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Case Report

PERSISTENT MICROSCOPIC HEMATURIA IN A FEMALE ASSOCIATED WITH COL4A1GENE MUTAYION: A CASE REPORT

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Abstract: Background: Hereditary angiopathy, nephropathy, aneurysms, and muscle cramps (HANAC) syndrome is an autosomal dominant syndrome caused by mutations in COL4A1. COL4A1 gene mutation leads to a rare, multi-system disorder characterized by abnormal brain, eyes, kidneys, and blood vessels in muscles.

Case Presentation: We are presenting a 7-year-old child with this rare medical condition who presented with persistent microscopic hematuria and was diagnosed through genetic screening early in life. Although she had limited clinical presentation due to her early age, the genetic testing revealed a pathogenic mutation in the COL4A1 gene, which is a known cause of HANAC syndrome.

Conclusion: COL4A1 gene mutation should be suspected in patients with unexplained persistent hematuria, especially with a strong family history of the same complaint without a clear underlying reason. Early in-life diagnosis is important for prognosis, health monitoring, and management.

Keywords: HANAC syndrome; pediatric; persistent hematuria.

INTRODUCTION Hereditary angiopathy, nephropathy, aneurysms, and muscle cramps (HANAC) syndrome is an autosomal dominant syndrome caused by mutations in COL4A1[1]. COL4A1 encodes the α1 chain of collagen IV, a major component of basement membranes[1]. Type IV collagen is important in humans' glomerular basement membrane integrity [2]. COL4A1 gene mutation leads to a multi-system disorder. Findings and age of onset vary within and between families with a wide variety of renal manifestations, including isolated hematuria, renal cysts, and mild late-onset renal failure[3]. COL4A1-related disorders are rare, as fewer than 100 families have been described [3]. Diagnosis is based on clinical findings and molecular genetic testing of COL4A1 [3]. Management is mainly supportive of a multidisciplinary team approach.

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CASE PRESENTATION A 7-year-old girl was referred to the pediatric nephrology clinic with a main complaint of persistent microscopic hematuria. Hematuria was discovered incidentally through urine analysis due to a concern of urinary tract infection and persisted over time. Although her past medical history was unremarkable, her family history was significant for persistent microscopic hematuria in her paternal aunt. She was well-grown and non-dysmorphic on clinical examination, with stable vital signs and an unremarkable physical exam. Baseline tests were unremarkable, including full blood count and complete metabolic panel. Rheumatological/ autoimmune diseases workup, including Antinuclear Antibody panel, C3, C4, and anti-streptolysin O titer, were all within the acceptable ranges.

Renal ultrasound was significant for mild left pelviectasis. Because of normal renal function and undetectable proteinuria, and after a risk-benefit assessment, a plan was made to do genetic testing to identify the precise diagnosis and avoid doing a kidney biopsy. Genetic testing revealed a heterozygous pathogenic mutation in the COL4A1 gene, which is related to HANAC syndrome.

The syndrome has autosomal dominant inheritance. Its symptoms vary from muscle cramps and microhematuria that may manifest from early in childhood to sometimes until later in life.

Genetic Variants: In genetic testing, we observed an autosomal recessive heterozygous mutation (c.1730G>T) of COL4A1. This mutation disturbs the range of structural support functions (Table 1).

introduces a premature stop codon, likely leading to a truncated and non-functional integrin alpha-6 protein. This variant's pathogenic classification highlights its potential to contribute to pathological conditions, reinforcing the importance of genetic screening in individuals presenting with kidney disorders. The **TP53RK,** c.640A>C (p.Thr214Pro) variant has an unknown significance but is noteworthy due to the gene's role in regulating the tumor suppressor protein TP53. It is

Gene	Chromosome location	Variants	Amino acid changes	Zygosity	Inheritance	Significance
COL4A1	Chr13(NM_001845.6):	c.1730G>T	p. Gly577Val	Heterozygous	Autosomal Dominant	Likely pathogenic
ITGA6	Chr2(NM_000210.4):	c.2926C>T	p. Arg976*	Heterozygous	Autosomal Recessive	Likely pathogenic
TP53RK	Chr20(NM_033550.4)	c.640A>C	p. Thr214Pro	Heterozygous	Autosomal Recessive	Unknown
FATA4	Chr4(NM_024582.5)	c.10333G>A	p. Gly3445Arg	Heterozygous	Autosomal Recessive	Unknown
	Chr4(NM_024582.5)	c.12023A>C	p. His4008Pro	Heterozygous	Autosomal Recessive	Unknown
MAGI2	Chr7(NM_012301)	c.3686C>A	p. Thr1229Lys	Heterozygous	Autosomal Recessive	Unknown
NPHP4	Chr1(NM_015102.5)	c.1956C>T	p.?	Heterozygous	Autosomal Recessive	Unknown

Table 1: Details of genetic variants of the patient.

