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COL4A1 and COL4A2-Related Disorders – Clinical Features, Diagnostic Guidelines, and Management.

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Abstract:**Purpose:**

Collagen type IV 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 $\geq 70\%$ 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.

Keywords: COL4A1, COL4A2, Guidelines, Delphi, genotype-phenotype.

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 IV, a critical part of all basement membranes, is a heterotrimer classically composed of two alpha 1 chains and one 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 IV alpha 1 and alpha 2 are proteins with shared structure, comprised of a large triple-helical domain defined by repeats of highly conserved glycine residues in Gly-X-Y motifs flanked by non-collagenous domains at the carboxy and amino termini (called NC1 and 7S domains, respectively). Missense variants impacting these glycine residues are the most common class of pathogenic variants², however other classes including splicing perturbations, premature stop codons, structural defects (deletions or duplications), and variants involving NC1 domain have been reported. Variants involving non-glycine 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 heterogeneity⁵. Notably, allelic heterogeneity extends to an important class of non-coding variants whereby single nucleotide mutations or alleles with Alu elements can cause highly penetrant cerebrovascular small-vessel disease (cSVD) mediated by de-repression 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 expression⁸ 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 cataracts⁹, retinal arterial tortuosity¹⁰, 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 as they impact 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 (OMIM:175780)
- Autosomal dominant brain small-vessel disease with hemorrhage (OMIM: 175780)
- Hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC) syndrome¹² (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 cSVD¹² 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 (3'UTR) of *COL4A1* (NM_001845) in PADMAL patients, including variants that disrupt miR-29 microRNA binding, leading to overproduction of collagen IV 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 publications¹⁷, 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 employed 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 prior to 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, where 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 $\geq 70\%$ agreement, and statements that reached consensus were included in the final recommendations, while 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. IRB approval was not sought as 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 26/31 (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 non-clinician 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 **two 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^{18,19,20,21, 22,23}
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 non-preterm children^{13,14}
5. Intracranial calcifications (may be identified on head CT or susceptibility-weighted imaging on brain MRI)²⁶
6. Bilateral white matter hyperintensities/abnormalities, unexplained white matter hyperintensities²⁷
7. Pediatric stroke and neonatal stroke²⁸ due to small vessel alteration²⁹ 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 factors³⁰
2. Pontine ischemic injury in young patients (<65 years) and/or in absence of risk factors³¹
3. Sub-cortical intraparenchymal hemorrhage(s) of unknown cause, especially in young patients with well-controlled or no known vascular risk factors^{30,12}
4. MRI markers of cSVD³² (leukoencephalopathy with presence or absence of deep microbleeds, old or acute small deep or subcortical infarcts, dilated perivascular spaces involving deep nuclei or hemispheric WM) discordant with vascular risk factors
5. Intracranial porencephalic cavity or ventricular cyst³³
6. Multiple intracranial carotid or vertebrobasilar system aneurysms³⁴ 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 extra-neurological manifestations involving the kidney (renal cysts, hematuria, proteinuria, renal failure of unexplained origin), eye (Axenfeld Rieger malformation³⁵, early-onset cataract or glaucoma, retinal hemorrhage, retinal arterial tortuosity), and/or muscle (unexplained cramps or myalgia, 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, 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, as 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/MRA and MRA of the neck
4. **Ophthalmologic evaluation**

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

1. Serum labs including CPK 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 (VUS).

Specific diagnostic rates for *COL4A1* and *COL4A2* variants across each phenotype are not yet known due to 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, as consensus on its clinical management has not yet been established. Care for an individual with a *COL4A1* or *COL4A2* variant requires a multidisciplinary healthcare 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 disease³⁶, 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 hemorrhage²⁵, hydrocephalus²¹, hypoplasia/agenesis of corpus callosum, schizencephaly, or porencephalic cysts, identified on fetal ultrasound³³ or brain MRI¹¹. 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, autism spectrum disorder), pyramidal and/or extrapyramidal motor abnormalities, epilepsy, intracranial aneurysms³⁴, 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 (e.g., 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, but 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 in other collagen vascular conditions.
5. Provide anticipatory guidance regarding potential for epileptic seizures. Epilepsy should be managed based on the electroclinical presentation, as 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 anti-thrombotic 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, as 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 EEG, 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 prior to 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 problems³⁹. 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 issues⁴⁰, 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 due to 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 (RATOR) is variably present in individuals with cSVD related to pathogenic *COL4A1* or *COL4A2* variants¹⁰ and can occur as the singular manifestation. A fundus examination may reveal significant tortuosity in the second- and third-order retinal arteries, while 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 following 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 impact 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, intra-ocular 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 hyperbilirubinemia⁴² 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 but 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 hemorrhage⁴³, 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 NSAIDs 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 (GFR).
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 RAAS 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 though asymptomatic, and persist over time, though 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, though 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, as existing estimates may be biased due to 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 Caesarean section 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 mice⁴⁸. There are several active areas of clinical research related to COL4A1/A2-related disorders, including 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 manuscript is based on established clinical practice information, expert consensus, and literature review from cited references.

