Genetics in Medicine (2025) 27, 101514

ELSEVIER

Genetics in Medicine
An Official Journal of the ACMG

www.journals.elsevier.com/genetics-in-medicine

ARTICLE

COL4A1 and COL4A2-related disorders: Clinical features, diagnostic guidelines, and management

Diana Tambala[1,2], Rachel Vassar[3], John Snow[1,4], Simona Balestrini[5,6], Anna Bersano[7], Stéphanie Guey[8], Eleonora Bonaventura[9], Sabrina Signorini[10,11], Stefano Sartori[12], Enrico Bertini[13], Davide Tonduti[9,14], Cecilia Parazzini[15], Marina Macchiaiolo[16], Maria Federica Pelizza[12], Anna Pichiecchio[17,18], Laura Massella[19], Thibault Coste[20,21], Simona Orcesi[11,17], Davide Politano[11,17], Giacomo Bacci[22], Elisa Marziali[22], Helene Dollfus[23], Anna Mandelli[24], Marcello Chinali[25], Emmanuelle Plaisier[26], Paolo Simioni[27], Raffaella Colombatti[28], Renzo Guerrini[5,6], Elisabeth Tournier-Lasserve[29,30], Douglas B. Gould[31,32,33,34], Patricia L. Musolino[1,2,4,*]

ARTICLE INFO

Article history:
Received 18 November 2024
Received in revised form
11 June 2025
Accepted 20 June 2025
Available online 2 July 2025

Keywords:
COL4A1
COL4A2
Delphi
Genotype-phenotype
Guidelines

ABSTRACT

Purpose: Collagen type 4 alpha 1 (COL4A1) and alpha 2 (COL4A2) chains, encoded by *COL4A1* and *COL4A2*, are essential for basement membrane integrity, contributing to structural stability and cell regulation. Pathogenic variants in these genes cause a spectrum of autosomal dominant and, more rarely, autosomal recessive disorders, which are collectively known as COL4A1/A2-related disorders. These multisystem disorders can include neurologic, ophthalmologic, renal, and other organ system pathology and vary widely in symptoms, complicating diagnosis and management.

Methods: Using a modified eDelphi method, we obtained consensus from international experts across medical subspecialties on the evaluation and management of COL4A1/A2-related disorders, with consensus set at ≥70% agreement.

Results: Consensus was achieved on recommendations for evaluating and managing these conditions.

Conclusion: Genetic testing and counseling are advised for individuals showing symptoms of COL4A1/A2-related disorders and for at-risk relatives. Given the complexity and rarity of these disorders, management requires a multidisciplinary approach informed by current understanding of disease mechanisms. Recommended care includes neurological and ophthalmological imaging and monitoring of cardiovascular and renal function. Ongoing research is critical to uncover genotype-phenotype links and potential modifiers, with clinical research participation encouraged to advance knowledge and treatments.

The Article Publishing Charge (APC) for this article was paid by Patricia L. Musolino.

Diana Tambala and Rachel Vassar are co-first authors.

*Correspondence and requests for materials should be addressed to Patricia L. Musolino, Pediatric Stroke and Cerebrovascular Program, Department of Neurology, Harvard Medical School, 185 Cambridge St, Suite 5248, Boston, MA 02214. *Email address:* pmusolino@mgh.harvard.edu

Affiliations are at the end of the document.

doi: https://doi.org/10.1016/j.gim.2025.101514

Introduction

Basement membranes are a specialized form of extracellular matrix that are essential biologic structures, covering all basal endothelial and epithelial surfaces. Mature collagen type 4, a critical part of all basement membranes, is a heterotrimer classically composed of 2 alpha 1 chains and 1 alpha 2 chain. These subunit proteins are respectively encoded by *COL4A1* (HGNC:2202, OMIM 120130) and *COL4A2* (HGNC:2203, OMIM 120090), genes that are tightly linked on a shared locus of human chromosome 13. Pathogenic variants in these genes underlie COL4A1/A2-related disorders, an entity with multisystem involvement and highly variable expressivity.[1]

Collagen type 4 alpha 1 and alpha 2 are proteins with shared structure, comprising a large triple-helical domain defined by repeats of highly conserved glycine residues in Gly-X-Y motifs flanked by noncollagenous domains at the carboxy and amino termini (called NC1 and 7S domains, respectively). Missense variants affecting these glycine residues are the most common class of pathogenic variants[2]; however, other classes, including splicing perturbations, premature stop codons, structural defects (deletions or duplications), and variants involving NC1 domain, have been reported. Variants involving nonglycine residues are also described, but interpretation of their causality requires caution and deserves additional research. Most pathogenic variants are de novo and autosomal dominant; however, recessive inheritance and reduced penetrance are also reported.[3,4] Phenotypic variability and incomplete penetrance in COL4A1/A2-related disorders may be shaped by both genetic and environmental factors, with studies in model organisms highlighting the roles of modifier genes and allelic heterogeneity.[5] Notably, allelic heterogeneity extends to an important class of noncoding variants, whereby single-nucleotide mutations or alleles with Alu elements can cause highly penetrant cerebrovascular small-vessel disease (cSVD) mediated by derepression of *COL4A1* expression.[6,7]

Clinically, COL4A1/A2-related disorders are primarily characterized by cerebrovascular disease, ocular dysgenesis, skeletal myopathy, and nephropathies; however, other organs can also be affected. Among the neurological manifestations, the most typical involves cSVD with predominant hemorrhagic expression[8] characterized by a highly variable severity and age at onset, from the fetal period to adulthood. Malformations of cortical development (mainly unilateral schizencephaly and polymicrogyria, secondary to early fetal cerebrovascular events), and intracranial aneurysms may also be encountered. Ophthalmologically, patients can develop eye defects (congenital cataracts,[9] retinal arterial tortuosity,[10] and anterior segment anomaly of Axenfeld) of variable penetrance and expression. Further systemic findings may include muscle cramps and/or elevated serum creatine kinase (CK) and kidney involvement characterized by renal cysts of capsular origin, hematuria, proteinuria, and renal failure. Cardiovascular and hematological manifestations may occur, including Raynaud phenomenon, cardiac arrhythmias, and neonatal hemolytic anemia. As research and clinical care evolves, abnormalities and associations linked to these variants continue to emerge and the full spectrum of disease is still only partially understood.

