

CASE REPORT

Legg-Calvé-Perthes disease in a patient with Bardet-Biedl syndrome: A case report of a novel *MKKS/BBS6* mutation

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Funding information

This work was supported by AMED under the grant numbers JP19ek0109280, JP19dm0107090, JP19ek0109301, JP19ek0109348, and JP18kk020501 (to N. Matsumoto); JSPS KAKENHI under the grant numbers JP17H01539 (to N. Matsumoto) and JP19H03621 (to N. Miyake); grants from the Ministry of Health, Labour, and Welfare (to N. Matsumoto); and the Takeda Science Foundation (to N. Matsumoto and N. Miyake).

Abstract

This article reports a girl with Bardet-Biedl syndrome (BBS) having a novel causative mutation who developed Legg-Calvé-Perthes disease (LCPD). There exists a possibility that the prognosis of LCPD had been adversely affected by the concomitant BBS.

KEYWORDS

Bardet-Biedl syndrome, Legg-Calvé-Perthes disease, *MKKS/BBS6* gene, osteochondrosis, surgical containment

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1 | INTRODUCTION

We report on a girl with Bardet-Biedl syndrome (BBS) harboring a novel MKKS/BBS6 mutation who developed Legg-Calvé-Perthes disease (LCPD). Although she was adequately treated with surgical containment, the proximal femur significantly deformed. There exists a possibility that the prognosis of LCPD had been adversely affected by the concomitant BBS.

Bardet-Biedl syndrome (BBS; MIN#209900) is an autosomal recessive disorder characterized by genetically and phenotypically heterogeneity with a prevalence of about 1 case per 125 000 live births.¹ The syndrome belongs to the group of ciliopathies that is caused by dysfunction and/or structural deficiency of the primary cilium. Reflecting versatile biological functions of the cilia, BBS compromises multiple organs and tissues, primarily manifesting as retinal dystrophy, obesity, renal malformation, and hypogonadism.² Orthopedic presentation of BBS mainly includes congenital hand anomalies, especially postaxial polydactyly, and sometimes syndactyly, brachydactyly, and/or clinodactyly. Legg-Calvé-Perthes disease (LCPD) is a juvenile form of idiopathic femoral head osteonecrosis due to compromise of blood supply to the osseous epiphysis with an annual incidence of 0.9 per 100 000 children aged <15 years in Japan.³ To our knowledge, there has been only one previously identified case of LCPD in a patient diagnosed with BBS.⁴ In this paper, we report on a Japanese patient with BBS complicated by LCPD who had a novel homozygous mutation in the *BBS6/MKKS* gene. The patients and their families were informed that data from the case would be submitted for publication and gave their consent.

2 | CASE PRESENTATION

The patient was born by vaginal delivery at forty weeks of gestational age. She was the first child of healthy nonconsanguineous parents. The family history was unremarkable for any genetic conditions, and no prenatal abnormalities were identified through routine sonographic assessments. At birth, she showed no signs of birth asphyxia with a weight of 2545 g and a length of 49 cm, but she exhibited bilateral postaxial synpolydactyly in the lower limbs. She could walk independently before the age of one year, but growth retardation was gradually apparent, with her body falling below $-2SD$ of the Japanese standard. At thirteen months of age, she underwent resection of the additional 6th digit in the right foot and the hypoplastic 5th digit in the left foot (Figure 1A,B). Speech and cognitive development were normal. At three years of age, she was referred to a pediatric ophthalmologist for strabismus and amblyopia, where she was diagnosed as early stage of retinitis

pigmentosa. Although growth hormone (GH) deficiency had not been confirmed, she had received GH therapy for $-3SD$ shorter than the mean since the age of five years. She was referred to our institution for continued growth disturbance and various skeletal malformations at four years of age. Facial appearance was dysmorphic with a round face, midface hypoplasia, and micrognathia. She had malaligned or malformed teeth and a high-arched palate (Figure 1C). Physical examination revealed proportionate short stature with increased lumbar lordosis and genu recurvatum in addition to hairiness of the back and hypoplastic digits. A full radiographic skeletal survey demonstrated mild generalized epiphyseal dysplasia of the long bones and brachydactyly in the hands and feet (Figure 1D,E,F). Based on the physical findings such as postaxial polydactyly, brachydactyly, and dysplastic teeth, Weyers acrofacial dysostosis, a similar but milder form of Ellis-van Creveld syndrome (EvC), was first considered in the differential diagnosis. Subsequent cardiovascular examination demonstrated no congenital cardiac defects, commonly seen in EvC. At the age of seven years, she was suspected to have Bardet-Biedl syndrome (BBS) through investigation by a medical geneticist based on the presence of retinitis pigmentosa, congenital anomalies of the hands and feet, and obesity trends. Whole-exome sequencing, which was performed as previously described,⁵ and conventional Sanger sequencing revealed that the presence of a novel homozygous and heterozygous nonsense mutation (NM_018848:c.589G>T:p.Gly197*) in exon 3 of the *MKKS/BBS6* gene, a causative gene of McKusick-Kaufman syndrome and BBS, in the patients and her parents, respectively (Figure 2).

