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Novel compound heterozygous mutations identified by whole exome sequencing in a Japanese patient with geroderma osteodysplastica

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ABSTRACT

Geroderma osteodysplastica (GO) is a subtype of cutis laxa syndrome characterized by congenital wrinkly skin, a prematurely aged face, extremely short stature, and osteoporosis leading to recurrent fractures. GO exhibits an autosomal recessive inheritance pattern and is caused by loss-of-function mutations in *GORAB*, which encodes a protein important for Golgi-related transport. Using whole exome sequencing, we identified novel compound heterozygous nonsense mutations in the *GORAB* in a GO patient.

The patient was a 14-year-old Japanese boy. Wrinkled skin and joint laxity were present at birth. At 1 year of age, he was clinically diagnosed with cutis laxa syndrome based on recurrent long bone fractures and clinical features, including wrinkled skin, joint laxity, and a distinctive face. He did not show retarded gross motor and cognitive development. At 11 years of age, he was treated with oral bisphosphonate and vitamin D owing to recurrent multiple spontaneous fractures of the vertebral and extremity bones associated with a low bone mineral density (BMD). Bisphosphonate treatment improved his BMD and fracture rate. Whole exome sequencing revealed two novel compound heterozygous nonsense mutations in the *GORAB* gene (p.Arg60* and p.Gln124*), and the diagnosis of GO was established. GO is a rare connective tissue disorder. Approximately 60 cases have been described to date, and this is the first report of a patient from Japan. Few studies have reported the effects of bisphosphonate treatment in GO patients with recurrent spontaneous fractures. Based on this case study, we hypothesize that oral bisphosphonate and vitamin D are effective and safe treatment options for the management of recurrent fractures in GO patients. It is important to establish a precise diagnosis of GO to prevent recurrent fractures and optimize treatment plans.

1. Introduction

Geroderma osteodysplastica (GO; MIM #231070) is a very rare autosomal recessive connective tissue disorder characterized by congenital wrinkled skin, a distinctive prematurely aged face, variable degrees of growth retardation, osteoporosis leading to recurrent fractures, and normal intellectual development (Berk et al., 2012). Bamatter et al. first described GO in 1950 and more than 60 cases have been described to date (Alazami et al., 2016; Al-Dosari and Alkuraya, 2009; Bamatter et al., 1950; Rajab et al., 2008). The majority of previously reported GO patients were born to consanguineous parents in the Middle East or in Mennonite communities. The clinical characteristics of GO overlap substantially with those of hereditary cutis laxa syndromes, including autosomal dominant cutis laxa (ADCL; MIM #123700), autosomal recessive cutis laxa (ARCLI; MIM #219100, ARCLII; MIM #219200, ARCLIII; MIM #219150), and wrinkly skin syndrome (WSS; MIM #278250) (Goyal et al., 2015). It is important to distinguish GO from other cutis laxa syndromes to select the appropriate treatment for the prevention of osteoporosis, which leads to recurrent bone fractures.

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We identified novel compound heterozygous nonsense mutations in the *GORAB* gene (NM_001320252.1; MIM*607983) by whole exome sequencing (WES) in a patient with GO. The patient was treated with bisphosphonate and vitamin D, which successfully reduced the recurrence of fractures. This is the first case of a Japanese GO patient with nonconsanguineous parents; the results support the use of oral bisphosphonate and vitamin D to treat GO.

2. Clinical report

The patient was a 14-year-old Japanese boy born via a normal delivery at 38 weeks of gestation to nonconsanguineous parents with a birth weight of 2680 g (−0.8 SD), length of 50.6 cm (+0.8 SD), and head circumference of 32 cm (−0.9 SD). There was no family history of bone or skin disorders. Joint laxity and wrinkly skin, especially on the dorsum of the hands, feet, and abdomen, were present at birth. At 5 months of age, he was referred our hospital and clinically diagnosed with cutis laxa syndrome based on recurrent bone fractures and clinical features, such as wrinkled skin, joint laxity, and a distinctive face (Fig. 1). Between 8 and 10 years of age, he suffered from three low-energy hand and foot bone fractures and a vertebral compression fracture. At 11 years of age, his height was 141.6 cm (−0.1 SD) and weight was 30.4 kg (−0.8 SD). His gross motor and cognitive development were not retarded, and his full-scale intelligent quotient score was 96 (normative). His facial features included a prematurely aged appearance, including maxillary hypoplasia, prognathism, and ear protrusion, but wrinkly skin and joint laxity were not evident. Radiographs showed the presence of multiple vertebral compression fractures and moderate osteopenia (Fig. 2). Bone mineral density (BMD), as measured by dual energy X-ray absorptiometry of the lumbar spine, revealed an age- and gender-matched z-score of −3.0 SD, and his serum N-telopeptide of type 1 collagen value, a bone resorption marker, was 80 nmolBCE/L (reference range: 9.5–17.7). He was diagnosed with osteoporosis, and treated with oral bisphosphonate (alendronate sodium, 1 mg/kg per week) and vitamin D (alfacalcidol, 0.03 μg/kg daily). Three years after the initiation of treatment, his lumbar spine BMD z-score increased to −1.5 SD, serum N-telopeptide of type1 collagen value decreased to 22 nmolBCE/L, and the incidence of bone fracture was not observed.

