



Letter to the Editor

An Italian family carrying a new mutation in the *COL4A1* gene

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Dear Editor,

Cerebral small vessel disease (SVD) is a group of pathologies affecting small arteries, arterioles, capillaries and small veins in the brain [1]. Neurological findings include cognitive impairment, dysfunction of gait and balance, mood disorders, and increased risk of stroke and dementia. Cerebral SVD is driven by a complex mix of environmental and genetic risk factors; both familial and sporadic conditions have been reported [2]. Mutations in the *NOTCH3*, *HTRA1*, *COL4A1*, *COL4A2* and *TREX1A* genes are known to cause the familial forms of SVD [2].

The *COL4A1* gene (chromosome13q34) encodes type IV collagen $\alpha 1$ chain, a crucial component of nearly all basement membranes including those of the vasculature, renal glomerules and eye structures [3].

Variant in *Col4a1* lead to very different clinical pictures, which are much more severe in children than in adults. Children mainly show perinatal intracerebral hemorrhages and porencephaly, whereas adults may manifest retinal bleeding with tortuous retinal vessels and bilateral cataracts, renal cysts (ranging from microhematuria to severe renal failure), ischemia and/or cerebral hemorrhages, leukoencephalopathy and elevated serum CK levels associated with muscle cramps [4].

Here we describe a new Italian family with wide variations in intra-familial phenotypic expressivity among members harboring a new variant in *COL4A1*.

The proband is a 26-year-old woman referred to our department for investigation of sweating, headache, muscle weakness, breathlessness, hemisomal paresthesia and visual disturbance. The EEG showed minimal diffuse paroxysmal activity, sensitive to SLI; brain MRI revealed severe areas of leukoencephalopathy in the semi-oval centres and bilaterally in the Rolandic areas. Fundus oculi examination displayed remarkable vessel tortuosity; a CT scan of the abdomen for liver or kidney cysts and abdominal aneurysms, was negative for parenchymal and vascular lesions.

We also examined the mother of the patient whose symptoms were limited to isolated episodes of headache. EEG was negative; fundus

oculi examination, CT scan of abdomen and brain MRI were normal. The patient's grandmother reported episodes of headache associated with scotomas, hemisomal paresthesia and phonemic paraphonesia since the age of 15 years. EEG, fundus examination and CT scan of the abdomen were negative; brain MRI showed some sporadic post-ischemic gliotic lesions in the basal nuclei and the white matter of both hemispheres.

Headache with characteristics similar to that of the proband was reported in a maternal cousin and the brother of the maternal grandmother.

Analysis of a NGS panel of 55 genes related to leukoencephalopathies revealed a heterozygous variant c.1055A > G, p.(Asn352Ser) in the *ARSA* gene, already reported in the literature in compound heterozygous or homozygous state with metachromatic leukodystrophy [5].

In light of the retinal vascular anomalies found in the proband, we analysed an NGS panel of 10 genes associated with vascular abnormalities and identified a variant c.3058A > G (p.(Thr1020Ala)) of uncertain significance in the *FBN1* gene (rs111801777), and previously unreported variants c.1473A > G (p.(Glu491=)) in the *TGFBR2* gene, and c.1619A > G, p.(Lys540Arg) in exon 25 of the *COL4A1* gene. Regarding the *FBN1* gene variant, transcript analysis did not reveal anomalies in mRNA processing.

The *COL4A1* variant (rs771824175) was predicted to be damaging by CADD-phred prediction tools (CADD-phred = 21.1) and the minor allele frequency (MAF) of the variant was 0.002%.

All three members of the family carried the same *COL4A1* variant, c.1619A > G, p.(Lys540Arg), in line with its causative role.

COL4A1-related disorders are transmitted by autosomal dominant inheritance and 27% of cases are associated with de novo pathogenic variants [2]. Intra- and inter-familial neurological variability has been reported including ischemic as well as hemorrhagic stroke. Thus, the distinction between de novo and familial cases on the basis of medical history, can be challenging.

Triple helical glycine substitutions are the most frequent class of genetic variant. Glycine is most often replaced by a charged amino acid

although the position of the variant appears to be more important than the identity of the substituting amino acid. Indeed, all the *COL4A1* pathogenic variants associated with hereditary angiopathy, nephropathy, aneurysms and muscle cramps are in exons 24 and 25 [6,7]. Variants associated with porencephaly and small-vessel brain disease are mostly between exons 25 and 51 [8]. In addition to being located on exon 25, the variant found in our family, is very close to the already reported pathogenic variant p.R538G [9].

The three members of the new family showed different phenotypes confirming high intrafamilial heterogeneity. Genetic anticipation is not reported in the literature. The penetrance of *COL4A1*-related disorders is probably close to 100%, with expression varying in age of onset and severity of clinical symptoms, even in the same family. Finally we confirmed the importance of fundus oculi examination in patients with vascular pathology, irrespective of how young they are, since it is often a hallmark of SVD.

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