pediatric stroke

Case Report

COL4A1/COL4A2 variants in 16 new pediatric patients: A Case Series of Stroke, Porencephaly, Schizencephaly and Other Findings

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Abstract:

The *COL4A1* and *COL4A2* genes encode subcomponents of collagen IV, abundant in basement membrane of vessels. Pathogenic variants in these two genes result in abnormal vasculature, causing a variable phenotype primarily involving the central nervous system, eyes, and kidneys. Central nervous system involvement typically manifests as small vessel disease, microhemorrhages, stroke, porencephaly, schizencephaly among other findings. Although cases of stroke have been described in a wide age range, ischemic/hemorrhagic stroke recurrence risk and standard of care for stroke prevention is not established for these patients. In this report, we describe 16 pediatric patients, including one family with three and another with four affected members, seen at our tertiary center with *COL4A1/2* variants with porencephaly, schizencephaly, and other brain abnormalities. Our cohort shows developmental issues in all patients, a high percentage of patients with epilepsy, and a significant portion with cataracts. Notably, none of our patients with perinatal brain injury had recurrence of stroke during follow-up in clinic. Further understanding of the phenotypic spectrum of *COL4A1/2* variants is critical to facilitate directed genetic work-up and early diagnosis for patients.

1. Introduction:

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The *COL4A1* and *COL4A2* genes, located in tandem on chromosome 13q34, encode collagen IV alpha 1 and 2 chains, subunits of collagen IV[1]. Collagen IV, a triple helix comprised of three alpha chains, constitutes the main component of basement membrane (BM) across all tissue including vascular endothelial BM[1].

COL4A1 variants, inherited most commonly in an autosomal dominant pattern, have a wide phenotypic spectrum[2,3], which includes HANAC (hereditary angiopathy, nephropathy, aneurysms, and muscle cramps) syndrome[4], cerebral small-vessel disease, malformation of cortical development, periventricular leukomalacia, microbleeds, ischemic or hemorrhagic stroke, porencephaly[1,5–8], PADMAL (pontine autosomal dominant microangiopathy and leukoencephalopathy)[9] and other systems involvement: most commonly with ocular and renal abnormalities[2]. More recently described, *COL4A2* variants have similarly been associated with brain small-vessel disease, porencephaly, and leukoencephalopathy and are inherited in autosomal dominant pattern[10–12].

Despite the clinical significance, there remain gaps in knowledge about *COL4A1/2* with novel reports still expanding the list of known variants, and the phenotypic spectrum. Thus, here we report our center's experience with *COL4A1/2* variants in a pediatric population.

2. Methodology:

We report a case series of 16 patients with *COL4A1* or *COL4A2* -related disorder seen at our institution between 2006 and 2023. Only patients with confirmed pathogenic variants in *COL4A1* were included in the report. One patient with a variant of uncertain significance (VUS) in *COL4A2* and consistent clinical phenotype was included after family genetic testing. Charts were reviewed in the electronic medical records system, and information was deidentified. Developmental delay was defined as failure to attain developmental milestones in gross motor, fine motor, language, and cognitive domains compared to peers. Severe developmental delay was defined as falling two or more typical milestones[13] behind expected for age.

3. Case Reports:

3.1. COL4A1:

Case 1:

Case 1 was a 3-year-old female, born at 35w6 gestational age (GA), who was discovered to have a unilateral open-lip schizencephaly and bilateral ventriculomegaly in-utero. In early infancy, she developed seizures and hydrocephalus requiring a ventriculoperitoneal (VP) shunt. She had sparse white matter and diffusely thin corpus callosum on imaging. At 3 years of age, she had severe global developmental delay, focal intractable epilepsy (onset at 1 year old), and cortical visual impairment. She did not have any family history of genetic neurologic problems. A brain

malformations genetic panel revealed a novel heterozygous de novo likely pathogenic missense variant c.3655G>C, p.(Gly1219Arg) in the *COL4A1* gene.

Case 2:

Case 2 was a 4-year-old-male who presented for developmental delay, who was subsequently diagnosed with autism spectrum disorder and mild global developmental delay. He was born at 39w GA without any perinatal complications. He had no known family history of genetic neurologic abnormalities. He did not develop seizures, ophthalmologic, or other medical complications. MRI brain and magnetic resonance angiography (MRA) at 4 years old were unremarkable except mild gliosis. A neurodevelopmental disorders genetic panel revealed a novel heterozygous de novo likely pathogenic variant c.903+1G>A, (Splice donor) in the *COL4A1* gene, which is expected to disrupt splicing.

Case 3:

Case 3 was a 4-year-old-male, born at 39w1d GA, who developed ventriculomegaly in-utero and was found to have intrauterine intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), thinned corpus callosum and a unilateral iris coloboma. He developed hypertrophic cardiomyopathy in the infantile period and focal seizures at age 3 years old. He had mild global developmental delay. There was no known family history of genetic neurologic conditions. A

genetic panel for microphthalmia, anophthalmia and anterior segment dysgenesis showed a previously reported heterozygous de novo likely pathogenic missense variant c.3307G>A, p.(Gly1103Arg) in *COL4A1*.

