Skeletal Radiology
https://doi.org/10.1007/s00256-018-2963-z

CASE REPORT

Widespread and debilitating hemangiomas in a patient with enchondromatosis and D-2-hydroxyglutaric aciduria

Patra Yeetong [1] · Teerasak Phewplung [2] · Wuttichart Kamolvisit [3,4] · Kanya Suphapeetiporn [3,4] · Vorasuk Shotelersuk [3,4]

Received: 6 February 2018 / Revised: 24 April 2018 / Accepted: 25 April 2018

Abstract

Metaphyseal chondromatosis with D-2-hydroxyglutaric aciduria (MC-HGA) (OMIM 614875) is a severe chondrodysplasia combined with a urinary excretion of D-2-hydroxyglutaric acid. Here, we reported the tenth case of this disease. A 15-year-old boy had symmetric radiolulencies in the metaphyses of the long bones suggesting enchondromatosis and platyspondyly. Remarkably, he manifested widespread cavernous hemangiomas including scalp, lips, tongue, larynx, and prepuce, with the onset of 3 years of age. Hemangiomas at the larynx had caused dyspnea and those in the oral cavity led to recurrent bleeding, requiring several surgical removals. These multiple and debilitating hemangiomas have never been previously reported in patients with MC-HGA. Mutation analyses including Sanger sequencing of genes involving in enchondromatosis and the metabolic pathway of D-2-hydroxyglutarate including *PTHR1*, *D2HGDH*, *HOT*, and *IDH1*, as well as whole-exome sequencing for proband-parent trio analysis and paired blood versus hemangioma studies showed no pathogenic variants. In summary, we reported the tenth patient with MC-HGA who manifested widespread and debilitating hemangiomas in several organs, expanding the clinical spectrum of MC-HGA.

Keywords Metaphyseal chondromatosis · D-2-Hydroxyglutaric aciduria

Introduction

Metaphyseal chondromatosis with D-2-hydroxyglutaric aciduria (MC-HGA) (OMIM 614875) is a rare disease with severe chondrodysplasia and a urinary excretion of D-2-hydroxy-glutaric acid [1]. Until now, nine patients have been reported [1–5]. In 2011, Vissers et al. performed exome sequencing of blood DNA in four unrelated patients, and two of them were found to be somatic mosaic for mutations p.R132H and p.R132S in *IDH1* [1].

Case report

The patient was a Thai boy presented to King Chulalongkorn Memorial Hospital for the first time at 16 months of age because of an abnormal gait. He was the first child of non-consanguineous parents and there was no family history of this disease. Physical examination revealed normal height and weight, but enlarged wrists, broadening and shortening of fingers (Fig. 1), and a malformed right ankle. At 2 years of age, he developed knock knees, pectus carinatum, scoliosis and enlarged shoulders, elbows, wrists, and all proximal and distal interphalangeal joints. He had strabismus of the right eye when he was four.

The X-ray of his chest and extremities at the age of 16 months showed multiple calcified expanding radiolucent lesions at the ends of long bones. At the age of 7 years (Figs. 2, 3, and 4), the posteroanterior chest radiograph revealed bulbous, expansive costovertebral junctions at several levels together with stippled calcification in the area of noncalcified

✉ Patra Yeetong
patra.y@chula.ac.th

[1] Division of Human Genetics, Department of Botany, Faculty of Science, Chulalongkorn University, Bangkok 10330, Thailand

[2] Department of Radiology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

[3] Center of Excellence for Medical Genetics, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

[4] Excellence Center for Medical Genetics, King Chulalongkorn Memorial Hospital, the Thai Red Cross Society, Bangkok 10330, Thailand

