Received: 22 May 2018 | Accepted: 22 May 2018
DOI: 10.1002/ajmg.a.40358

WILEY AMERICAN JOURNAL OF medical genetics PART A

CASE REPORTS IN DIVERSE POPULATIONS

Cole-Carpenter syndrome in a patient from Thailand

Thantrira Porntaveetus[1] | Thanakorn Theerapanon[2] | Chalurmpon Srichomthong[3,4] | Vorasuk Shotelersuk[3,4]

[1]Genomics and Precision Dentistry Research Unit, Department of Physiology, Faculty of Dentistry, Chulalongkorn University, Bangkok, Thailand

[2]Excellence Center in Regenerative Dentistry, Faculty of Dentistry, Chulalongkorn University, Bangkok, Thailand

[3]Center of Excellence for Medical Genomics, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

[4]Excellence Center for Medical Genetics, King Chulalongkorn Memorial Hospital, the Thai Red Cross Society, Bangkok, Thailand

Correspondence
Vorasuk Shotelersuk, Center of Excellence for Medical Genomics, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.
Email: vorasuk.s@chula.ac.th

Funding information
Thailand Research Fund (TRF), Grant/Award Number: DPG6180001; Office of Higher Education Commission (OHEC) Thailand, Grant/Award Number: MRG6080001; the Newton Fund, and Chulalongkorn Academic Advancement into its 2nd Century Project.

Cole-Carpenter syndrome (CCS), commonly classified as a rare type of osteogenesis imperfecta, is a disorder with severe bone fragility, craniosynostosis, and distinct facial features. Recently, the heterozygous missense mutation, c.1178A>G, p.Tyr393Cys, in exon 9 of *P4HB* which encodes protein disulfide isomerase, has been found in three Caucasian patients with CCS. Ethnic background is known to affect clinical manifestations, especially facial features of dysmorphic syndromes. Here, we describe the first Asian CCS patient possessing the recurrent mutation in *P4HB*. Although she had several common features of CCS including bulging forehead, ocular proptosis, midface hypoplasia, long bone deformity, popcorn epiphyses, vertebral fractures, and scoliosis, she did not have hydrocephalus, wormian bones, and dentinogenesis imperfecta, commonly seen in Caucasian patients. Interestingly, she is the only one without macrocephaly. Radiologically, metadiaphyseal fractures of the long bones with metaphyseal sclerosis were found, substantiating that they provide a definitive radiological feature of CCS. In addition, we showed for the first time a three-dimensional facial scan of a patient with CCS. She had been given intravenous bisphosphonate since the age of 9 months and had responded well. Our study presents the clinical features of the first Asian patient, supports metaphyseal scleroses and fractures as radiological clues, strengthens early bisphosphonate administration, and confirms the etiologic role of the c.1178A>G variant in *P4HB* across populations.

KEYWORDS
bisphosphonate, dentinogenesis imperfecta, hydrocephalus, osteogenesis imperfecta, *P4HB*

In 1987, Cole-Carpenter syndrome (CCS; OMIM 112240) was first described in two infants who developed multiple fractures of the long bones shortly after birth, recurrent diaphyseal fractures of the weight-bearing bones, ocular proptosis, craniosynostosis, hydrocephalus, and distinctive facial features (Cole & Carpenter, 1987). Neurological development was reported to be unaffected. Balasubramanian et al. recently reported the third CCS patient and proposed the "crumpling" metadiaphyseal fractures of the long bones with metaphyseal sclerosis as the phenotypic clue of CCS (Balasubramanian et al., 2018). These patients were recently found to be heterozygous for a missense variant, c.1178A > G, p.Tyr393Cys, in the *P4HB* gene, encoding prolyl 4-hydroxylase, subunit beta (Balasubramanian et al., 2018; Rauch et al., 2015).

