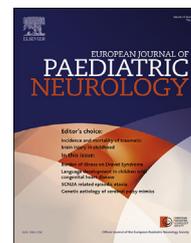




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Original article

Cortical malformations and COL4A1 mutation: Three new cases



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ABSTRACT

Aim: The COL4A1 gene (13q34) encodes the $\alpha 1$ chain of type IV collagen, a crucial component of the basal membrane. COL4A1 mutations have been identified as a cause of a multisystem disease.

Brain MRI in COL4A1-mutated patients typically shows vascular abnormalities and white matter lesions. Cortical malformations (specifically schizencephaly) have also recently been described in these patients, suggesting that these, too, could be part of the phenotypic spectrum of COL4A1 mutations.

The aim of our work was to retrospectively evaluate COL4A1-mutated subjects diagnosed at our centers in order to assess the frequency and define the type of cortical malformations encountered in these individuals.

Method: We retrospectively reviewed MRI data of 18 carriers of COL4A1 mutations diagnosed in our centers between 2010 and 2016.

Results: We identified polymicrogyria in two patients, and schizencephaly in the mother of a further patient.

Interpretation: Our findings confirm that cortical malformations should be considered to fall within the phenotypic spectrum of COL4A1 mutations and show that not only schizencephaly but also polymicrogyria can also be found in mutated individuals. Although further studies are needed to clarify the underlying pathogenetic mechanism, independently of this, the timing of the brain damage could be the crucial factor determining the type of lesion.

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1. Background

The *COL4A1* and *COL4A2* genes encode, respectively, $\alpha 1$ and $\alpha 2$ chains of type IV collagen, which is a crucial component of the basal membrane in many tissues. They share a common locus at 13q34. In 2005, a semi-dominant *Col4A1* mutation in an animal model was shown to induce perinatal cerebral hemorrhages and predispose to porencephaly.¹ Monoallelic *COL4A1* and *COL4A2* mutations have since been identified as the cause of a group of multisystemic conditions in humans variably involving the brain, eyes, muscles, kidneys and heart. They are collectively referred to as “collagen IV-related disorders”.^{2,3} Affected individuals have been found to show a broad spectrum of cerebrovascular disease, whose onset occurs from fetal life onward and whose severity may range from small-vessel disease to fatal intraparenchymal hemorrhage. Brain MRI is usually abnormal in *COL4A1*- and *COL4A2*-mutated patients, even in the absence of neurological signs and symptoms. Characteristic intracranial findings are porencephaly and white matter abnormalities, isolated in association with other abnormalities. Silent microbleeds and calcification have also been reported.^{3–9} The neurological picture is also variable, with features directly related to the location and extension of the encephaloclastic changes. Extraneurological features are commonly observed and are useful diagnostic pointers. In particular, congenital cataract and other eye abnormalities (retinal tortuosity, retinal hemorrhages, anterior chamber abnormalities, microcornea) are often observed, as are muscular cramps, raised CK levels and kidney involvement. *COL4A1* mutations have also been found in two individuals with a muscle-eye-brain/Walker-Warburg syndrome phenotype.¹⁰ In addition, there have been rare reports of hepatic cysts and cardiac arrhythmias.¹¹ The severity of the global clinical picture is highly variable, ranging from a severe, early-onset and rapidly fatal disorder to asymptomatic situations.^{3,12,13}

We first suggested that malformations of cortical development (MCD) might occur in collagen IV-related disorders, specifically unilateral schizencephaly, in 2012,¹³ and since then reports of other new patients have confirmed that *COL4A1* mutations are likely to cause mainly schizencephaly.^{3,4,10,13–16} Recent descriptions of polymicrogyria, focal cortical dysplasia and nodular heterotopia have further expanded the phenotypic spectrum.⁴

We retrospectively reviewed MR images in a cohort of pediatric patients and relatives with mutations in *COL4A1* diagnosed in our centers, looking for cortical involvement. Our aim was to assess the frequency and define the type of cortical malformations encountered in this population.

2. Methods

In this study, we retrospectively evaluated MR images of 18 individuals who, having been submitted to genetic testing for clinical purposes in our centers in the period 2010–2016, were known to carry *COL4A1* mutations (13 children and 5 adults, described in detail in Table 1).