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Ethics Declarations:

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

Conflict of interest:

No potential conflicts of interest were reported by the authors.

Additional Information:

Supplemental Table 1

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Supplemental Table 1

Recommendation	Participants who agreed with recommendation, n=	Participants who answered question about recommendation, n=	Degree of consensus
Indications for testing			
Disorders of structural brain development including anencephaly, polymicrogyria, schizencephaly, porencephaly, periventricular nodular heterotopias, hypoplasia/agenesis of corpus callosum, and/or cerebellar hypoplasia	25	26	96%
Epilepsy or infantile spasms, and associated structural brain abnormality	26	26	100%
Intracerebral hemorrhage in absence of underlying vascular malformation or coagulation disorder	26	26	100%
Periventricular leukomalacia-like pattern of brain injury in non-preterm children	26	26	100%
Intracranial calcifications (may be identified on head CT or susceptibility-weighted imaging on brain MRI)	25	26	96%
Bilateral white matter hyperintensities/abnormalities	19	26	73%

Pediatric stroke and neonatal stroke due to small vessel alteration or medullary vein congestion	26	26	100%
Unexplained, episodic irritability suggestive of muscle cramps with increased CK	22	26	85%
Congenital anomalies of the anterior segment of eye, cataract, glaucoma, optic nerve atrophy, retinal arterial tortuosity	26	26	100%
Hyperbilirubinemia and hemolytic anemia at birth (in association with signs listed above)	26	26	100%
First-degree relatives with known or suspected COL4A1/A2 variant (after consideration of personal preferences, adherence to local regulations, and approval if needed from relevant ethics committees)	26	26	100%
Indications for testing in adults			
Presence of any two or more of the above symptoms in childhood	23	25	92%
Ischemic brain lesions in multiple vascular territories and/or various ages in the absence of vascular risk factors	25	25	100%

Pontine ischemic injury in young patients (< 65 years) and/or in absence of risk factors	25	25	100%
Sub-cortical intraparenchymal hemorrhage(s) of unknown cause, especially in young patients with well-controlled or no known vascular risk factors	25	25	100%
MRI markers of cSVD (leukoencephalopathy with presence or absence of deep microbleeds, old or acute small deep or subcortical infarcts, dilated perivascular spaces involving deep nuclei or hemispheric WM) discordant with vascular risk factors	25	25	100%
Intracranial porencephalic cavity or ventricular cyst	25	25	100%
Multiple intracranial aneurysms or dolichoectasia (after ruling out PKD1/2 mutation if association with renal cysts)	25	25	100%
Carotid or basilar aneurysm in association with white matter hyperintensities and/or systemic features	25	25	100%
Suggestive extra-neurological manifestations involving either kidney (renal cysts, hematuria, proteinuria, renal failure of unexplained origin), and/or eye (Axenfeld Rieger malformation, early-onset cataract or	25	25	100%

glaucoma, retinal hemorrhage, retinal arterial tortuosity), and/or muscle (unexplained cramps or myalgia, rhabdomyolysis).			
Strong family history of any of the above symptoms	24	24	100%
Initial work-up for suspected COL4A1/A2:			
COL4A1/A2 genetic testing (may be performed in setting of cerebral small vessel disease panel, epilepsy gene panel, exome, or genome sequencing)	25	25	100%
Detailed family history, specifically regarding early-onset cerebrovascular disease/intracerebral hemorrhage, cerebral palsy, early-onset dementia, eye abnormalities, muscle cramps, hematuria, kidney failure, recurrent miscarriage	25	25	100%
CPK levels, urinalysis, standard coagulation tests	25	25	100%
Neuroimaging, preferably brain MRI/MRA and MRA of the neck	25	25	100%
Ophthalmologic evaluation	25	25	100%
Renal ultrasound	25	25	100%
Cardiovascular screening including ECG, and echocardiogram	25	25	100%
If high suspicion for COL4A1/A2-related symptoms and negative prior testing, consider genome sequencing (if not already performed)	25	25	100%

Skin fibroblast sampling might be considered for evaluation of COL4A1/A2 expression levels to interpret a Variant of Uncertain Significance	25	25	100%
Neurologic evaluation and management			
At diagnosis, individuals should undergo screening neuroimaging (MRI/MRA Head and Neck preferred). Frequency of imaging has not been established, but 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 advised).	24	24	100%
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	24	24	100%
If intracranial aneurysms are present, consider screening chest/abdomen/pelvis vasculature for presence of additional aneurysms.	23	23	100%
For management of unruptured intracranial aneurysms, safety of endovascular procedures is not well established but extra caution may be advised, similar to in another collagen vascular conditions.	24	24	100%
Provide anticipatory guidance regarding potential for epileptic seizures. Epilepsy should be managed based on the electroclinical presentation, as no specific medication regimens have been established for COL4A1/A2-related epilepsy	24	24	100%