Case 4:

Case 4 was a 13-year-old-male with history of severe intellectual disability, spastic quadriparesis, Lennox-Gastaut syndrome (seizure onset at 3 months of age with infantile spasms), cataracts, nephrolithiasis. He was born at 40w GA with in-utero ventriculomegaly, which post-natal MRI confirmed. He had not had any strokes. Neurologic family history was positive for mother and maternal uncle with seizures. Past whole exome sequencing, chromosomal microarray (CMA) and Fragile X testing had been negative, however repeat trio whole exome sequencing (WES) at 12 years old returned positive for a heterozygous previously reported de novo pathogenic missense variant c.2317 G>A, p.(Gly773Arg) in *COL4A1*.

Case 5:

Case 5 was an 8-year-old-male who was born at 34 weeks GA with concern for intrauterine hemorrhagic stroke. His mother had anti-phospholipid syndrome and pregnancy was complicated by placental ischemic infarcts. At 1 year-old, MRI brain revealed a large porencephalic cyst lined with dystrophic calcification and multifocal white matter gliosis. He

developed focal intractable epilepsy with onset of seizures at 6 months of age, severe intellectual disability, spastic quadriparesis, and cataracts. Neurologic family history was only positive for multiple sclerosis in maternal aunt. Cytomegalovirus testing during early infancy was negative. A congenital cataracts gene panel test and CMA were negative. A trio WES revealed a heterozygous de novo likely pathogenic de novo missense variant c.3208G>A, p.(Gly1070Arg) in *COL4A1*, previously reported in one other patient in the literature.

Family 1 (Cases 6-8)

Case 6:

Case 6 was a 15-year-old-female with mild intellectual disability, hemiparesis, focal epilepsy (seizure onset at 4-years-old). She was born at 39 weeks GA after an intrauterine stroke noted on fetal MRI. Whole exome sequencing revealed a previously reported heterozygous pathogenic missense variant in *COL4A1* gene c.3307G>A, p.(Gly1103Arg). Her brother, her sister (case 7 and case 8) and her mother with cerebral palsy were then confirmed to have the same variant.

Case 7:

Case 7 was a 13-year-old-male with mild intellectual disability, focal epilepsy (seizure onset at 2 years of age), ADHD, and hemiparesis. He had intraventricular hemorrhage on fetal imaging. A

porencephalic cyst, periventricular leukomalacia and thinning of body of corpus callosum were reported on MRI brain at 2-years old. *NOTCH3*, Factor V Leiden gene, and prothrombin gene sequencing, and CMA were negative. Genetic diagnosis was made after older sister's WES revealed a *COL4A1* variant (see above).

Case 8:

Case 8 was a 12-year-old-female with autism spectrum disorder. She was born at 40 weeks GA. Pregnancy was only complicated by fetal stroke. MRI at 4 years of age revealed mild periventricular gliosis and unilateral porencephaly. She was initially evaluated for mild speech delay and subsequently diagnosed with autism. She did not develop seizures, stroke, or hemiparesis. She developed bilateral cataracts at 6 years old. Initial evaluation with CMA, MECP2 and Fragile X gene testing were planned. However, family history was positive for two siblings and mother as described above, which led to the genetic diagnosis with confirmation of the same variant.

Family 2 (Cases 9-12):

Case 9:

Case 9 was an 11-year-old-female with mild intellectual disability, who had an uncomplicated birth at 39 weeks GA. She was mildly developmentally delayed during early childhood, was noted at 4 years old to have microcephaly and MRI brain revealed mild scattered white matter gliosis. She did not have seizures. Family history was positive for two siblings with microcephaly and mild delays (case 10 and case 11) and mother (case 12) with history of large hemispheric stroke at 14 years old. CMA at 5 years of age revealed a novel 573 kb deletion spanning 13q33.3 to 13q34 involving 5 exons of the *COL4A1* gene.

Case 10:

Case 10 was a 10-year-old-male who was born at 28 weeks GA due to preterm labor, required intubation after delivery and stayed in the NICU for 2 months, complicated by retinopathy of prematurity. He had mild global developmental delay, microcephaly, and did not develop new stroke or seizures. MRI brain showed mild scattered white matter gliosis, MRA was unremarkable. Given family history as above, he was confirmed at 4 years old with CMA to have the same novel deletion as sister (see above).

Case 11:

Case 11 was an 8-year-old-female, born full-term without complication. During infancy she had intestinal malrotation. She was noted to have mild global developmental delay, and mild spastic

hemiparesis at 18 months of age. She did not develop new seizures, or stroke. MRI brain revealed focal polymicrogyria & pachygyria, mild scattered white matter gliosis. MRA neck showed an aberrant subclavian artery. CMA at 2-years-old verified the same deletion as other family members (case 9, 10, and 12).

