FULL-LENGTH ARTICLE NPub.org/y1str3

Neurologic phenotypes associated with *COL4A1/2* mutations

Expanding the spectrum of disease

Sara Zagaglia, MD, Christina Selch, MD, Jelena Radic Nisevic, MD, et al.

Cite as: *Neurology*® 2018;91:e2078-e2088. doi:10.1212/WNL.0000000000006567

Correspondence
Dr. Sisodiya
s.sisodiya@ucl.ac.uk

Study objective

To characterize the neurologic phenotypes associated with *COL4A1/2* mutations.

Summary results

COL4A1/2 mutations are associated with a typical severe neurologic presentation and a broad spectrum of milder phenotypes with epilepsy as the predominant feature.

What is known and what this paper adds

COL4A1/2 mutations cause a broad spectrum of cerebrovascular diseases. This study clarifies the neurologic phenotypes associated with these mutations.

Participants and setting

This study analyzed 55 previously reported patients with *COL4A1/2* mutations and epilepsy who were identified through a PubMed search. This study also analyzed 44 previously unreported patients with pathogenic *COL4A1/2* mutations who were identified through informal links and contact with established consortia. The previously unreported patients lived in Germany, the UK, Italy, Denmark, Australia, the USA, Estonia, Japan, and Portugal.

Design, size, and duration

A customized questionnaire was used to collect clinical and genetic data. Additional clinical data, including seizure history data, were collected for the previously unreported patients. EEG and MRI data were analyzed when available.

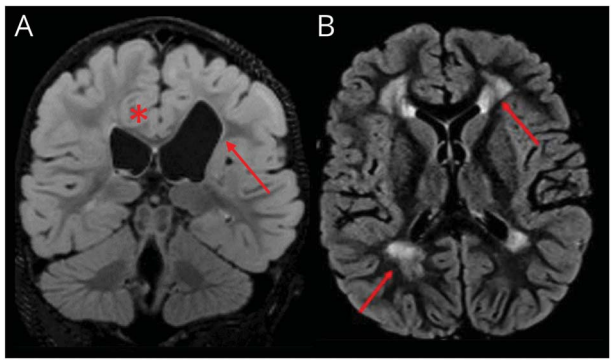
Primary outcome measures

The primary outcomes were neurologic presentations.

Main results and the role of chance

The most common phenotype involved childhood-onset focal seizures, with status epilepticus and resistance to antiepileptic drugs being frequent complicating factors. EEG typically revealed focal epileptiform discharges in the context of other abnormalities. Of the previously unreported patients who experienced focal seizures, approximately half had a porencephalic cyst or a malformation of cortical development colocalized with the area of the focal epileptiform discharges in brain MRIs, and these patients often exhibited extensive white matter abnormalities as well. This study also identified a subgroup of patients who had epilepsy as their main clinical feature and nonspecific findings in brain MRIs.

Figure MRI-detected brain abnormalities in 2 patients with *COL4A1* mutations



(A) The arrows point to enlarged ventricles, and the asterisk indicates callosal thinning (B) The arrows point to periventricular leukoencephalopathy.

Bias, confounding, and other reasons for caution

This study had a relatively small sample size and limited follow-up data.

Generalizability to other populations

This study's participants were predominantly young, so the generalizability of the results to older patients may be limited.

Study funding/potential competing interests

This study was funded by the EU and by the UK, and Estonian governments, and by various foundations. Some authors report receiving honoraria and research funding/support from various healthcare companies, having an academic collaboration with Congenica, and serving on journal editorial boards. Go to Neurology.org/N for full disclosures.

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.