

Porencephaly in a Fetus and HANAC in Her Father: Variable Expression of *COL4A1* Mutation

Toshiki Takenouchi,^{1,2} Masaki Ohyagi,³ Chiharu Torii,² Rika Kosaki,⁴ Takao Takahashi,¹ and Kenjiro Kosaki^{2*}

¹Department of Pediatrics, Keio University School of Medicine, Tokyo, Japan

²Center for Medical Genetics, Keio University School of Medicine, Tokyo, Japan

³Department of Internal Medicine, Tokyo Metropolitan Bokutoh Hospital, Tokyo, Japan

⁴Division of Medical Genetics, National Center for Child Health and Development, Tokyo, Japan

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COL4A1-associated disorders encompass a wide range of hereditary vasculopathy, including porencephaly and HANAC (adult-onset hemorrhagic stroke with cerebral aneurysm and retinal arterial tortuosity, renal cysts, and thenar muscle cramp). It remains elusive whether or not porencephaly and HANAC are molecularly distinctive disorders due to different classes of mutations. We report on a girl with porencephaly and an episode of microangiopathic hemolysis in infancy and her father with HANAC, both of whom had a heterozygous missense mutation of *COL4A1* (c.3715G>A, p.G1239R). The current observation implies phenotypic diversities of *COL4A1* mutations.

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Key words: HANAC; *COL4A1*; Porencephaly

INTRODUCTION

HANAC (hereditary angiopathy with nephropathy, aneurysms, and muscle cramps) [OMIM611773] is a recently established genetic condition characterized by cerebrovascular events and cerebral aneurysm formation, hematuria and cystic kidney disease, and retinal arterial tortuosity [Plaisier et al., 2007]. The mechanistic basis of this systemic vascular disorder is disruption of vascular wall integrity as a result of heterozygous *COL4A1* mutations. In the mean time, heterozygous *COL4A1* and *COL4A2* mutations have attracted attention as a cause of porencephaly due to prenatal cerebrovascular events [Gould et al., 2005; Gould et al., 2006; Plaisier et al., 2010; Yoneda et al., 2012]. It is known that *COL4A1* mutations are responsible for not only familial cases with porencephaly but also a substantial portion (i.e., 21%) of the sporadic cases [Yoneda et al., 2013]. Here, we report a family with a *COL4A1* mutation in which the father manifested with HANAC and his child with porencephaly.

CLINICAL REPORT

A female fetus was found to have intracranial hemorrhage with cystic changes on prenatal ultrasonography and magnetic resonance

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imaging (MRI) at 33 weeks of gestation (Fig. 1A,B). She was born at 35 weeks and 6 days of gestation by cesarean because of arrested fetal growth. Birth weight was 1878 grams (–1.5 SD), length was 42.6 cm (–1.4 SD), and head circumference was 29.6 cm (–1.6 SD). Physical examination at birth was unremarkable. A postnatal brain MRI showed porencephaly in the left hemisphere (Fig. 1C). She developed jaundice and anemia with evidence of intravascular hemolysis at age of 1 month, which was suggestive of microangiopathy. She later developed right hemiparesis at 12 months and seizure at 15 months of age. The combination of porencephaly and progressive hemolytic anemia led to a suspicion of basement membrane disease, and a *COL4A1* mutation analysis was performed.

Her father presented with a cerebrovascular event of adult onset, that is, sudden onset of transient left hemiparesis and difficulty in speaking, at age 38 years. He had the past history of microscopic hematuria and nephrotic syndrome. He also experienced muscle cramp in the left thumb while playing a videogame, which had

Conflict of interest: none

Abbreviations: HANAC, hereditary angiopathy with nephropathy, aneurysms, and muscle cramps; MRI, magnetic resonance imaging.

*Correspondence to:

Kenjiro Kosaki, M.D., Center for Medical Genetics, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, 160-8582, Japan.