We report the first Asian patient with CCS. She is the first child of non-consanguineous healthy Thai parents. The pregnancy was unremarkable and she was born without complications at 38 weeks of gestation with a birth weight of 3,260 g (50th centile) and Apgar scores of 10 and 10. At eight months of age, she was referred due to deformities of her extremities, difficulty sitting up, and gross motor delay (Figure 1). Her weight was 5,900 g (< 3rd centile); length 59 cm (< 3rd centile); and head circumference 41 cm (10–25th centile). On physical exam, she had marked limb deformities, bluish sclerae, depressed nasal bridge, broad face, angulated ankles, broad fingers and toes, and relatively long fingers. The deformed limbs were not tender or swollen. Dentinogenesis imperfecta was absent (Figure 1f). On skeletal survey, she had generalized osteopenia, numerous deformities of the long bones with flaring, sclerosis, and irregularity of metaphyses, popcorn epiphyses, and significant angulation at the junction of metaphyses and diaphyses of the forearm and leg bones including ulnae, radii, tibiae, and fibulae (Figure 2a–g). She had fractures with callus formation at the metadiaphyseal junctions of the ulnae and right humerus and vertebral compression fractures

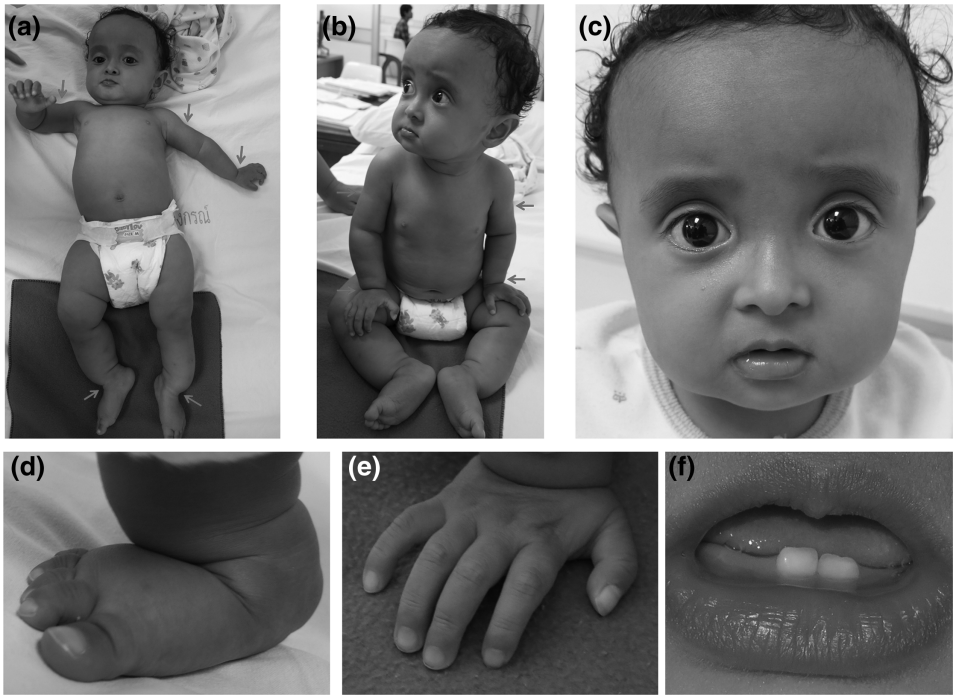

FIGURE 1 Clinical features of the proband at 11 months of age. (a, b) Severe limb deformity and angulated wrists and ankles (arrows). (c) Broad face, depressed nasal bridge, and blue sclerae. (d) Severely angulated ankle when standing (e) Broad and long fingers; (f) Normal tooth crowns without dentinogenesis imperfecta

(Figure 2h, i). She had an open anterior fontanelle (2 × 3 cm) and a closed posterior fontanelle. Wormian bones and hydrocephalus were not detected via radiological studies (Figure 2j–m and Supplementary Figure S1).

Dual-energy X-ray absorptiometry scanning revealed low lumbar spine BMD (0.196 g/cm^2, *z*-score −6.80). The levels of alkaline phosphatase 237 U/L (110–320 U/L), calcium 10.5 mg/dL (8.0–10.7 mg/dL), and phosphate 5.7 mg/dL (4.8–8.1 mg/dL) were within normal ranges. The serum procollagen type I N-terminal propeptide 636.4 ng/ml and serum carboxy terminal telopeptide of collagen type I 0.69 ng/ml were detected. A clinical diagnosis of osteogenesis imperfecta was made. Intravenous pamidronate was initiated at nine months of age, and then every two months. No bone fractures were observed during the last eight months. Her development has progressed appropriately. The radiographs at age 15 months showed dense periphery of the long bones, angulated long bones, irregular sclerosis around the old fracture, and "zebra stripe signs" at the proximal tibiae (Figure 3a–c).

