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Somayeh Bakhtiari

Abbas Tafakhori

Sheng Chih Jin

Brandon S. Guida

Elham Alehabib

*See next page for additional authors*

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**Authors**

Somayeh Bakhtiari, Abbas Tafakhori, Sheng Chih Jin, Brandon S. Guida, Elham Alehabib, Saghar Firouzabadi, Kaya Bilguvar, Michael C. Fahey, Hossein Darvish, and Michael C. Kruer

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# Recessive *COL4A2* Mutation Leads to Intellectual Disability, Epilepsy, and Spastic Cerebral Palsy

Somayeh Bakhtiari, PhD, Abbas Tafakhori, MD, Sheng Chih Jin, PhD, Brandon S. Guida, PhD, Elham Alehabib, PhD, Saghar Firouzbad, PhD, Kaya Bilguvar, MD, Michael C. Fahey, PhD, Hossein Darvish, PhD,\* and Michael C. Kruer, MD\*

## Correspondence

Dr. Kruer  
mkruer@phoenixchildrens.com

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Dominant negative or haploinsufficient mutations in the collagen genes *COL4A1* and *COL4A2* are characterized by arterial basement membrane thickening resulting in a multisystem microangiopathy targeting the CNS but also potentially affecting the ocular, renal, cardiac, and muscular systems. Within the brain, such changes predispose affected individuals to recurrent ischemic and/or hemorrhagic strokes beginning during early fetal development but extending into the postnatal period and even into adulthood.<sup>1</sup> Mutations affecting glycine residues of the Gly-Xaa-Yaw (typically representing glycine-proline-4-trans-hydroxyproline in vertebrates) repeat domains that typify collagens usually manifest in an autosomal dominant (AD) fashion. However, recent work suggests that tissue-specific mutation effects may also occur, with mutations leading to gain of function effects in some tissues and loss of function effects in others.<sup>2</sup> Stroke-related complications may be insidious and clinically silent. Neuroimaging phenotypes of *COL4A*-associated disease include chronic white matter disease, porencephaly/hydranencephaly, encephalomalacia, cerebral calcifications, schizencephaly and hydrocephalus and corresponding clinical diagnoses of cerebral palsy, intellectual disability, cortical visual impairment, and epilepsy.<sup>3</sup>

Type IV collagen  $\alpha$  chains form heterotrimers with  $\beta$  chains in a 2:1 ratio, and incompletely penetrant AD inheritance is typical. Although autosomal recessive mutations of *COL4A1* have been described,<sup>4</sup> prior reports of *COL4A2*-associated disease have all featured AD inheritance. We describe 2 children from a consanguineous Iranian family with intellectual disability, spastic cerebral palsy, and epilepsy who each harbored the same homozygous mutation in *COL4A2*.

Pregnancies for both children were uncomplicated, and both were born at term by vaginal delivery. The couple's 8 year-old son was bedridden and exhibited cortical visual impairment. He did not fix or track stimuli. He had never been able to sit unassisted or control his head. He did not speak or demonstrate communicative intent. He had focal epilepsy that began at age 6 months, partially controlled with carbamazepine. Motor examination revealed spastic quadriplegia with ophthalmoplegia, nystagmus, and skew deviation. Brain MRI revealed bilateral colpocephaly and irregular ventricular contours. His sister was 20 years old at the time of evaluation. Milestone attainment had been globally delayed. She also had focal epilepsy with onset at 18 months. Seizures were controlled with phenobarbital and carbamazepine. She began walking independently at age 3 years. At the time of evaluation, she did not speak, and her

\*Both authors jointly supervised this work.

From the Pediatric Movement Disorders Program (S.B., B.S.G., M.C.K.), Barrow Neurological Institute, Phoenix Children's Hospital, AZ; Departments of Child Health (S.B., B.S.G., M.C.K.), Neurology, Genetics, and Cellular & Molecular Medicine, University of Arizona College of Medicine Phoenix, Phoenix, AZ; Iranian Center of Neurological Research (A.T., H.D.), Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran; Department of Genetics (S.C.J.), Washington University School of Medicine, St. Louis, MO; Student Research Committee (E.A.), School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran; Genetics Research Center (S.F.), University of Social Welfare and Rehabilitation Sciences, Tehran, Iran; Department of Genetics (K.B.), Yale University, New Haven, CT; and Department of Paediatrics (M.C.F.), Monash University, Melbourne, Victoria, Australia.