Case 12:

Case 12 was the mother of the three aforementioned siblings, who was 31 years old at the time of the report. She was born full term, was healthy with normal growth and development. At 14 years of age, she presented to an OSH with headache, facial twitching, and syncopal event. She was discharged from ED, however presented to our center with a massive MCA stroke. She had no personal or family history of stroke, clotting disease, miscarriages, neurologic conditions. Cardiac and hypercoagulability workups were negative. Mildly irregular, diminutive proximal MCA, ACA and petrous ICA segments were noted unilaterally on MRA of head & neck. The etiology of stroke was considered unclear, she was placed on low-dose aspirin and followed. Her course was complicated by seizures, spastic hemiplegia. She self-discontinued aspirin after a few years. At 25 years-of-age, after her children were diagnosed with a deletion involving the *COL4A1* gene (see above), she was tested and shown to have the same deletion as well.

Case 13:

Case 13 was a 15-week-old male, born at 34 weeks GA. He was diagnosed with bilateral IVH in-utero with fetal ultrasound and schizencephaly with fetal MRI during an otherwise uncomplicated pregnancy to a healthy mother. After delivery, he was admitted to NICU due to prematurity and neonatal alloimmune thrombocytopenia. Post-partum CT brain imaging confirmed an extensive unilateral frontoparietal schizencephaly, lined with calcification. He was also found to have microcephaly and bilateral cataracts. At approximately 15 weeks of life, he developed focal seizures. Family history was positive for spontaneous abortion of sibling and father with epilepsy in childhood. CMV testing during neonatal period was negative. A cerebral palsy spectrum disorders panel resulted with a novel heterozygous de novo likely pathogenic missense variant c.3095G>A, p.(Gly1032Asp) in the *COL4A1* gene, confirming the diagnosis.

Case 14:

Case 14 was an 11-year-old male, with spastic quadriparesis, intellectual disability, epilepsy, microcephaly, and congenital cataracts. He was born at 39 weeks GA after an uncomplicated pregnancy to a healthy mother. After birth, he was noted to have microcephaly, cataracts, developed hyperbilirubinemia and required NICU care. In the NICU, head ultrasound revealed bilateral IVH. At 2 months, brain MRI showed ventriculomegaly, diffusely thin corpus callosum and scattered white matter gliosis. Initial genetic testing with chromosomal microarray,

karyotype was negative. At 7 years of age, a leukodystrophy and leukoencephalopathy gene panel revealed a novel heterozygous de novo likely pathogenic *COL4A1* gene missense variant c.2788G>C, p.(Gly930Arg), confirming the diagnosis.

Case 15:

Case 15 was a 9-year-old female with a history of intrauterine stroke, neonatal seizures, and subsequent intractable focal epilepsy, bilateral cataracts with anterior segment dysgenesis and bicuspid aortic valve. After an uncomplicated pregnancy, she was born at 40 weeks GA to a healthy mother. She then developed seizures on the second day of life and was found to have had hemorrhagic and ischemic strokes in-utero. She developed bilateral cataracts in early childhood. She had delays in gross and fine motor domains during early childhood and was later diagnosed with ADHD and autism. Most recent MR brain imaging at 9 years of age showed a unilateral porencephalic cyst, bilateral white matter gliosis and thinning of the body of corpus callosum. MRA brain showed a small aneurysm arising from cavernous segment of internal carotid artery, was otherwise unremarkable. There was no family history of early onset stroke, epilepsy, or genetic conditions. Genetic panel testing for microphthalmia, anophthalmia and anterior segment dysgenesis showed a previously reported heterozygous de novo pathogenic missense variant c.2263G>A, p.(Gly755Arg) in the *COL4A1* gene at 9-years-old.

3.2. COL4A2:

Case 16:

Case 16 was a 16-month-old male who was born at 39 weeks GA after an unremarkable pregnancy except prenatal diagnosis of ventriculomegaly. Postnatal MRI brain revealed an entrapped, asymmetrically enlarged lateral ventricle unilaterally, evidence of remote intraventricular hemorrhage. He was followed in Neurology clinic for gross and fine motor delays, early handedness, spastic hemiplegic cerebral palsy. He did not have any seizures. Family history was positive for his mother who had epilepsy secondary to a perinatal brain injury of unknown etiology. Due to atypical asymmetric pattern on imaging and the family history, a cerebral palsy gene panel was sent. Genetic panel showed a novel heterozygous VUS in the *COL4A2* gene c.3155G>T p.(Gly1052Val). Genetic testing of the mother, who had a past history of perinatal brain injury and epilepsy, revealed her to carry the same novel missense variant, and the variant was considered to be disease causing.

