genetic testing and management of Alport syndrome. *Clin J Am Soc Nephrol* 2022; 17(1): 143–154.
17. Savige J. Alport syndrome: deducing the mode of inheritance from the presence of haematuria in family members. *Pediatr Nephrol Berl Ger* 2020; 35(1): 59–66.
18. Pierides A, Voskarides K, Kkolou M, et al. X-linked, COL4A5 hypomorphic Alport mutations such as G624D and P628L may only exhibit thin basement membrane nephropathy with microhematuria and late onset kidney failure. *Hippokratia* 2013; 17(3): 207–213.