Published online: 10 May 2018

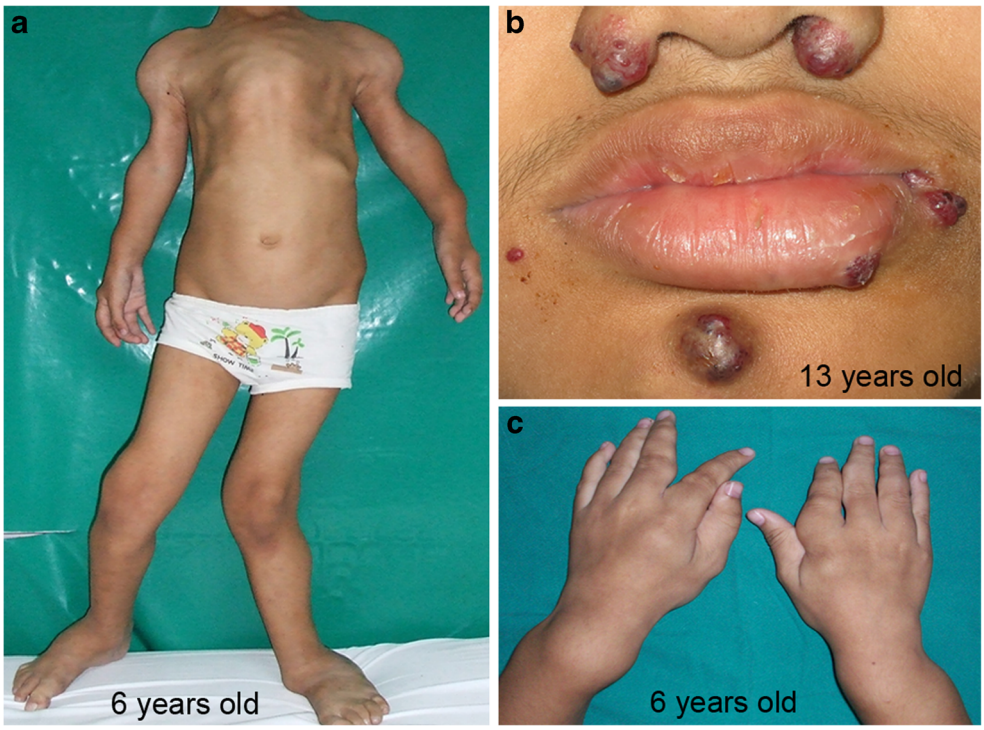

Fig. 1 Clinical manifestations. **a** At age 6 years, he showed pectus carinatum, deformed limbs, and short stature. **b** Multiple hemangiomas were seen at perioral area and ala nasi. **c** The patient's hands showed broadening and shortening of fingers

costal cartilages. Both proximal humeri also showed splaying columns of lucencies and streaks through the metaphyses associated with punctate calcifications in the area of deficient ossification. On the anteroposterior radiograph of the abdomen and pelvis, the levoconvex scoliosis of the thoracolumbar region was observed. There were mild platyspondyly, mild irregularities of the endplates, and speckled calcification. The presence of multiple enchondromas with platyspondyly is known as spondyloenchondrodysplasia [6]. There were multiple columnar lucencies at bilateral iliac crests with dot-like calcifications at nonossified iliac apophyses. The shallow and irregular acetabuli without narrowed sciatic notches were noted. The epiphyses of bilateral femora appeared normal. The radiographs of left arm, right wrist, both hands, both legs, left ankle, and left foot exhibited the same abnormalities, which were uneven, bulbous expansive metaphyses of long bones as well as irregular lucencies of metaphyses interspersed with stippled calcification. Some fingers revealed bulbous enlargement and streaks of lucencies through the metaphyses. Shortening of metacarpal and metatarsal bones was also observed.

At the age of 3 years, multiple dark purple masses (the estimated size 0.5 × 0.5 cm to 1 × 1 cm) appeared at the tip of prepuce, the right popliteal fossa, and the back of the left thigh. At that time, these masses were asymptomatic and conservative treatment was initiated. Subsequently, a biopsy of the masses was performed and the histopathology revealed hemangiomas. Their number and sizes increase with age. At 6 years old, hemangiomas spread through all of the patient's body, back, neck, arms, legs, and scrota (Fig. 1). When he was 12 years old, he had obstructive sleep apnea and hoarseness. Bronchoscopy revealed laryngeal hemangiomas, which originated from the right true vocal cord and anterior commissure and extended to the subglottic area. Four surgical removals were required during the ages of 12 and 14 years. At 13 years of age, hemangiomas had been increasing in size and number including those at bilateral alar nasi, left columella, oral commissure, arms, and legs (Fig. 1b, c, e). These masses became more painful. As a result, surgical excision of the masses was performed without complications. The histopathological examination revealed hemangiomas. At his last follow-up visit, at 15 years of age, he was 127 cm tall ($P < 3$rd centile).

His cognitive development was normal. At 15 years of age, he could read books, speak normally, and do proper mathematics. He was the second child of non-consanguineous parents. No other family members had similar manifestations.

MRI of the brain at the age of 13 years showed expansive clivus and lesions at bilateral posterior clinoid processes associated with heterogeneous enhancing soft tissue masses with cystic components, corresponding with enchondroma causing pressure to adjacent structures. Echocardiography and ultrasonography of the kidneys performed at the ages of 7 and 12 years, respectively, were unremarkable.