She showed a dull pain in the right thigh and limping without a history of trauma at eight years of age. The range of motion (ROM) of the right hip was limited in all planes except for flexion. Anteroposterior and frog-leg lateral radiographs of the hip demonstrated sclerosis, loss of height, and subchondral radiolucent zone (ie, crescent sign) in the right proximal femoral epiphysis. Magnetic resonance imaging (MRI) revealed homogenous hypointensity of the entire capital epiphysis on T1-weighted images and intra-articular joint effusion associated with lateralization of the femoral head on STIR-images, which was compatible with the diagnosis of LCPD (Figure 3). She was immediately hospitalized to undergo skin traction of the lower limbs for the purpose of reducing intracapsular synovitis. After the improvement of the ROM of the affected hip, we performed Salter innominate osteotomy with tenotomies of the adductor longus and the iliopsoas, which we have adopted as a method of containment for school-age children with LCPD.⁶ Postoperatively, the hip was immobilized in one and one-half hip spica cast for three weeks, followed by aggressive ROM exercises, and partial weight bearing was commenced eight weeks after

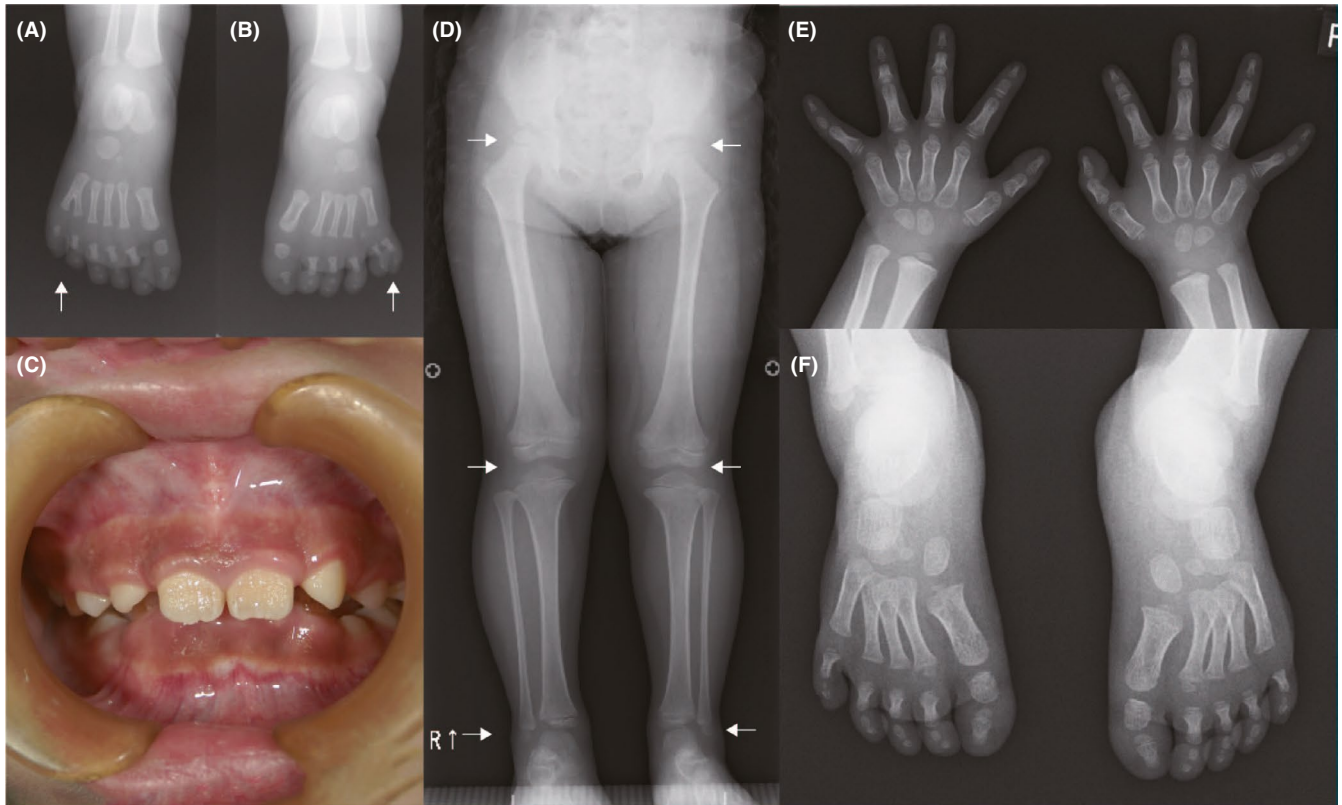


FIGURE 1 Clinical and radiological features of the patient. Radiographs of the patient's feet at 9 mo of age, indicating postaxial synpolydactyly (arrow) of the right foot (A) and left foot (B). Dental photographs of the patient at 10 y of age (C). Note an abnormally formed dentition. Radiographs of the upright full-length lower limbs (D), hands (E), and feet (F) at 4.5 y of age, showing mild multiple epiphyseal dysplasia of the long bones (arrow) and distal phalangeal hypoplasia

the surgery. The patient gradually became obese during the postoperative rehabilitation period and reached more than 2 SD of the mean value by age of nine years. Hip

radiographs at the fragmentation period demonstrated diminished epiphyseal height of the lateral portion of the femoral head, representing the modified lateral pillar

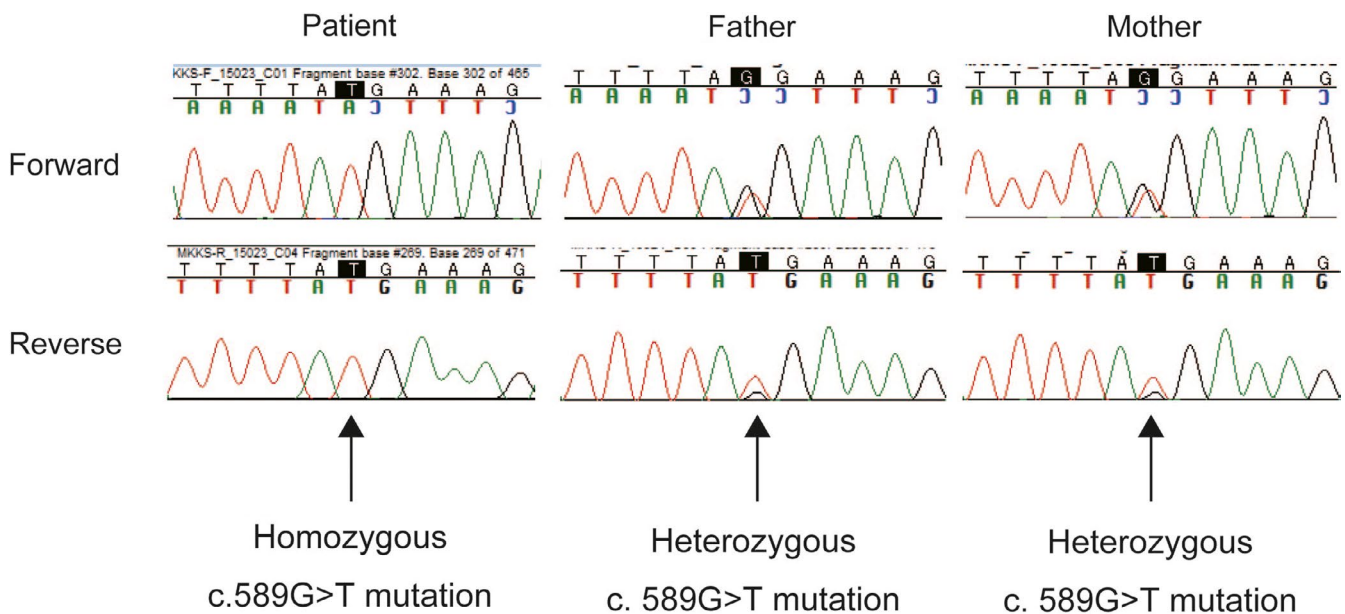


FIGURE 2 Partial sequence chromatograms of PCR products from the patient and her parents. The position of the homozygous or heterozygous mutation in exon 3 is marked by arrows in the chromatograms