The syndromes caused by pathogenic variants in *COL4A1* and *COL4A2* and are often considered part of a single disease spectrum because they affect the same protein heterotrimer. However, observations suggest potentially relevant differences between syndromes attributed to either *COL4A1* and *COL4A2* variants, particularly regarding inheritance patterns and disease severity. For example, pathogenic variants in *COL4A1* are frequently de novo and associated with more severe phenotypes, such as schizencephaly and early-onset epileptic encephalopathy. In contrast, several *COL4A2* variants appear to be inherited, often from asymptomatic or mildly affected parents.[11] These observations are based on relatively small cohorts, however, and further research is required to fully elucidate genotype-phenotype correlations. High clinical heterogeneity, even among members of the same family, further complicates the complex management and care for individuals with COL4A1/A2-related disorders.

Current expert opinion acknowledges the following clinical syndromes associated with pathogenic variants in COL4A1 and COL4A2:

- Autosomal dominant familial porencephaly type 1 (OMIM175780)
- Autosomal dominant brain small vessel disease with hemorrhage (OMIM 175780)
- Hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC) syndrome[12] (OMIM 611773)
- Isolated retinal artery tortuosity and/or congenital cataract
- Pontine autosomal dominant microangiopathy and leukoencephalopathy (PADMAL)[12] (OMIM 618564)
- *COL4A1* and *COL4A2* copy-number duplications/triplications leading upregulation of these genes and cSVD

PADMAL represents a distinct stereotyped adult-onset cSVD[12] phenotype, presenting differently than other COL4A1/A2-related disorders with an early adult onset (35-45 years old) and evidence of recurrent small pontine infarcts, hemispheric lacunar infarcts, vascular leukoencephalopathy,[3,13,14] cervical spine ischemic lesions, and absence of cerebral hemorrhages. Recent studies have identified variants in the 3′ untranslated region of *COL4A1* (NM_001845) in PADMAL patients, including variants that disrupt miR-29 microRNA binding, leading to overproduction of collagen 4 in this syndrome.[15,16]

This document summarizes the current knowledge about COL4A1/A2-related disorders and their underlying pathophysiology, clinical manifestations, and management based

on genereviews,[1] peer-reviewed publications,[17] and international expert consensus established at the 2024 1st COL4A1-COL4A2 European Conference (19.02.2024, Rome, Italy) and subsequent modified Delphi consensus survey. These recommendations aim to bridge the gaps between published research and clinical practice, while acknowledging that future research will continue to inform clinical management.

Materials and Methods

This study used a modified eDelphi consensus process to develop expert recommendations on COL4A1/A2-related disorders in pediatric and adult populations. The process began with a roundtable discussion on 19 February 2024, during the 1st COL4A1-COL4A2 European Conference in Rome, Italy, where open, focused discussions were held by pediatric and adult specialists with expertise in COL4A1-COL4A2 related disorders. Represented specialties included neurology, cardiology, hematology, nephrology, neuroimaging, clinical genetics, neuropsychology, ophthalmology, pediatric oncology, internal medicine, neuromuscular, and parent advocates from the Associazione Famiglie COL4A1-A2. These recommendations were extensively discussed and deliberated upon by the group of authors before the formal eDelphi process, ensuring that all included items had already achieved relatively high consensus.

The modified eDelphi consensus was executed in July 2024 using an anonymized online survey in a single round, in which participants were asked to respond "Yes" or "No" to indicate agreement or disagreement with statements on clinical features, diagnosis, and management strategies initially drafted during the round table discussions. Participants included those present at the initial roundtable, as well as additional researchers and clinicians selected for their expertise in COL4A1/A2-related disorders. Consensus was predefined as ≥70% agreement, and statements that reached consensus were included in the final recommendations, whereas areas lacking consensus were noted for further investigation. Participation in this study was voluntary, and informed consent was implied by completion of the anonymous online survey. Institutional Review Board approval was not sought because the study involved expert panel discussions and surveys conducted under professional settings without patient data.

Results

Modified eDelphi process

Thirty-one individuals were contacted for participation in the eDelphi consensus, and 26 of 31 (84%) participated. International experts included pediatric and adult neurologists ($n = 14$), neuroradiologists ($n = 2$), geneticist ($n = 1$), ophthalmologist ($n = 1$), cardiologist ($n = 1$), nephrologists ($n = 2$), hematologist ($n = 1$), intensivist ($n = 2$), and nonclinician researchers ($n = 2$). Results of the eDelphi consensus survey can be found in Supplemental Table 1. Any edits made to the final version of the recommendations from the original survey were solely for clarity or brevity, with no material changes to the content.

Discussion

Diagnostic Strategy—Indications for *COL4A1* and *COL4A2* genetic testing

Genetic testing is recommended for patients who exhibit 2 or more of the following clinical symptoms. It should also be considered for fetal and neonatal patients who display any one of these manifestations without an alternative cause.

Fetal/neonatal/pediatric patients

1. Disorders of structural brain development including anencephaly, polymicrogyria, schizencephaly, porencephaly, periventricular nodular heterotopias, hypoplasia/agenesis of corpus callosum, and/or cerebellar hypoplasia[18-23]
2. Epilepsy or infantile spasms and associated structural brain abnormality
3. Intracerebral hemorrhage in absence of underlying vascular malformation, inherited platelet disorder, or coagulation disorder[24,25]
4. Periventricular leukomalacia-like pattern of brain injury in nonpreterm children[13,14]
5. Intracranial calcifications (may be identified on head CT or susceptibility-weighted imaging on brain magnetic resonance imaging [MRI])[26]
6. Bilateral white matter hyperintensities/abnormalities, unexplained white matter hyperintensities[27]
7. Pediatric stroke and neonatal stroke[28] due to small vessel alteration[29] or medullary vein congestion
8. Unexplained, episodic irritability suggestive of muscle cramps with increased CK
9. Congenital anomalies of the anterior segment of eye, cataract, glaucoma, optic nerve atrophy, retinal arterial tortuosity[18,19]
10. Jaundice and hemolytic anemia at birth.
11. First-degree relatives with known *COL4A1/A2* variant, high CK, hematuria, early cSVD, glaucoma and/or Axenfeld-Rieger Syndrome (after consideration of personal preferences, adherence to local regulations, and approval if needed from relevant ethics committees)