Urine organic acid analysis of the patient showed an elevated excretion of D-2-hydroxyglutaric acid (1848 mmol/mol creatinine; normal range, 2.8–17). L-2-hydroxyglutaric acid excretion was within the normal range. His parents had

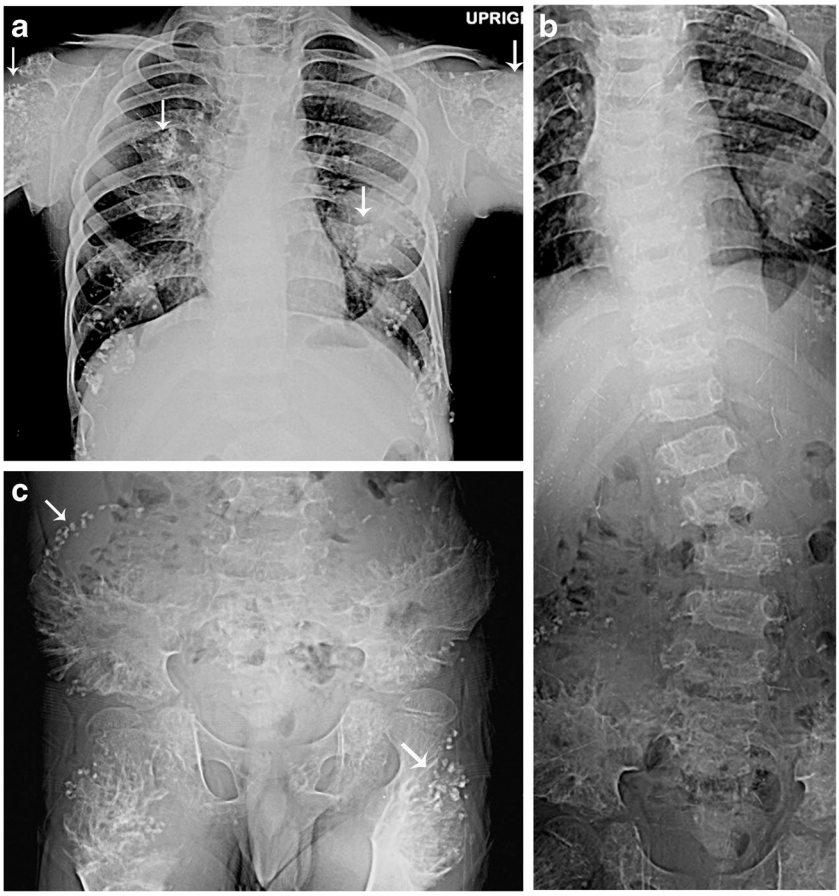

Fig. 2 Plain radiographs of the patient at 7 years of age. **a** The posteroanterior chest radiograph revealed bulbous, expansive costovertebral junctions at several levels together with stippled calcification in the area of noncalcified costal cartilages. Bilateral proximal humeri also showed splaying columns of lucencies and streaks through the metaphyses associated with punctate calcifications in the area of deficient ossification. **b**-**c** The radiographs of the spine and pelvis showed levoconvex scoliosis of the thoracolumbar region with mild platyspondyly, mild irregularities of the endplates, and speckled calcification, i.e., spondyloenchondromatosis, which was more pronounced at the lumbar spine. There were multiple columnar lucencies at bilateral iliac crests with dot-like calcifications at nonossified iliac apophyses. Shallow and irregular acetabuli without narrow sciatic notches were observed. The speckled calcification (*arrows*) is cartilage calcification in a typical "rings and arcs" pattern. *Vertical streaks of lucencies* represent columns of cartilages

normal excretions of both compounds. Karyotyping at a resolution of 400 bands showed normal 46, XY.