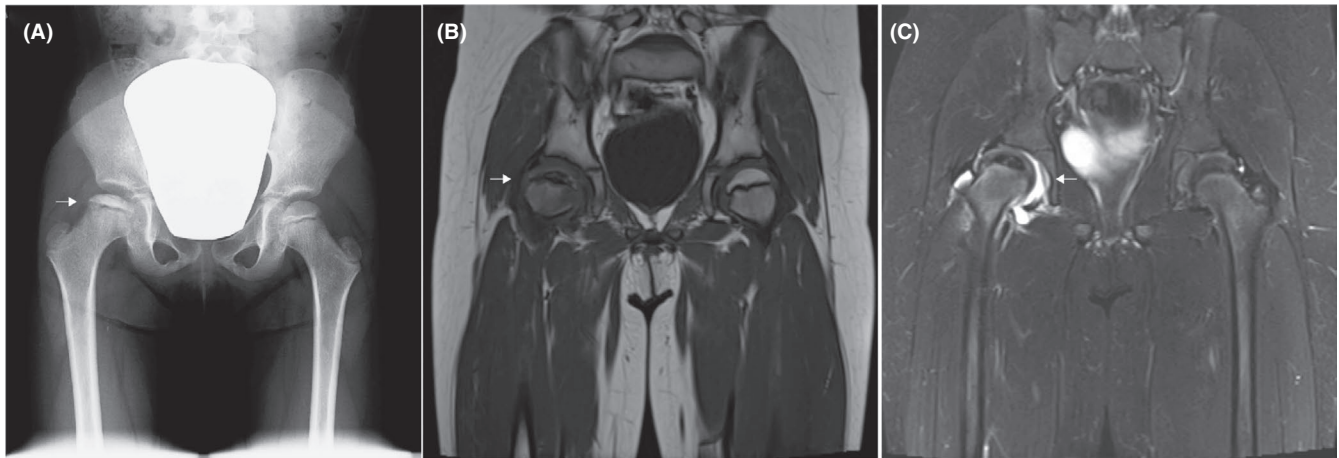


FIGURE 3 X-ray and MRI images of the patient made at diagnosis of Legg-Calvé-Perthes disease. Anteroposterior radiograph (A), coronal T1- (B) and STIR- (C) MR images at eight years of age, showing sclerosis and flattening (A, arrow) and homogenous hypointensity (B, arrow) of the right femoral head and an abundant intracapsular effusion (C, arrow)

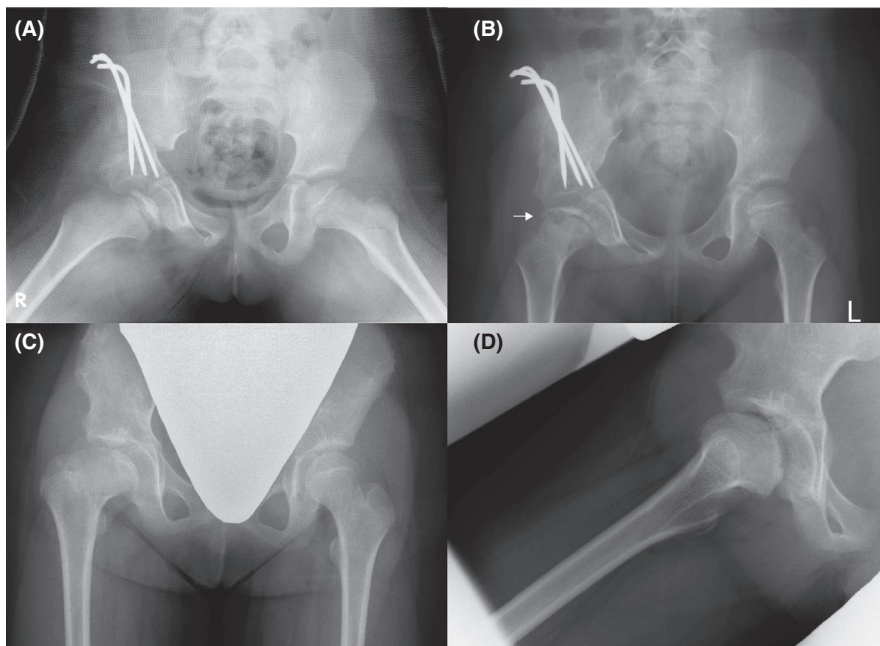


FIGURE 4 X-ray images of the patient made during the fragmentation (A and B) and healing (C and D) stages of Legg-Calvé-Perthes disease. Anteroposterior radiographs immediately (A) and six months (B) after the surgery. The right femoral head is fully contained within the displaced acetabulum (A). The lateral pillar height is decreased by <50% associated with a metaphyseal cyst formation (B, arrow). Anteroposterior (C) and frog-leg lateral (D) radiographs at latest follow-up, showing the right femoral capital epiphysis to be enlarged, confluent, and nonfragmented. Premature physeal closure and epiphyseal extrusion are evident