The variant c.1730G>T (p. Gly577Val) is classified as likely pathogenic due to its potential impact on the structural integrity of collagen IV, a crucial component of the basement membrane. This variant could disrupt the triple helical structure of collagen IV, leading to compromised basement membrane stability and increased susceptibility to glomerular disease. Given the heterozygous nature and autosomal dominant inheritance, individuals carrying this variant might be at risk if a second pathogenic variant is present. The c.2926C>T (p. Arg976*) variant of **ITGA6** involved in the phosphorylation of TP53, crucial for its activation and stabilization in response to DNA damage.

The identification of two heterozygous variants in FATA4, c.10333G>A (p.Gly3445Arg) and c.12023A>C (p.His4008Pro), presents an interesting case for further study. FATA4 is involved in transcriptional regulation during development, and mutations could potentially lead to developmental disorders of the GBM. The pathogenicity of these variants is currently unknown,

necessitating functional assays to determine their impact on gene expression and developmental processes. The c.3686C>A (p.Thr1229Lys) variant of **MAGI2 is** also of unknown significance. MAGI2 encodes a scaffolding protein involved in signaling and cell polarity during the development of the kidney. The p.Thr1229Lys variant may alter protein-protein interactions essential for synaptic function, but this requires confirmation through functional studies. The c.1956C>T variant in NPHP4, with an undetermined amino acid change, highlights the challenges of interpreting variants of unknown significance. NPHP4 mutations are linked to nephronophthisis, a ciliopathy affecting kidney function.

DISCUSSION Diagnosis of inherited medical conditions early in life is important for the patient's management and prognostic expectation, which needs to be discussed in genetic counseling. The child we presented had HANAC syndrome, which had limited clinical presentation due to the early age of onset. COL4A1 encodes the α1 chain of collagen IV, a major component of basement membranes [1]. Prevalence of COL4A1-related disorders cannot be established as fewer than 100 families have been described [3].

COL4A1-related disorders are inherited in an autosomal dominant manner. Most individuals diagnosed with COL4A1-related disorder have an affected parent. The proportion of cases caused by a de novo pathogenic variant is estimated at least 27% [3]. The patient, in our case, has a significant family history of persistent hematuria in her paternal aunt.

The classical presentations include muscle cramps, Raynaud phenomenon, kidney cysts, blood in the urine (typically not visible to the eye), leukoencephalopathy (a change in brain tissue that can be seen on MRI), retinal arterial tortuosity, headaches, and supraventricular arrhythmia [4].

A study done in the United Kingdom reported a novel frameshift mutation in COL4A1 in 20 family members, 17 of whom had confirmed hematuria and 5 of whom also had stage 4 or 5 chronic kidney disease [2]. This supports the fact that in our patient the mutation in the COL4A1 gene is related to her main complaint of hematuria.

COL4A1-related disorders vary widely and include neurological, ophthalmological, cardiological, and other systemic manifestations[3]. Presentations and systems involved vary between affected individuals. For example, as mentioned in a case report describing two patients aged one year and eight months with COL4A1 gene mutations who had convulsion, retinal arteriosclerosis, microscopic hematuria, and muscle cramps [5]. Another four affected individuals whose first manifestation of the disease was muscle cramps occurred in early childhood [6]. Minor ischemic stroke and bleeding complications with blood thinner use have been described as well [4].

There is no definitive treatment. Treatment is mainly supportive, using a multidisciplinary team approach, and includes practical help, emotional support, and counseling for affected individuals and their families.

Mutations in COL4A1 are traditionally associated with disorders affecting the vascular system, including cerebral small vessel disease [7]. However, COL4A1 is also a crucial component of the glomerular basement membrane in the kidneys. Variants in this gene can lead to defects in the collagen IV network, potentially causing Alport syndrome or other glomerulopathies [8]. The identified c.1730G>T (p.Gly577Val) variant may compromise the integrity of the glomerular basement membrane, resulting in proteinuria and progressive kidney disease [9]. While ITGA6 mutations are primarily linked to epidermolysis bullosa, integrins also play a vital role in renal glomeruli. Integrin alpha-6 partners with integrin beta-4 to form a receptor for laminin in the extracellular matrix, which is crucial for the structural integrity of the glomerular basement membrane [10]. The c.2926C>T (p.Arg976*) variant, resulting in a truncated integrin alpha-6 protein, could impair this interaction, potentially leading to glomerular basement membrane abnormalities and renal dysfunction [11]. Variants in COL4A1 and ITGA6 may disrupt the structural integrity of the glomerular basement membrane. This disruption can lead to defects and infiltration, resulting in proteinuria, hematuria, and progressive kidney disease[12]. Alport syndrome, caused by COL4A1 mutations, exemplifies how defects in basement membrane collagen can lead to renal pathology [9] (Figure 1).

