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A de novo COL4A1 Gene Mutation with Developmental Delay and Neuro-ophthalmologic Features

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INTRODUCTION

Pathogenic mutations of the COL4A1 gene cause COL4A1-related disorder, an autosomal dominant disease characterized by a broad phenotypic spectrum involving cerebrovascular, renal, ophthalmological, cardiac, and muscular systems. Cerebrovascular involvement includes autosomal dominant familial porencephaly and cerebral small-vessel disease, which may lead to neurodevelopmental delay.

CASE REPORT

An 18-month-old male with a de novo COL4A1 gene mutation (c.3742+1G>T, heterozygous)
was first referred to our clinic at the age of 6 months with chief complaint of delayed motor development accompanied by intermittent downward gaze deviation and poor visual fixation.

- **Birth history**

Full term - 2,675g - Cesarean section delivery with asymmetric intrauterine growth restriction

- **Brain MRI**

Porencephalic cystic lesion in the parietal white matter communicating with the right lateral ventricle, along with volume loss of the periventricular white matter, consistent with chronic periventricular leukomalacia (Figure 1)

- **Developmental evaluation**

The Bayley-III Scales was first performed at 6 months of age and repeated during follow-up at 12 and 18 months, demonstrating global developmental delay (Table 1).

- **Genetic evaluation**

In targeted next generation sequencing (NGS),
we detected variants in the SPAST gene (c.56C>G, heterozygous), WASHC5 gene (c.1275dup, heterozygous, likely pathogenic), and COL4A1 gene (c.3742+1G>T, heterozygous) in the patient.
Other genetic mutations were identified in his mother, but **COL4A1 gene mutation** was not detected in both parents (Table 2).

- **Neuro-ophthalmologic manifestations during follow-up**

- At 1 year of age, he developed seizure-like activity and was started on antiepileptic medication.
- On subsequent ophthalmologic evaluation, bilateral optic nerve atrophy, esotropia, and hyperopia were noted.

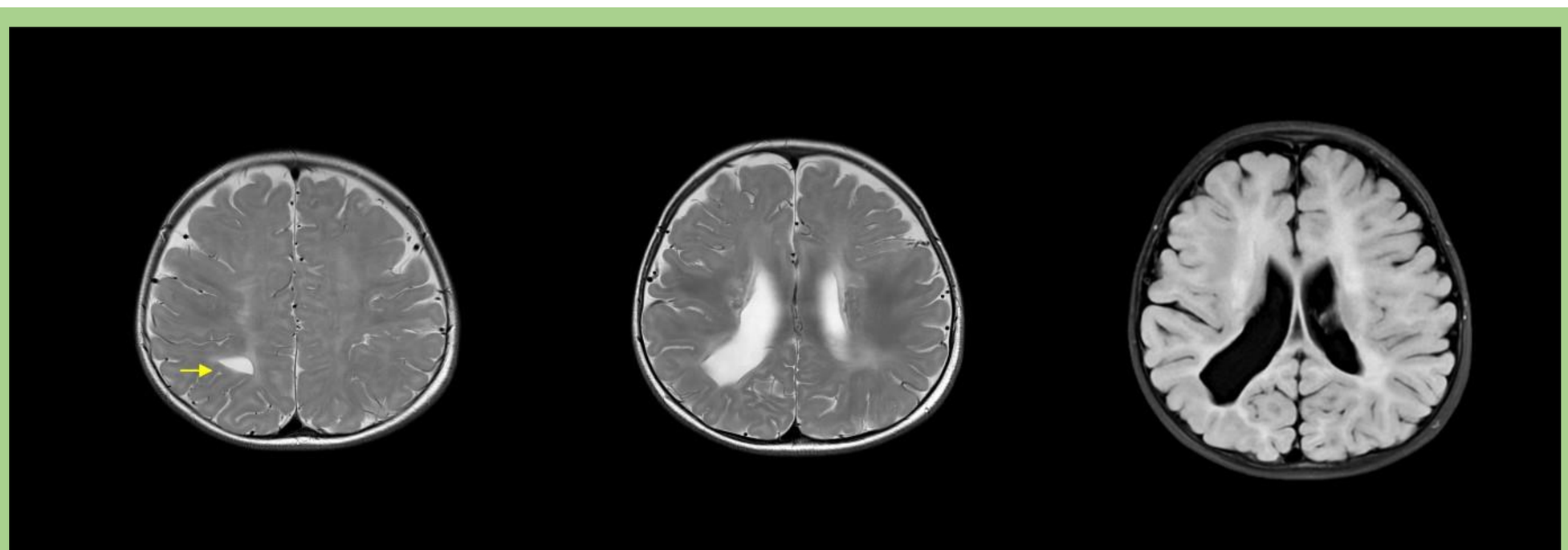

Figure 1. Brain MRI obtained at 9 months of age demonstrating abnormal findings.

Developmental evaluation (The Bayley III)	6 months of age		12 months of age		18 months of age	
	DAE	Composite score	DAE	Composite score	DAE	Composite score
Cognitive	6 months	90	6 months	60	9 months	60
Receptive communication	4 months	83	10 months	83	10 months	68
Expressive communication	5 months		8 months		10 months	
Fine motor	5 months	64	5 months	64	9 months	64
Gross motor	4 months		10 months		13 months	
Social-emotional	-	75	-	60	-	60
Adaptive behavior	-	70	-	69	-	62

DAE; Developmental age equivalent

Table 1. Developmental evaluation of the patient using the Bayley III.

	SPAST c.56C>G	*WASHC5* c.1275dup	*COL4A1* c.3742+1G>T
Patient's father			
Patient's mother			
The patient			

*Colored section means mutation was detected

Table 2. Findings of targeted next generation sequencing (NGS) in the patient's family.

CONCLUSION

We present a case of a de novo COL4A1 gene mutation (c.3742+1G>T) associated with developmental delay and ophthalmologic abnormalities. As the precise role of COL4A1 gene in ocular motor control and strabismus remains unclear, further research is needed to better define the ophthalmologic spectrum of COL4A1-related disorders.