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Short Report

Expanding the phenotypic spectrum of Caffey disease

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Infantile cortical hyperostosis (ICH) is an inherited disorder characterized by hyperirritability, acute inflammation of soft tissues, and massive subperiosteal new bone formation. It typically appears in early infancy and is considered a benign self-limiting disease. We report a three-generation Thai family with ICH, the oldest being a 75-year-old man. A heterozygous mutation for a 3040C→T in exon 41 of *COL1A1* was found in affected individuals, further confirming the autosomal dominance of Caffey disease that is caused by this particular mutation. The novel findings in our studies include short stature and persistent bony deformities in the elderly. The height mean Z-score of the five affected individuals was −1.75, compared to 0.53 of the other seven unaffected individuals giving a p-value of 0.008. Short stature may be partly due to progressive height loss from scoliosis, compression fractures of the spine and genu varus. These features, which have not previously been described, expand the phenotypic spectrum of the Caffey disease.

K Suphapeetiporn[a], S Tongkobpetch[a], A Mahayosnond[b] and V Shotelersuk[a]

[a]Department of Pediatrics and [b]Department of Radiology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

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Corresponding author: Vorasuk Shotelersuk, MD, Division of Medical Genetics and Metabolism, Department of Pediatrics, Sor Kor Building, 11th floor, King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand.
Tel.: 662-256-4989;
fax: 662-256-4911;
e-mail: vorasuk.s@chula.ac.th

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Infantile cortical hyperostosis (ICH) (Caffey disease; OMIM 114000) is characterized by hyperirritability, acute inflammation of soft tissues, and massive subperiosteal formation of the underlying bones typically involving the diaphyses of the long bones, mandible, clavicles, or ribs (1). Its clinical features usually begin before 5 months of age and resolve before 3 years of life (1, 2). It is benign and self-limited. It is inherited as autosomal dominance with incomplete penetrance and variable expressivity (3–5). Even though there are few reports describing the sequelae of the hyperostotic lesions in affected individuals, late recurrence or persistence of symptoms with deformity seems extremely rare (6–8).

A sporadic form of ICH has also been described. In addition, there are several conditions causing cortical bone lesions in children mimicking ICH including prolonged prostaglandin infusion, hypervitaminosis A, and hyperphosphatemia (9–12).

Recently, a novel missense mutation in *COL1A1*, the gene encoding the α1 chain of type 1 collagen, was found in all affected individuals from three unrelated families (13). All affected individuals were heterozygous for the identical mutation, a 3040C→T transition resulting in the substitution of an arginine by a cysteine at position 836 (R836C), within the helical domain of the α1 chain of type 1 collagen. Different mutations in *COL1A1* have been found in osteogenesis imperfecta and Ehlers–Danlos syndrome (EDS) (14, 15). Interestingly, some of the clinical features of EDS such as hyperextensible skin and joint hyperlaxity were found in some patients affected with ICH. It was shown that the R134C found in EDS and the R836C found in ICH gave a similar effect on synthesis and function of the collagen fibrils (13). However, the precise

functional link between the R836C mutation and the hyperostotic phenotype seen in ICH is still uncertain and awaits further exploration.

We report a three-generation Thai family with five members affected with ICH. A 3040C→T transition in exon 41 of *COL1A1* was identified. Short stature, persistent bony deformities, and rampant dental caries were present in this molecular proven ICH family.