type C hip,⁷ and metaphyseal cyst formation spanning the growth plate had occurred in the anterolateral portion (Figure 4A,B). Ten months after the surgery, she was allowed full weight bearing following the implant removal. At latest follow-up of twelve years of age (four years after diagnosis), she showed an ovoid right femoral head with preserved joint congruency, equivalent to Stulberg class 3 intermediate hip.⁷ When quantitatively determining the sphericity of the affected femoral head using the sphericity deviation score (SDS),⁸ on the other hand, its value of 45 agreed with the mean of the Stulberg class 4 unfavorable hip (Figure 4C,D). She was clinically asymptomatic, restoring a full painless ROM of the right hip without apparent gait abnormalities.

3 | DISCUSSION

The BBS is a genetically and phenotypically heterogeneous disorder characterized by up to 21 disease-causing BBS genes identified to date and six major defects such as retinal dystrophy, polydactyly, obesity, mental retardation, hypogonadism, and renal dysfunction called primary features, with secondary features that include hepatic fibrosis, diabetes mellitus, dental irregularities, and behavioral abnormalities. The proposed diagnostic criteria for BBS are defined as the presence of either four primary features or three primary and two secondary features,² which the present case did not meet at first presentation. A subset of the ciliopathy has been categorized as the skeletal ciliopathy

that share common skeletal features such as a narrow thorax, short ribs, polydactyly, and short limbs. It includes the short rib-polydactyly group, asphyxiating thoracic dysplasia, Ellis-van Creveld syndrome, Weyers acrofacial dysostosis, and cranioectodermal dysplasia.⁹ In the present case, the first presumptive diagnosis had been Weyers acrofacial dysostosis on the basis of the presence of post-axial polydactyly of the feet, mild short stature with short limbs, and dental anomalies. As opposed to other skeletal ciliopathies, the absence of a narrow thorax associated with short ribs and congenital heart defect in this case had also underpinned this entity.¹⁰ Because the skeletal ciliopathies generally lack of retinal involvement, clinicians should pay attention to visual acuity in addition to the presence of night blindness and peripheral visual field defects indicative of retinal abnormalities when encountering patients with suspected skeletal ciliopathies.

To our best knowledge, there has only one previously identified case exhibiting bilateral changes of the femoral head that were compatible with LCPD in a patient with genetically confirmed BSS caused by a mutation in the *BBS1* gene. Although it is likely that the occurrence of these two disorders in a single patient is a coincidence, despite successful surgical containment during the earlier phase of the disease, remodeling to a bigger mushroom-shaped femoral head than expected with marked shortening of the neck may be partly attributable to disruption of the basal body of ciliated chondrocytes within articular cartilage and growth plate in this patient. In mammalian cells, depletion of *BBS1*, *BBS4*, and *BBS6/MKKS*, which encode the basal body proteins of the cilium, has been shown to activate Wnt/ β -catenin signaling.¹¹ In a genetic mouse model in which chondrocyte-specific activation of Wnt/ β -catenin signaling can be induced for specific periods of time, abnormal growth plate closure and articular cartilage thickening were observed in postnatal mice,¹² Cartilage-specific activation of β -catenin signaling promoted perichondrial bone formation surrounding the growth plate as well.¹³ These changes of the cartilaginous tissues could have unfavorably affected the vulnerable head during the fragmentation and reossification stages by causing progressive extrusion of the femoral head, growth retardation of the capital femoral physis, and excessive metaphyseal widening, which may eventually retard successful remodeling of the hip. Metaphyseal cyst formation in the early stage of the disease, one of the five head-at-risk signs, could somewhat contribute to proximal femoral physeal growth disturbance that have been demonstrated in a piglet model of LCPD.^{14,15} Metabolic propensity toward obesity during a period of partial weight bearing could have an adverse impact on preservation of the lateral pillar height of the capital femoral epiphysis.⁷ We cannot conclude that a ciliopathy BBS had an appreciably negative effect on the

clinical course of LCPD in this case. Nonetheless, if diagnosed early with LCPD, combined pelvic and femoral osteotomy or triple pelvic osteotomy for more advanced containment and strict nonweight bearing management during the early phase of the disease may be preferable for patients with a ciliopathy.