4. Results:

4.1. Neurologic findings and brain imaging features:

The most common brain imaging finding was scattered white matter gliosis in eight patients (50%), along with two patients with periventricular leukomalacia (12%). Five patients with white matter gliosis also had thinning of the corpus callosum (31%). Four patients had porencephaly (Figure 1) (25%), two patients had schizencephaly (Figure 2) (12%). Five patients had hemosiderin deposition from prior hemorrhage (Figure 3) (31%). There was gliosis and atrophy of the central gray matter in five patients (31%). Three patients had imaging sequelae of past intraventricular hemorrhage (19%). Other findings noted were ventriculomegaly (5/16, 31%), intrauterine stroke (3/16, 19%), and one patient with an acute ischemic infarct in adolescence. The patient with *COL4A2* variant had ventriculomegaly and IVH, similar to the *COL4A1* patients (Figure 4). Patients from the same family had relatively similar findings on imaging (Figure 5, 6). All of the patients diagnosed in infancy or early childhood had some degree of developmental delay, excluding the single 15-week-old infant who will require developmental assessments over time. Four patients had microcephaly (25%). Three patients had autism spectrum disorder (19%). One patient had cortical visual impairment presumed secondary to her brain malformations (6%). Nine of sixteen patients had seizures (56%), which were most commonly focal (6/9, 67%).

4.2. Ocular and renal complications:

One patient had iris coloboma (6%), six had cataracts in infancy to early childhood (37%). One patient was reported to have unspecified anterior segment dysgenesis (6%). No other ocular findings were noted. One patient had nephrolithiasis (6%); no other renal abnormalities were reported in our cohort.

5. Discussion:

Brain imaging findings were variable in our cohort, with the most common finding being non-specific white matter gliosis. The white matter gliosis typically involved the periventricular and deep white matter with sparing of the juxtacortical u-fibers and cerebellar white matter. Other neuroimaging features included porencephaly, ventriculomegaly, cystic encephalomalacia, corpus callosum thinning, cerebral calcifications, schizencephaly, intraventricular/intraparenchymal hemorrhage, and malformations of cortical development. Hemosiderin staining observed in the margins of ventricles and encephalomalacia suggests that the brain changes are likely secondary to fetal, perinatal or childhood recurrent hemorrhagic strokes. Schizencephaly and polymicrogyria/pachygyria noted in these patients could be secondary to an acquired encephaloclastic process with the lesion type dependent on the timing of the insult[14,15]. Calcification on imaging, which has been described previously[16], along with the microcephaly initially raised concern of congenital CMV infection in two cases. We did

not observe extensive perivascular dilated spaces or microhemorrhages in most patients, although we had three patients with microhemorrhages, which have been described previously[17].

Developmental delay, spasticity, hemiparesis, epilepsy were common complications (Table 1). Cataracts were the most common early non-neurologic abnormalities in this cohort. A significant portion of our patients had multiple genetic tests prior to final diagnosis of *COL4A1/2* -associated disease. Gene panels used were diverse among patients. Furthermore, three patients and one family of four had previously unreported variants. Family history was crucial in many cases which otherwise may not have been easily elucidated. In our cohort, only one patient had an ischemic stroke outside of perinatal period and she was placed on aspirin as she did not have any history of hemorrhagic complications and was not known to have a *COL4A1* variant for many years. No stroke recurrence was seen in our cohort.

In a series of four cases with *COL4A1* related fetal demise, autopsy revealed placental villous dysmorphism, placental hypoplasia and fetal vascular malperfusion (thrombosis of placental vasculature)[18]. In another series of eight patients with fetal hemorrhagic stroke, three were shown to have placental abnormalities including chorioamnionitis, placental hypoplasia, one of whom had umbilical arteritis/phlebitis[19]. Thus, placental vasculature abnormalities could be

contributing to the pathophysiology of fetal stroke and other intracranial pathologies in the fetus. In our cohort, in case 5, the pregnancy was complicated by placental infarction, however the mother also had a history of anti-phospholipid syndrome which may have been contributing along with the patient's *COL4A1* variant. Overt placental pathology was not reported in other cases.

Although developmental delay is reported ubiquitously in *COL4A1/2* series, autism is infrequently reported[3]. In our case series, however, we had three cases from separate families with autism. The typical CNS pathology consists of cerebral small vessel disease, aneurysm, microhemorrhages. Thus, our findings of aberrant subclavian artery and diminutive large vessels in two members, and large-vessel stroke in one member of family 2 which carries a large deletion involving the *COL4A1* gene are curious, although the correlation between these atypical findings and the deletion variant is unclear at this time. Only one patient in our cohort had an aneurysm on vessel imaging.

Four of sixteen patients in our cohort were the result of premature delivery, which is higher than some previous cohorts, the etiology is unclear. One patient had intestinal malrotation and another patient had a bicuspid aortic valve. These have not been reported previously in

COL4A1/2; however, it is unclear if these are incidental findings or part of the phenotypic spectrum.

Our findings demonstrate the importance of maintaining a high degree of suspicion in making this challenging diagnosis. *COL4A1* & *COL4A2* gene testing should be strongly considered for patients with unexplained porencephaly, schizencephaly, intrauterine stroke or widespread white matter gliosis at birth. One of multiple available gene panels containing testing for the *COL4A1* and *COL4A2* genes could be utilized in practice. Of note, however, next generation sequencing techniques may not always capture large deletions or complex genetic variants involving these genes.