Nephronophthisis is a ciliopathy characterized by chronic kidney disease, and mutations in NPHP4 are directly implicated in this condition [13]. The c.1956C>T variant identified in this study could disrupt the normal function

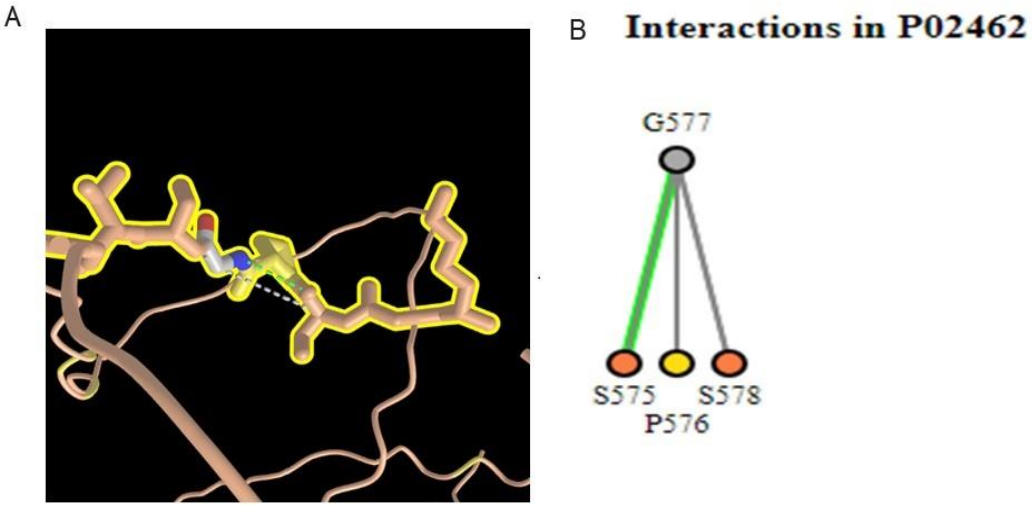

Figure 1: Effect of collagen variants on its structural stability. A) Interaction of mutant residue within the protein structure. B) The amino acid residues are involved in interaction with the mutated amino acid residue.

of NPHP4, leading to impaired ciliary function [14]. Cilia are essential for signaling pathways that regulate cell proliferation and differentiation in the kidneys[15]. Dysfunctional cilia due to NPHP4 mutations can lead to cyst formation and fibrosis, hallmark features of nephronophthisis [16].

It is also important to increase knowledge and widely introduce genetic testing in pediatric clinics for early diagnostic health management direction. The results of this study also have significant implications for genetic counseling. Individuals carrying likely pathogenic variants, such as those in COL4A1 and ITGA6, should receive genetic counseling to understand their risks and the potential implications for family members [11]. Moreover, personalized medicine approaches could be developed based on the specific genetic variants identified, leading to targeted therapies and improved management of inherited disorders [14].

CONCLUSION "HANAC syndrome" is a rare syndrome caused by mutations in the COL4A1 gene. COL4A1-related disorders vary widely and can include nephrological manifestations. Maintaining high suspicion may facilitate early diagnosis of the syndrome, especially in patients who present with persistent hematuria that other causes can't explain.

This study highlights the complex nature of genetic variants and their roles in disease. The identification of genetic variants in COL4A1, ITGA6, and NPHP4 highlights their potential role in kidney disease. Understanding these variants' pathogenic mechanisms is crucial for early diagnosis, personalized management, and the development of targeted therapies.

Declarations

Ethics approval and consent to participate

Written consent obtained from the patient's mother for publication of clinical details.

Consent for publication

Written consent obtained from the patient's mother for publication of clinical details.

Availability of data and materials

Not applicable.

Conflicts of interest

The authors declare that they have no competing interests.

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Authors' contributions

AH: Collected and interpreted the patient data regarding the case-related information and was a major contributor to writing the manuscript. MSI analyzed genetic data, explained, presented figures, and wrote partial manuscripts. TLV: Conceptualized, provided resources, patient communication, and final edited the manuscript; all authors read and approved the final manuscript.