Brain MRI studies had been performed using three different scanners: two 1.5T MRI systems (Gyrosan Intera, Philips

Medical Systems, Best, The Netherlands; Ingenia System, Philips Healthcare, Best, The Netherlands) and one 3T MRI system (Discovery MR 750, GE Healthcare, Milwaukee, WI). The routine diagnostic protocol, performed without contrast material, included multiplanar standard T1- and T2-weighted images. For the purpose of the present study the images were retrospectively evaluated by two neuroradiologists, each with 15 years' experience, and the following radiological variables were assessed: white matter abnormalities, porencephaly, MCD, ventricular dysmorphism and posterior fossa abnormalities.

This study was performed in accordance with the ethical standards detailed in the Declaration of Helsinki. The three subjects whose cases are described herein all gave their written informed consent for the publication of this study.

3. Results

Cortical malformations were found to be present in three of the 18 *COL4A1*-mutated individuals reviewed: polymicrogyria was found in two patients (cases 1 and 2) and schizencephaly in a relative (case 3).

3.1. Case 1

Case 1 is a six-year-old male. He is the only child of healthy consanguineous parents (first-degree cousins) with no family/personal medical history of note. He was born at term by natural delivery after a pregnancy complicated by oligohydramnios. Microcephaly was present at birth (head circumference 31 cm, <10th percentile); postnatally, neurological examination showed facial asymmetry, hypomobility of the right arm, and hypotonia and hyperreflexia of the right side of the body. Ophthalmological examination revealed esotropia of the right eye and optic sub-atrophy.

At the age of 12 months, the child developed infantile spasms with hypsarrhythmia on EEG; therapy with vigabatrin, valproic acid and nitrazepam led to complete control of seizures by the time he was 4 years old. At 6 years of age neurological examination confirmed microcephaly (47 cm, <3rd percentile, >-2SD), right hemiplegia, visual impairment, absent language and poor relational skills.

Furthermore, at the same age the child presented two episodes of asymptomatic macrohematuria without abnormalities on abdominal ultrasound.

MRI, performed at the age of 6 years, showed bilateral periventricular and deep white matter abnormalities, left nucleo-capsular porencephaly and fronto-insular polymicrogyria (Fig. 1A–D).

Genetic analysis in this patient, performed after exclusion of other causes of cerebral microangiopathy (coagulation factor screening), was prompted by the MRI finding of porencephaly and its association with episodes of macrohematuria. Sanger sequencing showed a de novo heterozygous mutation in the *COL4A1* gene: c.3715G>A (GeneBank Accession number: NM_001845.5), p.Gly1239Arg (GeneBank Accession number: NP_001836.3). Array CGH was not carried out. This mutation was previously reported in a girl with porencephaly and an episode of microangiopathic

Table 1 – MRI data of 18 carriers of COL4A1 mutations diagnosed between 2010 and 2016.

Case	Gender	Nucleotide mutation	Amino acid mutation	Age at first symptoms	Neurological clinical picture	Neuroradiological findings	Other features
1 Not previously described	M	c.3715G>A exon 42	p.Gly1239Arg	2 months of age	Microcephaly, right hemiplegia, esotropia, visual impairment, epilepsy, absent language and poor relational skills	Bilateral periventricular and deep white matter abnormalities, nucleo-capsular porencephaly and left frontal insular polymicrogyria	Optic sub-atrophy, asymptomatic macrohematuria
2 described in Zangaglia S et al. Neurology 2018 (4) Family 1	M	c.4105G>C exon 47	p.Gly1369Arg	2 years	Speech delay, dysarthria, drooling	White matter T2 hyperintensities and left frontal polymicrogyria	Absent
3 described in Tonduti et al. Neuropediatrics 2012 (13)	F	c.1973G>A exon 27	p.Gly658Asp	23 years (TIA)	Absent	Old pontine hematoma, multiple cerebrovascular lesions, both in the basal ganglia and in the hemispheric white matter bilaterally, and mesial frontal schizencephaly	Raised CPK, cramps, congenital cataract, microhematuria
4 described in Livingston J et al. Neuropediatrics 2011; 42 (6):227–233.	M	c.1973G>A exon 27	p.Gly658Asp	4 days	Spastic diplegia, epilepsy	Periventricular calcification, calcification of basal ganglia and thalami, white matter abnormalities	Raised CPK, cramps
5 described in Tonduti et al. Neuropediatrics 2012 (13)	M	c.2159G>A exon 29	p.Gly720Asp	15 days (dystonia)	Spastic-dystonic tetraparesis, cerebral visual impairment	Bilateral brain hemorrhage, dilatation of the right lateral ventricle, white matter abnormalities and calcification	Raised CPK, congenital cataract, altered kidney pyramids on US imaging
6 described in Tonduti et al. Neuropediatrics 2012 (13)	M	c.2159G>A exon 29	p.Gly720Asp	45 years (TIA)	Absent	Calcification and diffuse white matter abnormalities	Congenital cataract, raised CPK, renal cysts
7 described in Decio A et al. Am J Med Genet 2015. Part A 167A:810–815	M	c.3712C>T exon 42 (inherited), c.2458+1G>A intron 31 (de novo)	p.Arg1238Cys, donor splice-site variant	3 months	Epilepsy, spastic diplegia	White matter abnormalities, brain calcification	Congenital cataract, cramps, raised CPK, microhematuria
8 Not previously described	F	c.1537-2A>G intron 24	Acceptor splice-site variant	6 months	Cerebral visual impairment, epilepsy, cognitive disability	White matter abnormalities, basal ganglia calcification	Raised CPK, neonatal cutaneous steatonecrosis
9 described in Livingston J et al. Neuropediatrics 2011; 42 (6):227–233.	F	c.2969G>A exon 36	p.Gly990Glu	At birth	Spastic-dystonic tetraplegia, microcephaly, severe visual deficit and marked developmental delay	Irregular ventricular outline, small porencephalic cyst in communication with the body of the left lateral ventricle, high signal on T2 sequences within the periventricular and deep hemispheric white matter, calcification	Congenital cataract, microphthalmia and bilateral corneal and iris abnormalities, raised CK

