A COL4A1 variant in a neonate with multiple intracranial hemorrhages and congenital cataracts

Ayane Yakabe¹, Tamaki Ikuse¹,², Natsuki Ito¹, Hiromichi Yamada¹, Nobutomo Saito¹, Yuri Kitamura¹, Tomohiro Iwasaki¹, Mitsuru Ikeno¹, Hiroki Suganuma¹, Shinpei Abe¹, Nao Miyazaki¹, Ken Hisata¹, Hiromichi Shoji¹, Tomoyuki Nakazawa¹, Hidetaka Eguchi² and Toshiaki Shimizu¹

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A 2-year-old neonate presented with seizures, multiple intracranial hemorrhages, and bilateral congenital cataracts. Targeted next-generation sequencing of the collagen type IV alpha 1 chain (COL4A1) gene revealed a heterozygous de novo missense variant (NM_001845.6:c.2291G>A/p.Gly764Asp). This missense variant adds to the compendium of COL4A1 variants and is associated with a COL4A1-related disorder.

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Type IV collagen (COL4) is the most predominant and widely expressed protein in the basement membranes of systemic organ tissues. It has a helical heterotrimeric structure formed by three α chain sets of α1-6 and mainly consists of α1 and α2. The COL4A1 and COL4A2 genes reside on chromosome 13q, encoding the α1 and α2 chains of COL4, respectively. It is well known that pathogenic variations in COL4A1/A2 cause abnormalities in the basement membranes of systemic organs. For example, various cerebrovascular diseases, such as the development of porencephaly, schizencephaly, intracerebral hemorrhage, periventricular hyperintensity, ventricular enlargement, cerebellar atrophy, intracerebral calcification, cerebral infarction, and cerebral aneurysm, caused by the fragility of the basement membranes of cerebral blood vessels have been reported. Less lethal complications include cataracts, microphthalmia, tortuous retinal arterioles, retinal hemorrhages, hematuria, proteinuria, renal dysfunction, renal cysts, arrhythmia, elevated serum creatine kinase levels, muscle spasms, Raynaud’s phenomenon, and hemolytic anemia. Most COL4A1/A2 variants result from missense variants due to the substitution of glycine in the Gly-Xaa-Yaa triple-helical domain. In addition, splice-site mutations leading to haploinsufficiency and frameshift mutations have been reported, indicating that the haploinsufficiency of either COL4A1 or COL4A2 is another pathogenic mechanism. The resulting phenotype and severity vary from case to case, and neurological and other prognoses differ greatly depending on the severity of complications. Throughout life, the risk of cerebral hemorrhage is higher than that in the normal population, and the risk of bleeding is further increased by exercise, surgical intervention, and anticoagulant medication use. Investigations of treatments have been limited to nonclinical studies; therefore, no effective treatment has been established for this disorder.

We report the case of a 2-year-old male neonate who was born healthy at 36 weeks and 4 days of gestation with normal vaginal delivery in another hospital, with a birth weight of 2606 g (+0.14 standard deviation) and height of 46.6 cm (−0.11 standard deviation). On the second postnatal day, the patient presented with a generalized clonic seizure. Brain ultrasonography and computed tomography (CT) scans were suggestive of multiple intracranial hemorrhages with intraventricular perforation. On Day 3, the patient was transferred to our hospital (Juntendo University Hospital) for the management and treatment of multiple intracranial hemorrhages and seizures. A magnetic resonance imaging (MRI) scan revealed multiple parenchymal and subdural hemorrhages and dilation of the blood vessels in the semioval

Fig. 1 Magnetic resonance imaging (MRI) scan of the brain. Axial view, T1-weighted images show multiple parenchymal hemorrhages (arrows) and subdural hemorrhages (arrowheads).
The patient possessed a de novo mutation (PS2). The identification of sequence variants leads to a substitution of a glycine in the Gly-X-Y of pathogenic variants have accumulated substitutions in this Gly-4. Moreover, the diagnosis of a deleterious/damaging changes (PP3). In addition, the symptoms observed in the patient were typical of a cerebrovascular disease and bilateral congenital cataracts, regardless of the family history of COL4A1/A2-related disorders. Multiple intracranial hemorrhages experienced during the patient’s course of birth and the presence of bilateral congenital cataracts led us to perform molecular testing to identify the COL4A1/A2 variant, and we diagnosed the patient with a COL4A1-related disorder. Since the variant was not detected in the parents’ blood DNA, the risk of the disorder in future siblings could be considered low. However, future pregnancies should be carefully monitored because genome sequencing was performed only against blood DNA and not against tissue DNA.

In conclusion, we identified a de novo missense variant of the COL4A1 gene in a neonate leading to a COL4A1-related disorder manifesting as multiple intracranial hemorrhages and bilateral congenital cataracts.

**HGV DATABASE**

The relevant data from this Data Report are hosted at the Human Genome Variation Database at https://doi.org/10.6084/m9.gshare.hgv.3202.

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COMPETING INTERESTS
The authors declare no competing interests.

ADDITIONAL INFORMATION
Correspondence and requests for materials should be addressed to Tamaki Ikuse.

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