REFERENCES

1. Chen Z, Migeon T, Verpont MC, Zaidan M, Sado Y, Kerjaschki D, Ronco P, Plaisier E. HANAC Syndrome Col4a1 Mutation Causes Neonate Glomerular Hyperpermeability and Adult Glomerulocystic Kidney Disease. J Am Soc Nephrol 2016, 27(4):1042-1054. doi: 10.1681/ASN.2014121217.
2. Gale DP, Oygar DD, Lin F, Oygar PD, Khan N, Connor TM, Lapsley M, Maxwell PH, Neild GH. A novel COL4A1 frameshift mutation in familial kidney disease: the importance of the C-terminal NC1 domain of type IV collagen. Nephrol Dial Transplant 2016, 31(11):1908-1914. doi: 10.1093/ndt/gfw051.
3. Plaisier E, Ronco P: COL4A1-Related Disorders. In: GeneReviews((R)). edn. Edited by Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A. Seattle (WA); 1993.
4. Srivastava S WA, Naidu S.: Alexander Disease. In: GeneReviews® [Internet]. edn. Edited by Adam MP FJ, Mirzaa GM, et al., editors. Seattle (WA): University of Washington, Seattle; 2024: 1993-2024.
5. Shan LD, Peng J, Xiao H, Wu LW, Duan HL, Pang N, Miriam K, Yin F: [Clinical features and COL4A1 genotype of a toddler with hereditary angiopathy with nephropathy, aneurysms and muscle cramps syndrome]. Zhongguo Dang Dai Er Ke Za Zhi 2019, 21(8):754-760. doi: 10.7499/j.issn.1008-8830.2019.08.004.
6. Haga S, Takeguchi R, Tanaka R, Satake A, Makita Y, Yanagi K, Kaname T, Takahashi S. Clinical characteristics of muscle cramps in hereditary angiopathy with nephropathy, aneurysms, and muscle cramps syndrome associated with a novel COL4A1 pathogenic variant: A family case study. Brain Dev 2023, 45(7):390-394. doi: 10.1016/j.braindev.2023.02.008.
7. Gould DB, Phalan FC, Breedveld GJ, van Mil SE, Smith RS, Schimenti JC, Aguglia U, van der Knaap MS, Heutink P, John SW. Mutations in Col4a1 cause perinatal cerebral hemorrhage and porencephaly. Science 2005, 308(5725):1167-1171. doi: 10.1126/science.1109418.
8. Plaisier E, Gribouval O, Alamowitch S, Mougenot B, Prost C, Verpont MC, Marro B, Desmettre T, Cohen SY, Roullet E et al. COL4A1 mutations and hereditary angiopathy, nephropathy, aneurysms, and muscle cramps. N Engl J Med 2007, 357(26):2687-2695.doi: 10.1056/NEJMoa071906.
9. Kashtan CE. Alport syndrome. An inherited disorder of renal, ocular, and cochlear basement membranes. Medicine (Baltimore) 1999, 78(5): 338-360.doi: 10.1097/00005792-199909000-00005.
10. Pozzi A, Zent R. Integrins in kidney disease. J Am Soc Nephrol 2013, 24(7):1034-1039. doi: 10.1681/ASN.2013010012.
11. Tryggvason K, Zhou J, Hostikka SL, Shows TB. Molecular genetics of Alport syndrome. Kidney Int 1993, 43(1):38-44. doi: 10.1038/ki.1993.8.
12. Van Agtmael T, Bruckner-Tuderman L. Basement membranes and human disease. Cell Tissue Res 2010, 339(1):167-188. doi: 10.1007/s00441-009-0866-y.
13. Hildebrandt F, Otto E. Molecular genetics of nephronophthisis and medullary cystic kidney disease. J Am Soc Nephrol 2000, 11(9):1753-1761. doi: 10.1681/ASN.V1191753.
14. Hildebrandt F, Benzing T, Katsanis N: Ciliopathies. N Engl J Med 2011, 364(16):1533-1543. doi: 10.1056/NEJMra1010172.
15. Dell KM. The role of cilia in the pathogenesis of cystic kidney disease. Curr Opin Pediatr 2015, 27(2):212-218. doi: 10.1097/MOP.0000000000000187.
16. Hildebrandt F, Attanasio M, Otto E. Nephronophthisis: disease mechanisms of a ciliopathy. J Am Soc Nephrol 2009, 20(1):23-35. doi: 10.1681/ASN.2008050456.