10 Not previously described	M	c.2699G>A exon 33	p.Gly900Glu	6 months (psychomotor delay)	Hemiparesis (right side), epilepsy	Sequelae of prenatal/perinatal haemorrhage, calcification	Congenital cataract
11 Not previously described	F	c.2716 + G>T intron 33	Donor splice-site variant	4 months (seizures and psychomotor delay)	Spastic-dystonic tetraplegia, microcephaly, epilepsy, profound intellectual disability	Bilateral periventricular, cortical subcortical and cerebellar gliosis and porencephalic lesions, nucleo- capsular abnormalities, corpus callosum atrophy, calcification	Raised CPK, micro- hematuria, ocular abnormalities
12 Described in Shah et al. Dev Med Child Neurol 2012, Jun; 54 (6):569–74. Deml et al. Clin Genet 2014; Nov; 86 (5):475–81.	F	c.2317G>A exon 30	p.Gly773Arg	3rd trimester of gestation	Spastic-dystonic tetraparesis, epilepsy, profound intellectual disability	Ventricular dilatation, atrophy, nucleo-capsular lesions, corpus callosum atrophy, calcification	Congenital cataract, glaucoma, vesico-ureteral reflux
13 Described in Shah et al. Dev Med Child Neurol 2012, Jun; 54 (6):569–74. Deml et al. Clin Genet 2014; Nov; 86 (5):475–81.	M	c.2317G>A exon 30	p.Gly773Arg	25th week of gestation	Tetraparesis, drug-resistant epilepsy, microcephaly, severe developmental delay	Prenatal multifocal hemorrhages	Congenital cataract, microphthalmia
14 Not previously described	M	c.3383T>A exon 39	p.Ile1128Asn	31st week of gestation (brain hemorrhage)	Psychomotor delay, epilepsy, hemiparesis (left side), esotropia	Right fronto-parietal porencephaly with hypotrophic hemisphere, without calcification	Absent
15 Not previously described Family 1	F	c.4105G>C exon 47	p.Gly1369Arg	20th week of gestation (brain hemorrhage)	Psychomotor delay, epilepsy	Previous multifocal hemorrhages, calcification, white matter abnormalities	Absent
16 Not previously described Family 1	F	c.4105G>C exon 47	p.Gly1369Arg	Asymptomatic	Sporadic cramps	Vascular encephalopathy, old right occipital bleed	Mild mitral insufficiency
17 Not previously described Family 1	M	c.4308G>C exon 47	p.Gly1396Arg	Not available	Psychomotor delay, cognitive impairment, epilepsy	Not available	Not available
18 Not previously described Family 1	M	c.4308G>C exon 47	p.Gly1396Arg	Asymptomatic	Not available	Vascular encephalopathy	Not available