After informed consent was obtained, genomic DNA and RNA were isolated from peripheral leukocytes according to standard protocols. We sequenced genes related to isolated enchondromatosis and isolated D-2-hydroxyglutaric aciduria by Sanger sequencing. These included the p.R150C mutation of *PTHR1*, the coding regions of *D2HGDH, HOT* [7], and *IDH1*. No causative variants were identified; we then did whole-exome sequencing (WES) of the patient using DNA from his leukocytes and a hemangioma, and his parents. The samples were sent to Macrogen, Inc. (Seoul, Korea). Four μg of DNA samples were enriched by SureSelect Target Enrichment System and were sequenced onto Illumina Hiseq 4000. The raw data per exome were mapped to the human reference genome hg19 using Burrows–Wheeler alignment. Variants calling were detected with GATK. A total yield of 5.7–7.5 Gb per exome was achieved. The percent of on-target reads is 75.8–77.2 and the mean depth of target regions is 62.8–81.7X per exome. For trio-exome analysis, we explored de novo variants in the coding regions using *InteractiVenn* [8] and *Golden Helix Genome Browse*™. However, no likely pathogenic variants were found. For WES of a hemangioma and leukocytes of the patient, we searched for different variants or zygosity. No likely pathogenic variants were identified.

Discussion

We reported the tenth case of MC-HGA, confirmed by radiographs, demonstrating metaphyseal enchondromatosis and spondyloenchondromatosis as well as elevated concentrations of urine 2-hydroxyglutaric acid [1–5]. Our patient was found to have enchondromatosis and D-2-hydroxyglutaric aciduria at 16 months of age. At about 3 years of age, hemangiomas

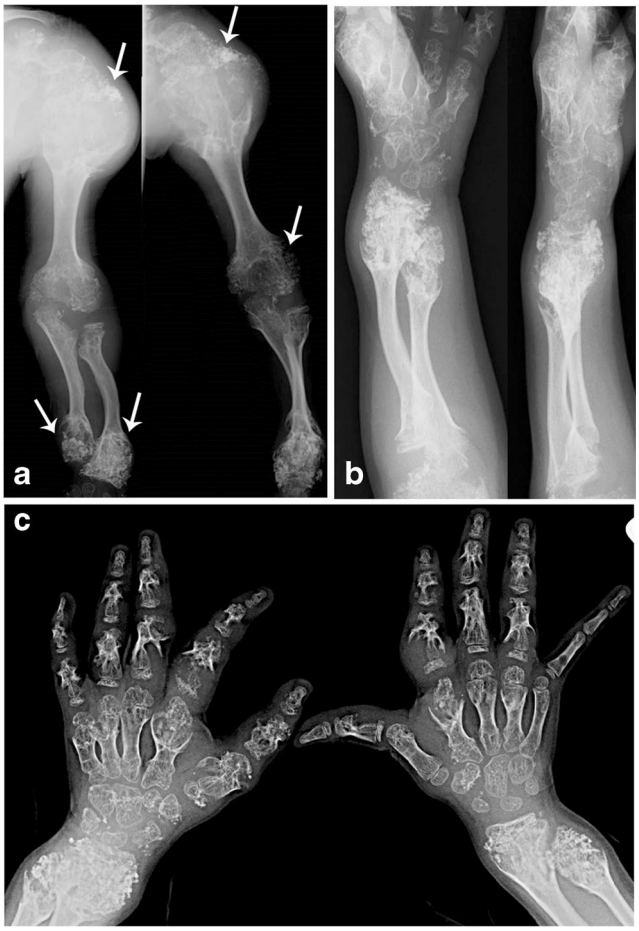

Fig. 3 Radiographs of the upper extremities. The radiographs of **a** left arm, **b** right wrist, and **c** both hands exhibited bulbous expansive metaphyses of long bones as well as irregular lucencies of metaphyses interspersed with stippled calcification. Some fingers revealed bulbous enlargement and streaks of lucencies through the metaphyses. Again noted, the speckled calcification (*arrows*) is cartilage calcification in a typical "rings and arcs" pattern. *Vertical streaks of lucencies* represent columns of cartilages

developed and progressed. If the patient was considered to have enchondromatosis with D-2-hydroxyglutaric aciduria, he would be the tenth of such cases and the first with widespread hemangiomas. If he was considered to have Maffucci syndrome (hemangiomatosis with multiple enchondromatosis), he would be the first having such a syndrome with D-2-hydroxyglutaric aciduria. Whether other patients with Maffucci syndrome do not have D-2-hydroxyglutaric aciduria or they did not undergo the test to determine the presence of D-2-hydroxyglutaric acid awaits further studies. In any case, our patient is the first who has all the three main features of enchondromatosis, D-2-hydroxyglutaric aciduria, and widespread hemangiomas.

All reported patients with enchondromatosis and D-2-hydroxyglutaric aciduria presented with limb shortening, bulbous metaphyses, short metacarpals/metatarsals, short phalanges, hand anomalies, and difficulty in walking. Most patients developed short stature and genu valgum/varum. Developmental delay, visceral abnormalities, CNS abnormalities, scoliosis, platyspondyly/irregular endplates, and narrow sciatic notches have been found in about half of the patients (Table 1).