Once a *COL4A1* or *COL4A2* variant is discovered (Table 2): High prevalence of developmental delay and epilepsy in our cohort and reports of recurrent ischemic or hemorrhagic stroke in literature[20,21] should raise concern and warrant close follow-up by Neurology. The wide phenotypic spectrum and incomplete penetrance of the variants make prognostication challenging. Stroke prevention and management remains a challenge as well, given phenotypic variability among patients, unclear risk of stroke recurrence in patients effected perinatally and increased propensity for both hemorrhagic and ischemic strokes. Previously published guidelines do not support antiplatelet, anticoagulant, or thrombolytic use in these patients[22].

MR imaging of the brain and the vessels of the head and neck should be obtained. Ophthalmology evaluation should be performed to screen for ocular complications. Renal function testing, and screening for hematuria, proteinuria should be considered, especially in those with variants in exon 24 or 25 of the gene[23]. Family member testing with the help of genetic counseling is vital.

6. Conclusion:

COL4A1/2 variants should be considered in the differential when assessing cases of perinatal stroke, porencephaly and/or schizencephaly, cataracts and even patients with a combination of non-specific white matter gliosis, developmental delays, and epilepsy.

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Legends:

Table 1: Select clinical, genetic, radiologic findings from the cohort. IVH: Intraventricular hemorrhage, PVL: periventricular leukomalacia, CC: corpus callosum.

Table 2: Findings in patients with *COL4A1/*2 variants in our cohort and in literature, and recommendations to address the findings.

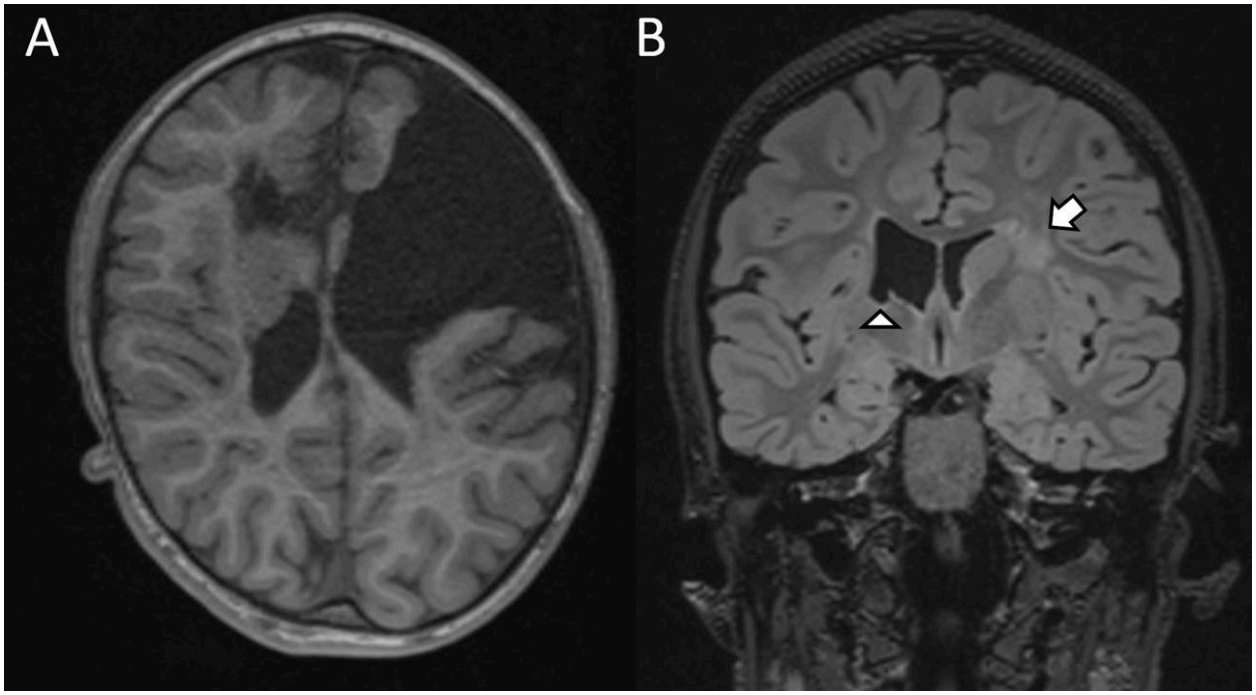

Figure 1: Porencephaly in *COL4A1* variants. (A) Axial T1 shows left-sided large porencephaly and cystic encephalomalacia on contralateral medial frontal lobe, case 5 at 7 years old. (B) Coronal

T2 FLAIR shows right sided porencephalic cyst of the superior putamen communicating with the right lateral ventricle (arrowhead), atrophy of the right basal ganglia, bilateral white matter gliosis (arrow), case 15 at 9 years old.