At 17 months, she weighed 7.3 kg (< 3rd centile); her length was 65.5 cm (< 3rd centile); and head circumference was 44 cm (10th centile). Anterior fontanelle was 1 × 1 cm. Her lumbar spine BMD was low (0.296 g/cm^2, z-score −4.56), but improved compared to that at eight months of age. Tooth eruption was delayed. Exome sequencing performed on research basis identified that the proband had the same *de novo* heterozygous missense pathogenic variant, c.1178A > G, p.Tyr393Cys, in the *P4HB* gene (Supplementary Figure S2) that was previously reported in three patients with CCS (Supplementary Table).

Of the four CCS patients with the same *P4HB* pathogenic variant, ocular proptosis, midfacial hypoplasia, severe limb deformities, and postnatal fractures were the consistent clinical phenotypes and metadiaphyseal anomalies/fractures of long bone with metaphyseal sclerosis, angulated long bones, and popcorn epiphyses are constant radiological features. On the contrary, craniosynostosis, hydrocephalus, macrocephaly, blue sclerae, and dentinogenesis imperfecta were inconsistently present among the four cases. Notably, in contrast to the previous three Caucasian CCS patients, our proband with Asian background did not have macrocephaly (head circumference *z*-scores of −2.0 at 8 and 17 months of age). In contrast to osteogenesis imperfecta, wormian bones were not commonly observed in CCS patients (Supplementary Table).

All four patients including our proband received pamidronate therapy. The first two patients showed an improved *z*-score of lumbar spine BMD. However, they did not have obvious clinical benefit from the treatment, which could be due to the fact that pamidronate was initiated after skeletal maturity (Rauch et al., 2015). The third patient, who received pamidronate from seven months of age, had not sustained any bone fractures in the last 18 months and showed improved remodeling of vertebral bodies (Balasubramanian et al., 2018). Our patient had intravenous pamidronate starting at nine months and every two months afterwards. When last seen at 19 months of age, her clinical and radiological findings had improved with no new bone fractures. We believe early pamidronate therapy to be effective for CCS.

In conclusion, our report of the first Asian patient with CCS shows that macrocephaly is not an essential feature, that metadiaphyseal fractures of long bones and metaphyseal sclerosis are a

