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

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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.[1] 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.[2] 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.[3]

Type IV collagen α chains form heterotrimers with β chains in a 2:1 ratio, and incompletely penetrant AD inheritance is typical. Although autosomal recessive mutations of *COL4A1* have been described,[4] 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

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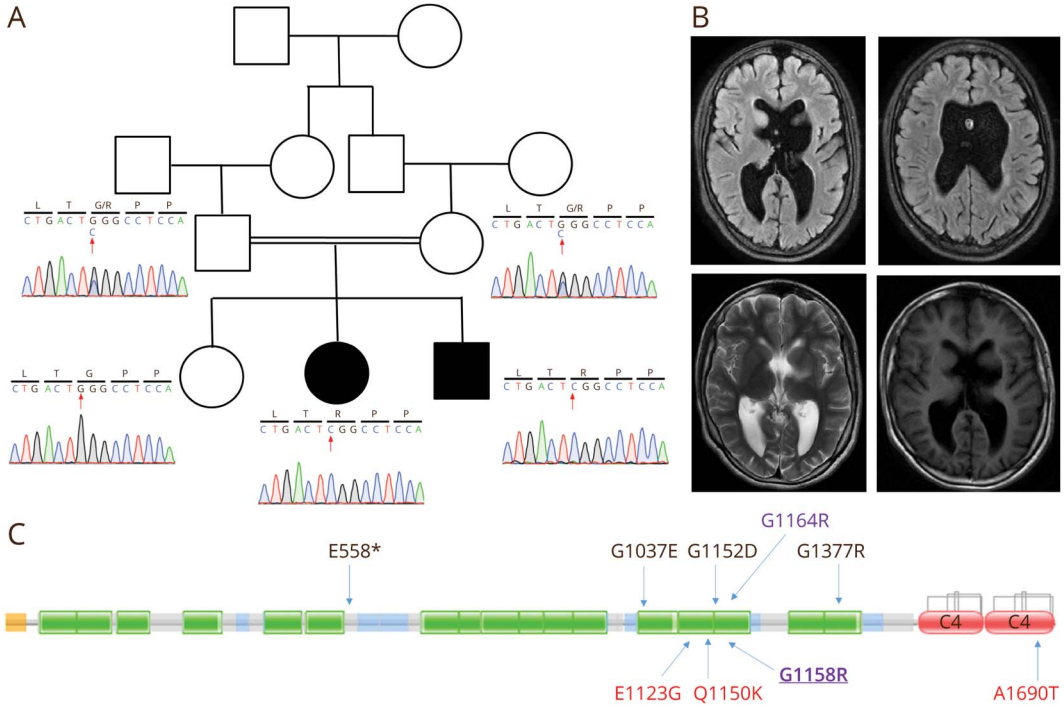
Figure Clinical, Neuroimaging, and Genetic Findings in the Index Family



(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.[5] 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.[6]

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.[7]

Data Availability

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

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Disclosure

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Hossein Darvish, PhD	Tehran University of Medical Sciences	Designed and conceptualized the study; integrated clinical and genomic findings; and revised the manuscript for important intellectual content
Michael C. Kruer, MD	Phoenix Children's Hospital	Designed and conceptualized the study; integrated clinical and genomic findings; and drafted and revised the manuscript

References

1. van der Knaap MS, Smit LM, Barkhof F, et al. Neonatal porencephaly and adult stroke related to mutations in collagen IV A1. *Ann Neurol* 2006;59(3):504-511.
2. Labelle-Dumais C, Schuitema V, Hayashi G, et al. *COL4A1* mutations cause neuromuscular disease with tissue-specific mechanistic heterogeneity. *Am J Hum Genet* 2019;104(5):847-860.
3. Zagaglia S, Selch C, Nisevic JR, et al. Neurologic phenotypes associated with *COL4A1/2* mutations: expanding the spectrum of disease. *Neurology* 2018;91(22):e2078-e2088.
4. Yaramis A, Lochmüller H, Töpf A, et al. *COL4A1*-related autosomal recessive encephalopathy in 2 Turkish children. *Neurol Genet* 2020;6(1):e392.
5. Jin SC, Lewis SA, Bakhtiari S, et al. Mutations disrupting neuritogenesis genes confer risk for cerebral palsy. *Nat Genet* 2020;52:1046-1056.
6. Jeanne M, Gould DB. Genotype-phenotype correlations in pathology caused by collagen type IV alpha 1 and 2 mutations. *Matrix Biol* 2017;57-58:29-44.
7. Fahey MC, Maclennan AH, Kretzschmar D, Gecz J, Kruer MC. The genetic basis of cerebral palsy. *Dev Med Child Neurol* 2017;59(5):462-469.