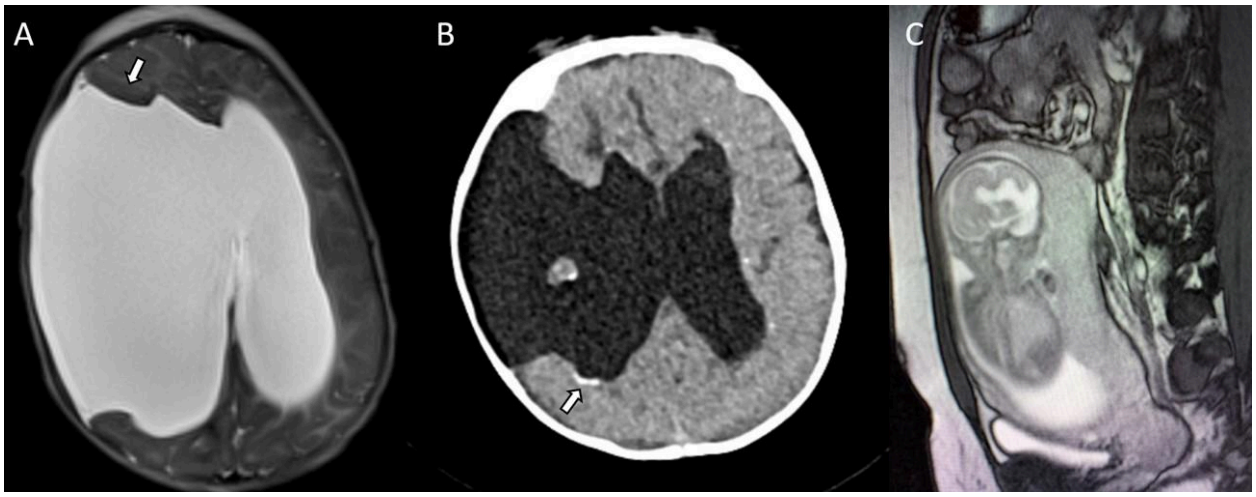

Figure 2: Schizencephaly in *COL4A1* variants. (A) Axial T2 image shows a large right-sided schizencephaly, see abnormal gray matter lining (arrow), case 1 at 3 months old. (B) CT shows large right-sided schizencephaly with surrounding calcification (arrow), case 13 at 15 weeks old. (C) Fetal MRI of same patient (B) shows schizencephaly.