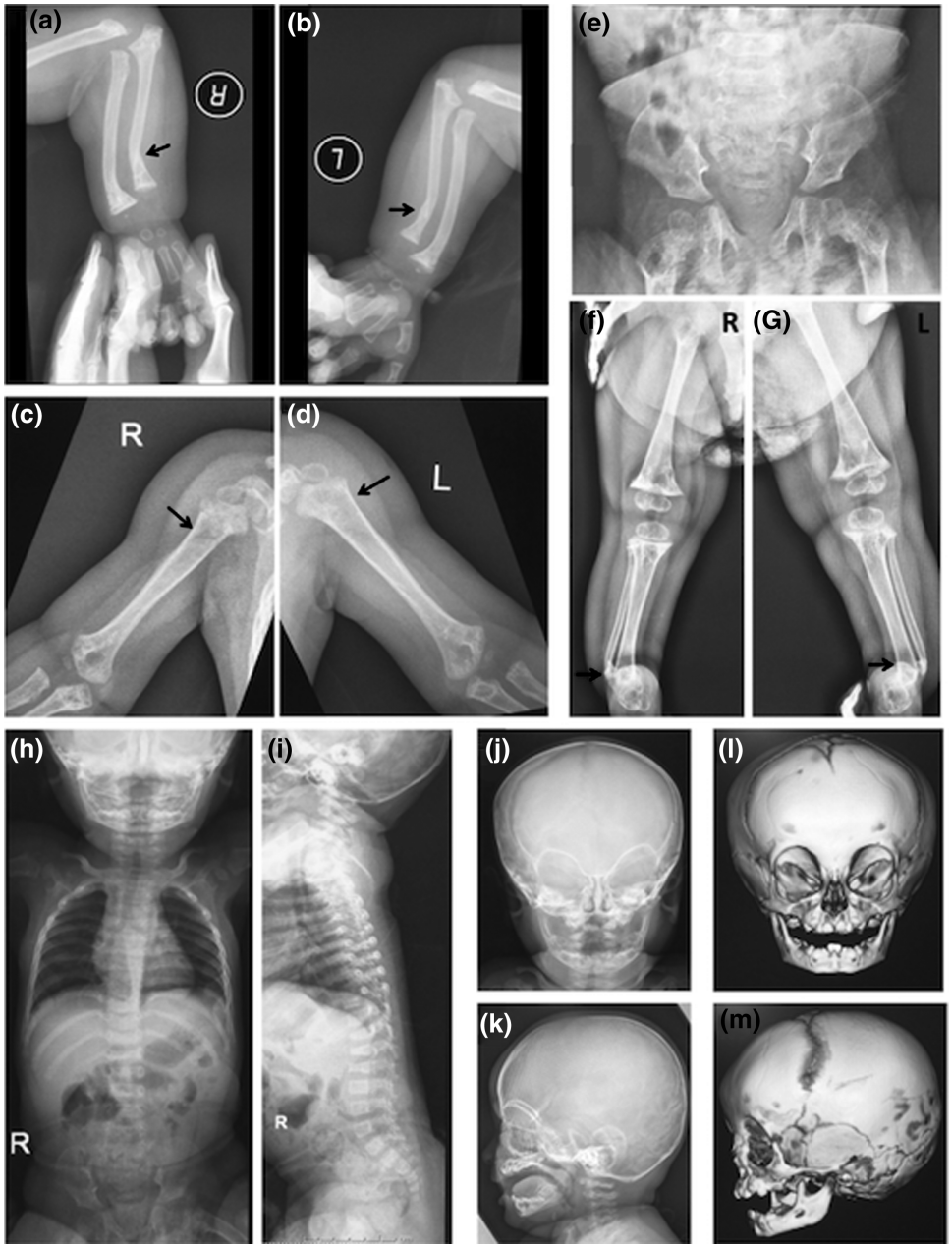

FIGURE 2 Radiographs of the proband at 8 months of age showed generalized osteopenia. (a, b) fractures with callus formation at the metadiaphyseal junction of the ulnae and right humerus (arrows). (c, d) metaphyseal sclerosis (arrows) and popcorn epiphyses. (e–g) Sharp bending of ankles (arrows) observed on the pelvis and lower extremity. (h, i) Vertebral compression fractures (j, m) Opened anterior fontanelle without wormian bones (j-m). (A) right forearm, (b) left forearm, (c) right arm, (d) left arm, (e) hip, (f) right leg, (g) left leg, (h) AP spine, (I) lateral spine, (j) AP skull, and (k) Lateral skull, (l, m) 3D facial scans at 13 months of age

TABLE 1 Comparison of clinical, radiological, molecular diagnosis in our proband and patients reported with CCS

	Present report	Patient 3 (Balasubramanian et al., 2018)	Patient 2 (Cole & Carpenter, 1987)	Patient 1 (Cole & Carpenter, 1987)
Age at the last follow-up	17 months	3 years and 8 months	18 years	4 years
Sex	F	F	M	M
Ethnicity	Asian	Caucasian	Caucasian	Caucasian
Consanguinity	No	No	No	No
Genetic mutation	*P4HB* c.1178A>G, p.Tyr393Cys	*P4HB* c.1178A>G, p.Tyr393Cys	*P4HB* c.1178A>G, p.Tyr393Cys	*P4HB* c.1178A>G, p.Tyr393Cys
Inheritance	AD	AD	AD	AD
De novo	Yes	Yes	Yes	Yes
Growth				
Prenatal fractures	-	-	-	-
Postnatal fractures	+	+	+	+
Age at first fracture (months)	< 8	6	2	1
Intelligence	Normal	Normal	Normal	Normal
Craniofacial features				
Craniosynostosis	Coronal sutures	-	+	Coronal and frontal sutures
Macrocephaly	-	+	+	+
Hydrocephalus	-	-	+	+
Wormian bones	-	+	-	+
Ocular proptosis	+	+	+	+
Sclerae	Blue	Blue	White	White
Midface hypoplasia	+	+	+	+
Dentinogenesis imperfecta	-	-	-	+
Micrognathia	-	NA	+	+
Radiological features				
Long bone deformity	+	+	+	+
Metadiaphyseal fractures	+	+	+	+
Vertebral fractures/Scoliosis	+	+	+	+
Osteopenia	+	+	+	+
Widening and irregularity of metaphyses	+	+	NA	NA
Popcorn epiphyses	+	+	+	+
Bisphosphonate therapy				
Clinical and radiological improvement	+	+	-	-
Pamidronate period (months)	6	37	36	12
Lubmar spine BMD (before/after)	−6.8 / −4.6	NA	−5.0 / −4.2	−3.9 /2.4
Serum biochemistry				
Calcium, phosphate, and alkaline phosphatase	Normal	NA	Normal	Normal