Material and methods

Clinical subjects

We report a three-generation family with affected members having clinical findings consistent with Caffey disease (see pedigree, Fig. 1, Table 1). Individual I-3 reported to have bow legs since childhood. The deformity persisted and progressed till 75 years of age (Fig. 2a). He had fractures around his left knee twice at the ages of 39 and 43, due to pedestrian struck. His hands were short and stubby. He also had kyphoscoliosis and compression fractures of vertebrae that had not undergone surgery. His radiographs are shown in Fig. 2b–i. II-2 had short, stubby forearms and hands, and bow legs. He had two fractures. The first fracture was on his left forearm that he sustained from playing jumping rope at the age of 13. The second was on his right leg, due to a motorcycle accident, at the age of 19. Although his scoliosis was more severe than that of his father, he did not require surgery (Fig. 2j,k). His radiographs revealed cortical thickening of the affected long bones (data not shown). II-7 was clinically unaffected. However, the radiographs revealed abnormalities of ribs and hands albeit milder severity compared with those of I-3 and II-2 (data not shown). II-11 was noted to have non-painful bowed right leg soon after birth. She easily dislocated and self-reduced her right shoulder. III-3 was a 22-year-old woman who reported to have non-painful curved forearms, and valgal halluces since infancy. III-15 was the proband referred to us at 11 days of age due to swelling and bowing of the right leg (Fig. 2l). She became irritable and cried when passively moving the affected limb. Bone radiographs revealed periosteal elevation and cortical thickening of the diaphyses of the right tibia (Fig. 2m). Other long bones, mandible, clavicles and ribs were unremarkable. Without any medications, swelling and pain on the right leg resolved when she was 2 months old. At 7 months of age, her left leg was swollen and appeared bowed. The radiographs showed her affected left tibia compared with the right (Fig. 2n,o). Again, without any medications, her symptoms gradually subsided and, at 18 months of age, resolved. Some angular deformities of bilateral tibias, however, still persisted (data not shown). The other seven members whose data were available (five were examined by us and two were seen at other medical centers) had normal clinical features, with the mean of the Z score for their height being 0.53 compared to the height mean Z score of −1.75 in the five affected members with the *COL1A1* mutation.

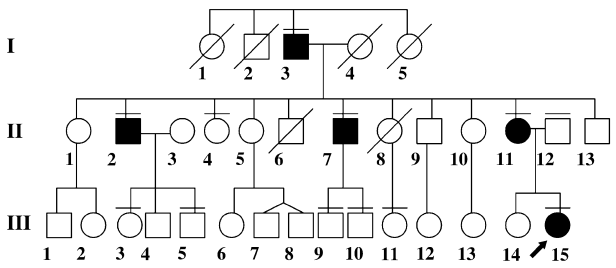

Fig. 1. Pedigree of the family with an autosomal dominant form of Caffey disease. Arrow, proband; blackened symbols, affected individuals; bar above symbol, individuals clinically examined in our center.

Mutation analysis

After informed consent was obtained, genomic DNA was extracted from peripheral leukocytes according to standard protocols. We screened genomic DNA from affected family members and unaffected controls by restriction enzyme digestion of polymerase chain reaction products as previously described (13). One sample from either group with different pattern of restriction enzyme digestion was selected for direct sequencing to further confirm the mutation.

Results

Five affected individuals were heterozygous for a 3040C→T transition in exon 41 of *COL1A1* (Table 1, Fig. 3). Surprisingly, patient III-3 who had clinical features consistent with ICH did not have the mutation as shown by the restriction enzyme digestion (Fig. 3) and direct sequencing (data not shown). The mutation analyses of this individual were confirmed by repeated studies using DNA from two separate blood collections.

Discussion

We described a Thai family with the proband presented with clinical and radiographic features

Table 1. Clinical, radiological and molecular findings of affected members

Features	I-3	II-2	II-7	II-11	III-15
Sex	M	M	M	F	F
Age (years)	75	50	44	30	1
Height (cm)	147	150	156.7	150.6	71.5
Z-score	−3.20	−2.68	−1.39	−0.61	−0.88
Head circumference (cm)	56.5	58	59.5	55.5	45
Onset of cortical hyperostosis	NA	NA	NA	Soon after birth	Soon after birth
Angular deformity	Both forearms and legs	Both forearms and legs	N	Right leg	Both legs
History of fractures	Twice	Twice	N	N	N
Blue sclerae	N	N	N	N	N
Rampant dental caries	Y	Y	Y	Y	N
Hyperextensible skin	N	N	N	N	N
Joint hyperlaxity	Y	N	N	Y	N
Scoliosis	Y	Y	N	N	N
3040C→T (R836C)	Y	Y	Y	Y	Y

M, male; F, female; Y, yes; N, no; NA, not applicable.

consistent with ICH. There were multiple affected members showing an autosomal dominant condition.

We had an opportunity to examine 11 members of this family. Five were found to have the *COL1A1* 3040C→T mutations. Additional striking phenotype that we observed in this family was short stature. Short stature was not previously found to be part of the disorder (13). Comparing height of these five individuals with that of the other seven clinically unaffected, we found that the means of the Z scores for their heights were statistically different ($p = 0.008$). We did not include III-3, who had curved forearms but did not have the *COL1A1* 3040C→T mutations in her leukocytes, in either group. Short stature could partly be caused by loss of adult height from kyphoscoliosis, compression fractures of vertebrae, and lower limb deformities as seen in our oldest 75-year-old man and his affected first son.