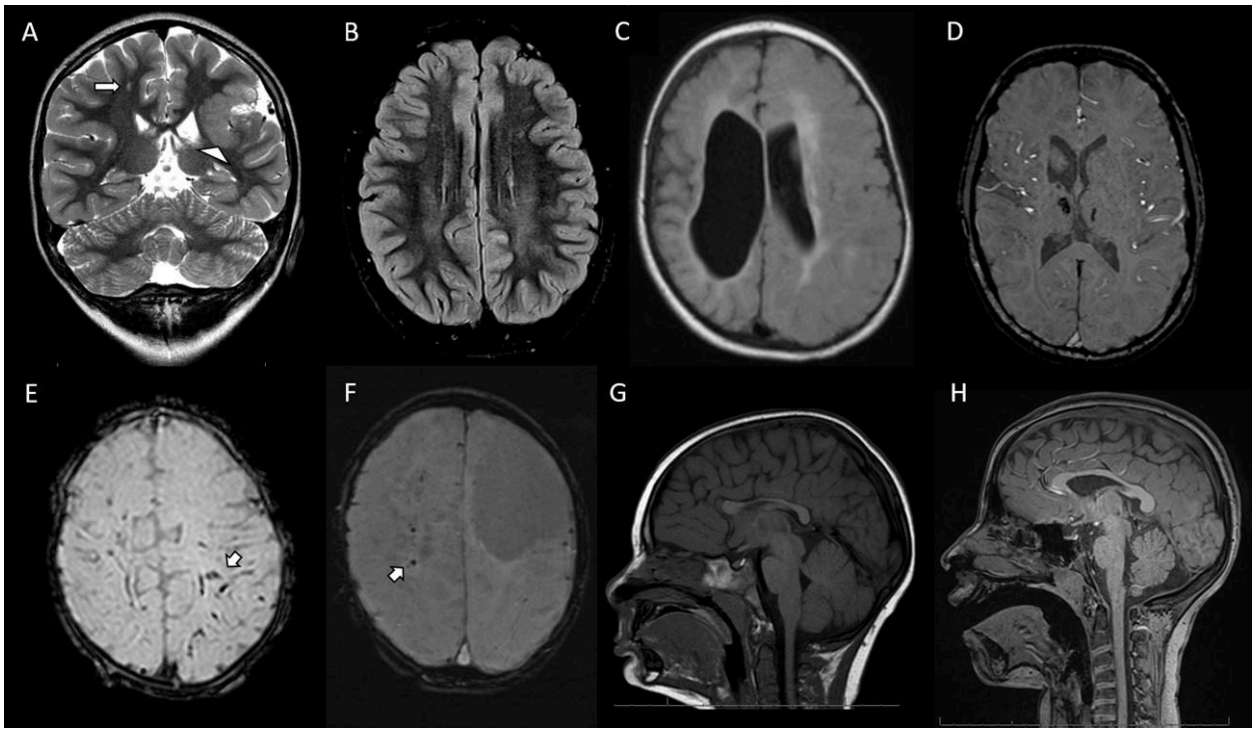

Figure 3: Other imaging findings in *COL4A1* variants. (A) Coronal T2 shows left insular polymicrogyria/pachygyria (arrowhead), small right contralateral white matter gliosis (arrow), case 11 at 6 years old. (B) Axial T2 FLAIR shows non-specific bilateral scattered white matter gliosis, case 10 at 8 years old. (C) Axial T2 FLAIR shows right-sided ex vacuo ventriculomegaly, bilateral scattered white matter gliosis affecting periventricular and deep white matter, case 14 at 1 year old. (D) Axial SWI shows hemosiderin deposits in bilateral thalami related to prior hemorrhages, case 15 at 9 years old. (E) Axial SWI shows scattered hemosiderin deposits across

cerebral white matter (arrow), case 14 at 2 months old. (F) Axial SWI shows tiny areas of hemosiderin deposit in periventricular white matter in areas of gliosis (arrow), case 5 at 7 years old. Thinning of corpus callosum, seen in sagittal T1 sequence in (G) case 7 at 2 years old, and (H) case 15 at 9 years old.

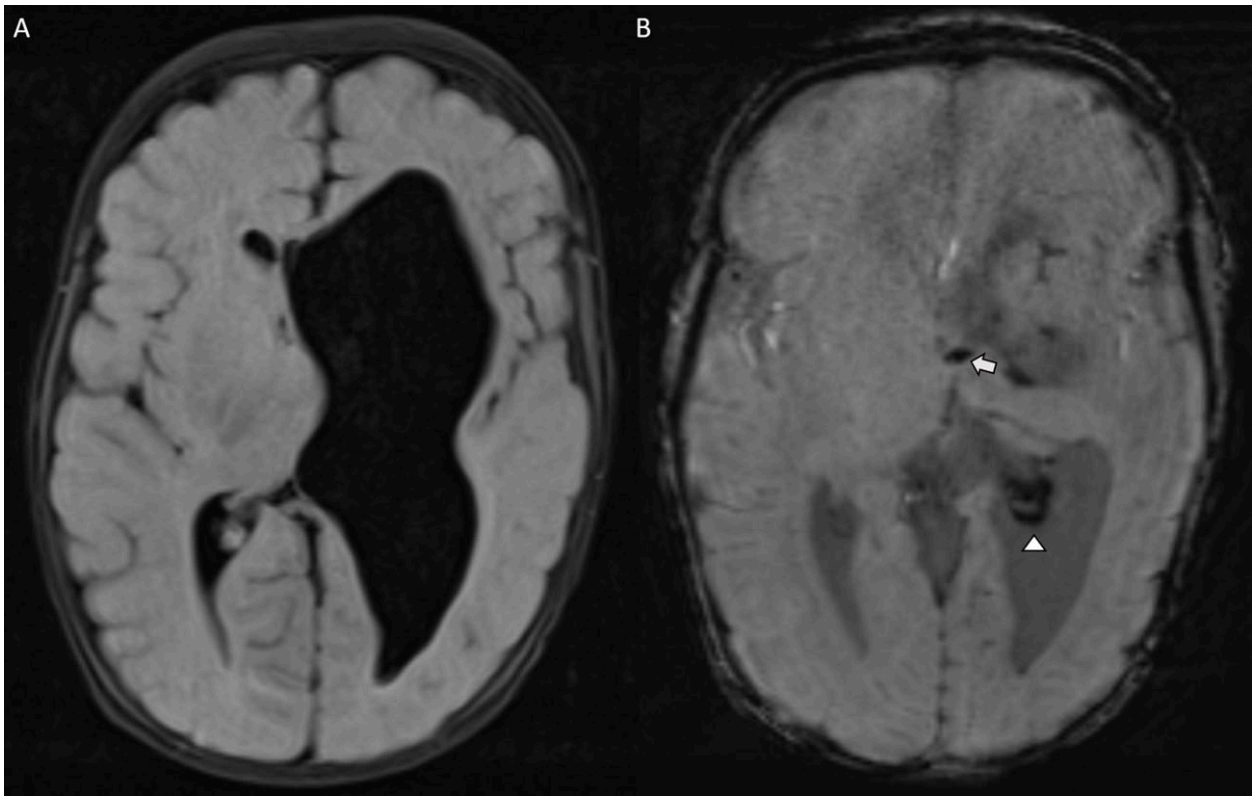

Figure 4: Imaging findings in *COL4A2* variants, case 16 at 2 months old. (A) Axial T2 FLAIR shows left lateral asymmetric, entrapped ventriculomegaly. (B) Axial SWI shows signal consistent with

remote intraventricular hemorrhage (arrow) and susceptibility artifact involving the choroid plexus (arrowhead).