3. Results

Written consent was obtained from the parents for the sequencing analysis. We initially sequenced 13 genes previously identified in osteogenesis imperfecta (*BMP1, COL1A1, COL1A2, CRTAP, FGFR2, FGFR3, FKBP10, LEPRE1, LRP5, PPIB, SERPINF1, SERPINH1,* and *SP7*). We did not detect any pathological mutations in these genes. We then performed WES as described previously (Nakamura et al., 2015). We found two novel compound heterozygous nonsense mutations (p.Arg60* and p.Gln124*) in *GORAB* (Fig. 3). To verify that these two mutations were different alleles, we cloned the PCR product from the patient. Arg60* and Gln124* mutations were found in different clones, indicating that they are located in trans. We established a diagnosis of GO.

4. Discussion

GO is inherited as an autosomal recessive disorder caused by loss-of-function mutations in the Golgin, RAB6-interacting (*GORAB*) gene on chromosome 1q24, which encodes a protein important for Golgi-related transport (Hennies et al., 2008). The genetic bases for various types of hereditary cutis laxa have recently been identified; for example, ADCL is caused by *ELN* and *FBLN5* mutations, ARCL is caused by *FBLN5, EFEMP2, ATP6V0A2, PYCR1,* and *ALDH18A1* mutations, and WSS is caused by *ATP6V0A2* mutations (Berk et al., 2012; Alazami et al., 2016). It is difficult to distinguish GO from other types of cutis laxa owing to shared clinical features, e.g., skinfold, hyperelastic skin, and joint laxity. Some authors have described differences in the phenotypes between GO and other cutis laxa syndromes. Morava et al. (2009) indicated that the dysmorphic features of GO become more prominent during the disease course, while improvements in disease phenotypes are observed in ARCLII. Rajab et al. (2008) reported that the skin symptoms of WSS patients improve with increasing age, similar to the symptoms of ARCLII. In contrast with these previous reports, the skin symptoms in our patient improved with age, similar to the symptoms of ARCLII and WSS. In GO patients, the frequency of bone fractures is not attenuated with age; accordingly, it is difficult to distinguish GO not only from other cutis laxa syndromes, but also from bone fragility disorders, e.g., osteogenesis imperfecta, especially in older children.

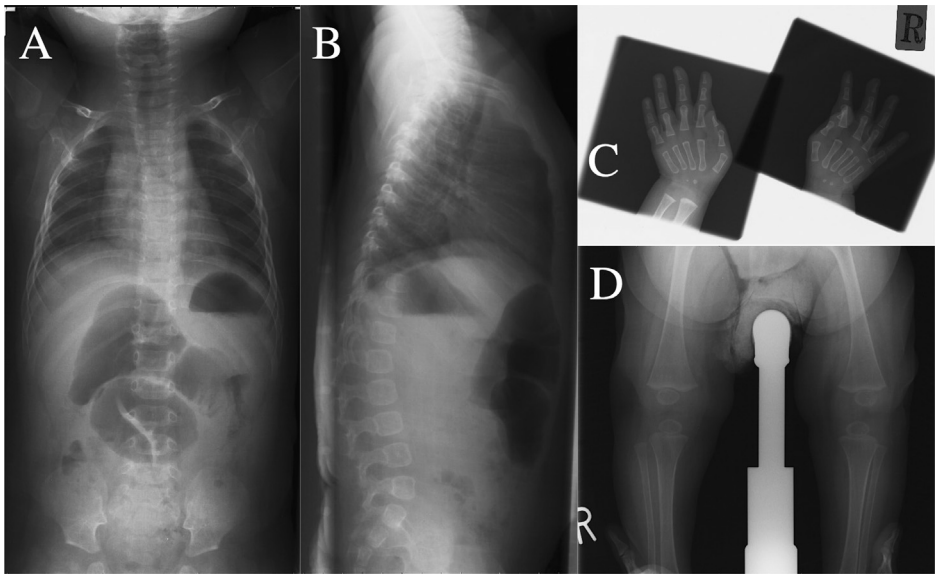

Fig. 1. Radiographs at 5 months of age.
A–D: Note modest osteopenia, tall vertebral bodies, and metaphyseal undermodeling of the knee.

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