ACKNOWLEDGMENTS

We greatly thank staff members of Department of Human Genetics, Graduate School of Medicine, Yokohama City University, Yokohama, Japan, for their great help in the genetic analysis of the patient and her parents.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTION

KM, SM, and HK: equally involved in clinical examination, literature search, and writing of the paper. AF, NM, and NM: equally involved in genomic sequencing and mutation analysis. MM, TN, YK, and SI: equally involved in clinical examination and drafting.

INFORMED CONSENT

The patient and her parents were informed that data concerning the case would be submitted for publication, and they consented.

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REFERENCES

1. Tsang SH, Aycinena ARP, Sharma T. Ciliopathy: Bardet-Biedl Syndrome. *Adv Exp Med Biol*. 2018;1085:171-174.
2. Khan SA, Muhammad N, Khan MA, Kamal A, Rehman ZU, Khan S. Genetics of human Bardet-Biedl syndrome, an updates. *Clin Genet*. 2016;90(1):3-15.
3. Kim WC, Hiroshima K, Imaeda T. Multicenter study for Legg-Calve-Perthes disease in Japan. *J Orthop Sci*. 2006;11(4):333-341.
4. Ramirez N, Marrero L, Carlo S, Cornier AS. Orthopaedic manifestations of Bardet-Biedl syndrome. *J Pediatr Orthop*. 2004;24(1):92-96.
5. Aoi H, Mizuguchi T, Ceroni JR, et al. Comprehensive genetic analysis of 57 families with clinically suspected Cornelia de Lange syndrome. *J Hum Genet*. 2019;64(10):967-978.
6. Kitakoji T, Hattori T, Kitoh H, Katoh M, Ishiguro N. Which is a better method for Perthes' disease: femoral varus or Salter osteotomy? *Clin Orthop Relat*. 2005;Res(430):163-170.
7. Herring JA, Kim HT, Browne R. Legg-Calve-Perthes disease. Part I: classification of radiographs with use of the modified lateral pillar and Stulberg classifications. *J Bone Joint Surg Am*. 2004;86(10):2103-2120.

8. Shah H, Siddesh ND, Pai H, Tercier S, Joseph B. Quantitative measures for evaluating the radiographic outcome of Legg-Calve-Perthes disease. *J Bone Joint Surg Am.* 2013;95(4):354-361.
9. Huber C, Cormier-Daire V. Ciliary disorder of the skeleton. *Am J Med Genet C Semin Med Genet.* 2012;160C(3):165-174.
10. Ye X, Song G, Fan M, et al. A novel heterozygous deletion in the EVC2 gene causes Weyers acrofacial dysostosis. *Hum Genet.* 2006;119(1-2):199-205.
11. Gerdes JM, Liu Y, Zaghoul NA, et al. Disruption of the basal body compromises proteasomal function and perturbs intracellular Wnt response. *Nat Genet.* 2007;39(11):1350-1360.
12. Majidinia M, Aghazadeh J, Jahanban-Esfahlani R, Yousefi B. The roles of Wnt/beta-catenin pathway in tissue development and regenerative medicine. *J Cell Physiol.* 2018;233(8):5598-5612.
13. Dao DY, Jonason JH, Zhang Y, et al. Cartilage-specific beta-catenin signaling regulates chondrocyte maturation, generation of ossification centers, and perichondrial bone formation during skeletal development. *J Bone Miner Res.* 2012;27(8):1680-1694.
14. Kim HK, Skelton DN, Quigley EJ. Pathogenesis of metaphyseal radiolucent changes following ischemic necrosis of the capital femoral epiphysis in immature pigs. A preliminary report. *J Bone Joint Surg Am.* 2004;86(1):129-135.
15. Rampal V, Clement JL, Solla F. Legg-Calve-Perthes disease: classifications and prognostic factors. *Clin Cases Miner Bone Metab.* 2017;14(1):74-82.

How to cite this article: Mishima K, Fujita A, Mizuno S, et al. Legg-Calvé-Perthes disease in a patient with Bardet-Biedl syndrome: A case report of a novel *MKKS/BBS6* mutation. *Clin Case Rep.* 2020;8:3109–3114. <https://doi.org/10.1002/ccr3.3357>