E-mail: kkosaki@z3.keio.jp

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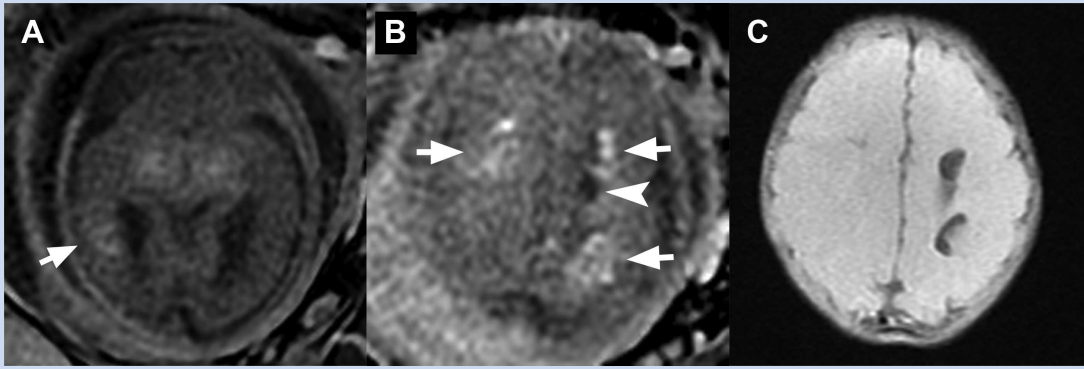


FIG. 1. Fetal and postnatal neuroimaging of the probanda. Fetal brain MRI obtained at 33 weeks of gestation (A and B) showing scattered T1 hyperintense lesions (arrows), likely representing hemorrhage, and a hypodensity suggestive of porencephaly (arrowhead). A postnatal brain MRI shows left hemispheric porencephaly (C).

started at the age 22 years, and lasted for one minute, causing significant disabilities in his everyday life. Creatinine kinase level was within the normal limits. Fundoscopic examination showed mild retinal arterial tortuosity. Renal ultrasound examination revealed small cysts measuring less than 5 mm. Brain MRI demonstrated extensive white matter lesions, multiple chronic hemorrhagic foci, and a cerebral arterial aneurysm at the left carotid siphon (Fig. 2). These vascular phenotypes were consistent with a diagnosis of HANAC.

MOLECULAR ANALYSIS

Genomic DNA was extracted from whole blood samples from the probanda and her parents. A mutation analysis panel (SureSelect XT-Auto custom; Agilent Technologies, Santa Clara, CA) was custom-

designed to include major causative genes of congenital disorders primarily affecting the central nervous system, including *COL4A1* (the list of genes is available upon request). The sequencing of their PCR products using the panel and a next-generation sequencer (MiSeq; Illumina, Inc. San Diego, CA) identified a heterozygous missense mutation in exon 42 of *COL4A1* (NM_001845), that is, c.3715G>A p.Gly1239Arg in the probanda and her father, but not in her mother (Fig. 3). Sanger sequencing of the same PCR products confirmed the result (Fig. 3). The p.Gly1239Arg was not present in the dbSNP137, 1000 genomes Project (<http://www.1000genomes.org/>), ESP6500, or the Japanese SNP dataset of 1208 normal individuals (Human Genetic Variation Browser, <http://www.genome.med.kyoto-u.ac.jp/SnpDB>). Although there is no direct evidence of pathogenicity of this specific mutation, three different bioinformatics programs all predicted that the p.Gly1239Arg mutation in *COL4A1* is