Adults

1. Ischemic brain lesions in multiple vascular territories and/or various ages in the absence of vascular risk factors[30]
2. Pontine ischemic injury in young patients (<65 years) and/or in absence of risk factors[31]

3. Subcortical intraparenchymal hemorrhage(s) of unknown cause, especially in young patients with well-controlled or no known vascular risk factors[12,30]
4. MRI markers of cSVD[32] (leukoencephalopathy with presence or absence of deep microbleeds, old or acute small deep or subcortical infarcts, dilated perivascular spaces involving deep nuclei, or hemispheric white matter) discordant with vascular risk factors
5. Intracranial porencephalic cavity or ventricular cyst[33]
6. Multiple intracranial carotid or vertebrobasilar system aneurysms[34] or dolichoectasia (if not high suspicion or diagnosis of alternative genetic cause, such as *PKD1/2*, Fabry's, or Loews-Dietz's syndrome)
7. Suggestive extraneurological manifestations involving the kidney (renal cysts, hematuria, proteinuria, and renal failure of unexplained origin), eye (Axenfeld-Rieger malformation,[35] early-onset cataract or glaucoma, retinal hemorrhage, and retinal arterial tortuosity), and/or muscle (unexplained cramps or myalgia and rhabdomyolysis)
8. Strong family history of any of the above symptoms

Initial work-up for suspected COL4A1/A2

1. *COL4A1* and *COL4A2* genetic testing may be performed using direct gene sequencing, panels inclusive of *COL4A1* and *COL4A2* (cerebral small vessel disease panel, epilepsy gene panel, and leukodystrophy panels) or exome/genome sequencing. Genome sequencing is recommended in patients with a negative panel or exome if there is high suspicion for COL4A1/A2-related disorder given symptoms ± family history because several intronic pathogenic variants exist. Preferred method of genetic testing may vary based on local clinical practice and testing accessibility, but *COL4A1* and *COL4A2* variants should be included in any panel-based testing for patients with compatible symptoms.
2. Detailed family history to identify relatives of the proband at risk, specifically regarding early-onset cerebrovascular disease, cerebral palsy, early-onset dementia, cerebral palsy, eye abnormalities, muscle cramps, hematuria, kidney failure, and recurrent miscarriage
3. Neuroimaging, preferably brain MRI/magnetic resonance angiography (MRA) and MRA of the neck
4. Ophthalmologic evaluation

Subsequent work-up of suspected or confirmed COL4A1/A2-related disorder

1. Serum labs including creatine phosphokinase levels, standard coagulation tests
2. Urinalysis, renal ultrasound
3. Cardiovascular screening including blood pressure evaluation, electrocardiogram, and echocardiogram
4. Skin fibroblast sampling might be considered for evaluation of *COL4A1* or *COL4A2* expression levels to interpret a variant of uncertain significance.

Specific diagnostic rates for *COL4A1* and *COL4A2* variants across each phenotype are not yet known because of phenotypic variability and limited access to genetic testing until recent years. This is an important area for future research, and we recommend further epidemiology studies to improve the understanding of overall prevalence of COL4A1/A2-related disorders.

Clinical features and management by systems

These consensus statements aim to provide recommendations for clinical management of individuals with either confirmed or highly suspected *COL4A1* or *COL4A2* variants. These recommendations may not be applicable to individuals with PADMAL because consensus on its clinical management has not yet been established. Care for an individual with a *COL4A1* or *COL4A2* variant requires a multidisciplinary health care team involving neurologists, ophthalmologists, nephrologists, and other specialists to address the diverse manifestations. Encouraging individuals and families affected by COL4A1/A2-related disorders to participate in research studies and clinical trials may contribute to the understanding of the condition and potentially advance treatment options.

Neurologic/cerebrovascular

COL4A1 and *COL4A2* variants cause a broad spectrum of cerebrovascular disease,[36] with variable onset from fetal life to adulthood. The timing of the cerebrovascular insult during different life stages (fetal, perinatal, pediatric, or adult) influences the clinical presentation of neurologic symptoms. Fetal presentation[22,37] of disease includes intracranial hemorrhage,[25] hydrocephalus,[21] hypoplasia/agenesis of corpus callosum, schizencephaly, or porencephalic cysts, identified on fetal ultrasound[33] or brain MRI.[11] In older patients, diffuse cSVD is the most common pattern of brain injury associated with COL4A1/A2-related disorders, including bilateral confluent or patchy periventricular leukomalacia-like white matter hyperintensities with anterior circulation predilection.

Neurologic symptom burden in these patients is highly variable between affected individuals and can include global developmental delay evolving into intellectual disability, other neurodevelopmental disorders (language disorders, learning disorders, and autism spectrum disorder), pyramidal and/or extrapyramidal motor abnormalities, epilepsy, intracranial aneurysms,[34] migraines, visual impairment, behavioral difficulties, and/or cognitive decline. A feature of the clinical picture that may often be present in pediatric patients is the simultaneous presence of visual impairment of central origin (due to brain malformations or lesions) and peripheral origin (due to ophthalmological abnormalities). Individuals may have a discrepancy between the clinical history and extent of brain damage (eg, minimal, or absent symptoms but notable structural brain abnormalities or injury).