ICH has been considered a benign and self-limited disorder. Our 75-year-old patient, the oldest individual ever reported with ICH, and his 50-year-old affected first son have been generally healthy despite persistent deformity of the long bones. Even though persistent deformities of the affected bones have been previously noted (6–8), this study described the first molecular proven Caffey family with persistent deformities. Based on these data, we propose that short stature and persistent bony deformity should be included in the clinical spectrum of Caffey disease.

Rampant dental caries were observed in all mutation positive members, except III-15 who was still very young. However, the dental problems were also observed in many other family members without the mutation. Therefore, whether this phenotype is part of ICH needs further studies.

A heterozygous mutation for a 3040C→T in a CpG dinucleotide of exon 41 of *COL1A1* was identified. This similar mutation was previously described in a study of three unrelated kindreds from Australia and Canada with an autosomal dominant form of ICH (13). Our study in a large Thai family further confirmed that familial Caffey cases are caused by this particular mutation. The fact that all the familial cases studied so far had the same mutation, regardless of their ethnicities, supports the previous observation that the 3040C→T transitions are recurrent, making it a mutational hot spot in *COL1A1*.

In this family, we found two members with discrepancy between genotype and phenotype. II-7 had some minor radiographic findings without clinical features of Caffey disease but had the mutation. Incomplete penetrance and variable expressivity have been previously observed in Caffey disease (3–5). It has been shown that 21% of the individuals carrying the R836C substitution do not develop the disease (13). More interestingly, the heterozygous *COL1A1* 3040C→T mutation was not found in a 22-year-old woman with curving deformity of bilateral forearms since early childhood. Radiographs taken during her first visit at 22 years of age revealed cortical thickening of the affected bones. Unexpectedly, the 3040C→T mutation was not detected in her genomic DNA extracted from the peripheral leukocytes in two separated DNA samples obtained from blood drawn on two occasions. One possibility is that she is a mosaic for the inherited mutation. The occurrence of the nucleotide substitution in an already