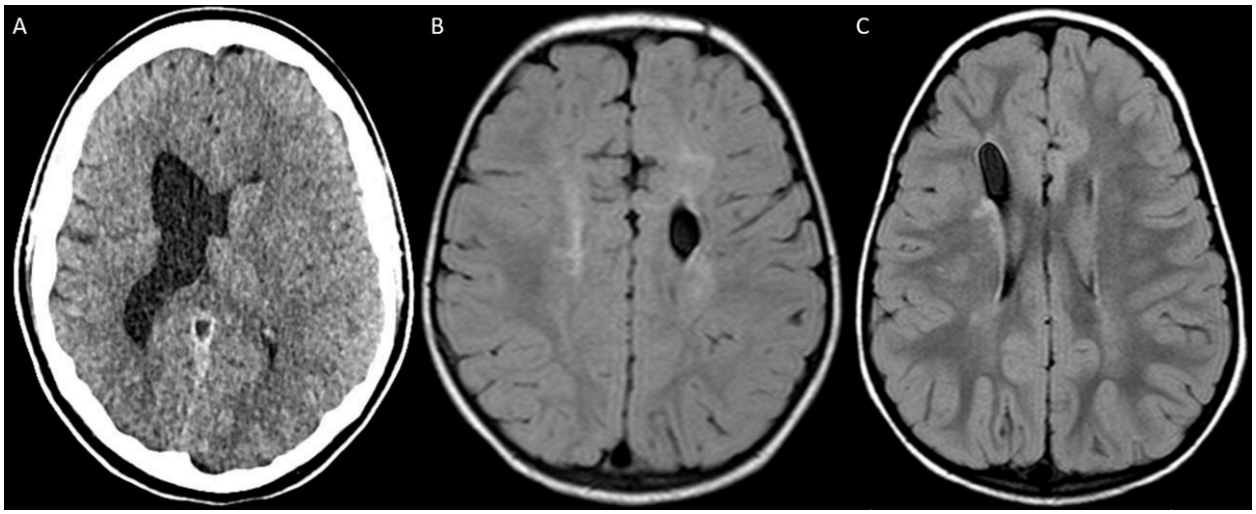

Figure 5: Select images from family 1 with G1103R variant. (A) CT head shows unilateral ex vacuo ventriculomegaly and mild cerebral volume loss (secondary to patient's intrauterine stroke), case 6 at 15 years old. (B) Axial T2 FLAIR shows unilateral porencephaly, bilateral white matter hyperintensity, case 7 at 2 years old. (C) Axial T2 FLAIR shows unilateral porencephaly, bilateral white matter hyperintensity, case 8 at 3 years old.

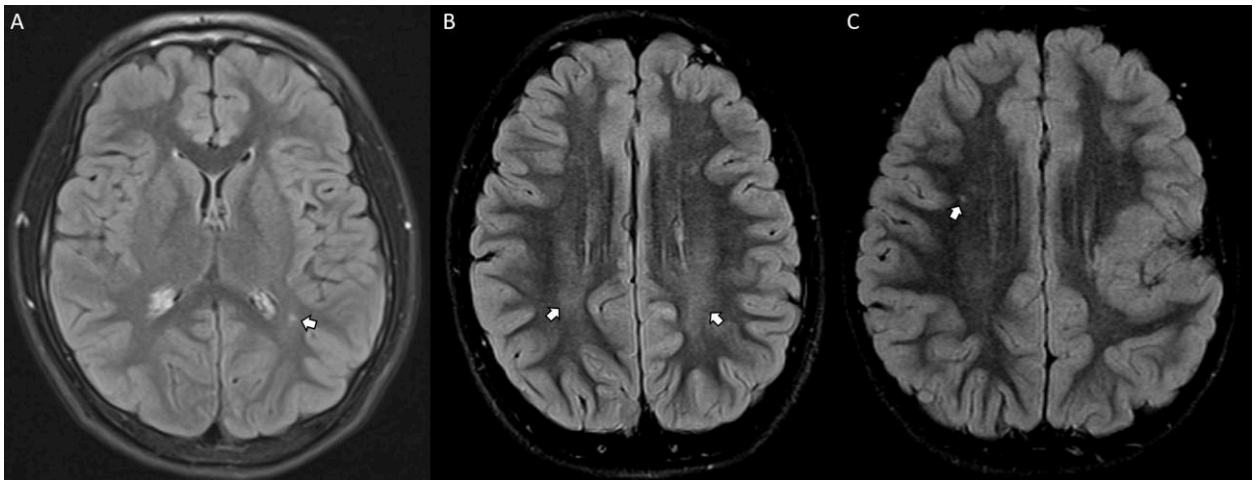

Figure 6: Select images from family 2 with 13q33.3-4 deletion involving *COL4A1* gene, Axial T2 FLAIR sequences. (A) Scattered few white matter hyperintensities, mild gliosis (arrow), case 9 at 11 years old. (B) Moderate white matter gliosis (arrows), case 10 at 8 years old. (C) Scattered few white matter hyperintensities (arrow), and left posterior insular focal polymicrogyria, case 11 at 6 years old.