Recommendations

1. At diagnosis, individuals should undergo screening neuroimaging (MRI/MRA head and neck preferred). Frequency of imaging has not been established; however, it is reasonable to perform screening imaging in infancy, adolescence, and then at regular intervals in adulthood (every 5 years, unless aneurysm is observed, in which case more frequent screening is advised).
2. Neuroimaging should include vessel imaging to assess for aneurysms and susceptibility-weighted imaging to assess for microhemorrhages or calcifications. Use established "stroke protocol" imaging when available, including, diffusion-weighted and susceptibility-weighted sequences, T2 FLAIR, and MRA imaging.[38]
3. If intracranial aneurysms are present, consider screening chest/abdomen/pelvis vasculature for presence of additional aneurysms.
4. For management of unruptured intracranial aneurysms, safety of endovascular procedures is not well established, but extra caution may be advised, similar to that in other collagen vascular conditions.
5. Provide anticipatory guidance regarding potential for epileptic seizures. Epilepsy should be managed based on the electroclinical presentation because no specific medication regimens have been established for epilepsy associated with COL4A1/A2-related disorders.
6. Aggressive management of additional cerebrovascular risk factors, particularly preventing elevated blood pressure and recommendation against smoking/sympathomimetic use, treatment of hypercholesterolemia, diabetes, and/or obesity.
7. There is no specific evidence for use of antithrombotic agents for primary or secondary stroke prevention (see Hematologic section for additional recommendations regarding antithrombotic safety and use).
8. Avoid high-intensity, prolonged physical activities and sports predisposing to high-risk for head injury because increased risk for provoked intracranial hemorrhage or other cerebrovascular events have been observed.
9. Providing emotional support and counseling is an essential aspect of supportive care for affected individuals and their families.

Specific fetal/pediatric considerations:

1. In cases of fetal intracranial abnormalities, such as cerebral hemorrhages of unknown cause identified on ultrasound, evaluate further with fetal brain MRI.
2. Counsel regarding potential for infantile spasms and treat promptly given high prevalence in infants with COL4A1/A2-related disorder. Maintain a low threshold for obtaining an electronencephalogram, particularly in the setting of developmental regression or paroxysmal episodes suggestive of seizure.

Other recommendations:

1. Prolonged recovery from anesthesia and complications during anesthetic events have been reported. Further investigation of the cause of these complications is ongoing, but consultation with anesthesiologists before any procedure and notification about specific genetic variants is advised. Anesthesiologists may consider strict peri-procedural blood pressure support to avoid hypotension.

Neuro-ophthalmologic

In COL4A1/A2-related disorders, brain areas involved in visual processing can lead to cerebral visual impairment (CVI), a broad term for brain-related visual problems.[39] These disorders are often linked with ophthalmological symptoms due to *COL4A1* or *COL4A2* variants. CVI is a visual dysfunction not attributed to anterior visual pathway issues[40] but related to damage or malfunction in the central visual system. CVI presents a range of visual impairments, including decreased acuity, contrast sensitivity issues, visual field defects, and cognitive dysfunctions; oculomotor disorders and fluctuating visual attention may also occur.[41] Symptoms may evolve over time because of brain maturation and adaptive neuroplasticity, especially in early life.

Recommendations

1. Early, multidisciplinary evaluation of visual function for prompt CVI diagnosis and treatment planning
2. Continuous monitoring and effective habilitation strategies for visual functions to support development
3. Strategies and environmental modifications tailored to the child's visual and overall profile should be shared with caregivers to support the child's development and adaptation in daily life.

Ophthalmologic

Ophthalmological manifestations are observed in a subset of COL4A1/A2-related disorders. Three distinct ocular features have been reported, as summarized below.

Bilateral retinal arterial tortuosity is variably present in individuals with cSVD related to pathogenic COL4A1 or COL4A2 variants[10] and can occur as the singular manifestation. A fundus examination may reveal significant tortuosity in the second- and third-order retinal arteries, whereas the first-order arteries and retinal veins appear normal. Fluorescein angiography typically shows no leakage or staining. Individuals affected by this condition may experience temporary episodes of visual loss, often due to spontaneous retinal hemorrhage or after minor stress or trauma.

Congenital or acquired cataract[9] may occur as a standalone ocular condition or be linked to other anterior segment eye abnormalities, such as Axenfeld-Rieger anomaly, in families with cSVD and porencephaly.

Axenfeld-Rieger anomaly[35] is a form of anterior segment dysgenesis, encompassing a range of ocular features that affect the anterior chamber. These can include congenital iris malformations, posterior embryotoxon, microcornea, and, in some cases, glaucoma.

Recommendations

1. Baseline screening ophthalmologic examination, including dilated indirect ophthalmoscopy, to assess for retinal vessel tortuosity and/or hemorrhages, and slit lamp examination, followed by further ophthalmologic evaluations according to the severity of clinical findings
2. Deeper ophthalmological evaluations may be performed as appropriate for age and level of cooperation, including best corrected visual acuity, intraocular pressure measurements and, where possible, optical coherence tomography
3. Counsel regarding transient visual loss which warrants urgent ophthalmology evaluation to identify possible retinal hemorrhage
4. Monitoring and management of identified ophthalmologic complications per standard guidelines

Cardiovascular

Manifestations that may occur in patients with *COL4A1* or *COL4A2* variants include supraventricular arrhythmia, mitral valve prolapse with associated mitral valve insufficiency, systemic hypertension, septal defects, coronary artery aneurysms or dissection, spontaneous coronary artery dissection, congenital heart defects, and/or Raynaud phenomenon.

Recommendations

1. Baseline electrocardiogram and transthoracic echocardiogram in all patients
2. In patients with history of syncope and/or palpitations, consider longer-duration, portable cardiac monitoring
3. In adolescence and adulthood, consider stress tests
4. Evaluation and close blood pressure monitoring with strict avoidance of hypertension (in adults, goal: <130/80; in children, goal <95th percentile for age)

Hematologic

Some patients may present with hemolytic anemia, especially in neonates with concomitant neonatal hyperbilirubinemia[42] and/or hemorrhagic stroke. In general, the use of fibrinolysis is not recommended in acute small deep ischemic lesions in patients with genetic cerebrovascular conditions, such as COL4A1/A2-related disorders and associated cSVD; however, its safety has not been studied specifically. Acute thrombolysis may be safe on a case-by-case basis in context of large artery occlusion in patients with no history of intracranial hemorrhage,[43] but further research is warranted to identify potential risk versus benefit.