Aggressive management of additional cerebrovascular risk factors, including recommendation against smoking/sympathomimetic use, and treatment of hypercholesterolemia, diabetes, elevated blood pressure, and/or obesity	24	24	100%
There is no specific evidence for use of anti-thrombotic agents for primary or secondary stroke prevention (See Hematologic section for additional recommendations regarding antithrombotic safety and use)	24	24	100%
Avoid high-intensity, prolonged physical activities, and sports predisposing to high-risk for head injury, as increased risk for provoked intracranial hemorrhage or other neurovascular events has been observed.	24	24	100%
Supportive care including emotional support and counseling are appropriate for affected individuals and their families.	24	24	100%
For fetal/pediatric cases, in cases of intracranial abnormalities such as cerebral hemorrhages of unknown cause identified on fetal ultrasound, evaluate further with fetal brain MRI.	24	24	100%
For pediatric cases, counsel regarding potential for infantile spasms and treat promptly given high prevalence in infants with COL4A1/A2	23	24	96%
Prolonged recovery from anesthesia and complications during anesthetic events have been reported. Further investigation of the cause of these	22	22	100%

complications is ongoing, but consultation with anesthesiologists prior to any procedure and notification about specific genetic variants is advised. Anesthesiologists may consider strict peri-procedural blood pressure support to avoid hypotension.			
Neuro-ophthalmologic evaluation and management			
Early, multidisciplinary evaluation of visual function for prompt cortico-visual impairment (CVI) diagnosis and treatment planning.	24	24	100%
Continuous monitoring and effective habilitation strategies for visual functions to support development.	24	24	100%
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.	24	24	100%
Ophthalmologic evaluation and management			
Baseline screening ophthalmologic examination including fundoscopic examination to assess for retinal vessel tortuosity and/or hemorrhages, and slit lamp examination, followed by annual ophthalmologic evaluations.	24	24	100%

Other ophthalmological evaluations may be performed as appropriate for age and level of cooperation, including best corrected visual acuity, intra-ocular pressure measurements, optical coherence tomography.	24	24	100%
Counsel regarding transient visual loss which warrants urgent ophthalmology evaluation to treat possible retinal hemorrhage.	24	24	100%
Monitoring and management of identified ophthalmologic complications per standard guidelines.	24	24	100%
Cardiac evaluation and management			
Baseline electrocardiogram and transthoracic echocardiogram in all patients.	24	24	100%
In patients with history of syncope and/or palpitations, consider longer-duration, portable cardiac monitoring.	24	24	100%
In adolescence and adulthood, consider stress tests.	22	24	92%
Evaluation and close blood pressure monitoring with strict avoidance of hypertension (in adults, goal: < 130/80; in children, goal < 95th percentile for age)	24	24	100%
Hematologic evaluation and management			

Antiplatelet and anticoagulant treatments are generally not recommended for primary or secondary cardiovascular or cerebrovascular prevention in COL4A1/A2, though risks/benefits should be discussed with a multidisciplinary team if they are felt to be strongly indicated	24	24	100%
Safety of intravenous thrombolysis has not been investigated in individuals with COL4A1/A2	24	24	100%
Safety of medications and supplements that may influence the coagulation pathway have not been formally evaluated, but occasional use of NSAIDs has been tolerated.	24	24	100%
Renal evaluation and management			
Baseline kidney and bladder US, urinalysis, serum creatinine concentration and estimated glomerular filtration rate (GFR).	23	24	96%
If COL4A1/A2 diagnosis established in childhood, consider repeating urinalysis and kidney ultrasound in adulthood or if symptomatic.	23	24	96%
If albuminuria is present, assess a quantitative evaluation (Urinary protein/creatinine ratio in children; in adults, urinary protein/creatinine or 24-hour urinalysis).	23	24	96%

If proteinuria is present, refer the patient to a nephrologist for consideration of RAAS blockade inhibition.	23	24	96%
Refer to nephrologist in cases of decreased kidney function, multi-cystic kidney disease, and/or hypertension.	23	24	96%
In pediatric patients, 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.	24	24	100%
Musculoskeletal evaluation and management			
Baseline measurement of serum CK	23	24	96%
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.	24	24	100%
Continue aerobic exercise while avoiding strenuous, prolonged activities.	24	24	100%
There is anecdotal evidence that medications that increase nitric oxide may improve muscle cramping, though further evaluation is necessary.	22	24	92%

In severely neurologically compromised children: episodes of irritability, unexplained crying, or sleep disturbance should raise suspicion for muscle cramps.	24	24	100%
Family planning			
Consultation with genetic counselor and geneticist, and if suspected fetal diagnosis of COL4A1/A2, consider consultation with fetal neurologist if available	25	25	100%
Delivery at a tertiary care center	25	25	100%
A Caesarean section delivery should be considered in women giving birth if either the mother or fetus has a known COL4A1/2 variant	25	25	100%