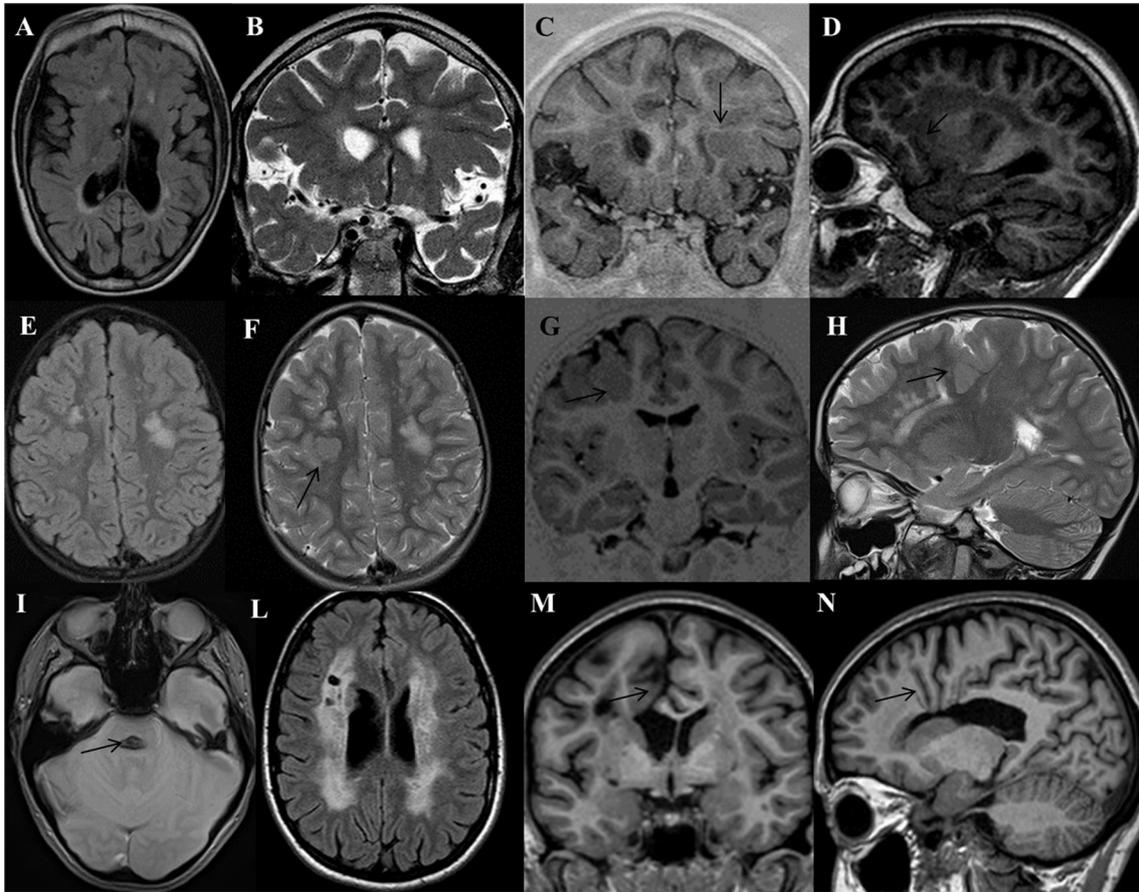


Fig. 1 – Non-contrast brain MRI: axial fluid-attenuated inversion recovery-FLAIR (A, E, L); coronal/sagittal T2-weighted turbo spin echo-TSE (B, F, H); coronal phase-sensitive inversion recovery-PSIR (C, G, M); axial T2-weighted fast field echo-FFE (I); sagittal magnetization-prepared rapid gradient echo-MPRAGE (D, N). Case 1 (A–D): bi-hemispheric leukoencephalopathy (A), left nucleo-capsular porencephaly (B) and left frontal insular polymicrogyria (C, D, black arrows); Case 2 (E–G): multifocal abnormalities of the white matter (E–F) and left frontal polymicrogyria (F, G, H, black arrows); Case 3 (I–N): old hematoma in the pons (I, black arrow), diffuse cerebrovascular lesions in the supratentorial white matter bilaterally (L), and mesial frontal schizencephaly (M, N, black arrow).

hemolysis in infancy, and also in her father, who was affected by HANAC (hereditary angiopathy with nephropathy, aneurysms and muscle cramps OMIM: 611773). p.Gly1239Arg was not present in population databases, and three different bioinformatics programs (PolyPhen2, SIFT, Mutation Taster) all predicted this mutation as pathogenic.

3.2. Case 2

Case 2 is a seven-year-old male born to healthy unrelated parents. The perinatal period was uneventful (head circumference 35 cm, 50th percentile).