Recommendations

1. Antiplatelet and anticoagulant treatments are generally not recommended for primary or secondary cardiovascular or cerebrovascular prevention in patients COL4A1/A2-related disorders. However, risks and benefits should be discussed with a multidisciplinary team in cases of ischemic stroke, in the absence of previous intracranial hemorrhage, or in presence of a strong indication (eg, coronary artery disease).[43]
2. Safety of intravenous thrombolysis has not been investigated in individuals with COL4A1/A2-related disorders. Safety of medications and supplements that may influence platelet aggregation and/or coagulation pathways have not been formally evaluated in these population, but occasional use of non-steriodal anti-inflammatory drugs has been reported as tolerated.

Genito-urinary system

Individuals with COL4A1/A2-related disorders may exhibit isolated microscopic hematuria along with occasional episodes of gross hematuria. A detailed examination of renal biopsy samples can reveal irregular and abnormal thickening of the basement membranes in structures such as tubules, Bowman's capsule, and interstitial capillaries. Small renal cysts may be seen, though their presence is variable. Mild renal failure, which may or may not be accompanied by proteinuria or hypertension, can develop in individuals over the age of 50.[44]

Bilateral renal cysts are commonly found in individuals with HANAC syndrome and less commonly in those with the cSVD phenotype. In some families, renal cysts are the primary clinical feature, often accompanied by hematuria and a decline in glomerular filtration rate.[45]

Hematuria has been observed in individuals with cSVD, porencephaly and HANAC.[11]

Unilateral renal atrophy and vesico-ureteral reflux have been also reported.

Glomerular filtration rate decreases typically seen in individuals over 40 years old has also been noted in patients with HANAC. This often occurs alongside renal cysts and hematuria, without any involvement of the brain or other extracerebral areas.[45]

Recommendations

1. Baseline kidney and bladder US, urinalysis, serum creatinine concentration, and estimated glomerular filtration rate.
2. If COL4A1/A2-related disorder is diagnosed in childhood, consider repeating urinalysis and kidney ultrasound in adulthood or if symptomatic.
3. If albuminuria is present, assess a quantitative evaluation (urinary protein/creatinine ratio in children; in adults, urinary protein/creatinine or 24-hour urinalysis).
4. If proteinuria is present, refer the patient to a nephrologist for consideration of renin-angiotensin-aldosterone system blockade inhibition.
5. Refer to nephrologist also in cases of decreased kidney function, cystic kidney disease, and/or hypertension.

Specific pediatric considerations:

1. In case of microscopic or macroscopic hematuria with or without proteinuria, renal cysts, or blood pressure greater or equal to 95th percentile, refer the patients to a pediatric nephrologist.

Musculoskeletal system

Affected individuals may experience spontaneous, episodic muscle cramps in various muscles, often beginning in early childhood. These cramps can occur during periods of rest or in cold conditions. Electromyography typically does not reveal any specific abnormalities, and muscle biopsies are often normal.[5] Serum CK levels in affected individuals may be mildly elevated, but asymptomatic, and persist over time, although there have been rare instances of severe rhabdomyolysis leading to acute renal failure.[46]

Recommendations

1. Baseline measurement of serum CK.
2. Monitor for increasing fatigue or muscle pain/cramps as skeletal muscle involvement may occur later in life, and if present, counsel regarding exacerbation of symptoms in cold temperatures.
3. Continue aerobic exercise while avoiding strenuous, prolonged activities.
4. There is anecdotal evidence that medications that increase nitric oxide may improve muscle cramping, although further evaluation is necessary.
5. In severely neurologically compromised children, episodes of irritability, unexplained crying, or sleep disturbance should raise suspicion for muscle cramps.

Genetic counseling and family planning

Individuals diagnosed with COL4A1/A2-related disorders should receive genetic counseling to assess the risk of passing the condition to offspring and discuss family planning options. Pathogenic variants in *COL4A1* and *COL4A2* are most commonly inherited in an autosomal dominant pattern (50% risk of inheriting the variant for each child of a parent with *COL4A1/A2* variant). More research is needed to accurately characterize the proportion of cases that are caused by de novo variants, because existing estimates may be biased because of a variety of factors, including testing biases.[24,33,47]

Recommendations

1. Consultation with genetic counselor and geneticist, and if there exists a suspected fetal diagnosis of COL4A1/A2-related disorder, consider consultation with fetal/neonatal neurologist if available.
2. Delivery at a tertiary care center maybe considered and a high-risk pregnancy obstetric follow-up is highly recommend.
3. A cesarean delivery may be considered in a case-by-case basis when a mother or fetus has a known pathogenic *COL4A1* or *COL4A2* variant.

Conclusion

COL4A1/A2-related disorders represent a complex, rare group of genetic diseases characterized by a wide spectrum of multisystemic manifestations, primarily affecting the neurological, ocular, renal, and cardiovascular systems. These disorders result from pathogenic variants in *COL4A1* and *COL4A2*, which encode essential components of basement membranes. The phenotypic variability and incomplete penetrance of these conditions often complicate diagnosis, management, and prognostication.

Given the multisystemic nature of the disease, management requires a coordinated approach involving specialists from various fields. This was highlighted in the development of expert recommendations through a modified eDelphi consensus process, initiated at the 1st COL4A1-COL4A2 European Conference in February 2024. Specialists from neurology, cardiology, nephrology, and other relevant fields collaborated to draft guidelines using an anonymized online survey in July 2024, reaching a consensus on key clinical features, diagnosis, and management strategies.

Individualized treatment plans based on clinical presentation, regular monitoring, and supportive care are crucial for improving patient outcomes. Participation in natural history registries and eventual clinical trials is encouraged to advance knowledge about COL4A1/A2-related disorders.

Future research on COL4A1/A2-related disorders should focus on refining diagnostics, understanding disease progression, and exploring new therapeutic options as they emerge and are studied in mice.[48] There are several active areas of clinical research related to COL4A1/A2-related disorders, including the assessment of the safety of delivery methods (cesarean section vs vaginal), and tolerance of anesthesia events in individuals with *COL4A1/A2* variants. Natural history registries aim to better assess risk of cerebral and systemic aneurysms across the lifespan, prevalence of gastrointestinal motility issues, sleep apnea, and other poorly characterized symptoms reported in affected individuals. Despite being grouped under a common name, COL4A1/A2-related disorders exhibit such clinical heterogeneity that overall prognosis remains unclear, highlighting the need for studies on genotype-phenotype correlations and outcomes. In conclusion, COL4A1/A2-related disorders demand an integrated and vigilant approach for early diagnosis, comprehensive care, and ongoing research to address the clinical variability and improve long-term outcomes for affected individuals.