The radiographic findings of our case are similar to the two prior well-described imaging studies [3, 5]. These abnormalities include bulbous, expansive costovertebral junctions and metaphyses of long bones with stippled calcification in the area of noncalcified cartilages. Splaying columns of lucencies and streaks through the metaphyses of long bones and bilateral iliac crests associated with punctate calcifications in the area of deficient ossification are observed. There are also levoconvex scoliosis of the thoracolumbar region with mild platyspondyly, mild irregularities of the endplates, and speckled calcifications. Shallow and irregular acetabuli, but normal sciatic notches and normal epiphyses of bilateral femora, are included.

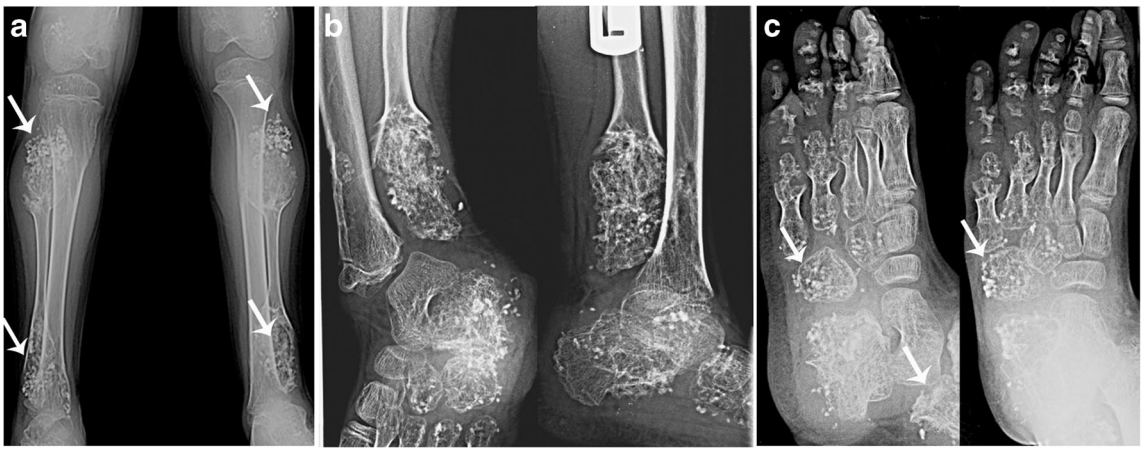

Fig. 4 Radiographs of the lower extremities. The radiographs of **a** both legs, **b** left ankle, and **c** left foot revealed splaying and enlargement of the metaphyses of the fibulae and metatarsal bones with irregular radiolucencies and stippled calcification, which were cartilage calcification (*arrows*). There was also scattering spot calcification in non-calcified cartilage of tarsal bones (*arrows*)

Table 1 Clinical and radiological summary of ten reported metaphyseal chondromatosis associated with 2-hydroxyglutaric aciduria

Clinical/radiological features	Previously reported case [3]	Our case	Total
Consanguinity	1/9	–	1/10
Age at exam	11 months to 17 years	15 years	11 months to 17 years
Short stature	7/9	+	8/10
Developmental delay	5/9	–	5/10
Mental retardation	1/8	–	1/9
Visceral abnormalities	3/9	+	4/10
CNS abnormalities	3/9	+	4/10
Walking difficulty	9/9	+	10/10
Limb shortening	9/9	+	10/10
Genu valgum/varum	7/9	+	8/10
Hand abnormalities	9/9	+	10/10
Other abnormalities	4/9	+ (hemangioma)	5/10
Scoliosis	4/9	+	5/10
Platyspondyly/irregular endplates	5/9	+	6/10
Hip subluxation	1/9	–	1/10
Narrow sciatic notch	6/9	–	6/10
Bulbous metaphyses	9/9	+	10/10
Short metacarpal/metatarsal	9/9	+	10/10
Short phalanges	9/9	+	10/10

Of these ten reported cases, our patient is the only one with hemangiomas in several organs. A previous study reported hemangiomas on hands [3]. These widespread lesions are progressive and laryngeal hemangiomas could lead to obstructive sleep apnea and hoarseness while those in the oral cavity could cause recurrent bleeding. However, the presence of multiple enchondromas combined with multiple hemangiomas is known as Maffucci syndrome [6].

