

## ‘De novo’ *Col4A2* mutation in a patient with migraine, leukoencephalopathy, and small carotid aneurysms

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Dear Sirs,

Collagen IV-related diseases affect the basement membrane and can be caused by *COL4A1* or *COL4A2* gene mutations. The phenotypic expression seems to be similar in both and encompass porencephaly, small-vessel disease, ocular involvement, peripheral myopathy, and kidney disease.

A 17-year-old boy presented with migraine headaches for 5 years. A brain MRI showed diffuse white matter hyperintensities on FLAIR sequence, while MRA revealed small aneurysms of both carotid siphons (Fig. 1). He had a completely normal physical exam. He never complained of muscular cramps, but a severe transient increase in CK level ( $\times 70$  the normal range) was recurrently measured 24–72 h after mild exercise (football). Myoglobinuria was ruled out at rest. Abdominal MRI and ophthalmologic examination with fluorescein angiography were normal. Sequencing of *COL4A1* did not identify any mutation. *COL4A2* gene sequencing identified the c.2105 G>A mutation in exon 28, at protein level resulting in a glycine

substitution: p.(Gly702Asp). This mutation has been found in a large family showing dominant porencephaly with reduced penetrance [1, 2]. The present report adds a distinct patient of Caucasian origin with the same mutation: this allows to confirm its pathogenicity (after molecular evidence—nucleotide and protein changes as impact on the triple helix formation—and cellular involvement). His healthy parents did not carry the mutation (‘de novo’). After 1-year follow-up, brain MRI and MRA remained unchanged.

Type IV collagens are a major component of all basement membranes. Six genes arranged by pairs encode for six alpha polypeptide chains. The *COL4A2* gene encodes the alpha 2 polypeptide chain which forms heterotrimers with two alpha 1 chains. Each polypeptide chain contains a triple helical domain, a short 7S domain and a globular non-collagenous (NC1) domain. The collagenous domain consists of Gly-Xaa-Yaa repeats with interruptions. Putative *COL4A2* gene mutations were found on X location of the repeats and in the NC1 domain in patients suffering from intra-cerebral haemorrhage (ICH) [3]. Significant differences in phenotypic expression of an individual mutation also suggest a role for environmental influences or genetic modifiers with a focus on the secretion’s regulation of mutant *COL4A2* from the endoplasmic reticulum [1]. Phenotypic variability (ICH, myopathy, etc.) seems to depend on different pathogenic mechanisms, and their respective severity may be correlated to the different locations of the mutation [4]. Increase CK level without cramps is well known in patients with HANAC syndrome [5]. A link between CK elevation and exertion has never been reported in patients with *COL4A2* gene mutation but was reported in mice with *COL4A1* gene mutations [6]. De novo mutations were found in two other patients [7, 8]. Our patient is up to now asymptomatic similar to adult carriers

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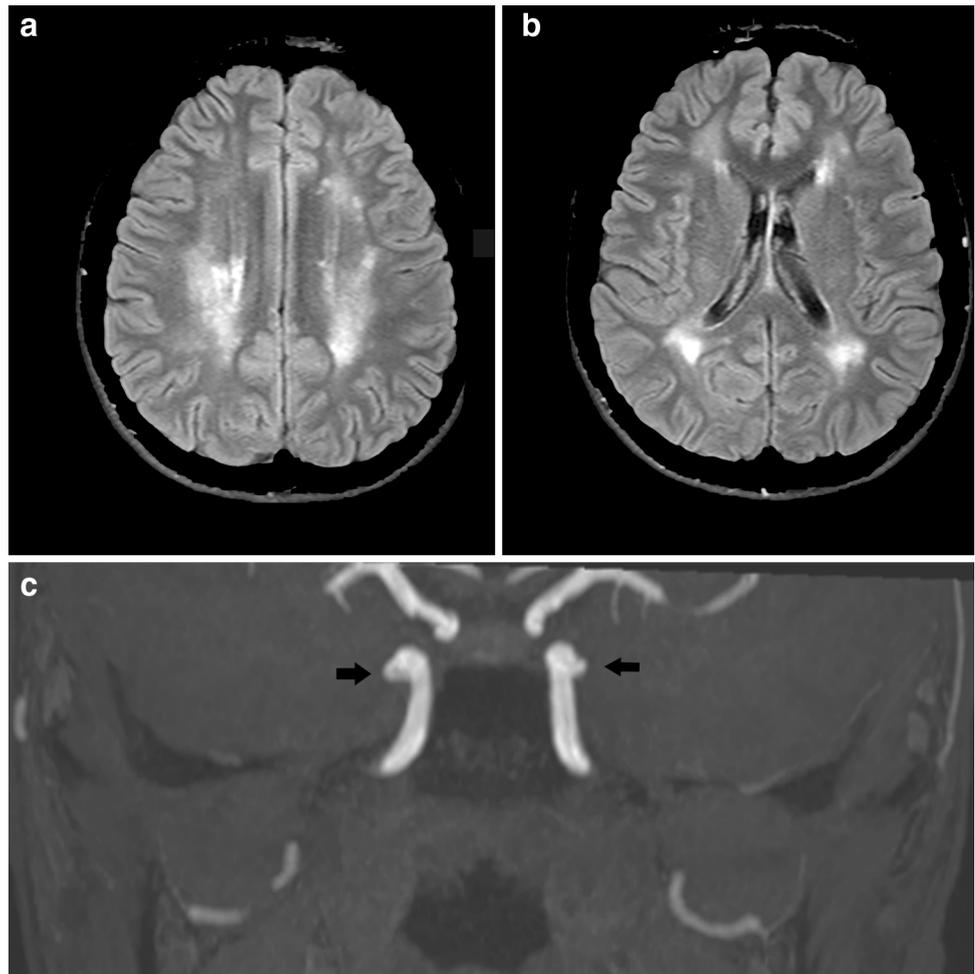
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**Fig. 1** Brain MRI (FLAIR sequence) shows leukoencephalopathy (a, b), and brain MRA shows small aneurysms of both carotid siphons (1.8 and 3.5 mm diameter) (c)



already identified [1, 2, 7, 9], but a carrier with the same mutation did not show any MRI anomaly suggestive of cerebral small-vessel disease at the time of the report (1–2) and in one sporadic patient (de novo mutation) a first deep ICH occurred at age 23 [8]. When considering the mutation's location near the C terminus of the triple helical domain, this may suggest a higher haemorrhagic risk [4]. An increase of ICH risk induced by intense exercise was recorded [4]. Two patients with *COL4A1* gene mutation and one with *COL4A2* mutation presented with ICH triggered by exercise [8, 10, 11]. Whether presymptomatic recommendations in patients with Collagen type IV mutations should address the caution for intense exercise still needs to be validated.

The finding of leukoencephalopathy and/or carotid siphon aneurysms in a patient should warrant *COL4A1* and *COL4A2* gene sequencing, even without a typical cerebral stroke event or family history. The case presented underlines the need for a comprehensive systemic evaluation, including CK quantification at rest and after exercise as well as ophthalmologic and kidney evaluation. Genetic counselling has to be provided to patients and (over time

with better phenotype delineation and correlation) even in asymptomatic carriers.

#### Compliance with ethical standards

**Ethical standards** Patient gave informed consent and details that might disclose the identity of the patient have been omitted. This case has been done in accordance with ethical standards stated in the 1964 Declaration of Helsinki and its later amendments.

**Conflicts of interest** None.

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