Data Availability

Data from the individual responses for the modified Delphi consensus will be made available upon request. The remainder of the content of the article is based on established clinical practice information, expert consensus, and literature review from cited references.

Acknowledgments

The authors are deeply grateful to Simona and Francesca Monodoro of the Associazione Famiglie COL4A1-A2 for organizing and facilitating the roundtable discussion at the COL4A1-A2 Conference held in Rome in February 2024.

Funding

This manuscript received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author Contributions

Study Conception and Design: D.T., R.V., J.S., S.B., A.B., S.G., E.B., S.S., E.B., D.T., C.P., M.M., M.F.P., A.P., L.M., T.C., S.O., D.P., G.B., E.M., H.D., A.M., M.C., E.P., P.S., R.C., R.G., E.T.-L., D.B.G., P.L.M.; Data Collection: D.T., R.V.; Analysis and interpretation of results: D.T., R.V.; Draft manuscript preparation: D.T., R.V., J.S., D.G., P.L.M.; Approval of the final version of the manuscript: D.T., R.V., J.S., S.B., A.B., S.G., E.B., S.S., E.B., D.T., C.P., M.M., M.F.P., A.P., L.M., T.C., S.O., D.P., G.B., E.M., H.D., A.M., M.C., E.P., P.S., R.C., R.G., E.T.-L., D.B.G., P.L.M.

Ethics Declarations

Participation in this study was voluntary, and informed consent was implied by completion of the anonymous online survey. Institutional Review Board approval was not sought because the study involved expert panel discussions and surveys conducted under professional settings without patient data.

Conflict of Interest

The authors declare no conflicts of interest.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gim.2025.101514) contains supplemental material, which is available to authorized users.

Affiliations

[1]Department of Neurology, Massachusetts General Hospital, Boston, MA; [2]Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA; [3]Department of Neurology, University of California San Francisco, San Francisco, CA; [4]Harvard Medical School, Boston, MA; [5]Neuroscience and Human Genetics Department, Meyer Children's Hospital IRCSS, Florence, Italy; [6]University of Florence, Florence, Italy; [7]Cerebrovascular Unit Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; [8]French Reference Center for Rare Vascular Diseases of the Brain and the Eye, Lariboisière Hospital, Paris, France; [9]Unit of Pediatric Neurology, C.O.A.L.A (Center for diagnosis and treatment of leukodystrophies), V. Buzzi Children's Hospital, Milan, Italy; [10]Developmental Neuro-Ophthalmology Unit, Child Neurology and Psychiatry Unit, IRCCS Mondino Foundation, Pavia, Italy; [11]Child Neurology and Psychiatry Unit, IRCCS Mondino Foundation, Pavia, Italy; [12]Pediatric Neurology and Neurophysiology Unit, Department of Women's and Children's Health, University of Padua, Padua, Italy; [13]Research Unit of Neuromuscular Disease, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy; [14]Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy; [15]Pediatric Radiology and Neuroradiology Department, Children's Hospital V. Buzzi, Milan, Italy; [16]Rare Diseases and Medical Genetics Unit, University-Hospital Pediatric Department (DPUO), Bambino Gesù Children's Hospital, IRCCS, Rome, Italy; [17]Department of Brain and Behavioral Sciences, University of Pavia, Italy; [18]Neuroradiology Department, IRCCS Mondino Foundation, Pavia, Italy; [19]Division of Nephrology, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy; [20]Department of Neurovascular Genetics, AP-HP, Paris, France; [21]Université Paris Cité, Inserm, NeuroDiterot, Paris, France; [22]Pediatric Ophthalmology Unit, Meyer Children's Hospital IRCCS, Florence, Italy; [23]ERN-EYE Centre de Référence Pour les Affections Rares en Génétique Ophtalmologique (CRMR CARGO), Institut de Génétique Médicale d'Alsace (IGMA), FSMR SENSGENE, Hôpitaux Universitaires de Strasbourg, Université de Strasbourg, Strasbourg, France; [24]Department of Pediatric Anesthesiology and Reanimation, "Vittore Buzzi" Children's Hospital, Milan, Italy; [25]Echocardiography Laboratory of the Department of Pediatric Cardiology and

Cardiac Surgery, Pediatric Hospital Bambino Gesù, Rome, Italy; [26]Department of Nephrology, Association pour l'Utilisation du Rein Artificiel Paris Plaisance, Paris, France; [27]General Internal Medicine and Thrombotic and Hemorrhagic Unit, Department of Medicine, University Hospital of Padova, Padova, Italy; [28]Pediatric Oncology Hematology Unit, Department of Women's and Children's Health, University of Padua, Padua, Italy; [29]Department of Neurovascular Molecular Genetics AP-HP, Saint-Louis Hospital, Paris, France; [30]Reference Center for Rare Vascular Diseases of the Central Nervous System and the Retina (CERVCO), APHP Lariboisière Hospital, Paris, France; [31]Departments of Ophthalmology and Anatomy, University of California San Francisco, San Francisco, CA; [32]Cardiovascular Research Institute, University of California San Francisco, San Francisco, CA; [33]Aging Research Institute, University of California San Francisco, San Francisco, CA; [34]Institute for Human Genetics, University of California San Francisco, San Francisco, CA