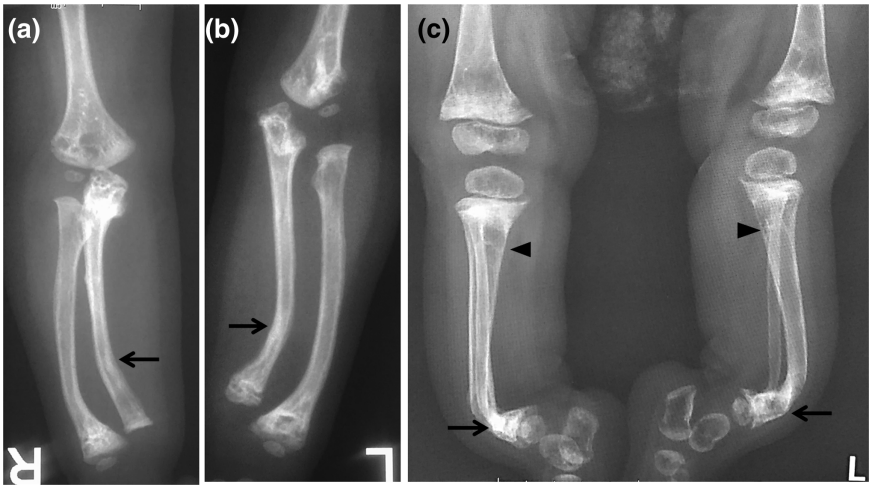

FIGURE 3 Radiographs of the proband at 17 months of age. (a, b) Irregular sclerosis observed around the previous fracture sites. The long bones showed dense periphery. Bisphosphonate lines were present at proximal tibiae. (a) right forearm, (b) left forearm, and (c) AP legs

radiological clue, supports early bisphosphonate administration, and confirms the etiologic role of the c.1178A > G, p.Tyr393Cys variant in *P4HB* across populations.

ACKNOWLEDGEMENTS

This study was supported by the Thailand Research Fund (TRF) (DPG6180001) and Office of Higher Education Commission (OHEC) Thailand (MRG6080001), the Newton Fund, and Chulalongkorn Academic Advancement into its 2nd Century Project.

AUTHOR'S CONTRIBUTIONS

TP, VS contributed to conception, data acquisition and analysis, drafting, and critical revision of the manuscript; TT, CS contributed to data analysis, and critical revision of the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

ORCID

Thantrira Porntaveetus http://orcid.org/0000-0003-0145-9801
Vorasuk Shotelersuk http://orcid.org/0000-0002-1856-0589

REFERENCES

Balasubramanian, M., Padidela, R., Pollitt, R. C., Bishop, N. J., Mughal, M. Z., Offiah, A. C., … Stephens, D. J. (2018). P4HB recurrent missense mutation causing Cole-Carpenter syndrome. *Journal of Medical Genetics*, *55*(3), 158–165. https://doi.org/10.1136/jmedgenet-2017-104899

Cole, D. E., & Carpenter, T. O. (1987). Bone fragility, craniosynostosis, ocular proptosis, hydrocephalus, and distinctive facial features: A newly recognized type of osteogenesis imperfecta. *Journal of Pediatrics*, *110*(1), 76–80.

Rauch, F., Fahiminiya, S., Majewski, J., Carrot-Zhang, J., Boudko, S., Glorieux, F., … Moffatt, P. (2015). Cole-Carpenter syndrome is caused by a heterozygous missense mutation in P4HB. *American Journal of Medical Genetics Part A*, *96*(3), 425–431. https://doi.org/10.1016/j.ajhg.2014.12.027

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Porntaveetus T, Theerapanon T, Srichomthong C, Shotelersuk V. Cole-Carpenter syndrome in a patient from Thailand. *Am J Med Genet Part A*. 2018;176A:1706–1710. https://doi.org/10.1002/ajmg.a.40358