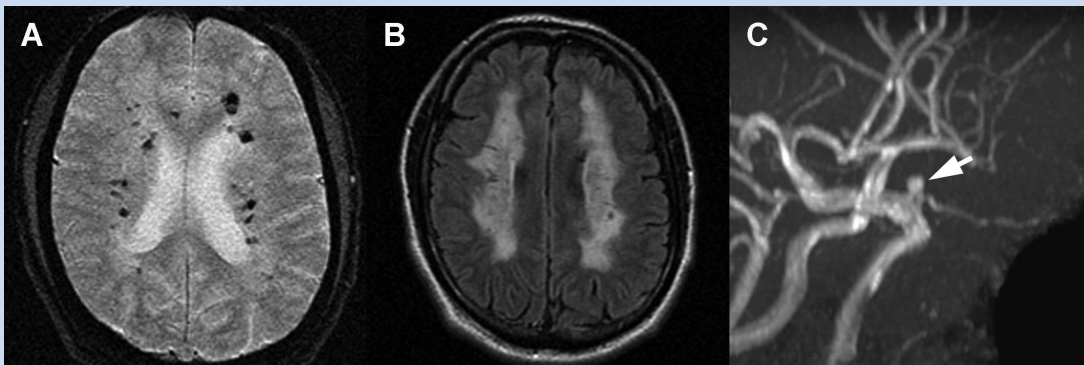


FIG. 2. Neuroimaging of the probanda's father. MRI of the brain showing scattered multiple hypodensities on T2* gradient echo imaging representing paramagnetic signals as a result of chronic hemorrhage (A) and a diffuse white matter lesion on a fluid-attenuated inversion recovery image (B). Magnetic resonance angiography shows a cerebral aneurysm at the left carotid siphon measuring approximately 3 mm (arrow, C). These radiographic features are compatible with a diagnosis of HANAC.

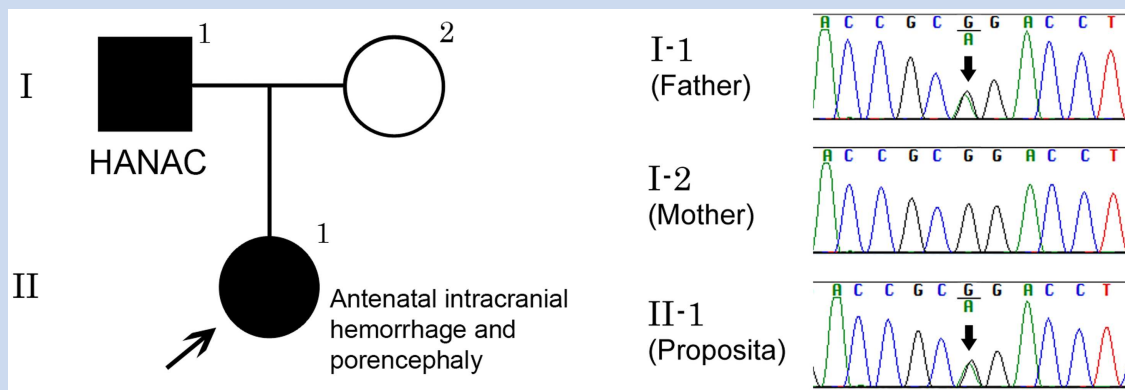


FIG. 3. Family pedigree and sequence chromatograms. The probanda had an antenatal intracranial hemorrhage, resulting in porencephaly. Her father had history of hematuria, an ischemic stroke at 38 years of age, cerebral aneurysm, and retinal arterial tortuosity, consistent with a diagnosis of HANAC. Sequence chromatograms shows that a single heterozygous nucleotide change, c.3715G>A, is present in the probanda (II-1) and her father (I-1), but not in her mother (I-2).

pathogenic (PolyPhen2, “probably damaging”; SIFT, “deleterious”; and MutationTaster, “disease-causing”).

DISCUSSION

We reported on a familial case of porencephaly and hemolysis in a girl and HANAC in her father, who had a heterozygous mutation causing substitution of arginine for glycine in the triple helical region of COL4A1. The p.Gly1239Arg mutation was highly likely to be disease-causing. It is the rule that a single amino acid substitution for glycine residue in the triple helical region of a major collagen is pathogenic [Gupta et al., 1997; Nussbaum et al., 2007]. All mutations previously reported in HANAC were the same type of mutations [Plaisier et al., 2010]. Furthermore, it is known that a similar missense mutation (p.Gly1236Arg) is responsible for COL4A1-related vasculopathy [Gould et al., 2005].

Our observation suggested a significant variability in the expression of COL4A1-related basement membrane diseases. In autosomal dominant disorders, intrafamilial variability is the rule rather than the exception. From the clinical viewpoint; however, antenatal porencephaly and adult-onset HANAC are discrete conditions. Thus, we have to be careful in genetic counseling for COL4A1-associated disorders, in that a patient with a late-onset manifestation may have an affected child with a congenital phenotype, and vice versa.

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