The family history was positive for intellectual disability and seizures (a maternal uncle). The patient was investigated at the age of 5 years for a severe isolated language disorder characterized by speech delay, dysarthria and drooling. Neurological examination was otherwise normal and microcephaly was not present.

Brain MRI, performed at the age of 5 years, showed multifocal white matter hyperintensities and right frontal polymicrogyria (Fig. 1E–H).

The polymicrogyria prompted us to carry out NGS analysis. Performed using a custom targeted resequencing panel covering 82 genes (Haloplex panel, Agilent) and Paired End protocol on MiSeq (Illumina), this resulted in the detection of a COL4A1 mutation — c.4105G>C (GeneBank Accession number: NM_001845.5), p.Gly1369Arg (GeneBank Accession number: NP_001836.3) — and allowed us to exclude other causes of the polymicrogyria. This mutation has not previously been reported in the literature or in the mutation databases, but has been considered probably pathogenic due to its absence in population databases and the involvement of a glycine residue of collagen protein⁴. The etiological importance of the COL4A1 mutation found was simultaneously suggested by the occurrence of a fetal subependymal hemorrhage at 20 weeks of gestation during the mother's second pregnancy (case 15, Table 1).

Subsequently, the mutation was sought in the child's family (Family 1, Table 1): it was detected in his mother (whose brain MRI, performed at the age of 36 years, showed mild supratentorial leukoencephalopathy and hemosiderin deposits) (case 16, Table 1), in the mother's uncle (case 17, Table 1), and in the child's maternal grandfather (case 18,

Table 1 (the latter showing only mild leukoencephalopathy on brain MRI, performed at the age of 65 years).

3.3. Case 3

Case 3 is a 31-year-old female, the mother of a COL4A1-mutated patient affected by congenital spastic diplegia (patient 3, **Table 1**). We have already described and illustrated this case in detail in a previous study.¹³ We have had no subsequent follow-up with this patient and therefore have no further information to add. Case 3 and her son carry the same heterozygous c.1973G>A mutation (GeneBank Accession number: NM_001845.5) in exon 27 leading to the p.G658D (GeneBank Accession number: NP_001836.3) aminoacidic change. This mutation results in the substitution of aspartic acid for the highly conserved glycine residue at position 658 within the triple helix domain. Direct sequencing of the coding exons and analysis of flanking intronic sequences of COL4A1 were conducted using Sanger sequencing.

4. Discussion

For the purpose of this study, we reviewed a cohort of pediatric patients and relatives with mutations in COL4A1, looking for cortical involvement. The patients showed a variable neuroradiological phenotype, with features including white matter lesions, hematoma and porencephaly. Among the 18 individuals analyzed (patients and relatives), three cases with cortical malformation were found. One case presented schizencephaly (case 3) and two showed polymicrogyria (case 1 and case 2). The latter, being a feature only recently been described in the literature,⁴ probably expands the phenotypic spectrum of COL4A1 mutations.

Mutations in COL4A1 are known to cause small-vessel fragility leading to hemorrhage and ischemic damage with ante-, peri- or postnatal onset.¹⁷ They are frequently associated with porencephaly especially in preterm infants, probably related to focal disruption of vascular basal membrane.^{1,18} It should be noted, however, that our patient with porencephaly (case 1) was born at term without a history of head trauma, and without evidence of fetal intracranial hemorrhage on routine ultrasound examinations. This suggests that subtle bleeding, silent prenatally, can also be responsible for the damage.

Our initial suggestion that MCD, specifically unilateral schizencephaly, might occur in collagen IV-related disorders dates back to 2012 (13), and since then reports of other new patients have confirmed that COL4A1 mutations are more likely to cause schizencephaly than polymicrogyria, and that the schizencephaly usually involves the anterior hemispheric regions (frontal, perirolandic or perisylvian).^{3,13–15,19–29} Recently, Zagaglia et al.⁴ reported various MCD, including schizencephaly, polymicrogyria, focal cortical dysplasia and nodular heterotopia, in 11/38 new and 7/55 published patients. In these studies, MCD, when present, were always associated with white matter vascular lesions.