References

1. Plaisier E, Ronco P. In: Adam MP, et al., eds. *GeneReviews(®) [Internet]*. University of Washington Seattle; 2024.
2. Jeanne M, Gould DB. Genotype-phenotype correlations in pathology caused by collagen type IV alpha 1 and 2 mutations. *Matrix Biol*. 2017;57-58:29-44. http://doi.org/10.1016/j.matbio.2016.10.003
3. Yaramis A, Lochmüller H, Töpf A, et al. COL4A1-related autosomal recessive encephalopathy in 2 Turkish children. *Neurol Genet*. 2020;6(1):e392. http://doi.org/10.1212/NXG.0000000000000392
4. Nicita F, Aiello C, Carboni A, Longo D, Bertini E, Travaglini L. Leukoencephalopathy with spot-like calcifications caused by recessive COL4A2 variants. *Clin Neurol Neurosurg*. 2023;225:107584. http://doi.org/10.1016/j.clineuro.2022.107584
5. Labelle-Dumais C, Schuitema V, Hayashi G, et al. COL4A1 mutations cause neuromuscular disease with tissue-specific mechanistic heterogeneity. *Am J Hum Genet*. 2019;104(5):847-860. http://doi.org/10.1016/j.ajhg.2019.03.007
6. Verdura E, Hervé D, Bergametti F, et al. Disruption of a miR-29 binding site leading to COL4A1 upregulation causes pontine autosomal dominant microangiopathy with leukoencephalopathy. *Ann Neurol*. 2016;80(5):741-753. http://doi.org/10.1002/ana.24782
7. Aloui C, Neumann L, Bergametti F, et al. An AluYa5 insertion in the 3′UTR of COL4A1 and cerebral small vessel disease. *JAMA Netw Open*. 2024;7(4):e247034. http://doi.org/10.1001/jamanetworkopen.2024.7034
8. Kuuluvainen L, Mönkäre S, Kokkonen H, et al. COL4A1 and COL4A2 duplication causes cerebral small vessel disease with recurrent early onset ischemic strokes. *Stroke*. 2021;52(10):e624-e625. http://doi.org/10.1161/STROKEAHA.120.033864
9. Yakabe A, Ikuse T, Ito N, et al. A COL4A1 variant in a neonate with multiple intracranial hemorrhages and congenital cataracts. *Hum Genome Var*. 2022;9(1):24. http://doi.org/10.1038/s41439-022-00199-5
10. Zenteno JC, Crespí J, Buentello-Volante B, et al. Next generation sequencing uncovers a missense mutation in COL4A1 as the cause of familial retinal arteriolar tortuosity. *Graefes Arch Clin Exp Ophthalmol*. 2014;252(11):1789-1794. http://doi.org/10.1007/s00417-014-2800-6
11. Meuwissen MEC, Halley DJJ, Smit LS, et al. The expanding phenotype of COL4A1 and COL4A2 mutations: clinical data on 13 newly identified families and a review of the literature. *Genet Med*. 2015;17(11):843-853. http://doi.org/10.1038/gim.2014.210
12. Guey S, Hervé D. Main features of COL4A1-COL4A2 related cerebral microangiopathies. *Cereb Circ Cogn Behav*. 2022;3:100140. http://doi.org/10.1016/j.cccb.2022.100140
13. Roos J, Müller S, Giese A, et al. Pontine autosomal dominant microangiopathy with leukoencephalopathy: Col4A1 gene variants in the original family and sporadic stroke. *J Neurol*. 2023;270(5):2631-2639. http://doi.org/10.1007/s00415-023-11590-9
14. Robinson LJ, Sudarshan D, Goold E, et al. A novel, pathogenic COL4A1 missense variant involving thrombotic microangiopathic leukoencephalopathy in a neonate. *J Neuropathol Exp Neurol*. 2023;82(10):880-883. http://doi.org/10.1093/jnen/nlad057
15. Li Q, Wang C, Li W, et al. A novel mutation in COL4A1 gene in a Chinese family with pontine autosomal dominant microangiopathy and leukoencephalopathy. *Transl Stroke Res*. 2022;13(2):238-244. http://doi.org/10.1007/s12975-021-00926-0
16. Sakai N, Uemura M, Kato T, et al. Hemorrhagic cerebral small vessel disease caused by a novel mutation in 3′ UTR of collagen type IV alpha 1. *Neurol Genet*. 2020;6(1):e383. http://doi.org/10.1212/NXG.0000000000000383
17. Gasparini S, Balestrini S, Saccaro LF, et al. Multiorgan manifestations of COL4A1 and COL4A2 variants and proposal for a clinical management protocol. *Am J Med Genet C*. 2024;196(4):e32099. http://doi.org/10.1002/ajmg.c.32099
18. Khan AO. col4a1 mutations in two infants with congenital cataracts and porencephaly: an ophthalmologic perspective. *J AAPOS*. 2019;23(6):362. http://doi.org/10.1016/j.jaapos.2019.07.002
19. Alavi MV, Mao M, Pawlikowski BT, et al. Col4a1 mutations cause progressive retinal neovascular defects and retinopathy. *Sci Rep*. 2016;6:18602. http://doi.org/10.1038/srep18602
20. Cavallin M, Mine M, Philbert M, et al. Further refinement of COL4A1 and COL4A2 related cortical malformations. *Eur J Med Genet*. 2018;61(12):765-772. http://doi.org/10.1016/j.ejmg.2018.10.004
21. Straka B, Vlčková M, Libá Z, et al. COL4A1 mutation-related disorder presenting as fetal intracranial bleeding, hydrocephalus, and polymicrogyria. *Epilepsia Open*. 2023;8(1):211-216. http://doi.org/10.1002/epi4.12681
22. Brock S, Michotte A, Doné E, et al. Novel variant in COL4A1 causes extensive prenatal intracranial hemorrhage and porencephaly. *J Neuropathol Exp Neurol*. 2021;80(8):807-810. http://doi.org/10.1093/jnen/nlab026
23. Takenouchi T, Ohyagi M, Torii C, Kosaki R, Takahashi T, Kosaki K. Porencephaly in a fetus and HANAC in her father: variable expression of COL4A1 mutation. *Am J Med Genet A*. 2015;167A(1):156-158. http://doi.org/10.1002/ajmg.a.36823
24. Maurice P, Guilbaud L, Garel J, et al. Prevalence of COL4A1 and COL4A2 mutations in severe fetal multifocal hemorrhagic and/or ischemic cerebral lesions. *Ultrasound Obstet Gynecol*. 2021;57(5):783-789. http://doi.org/10.1002/uog.22106
25. Campo-Caballero D, Rodriguez-Antigüedad J, Ekiza-Bazan J, et al. COL4A1 mutation as a cause of familial recurrent intracerebral hemorrhage. *J Stroke Cerebrovasc Dis*. 2020;29(4):104652. http://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104652
26. Kinoshita K, Ishizaki Y, Yamamoto H, et al. De novo p.G696S mutation in COL4A1 causes intracranial calcification and late-onset cerebral hemorrhage: a case report and review of the literature. *Eur J Med Genet*. 2020;63(4):103825. http://doi.org/10.1016/j.ejmg.2019.103825
27. Vitale G, Pichiecchio A, Ormitti F, et al. Cortical malformations and COL4A1 mutation: three new cases. *Eur J Paediatr Neurol*. 2019;23(3):410-417. http://doi.org/10.1016/j.ejpn.2019.02.006
28. Durrani-Kolarik S, Manickam K, Chen B. COL4A1 mutation in a neonate with intrauterine stroke and anterior segment dysgenesis. *Pediatr Neurol*. 2017;66:100-103. http://doi.org/10.1016/j.pediatrneurol.2016.04.010
29. England EC, Cornejo P, Neilson DE, Rao RP, Goncalves LF. Fetal brain small vessel disease 1 caused by a novel mutation in the COL4A1