Previous reports showed that most patients had normal cognitive function, similar to our patient [1–3, 5] (Table 1). The only patient with microcephaly and intellectual disability was reported by Vissers et al. [1].

We did Sanger sequencing for genes related to isolated enchondromatosis and isolated D-2-hydroxyglutaric aciduria. These included a hotspot mutation p.R150C, of *PTHR1* found in two of six individuals with Ollier enchondromatosis [9]; all coding regions of *D2HGDH*, a causative gene of D-2-hydroxyglutaric aciduria [10]; all coding regions of *HOT*, a gene encoding hydroxyacid-oxoacid transhydrogenase involved in the formation of D-2-hydroxyglutarate and metabolism of 4-hydroxybutyrate [7]; and all coding regions of *IDH1*, a gene encoding isocitrate dehydrogenase 1 (NADP+) catalyzing D-isocitrate to alpha-ketoglutarate [1]. Two of four patients with MC-HGA were previously found to have mutations in the *IDH1* gene [1]. However, no pathogenic mutations were identified in our patient.

We subsequently performed WES using DNA extracted from leukocytes of the patient and his parents. De novo variants were looked for but no likely pathogenic variants were detected. We also did WES using DNA extracted from the patient's hemangioma. Variants with different zygosity, especially those with loss of heterozygosity, and different variants between the leukocytes and the hemangioma suggesting a somatic mutation, were sought after. Unfortunately, no likely pathogenic variants were found.

In conclusion, we reported the tenth patient with MC-HGA who manifested widespread and debilitating hemangiomas in several organs, expanding the clinical spectrum of MC-HGA.

Acknowledgements We are grateful to Professor Dr. Cornelis Jakobs from the VU University Medical Center, Amsterdam, The Netherlands, for the D-2-HGA analyses. This study was supported by Royal Golden Jubilee Advanced Program under Grant No. RAP59K0008, Thailand Research Fund (DPG6180001) and the Chulalongkorn Academic Advancement into Its 2nd Century Project.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Vissers LE, Fano V, Martinelli D, Campos-Xavier B, Barbuti D, Cho TJ, et al. Whole-exome sequencing detects somatic mutations of IDH1 in metaphyseal chondromatosis with D-2-hydroxyglutaric aciduria (MC-HGA). Am J Med Genet A. 2011;155A(11):2609–16.
2. Bayar A, Acun C, Dursun A, Verhoeven N, Bonafe L, Keser S, et al. Metaphyseal enchondrodysplasia with 2-hydroxy-glutaric

aciduria: observation of a third case and further delineation. Clin Dysmorphol. 2005;14(1):7–11.
3. Choo HJ, Cho TJ, Song J, Tiller GE, Lee SH, Park G, et al. Metaphyseal chondromatosis combined with D-2-hydroxyglutaric aciduria in four patients. Skelet Radiol. 2012;41(11):1479–87.
4. Honey EM, van Rensburg M, Knoll DP, Mienie LJ, van de Werke I, Beighton P. Spondyloenchondromatosis with D-2-hydroxyglutaric aciduria: a report of a second patient with this unusual combination. Clin Dysmorphol. 2003;12(2):95–9.
5. Talkhani IS, Saklatvala J, Dwyer J. D-2-hydroxyglutaric aciduria in association with spondyloenchondromatosis. Skelet Radiol. 2000;29(5):289–92.
6. Pansuriya TC, Kroon HM, Bovee JV. Enchondromatosis: insights on the different subtypes. Int J Clin Exp Pathol. 2010;3(6):557–69.
7. Kardon T, Noel G, Vertommen D, Schaftingen EV. Identification of the gene encoding hydroxyacid-oxoacid transhydrogenase, an enzyme that metabolizes 4-hydroxybutyrate. FEBS Lett. 2006;580(9): 2347–50.
8. Heberle H, Meirelles GV, da Silva FR, Telles GP, Minghim R. InteractiVenn: a web-based tool for the analysis of sets through Venn diagrams. BMC Bioinforma. 2015;16:169.
9. Hopyan S, Gokgoz N, Poon R, Gensure RC, Yu C, Cole WG, et al. A mutant PTH/PTHrP type I receptor in enchondromatosis. Nat Genet. 2002;30(3):306–10.
10. Struys EA, Salomons GS, Achouri Y, Van Schaftingen E, Grosso S, Craigen WJ, et al. Mutations in the D-2-hydroxyglutarate dehydrogenase gene cause D-2-hydroxyglutaric aciduria. Am J Hum Genet. 2005;76(2):358–60.