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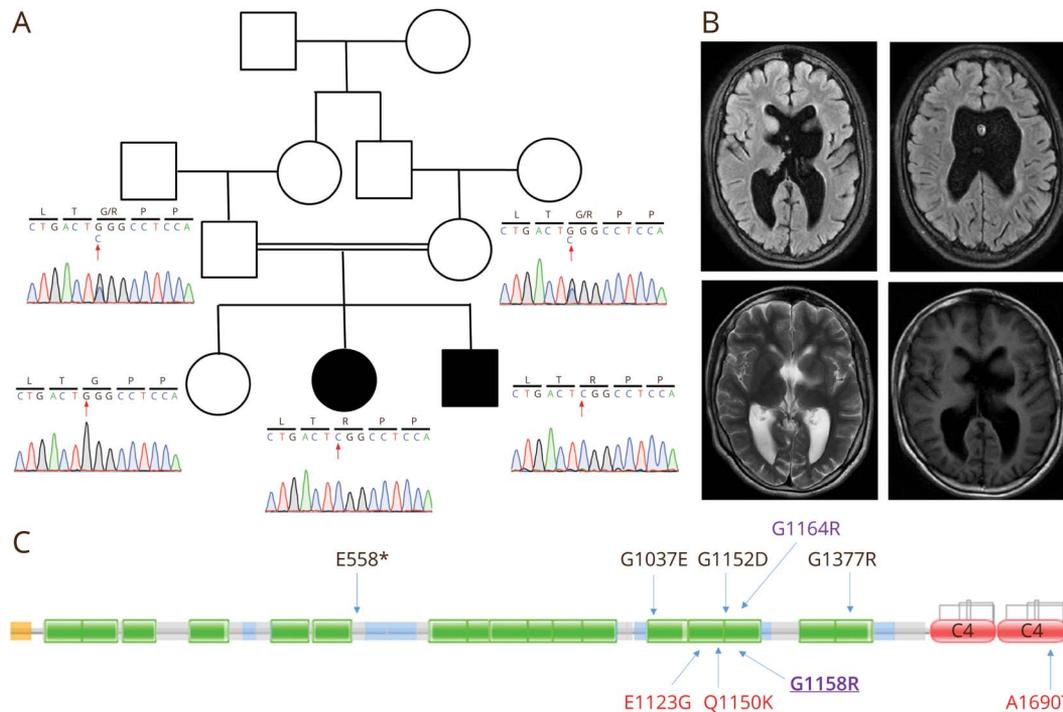
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Corresponding author Michael Kruer takes responsibility for the accuracy of the data presented, the conduct of the research, providing access to the original data, and the right to publish.

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(A) Pedigree demonstrating variant segregation. (B) Brain MRI findings from the affected sister demonstrate colpocephaly, irregular ventricular contours, encephalomalacia affecting the left greater than right caudate, putamen, globus pallidus, and thalamus, periventricular white matter injury, and thin corpus callosum. (C) Protein schematic with mapping of autosomal dominant mutations previously described and autosomal recessive variant described in this study (green = collagen triple helices; pink = procollagen C-terminal repeat domain; black variants indicate ischemic disease; red variants indicate hemorrhagic disease; purple variants indicate porencephaly; homozygous variant from this study bolded and underlined).

examination was significant for asymmetric spastic-dystonic quadriparesis with right-sided predominance. Her brain MRI showed irregular lateral ventricle contour with coalescent porencephaly and generalized cortical atrophy (figure, A). Neither patient was known to have ocular, kidney, skeletal, or cardiac muscle disease.

Both affected children and their parents provided informed consent for study participation in accordance with local ethics oversight and underwent whole-exome sequencing with filtering and variant prioritization as described previously.<sup>5</sup> This revealed a homozygous c.3472G>C (p.G1158R) variant in *COL4A2* (NM\_001846) segregating with disease status in the family (both parents are neurologically healthy, although neuroimaging was not able to be performed) (figure, B). This variant is novel (not found in gnomAD or the Greater Middle Eastern Variome server) and predicted to be deleterious (MetaSVM, CADD, SIFT, and PolyPhen), putatively by disrupting a glycine residue within a highly conserved Gly-Xaa-Yaw collagen triple helix repeat domain. Such glycine residues are known to be critical determinants of collagen stability and we anticipate that the substitution of an arginine residue to have a destabilizing effect.<sup>6</sup>

In comparison to previously described incompletely penetrant dominantly inherited mutations in *COL4A2*, this homozygous (p.G1158R) variant appears to exhibit autosomal

recessive inheritance, although our observations will benefit from subsequent confirmation. Our results indicate that both dominant and recessive forms of *COL4A2* disease exist. This finding has potentially important implications for the interpretation of clinical genetic testing in cases of porencephaly, hydrocephalus or idiopathic antenatal or perinatal ischemic/hemorrhagic stroke and for associated clinical phenotypes including epilepsy, intellectual disability, and cerebral palsy.<sup>7</sup>

### Data Availability

Full data are available to qualified investigators on reasonable request to the corresponding author.

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## Appendix Authors

Name	Location	Contribution
<b>Somayeh Bakhtiari, PhD</b>	Phoenix Children's Hospital	Designed and conducted bioinformatic analysis and revised the manuscript for important intellectual content
<b>Abbas Tafakhori, MD</b>	Tehran University of Medical Sciences	Enrolled participants; performed clinical phenotyping; and revised the manuscript for important intellectual content
<b>Sheng Chih Jin, PhD</b>	Washington University, St. Louis	Designed bioinformatic analysis and revised the manuscript for important intellectual content
<b>Brandon S. Guida, PhD</b>	Phoenix Children's Hospital	Designed and conceptualized the study and revised the manuscript for important intellectual content
<b>Elham Alehabib, PhD</b>	Shahid Beheshti University of Medical Sciences	Enrolled participants; performed clinical phenotyping; and revised the manuscript for important intellectual content
<b>Saghar Firouzabadi, PhD</b>	University of Social Welfare and Rehabilitation Sciences, Tehran	Enrolled participants; performed clinical phenotyping; and revised the manuscript for important intellectual content

## Appendix (continued)

Name	Location	Contribution
<b>Kaya Bilguvar, MD</b>	Yale University	Designed and conceptualized the study and revised the manuscript for important intellectual content
<b>Michael C. Fahey, PhD</b>	Monash University	Designed and conceptualized the study and revised the manuscript for important intellectual content
<b>Hossein Darvish, PhD</b>	Tehran University of Medical Sciences	Designed and conceptualized the study; integrated clinical and genomic findings; and revised the manuscript for important intellectual content
<b>Michael C. Kruer, MD</b>	Phoenix Children's Hospital	Designed and conceptualized the study; integrated clinical and genomic findings; and drafted and revised the manuscript

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