gene. *Pediatr Radiol*. 2021;51(3):480-484. http://doi.org/10.1007/s00247-020-04847-2
30. Lee JJ, Patel S, Hinman JD. Late-onset COL4A1 mutation with recurrent ischemic and hemorrhagic strokes. *Neurologist*. 2024;29(1):1-3. http://doi.org/10.1097/NRL.0000000000000514
31. Zhang H, Fan KL, Zhang YQ, Hao XY, Yuan XZ, Zhang SY. Case report: recurrent pontine stroke and leukoencephalopathy in a patient with de novo mutation in COL4A1. *Front Neurol*. 2023;14:1237847. http://doi.org/10.3389/fneur.2023.1237847
32. Hausman-Kedem M, Ben-Sira L, Kidron D, et al. Deletion in COL4A2 is associated with a three-generation variable phenotype: from fetal to adult manifestations. *Eur J Hum Genet*. 2021;29(11):1654-1662. http://doi.org/10.1038/s41431-021-00880-3
33. Itai T, Miyatake S, Taguri M, et al. Prenatal clinical manifestations in individuals with COL4A1/2 variants. *J Med Genet*. 2021;58(8):505-513. http://doi.org/10.1136/jmedgenet-2020-106896
34. Lanfranconi S, Markus HS. COL4A1 mutations as a monogenic cause of cerebral small vessel disease: a systematic review. *Stroke*. 2010;41(8):e513-e518. http://doi.org/10.1161/STROKEAHA.110.581918
35. Coupry I, Sibon I, Mortemousque B, Rouanet F, Mine M, Goizet C. Ophthalmological features associated with COL4A1 mutations. *Arch Ophthalmol*. 2010;128(4):483-489. http://doi.org/10.1001/archophthalmol.2010.42
36. Mancuso M, Arnold M, Bersano A, et al. Monogenic cerebral small-vessel diseases: diagnosis and therapy. Consensus recommendations of the European Academy of Neurology. *Eur J Neurol*. 2020;27(6):909-927. http://doi.org/10.1111/ene.14183
37. George E, Vassar R, Mogga A, et al. Spectrum of fetal intraparenchymal hemorrhage in COL4A1/A2-related disorders. *Pediatr Neurol*. 2023;147:63-67. http://doi.org/10.1016/j.pediatrneurol.2023.07.008
38. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12(8):822-838. http://doi.org/10.1016/S1474-4422(13)70124-8
39. Pilling RF. Make it easier: 3-word strategies to help children with cerebral visual impairment use their vision more effectively. *Eye (Lond)*. 2023;37(2):285-289. http://doi.org/10.1038/s41433-021-01920-4
40. Sakki HEA, Dale NJ, Sargent J, Perez-Roche T, Bowman R. Is there consensus in defining childhood cerebral visual impairment? A systematic review of terminology and definitions. *Br J Ophthalmol*. 2018;102(4):424-432. http://doi.org/10.1136/bjophthalmol-2017-310694
41. Ortibus E, Fazzi E, Dale N. Cerebral visual impairment and clinical assessment: the European perspective. *Semin Pediatr Neurol*. 2019;31:15-24. http://doi.org/10.1016/j.spen.2019.05.004
42. Kirimura A, Yasuhara H, Hachisuka S, et al. A neonatal patient diagnosed with a COL4A1 mutation presenting with hemorrhagic infarction and severe jaundice. *Case Rep Genet*. 2022;2022:1594364. http://doi.org/10.1155/2022/1594364
43. Guey S, Lesnik Oberstein SAJ, Tournier-Lasserve E, Chabriat H. Hereditary cerebral small vessel diseases and stroke: a guide for diagnosis and management. *Stroke*. 2021;52(9):3025-3032. http://doi.org/10.1161/STROKEAHA.121.032620
44. Plaisier E, Gribouval O, Alamowitch S, et al. COL4A1 mutations and hereditary angiopathy, nephropathy, aneurysms, and muscle cramps. *N Engl J Med*. 2007;357(26):2687-2695. http://doi.org/10.1056/NEJMoa071906
45. Gale DP, Oygar DD, Lin F, et al. 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. http://doi.org/10.1093/ndt/gfw051
46. Okano S, Shimada S, Tanaka R, et al. Life-threatening muscle complications of COL4A1-related disorder. *Brain Dev*. 2020;42(1):93-97. http://doi.org/10.1016/j.braindev.2019.09.001
47. Coste T, Vincent-Delorme C, Stichelbout M, et al. COL4A1/COL4A2 and inherited platelet disorder gene variants in fetuses showing intracranial hemorrhage. *Prenat Diagn*. 2022;42(5):601-610. http://doi.org/10.1002/pd.6113
48. Jones FE, Murray LS, McNeilly S, et al. 4-sodium phenyl butyric acid has both efficacy and counter-indicative effects in the treatment of Col4a1 disease. *Hum Mol Genet*. 2019;28(4):628-638. http://doi.org/10.1093/hmg/ddy369