It is known that porencephaly and schizencephaly can be concomitant with polymicrogyria.^{22,23} The possibility of a polymicrogyric neocortex bordering the schizencephalic cleft, and the association between acquired encephaloclastic defects

(including hemorrhage or bland ischemic infarction, which can also lead to porencephaly/schizencephaly) and subsequent polymicrogyria are well established.^{24–26} However, despite the identification of a growing number of genetic causes of polymicrogyria,^{27–30} no genetically determined vascular cause of this malformation has yet been described.^{14,31,32} Bilateral perisylvian/perirolandic polymicrogyria is usually considered genetic in origin, while unilateral forms are more likely acquired; that said, some cases with unilateral polymicrogyria of genetic origin have recently been reported.^{33,34} The finding of unilateral polymicrogyria variably combined with porencephaly, schizencephaly and calcification³¹ (without evidence of congenital CMV infection) suggests that the underlying trigger could be a destructive vascular insult (hypoxia-ischemia or hemorrhage), capable of resulting in different lesions depending on the severity of the brain damage and the timing of its onset (before, during or after neuronal migration).²⁶ This is similar to what is seen in twin–twin transfusion syndrome, which can result in various types of brain lesion of antenatal origin, including hydranencephaly, porencephaly, polymicrogyria, other sulcation abnormalities, germinal matrix-intraventricular hemorrhage and white matter injury, depending on the timing and mechanism of injury.^{35–37}

Nevertheless, a key or concurrent primary role of abnormal basal membrane in intracellular signaling pathways, also regulating cell migration,^{38,39} cannot be excluded. The difficulty in establishing such a relationship (even only temporal) is due, among other things, to the fact that the acquired encephaloclastic defect may be clinically obscure, as in our cases. Similarly, a vascular malformation found to be topographically associated with polymicrogyria cannot be taken to constitute a concrete proof-of-concept demonstration of vascular induction of a cortical malformation.⁴⁰ Despite this, the extension of cortical malformations, both in general⁴⁰ but also specifically in COL4A1-mutated patients, seems to respect vascular territories.

In line with a previous literature report,³ we found MRI abnormalities, namely schizencephaly and an old pontine hematoma, in a mutation carrier (case 3) without permanent neurological impairment; interestingly, MRI examination of case 3's son showed a periventricular leukomalacia-like pattern, but no cortical malformations, even though he carried the same mutation as his mother. This suggests that cortical involvement is not simply a consequence of a genetic impairment, but needs co-factors in order to develop. The same case showed multiple cerebrovascular lesions in the basal ganglia. This together, with the presence of pontine bleeding and periventricular porencephaly, may indicate a major susceptibility of the small vessels (e.g. perforator arteries, ventriculopetal penetrating arteries in the immature brain), although the periventricular porencephaly may also be explained by venous medullary infarction.

Our cases confirm that COL4A1 mutations may also cause cortical malformations, which should therefore be considered part of the spectrum of collagen IV-related disorders. Nevertheless, other genes potentially responsible for brain malformations were tested and ruled out in only one of our three cases, and we realize that COL4A1 mutations may not be the only cause of genetic predisposition to these malformations. Recent literature documented a second-hit pathogenesis in many MCD lesions, including polymicrogyria,⁴¹ with second

hits coming from brain somatic mutations. As none of patients in the present study underwent neurosurgery, this hypothesis cannot be tested. Moreover, some brain malformations (focal cortical dysplasia, pachygyria) have recently also been reported in patients with germline mutations in genes that usually cause epilepsy and neurodevelopmental features (i.e. *DEPDC5*, *SCN1A*, *PCDH19*).^{42–44} Such findings are obviously also related to improvements in the sensitivity of MRI technology and the experience of the radiologist.

In conclusion, although our understanding of the above issues needs to be refined, it may be opportune to analyze *COL4A1* in patients with cortical malformations, at least in selected scenarios characterized by other concomitant clinical (familiarity for juvenile stroke, cataracts, cramps and abnormal CPK) or neuroradiological (signs of ischemic and/or hemorrhagic insult, calcification, cortical malformation) findings.

What this paper adds

1. The phenotypic spectrum of *COL4A1* mutations includes cortical malformations.
2. Polymicrogyria and schizencephaly are both possible features.
3. An acquired encephaloclastic process seems the most likely mechanism.
4. The lesion type probably depends mainly on the timing of the damage.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Obtained.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

PA/OF wrote the manuscript, and analyzed and interpreted the radiological data; GV wrote the manuscript and reviewed the literature; OS wrote the manuscript, and analyzed and interpreted clinical data; PB analyzed and interpreted clinical data; TD/PL/FL analyzed and interpreted radiological data; PerA analyzed and interpreted genetic data; Study group members: analysis and interpretation of clinical, radiological

and genetic data; SB carried out the final revision. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejpn.2019.02.006>.

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