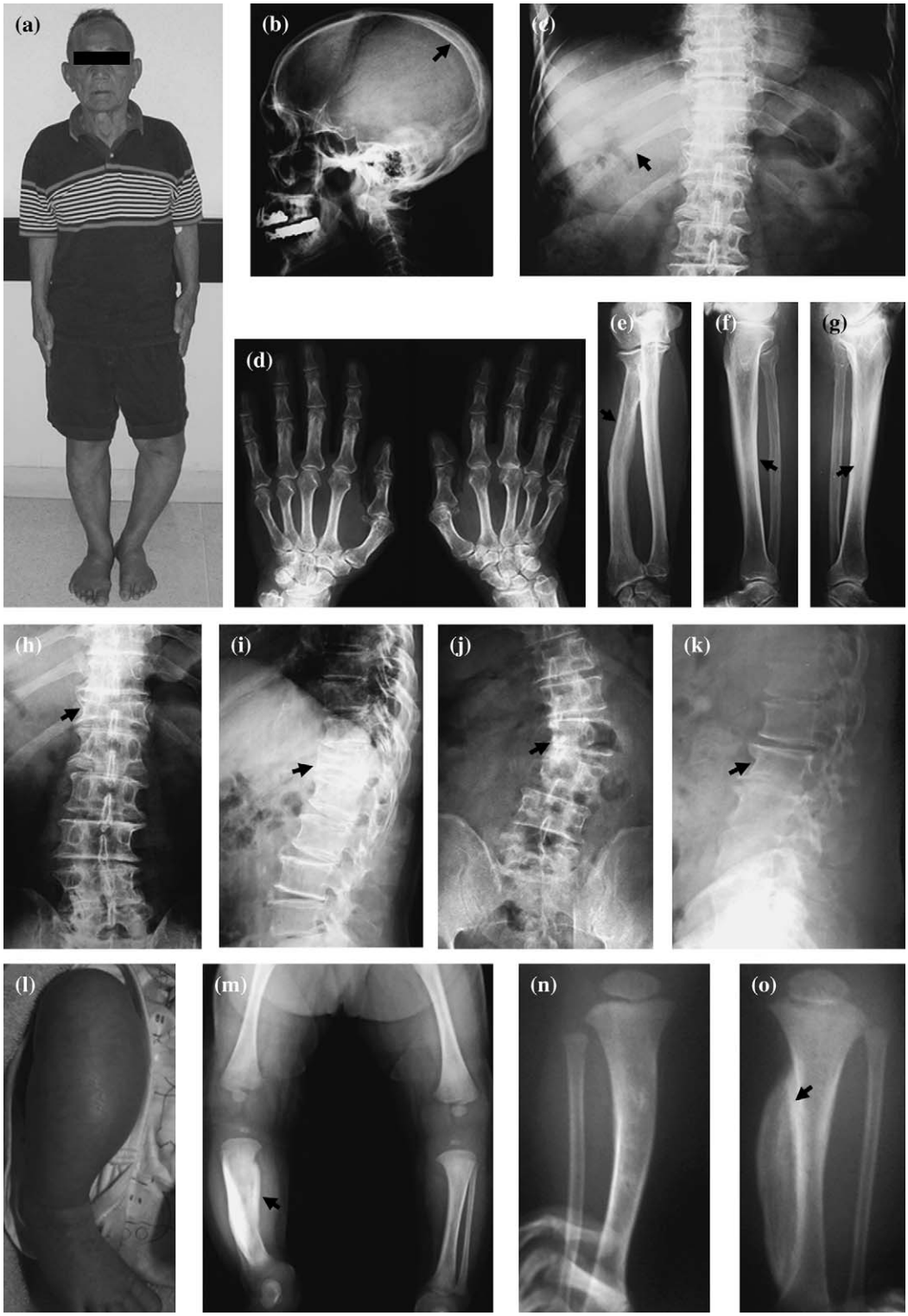

Fig. 2. Clinical and radiological features of affected individuals. (**a**) Photograph of the oldest individual (I-3) with Caffey disease. Radiographs of patients I-3 (**b–i**), II-2 (**j**, **k**), and the proband, III-15 (**l–o**) showing (**b**) cortical thickening of the cranial vault (**c**) ribs with paddle-like shape (**d**) hands with short metacarpals (**e**) angular deformity with cortical thickening of the radius (**f**, **g**) anterior bowing with cortical thickening of the right and left tibias respectively (**h**, **i**) kyphoscoliosis with compression fracture of T12 (**j**, **k**) scoliosis with spondylosis of L2. Photograph of the proband (**l**) showing swelling of the right leg, which is matched to the radiograph (**m**) showing periosteal elevation and cortical thickening of the diaphyses of the right tibia. Radiographs of bilateral legs showing (**n**, **o**) cortical hyperostosis with anterior curvature of the right tibia and periosteal elevation and cortical thickening of the left tibia, respectively. Arrows indicated the affected bones.

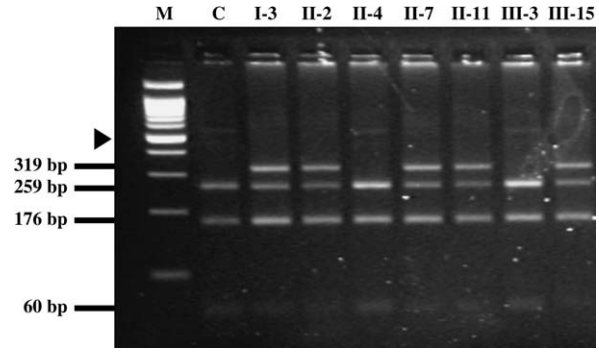

Fig. 3. Mutation analysis. M: 100-bp marker. The 500-bp band indicated by an arrow head. C: unaffected control. Restriction enzyme analysis of polymerase chain reaction products showing the mutant allele lacking one of the cleavage sites for the restriction endonuclease *HpyCH4IV* resulting in bands of 319 and 176 bp and the wild-type allele with bands of 259, 176 and 60 bp. Patients I-3, II-2, II-7, II-11 and III-15 were heterozygous for C→T mutation at nucleotide 3040 of *COL1A1*.

mutant nucleotide has been previously described (16). DNAs from other tissues are, unfortunately, unavailable. Another possibility is that she is affected by another disorder, not linked to the mutation.

The clinical and molecular characteristics of the inherited form of Caffey disease were further delineated in our study. Short stature and persistence of bony deformity were additional features found in Thai affected individuals.

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