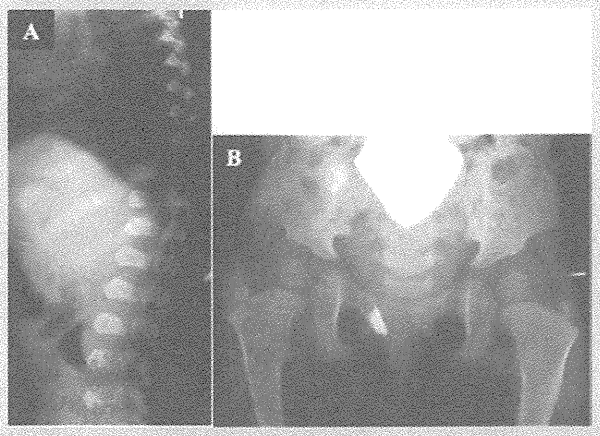

FIG. 5. Radiographs of Patient 3 compatible with the diagnosis of spondyloepipyseal dysplasia, Kozlowski type. A: Pelvis A-P at age 2 years. Persistent hypoplasia of the basilar portions of the iliac bones and round capital femoral epiphyses. The femoral necks are short, but have no overt metaphyseal abnormalities. B: Lateral spine at age 3 years. The vertebral bodies are flat with anterior wedging.

although there is large intra- and inter-familial variability [Dai et al., 2010a].

Patient 2 was diagnosed as having SEMD-M, but the mutation found, p799R, was identified previously in two cases of metatropic dysplasia by our group [Dai et al., 2010a]. The same *TRPV4* mutation shows considerably different skeletal phenotypes in different patients [Dai et al., 2010b]. We reviewed the records of the cases with the p799R mutations, but found nothing to suggest the association of peripheral neuropathy. The neurological phenotype in Patient 2 was compatible with a motor and sensory axonal neuropathy predominant in the lower limb. Patient 3 had a novel TRPV4 mutation and was diagnosed as having SMD-K and a neurological phenotype compatible with scapulo-humeral spinal muscular atrophy. Thus, the three cases have different *TRPV4* mutations and quite varied skeletal and neurological phenotypes.

Co-occurrence of skeletal and neurological phenotypes has been hinted at in a few instances. Chen et al. [2010] reported a three-generation family with six patients harboring an S542Y mutation. The patients in this family manifested as HMSN2C but in addition had moderate short stature. The diagnosis of the neuropathy was unequivocal, while characterization of skeletal changes was minimal and radiographic data were not presented. The description suggests to us that the family might have had brachyolmia or mild SMD-K. Zimon et al. [2010] reported an isolated Croatian patient (PN-1394.1 in the paper) who was diagnosed as having HMSN2, and also had scoliosis and short stature. Although the authors stated that skeletal abnormalities in the patient were too limited to make a formal diagnosis of a skeletal dysplasia, the radiographic description suggests brachyolmia. The patient had a de novo V620I mutation, which was previously shown to cause autosomal dominant brachyolmia [Rock et al., 2008; Dai et al., 2010a]. Recently, Unger et al. [2011] reported fetal akinesia as the presenting feature of severe metatropic dysplasia, which supported that certain *TRPV4* mutations can cause both skeletal and neuropathic phenotypes.

Earlier reports stressed that *TRPV4* mutations associated with neuropathy involve substitutions of arginine residues at the ankyrin repeats [Auer-Grumbach et al., 2010; Chen et al., 2010; Deng et al., 2010; Landoure et al., 2010; Berciano et al., 2011; Klein et al., 2011]. However, two neuropathic mutations have been reported in the TRPV4-transmembrane domain (S542Y and V620I) [Chen et al., 2010; Zimon et al., 2010]. Neither of them is an arginine substitution. Conversely, many *TRPV4* mutations identified in skeletal dysplasias are arginine substitutions and several are in the ankyrin repeats [Dai et al., 2010a]. Also, all mutations in our patients were not arginine substitutions, and the mutation in Patient 2 was not in the ankyrin repeat. Our conclusion from these findings is that genotype–phenotype association in TRPV4-pathies is not strict and may lead to clinical phenotypes manifesting with both skeletal and neurological abnormalities.

Pathogenesis remains enigmatic and contentious in TRPV4-associated neuropathies, where some in vitro experiments indicated a possible loss-of-function for specific TRPV4 variants [Auer-Grumbach et al., 2010]. In contrast, all mutations reported to date, including the mutations associated with isolated neurological disease, seemingly activate non-selective Ca^{2+} channel function of TRPV4. Although recent in vitro evidence demonstrates that the extent of functional channel gain in *Xenopus* oocytes correlates apparently well with disease severity in the skeleton [Loukin et al., 2011], clinical evidence of eminent intra- and inter-familial variability strongly contradicts a simple pathogenic mechanism. Our findings prove that clinical variability associated with specific *TRPV4* mutations may even extend to different organ systems. Understanding the molecular pathophysiology of pleiotropic TRPV4-pathies thus remains a challenge and awaits the generation of true disease models.

Thus, we have described clear-cut cases that show both skeletal dysplasia and axonal type peripheral neuropathy in association with *TRPV4* mutations. It implies that the pathogenic mechanisms of phenotypes in the two systems are not mutually exclusive. As the developmental skeletal phenotype may be detected earlier than degenerative neurologic disorder, those patients confirmed to have skeletal dysplasias of TRPV4-pathy should be paid special attention to their neurologic abnormality. Any deficit developing in TRPV4-pathy skeletal dysplasia patients should be differentiated between TRPV4-related peripheral neuropathy versus cord or spinal nerve compression from vertebral abnormalities.

Despite the presence of unequivocal radiographic changes in all our patients, their heights were within the normal range. As short stature is often the primary indication of a skeletal dysplasia, it is possible that more patients with TRPV4-related peripheral neuropathy have skeletal manifestations, but have simply never been investigated because they are not short. Radiographic examination should be considered as a part of the standard work-up for patients compatible with TRPV4-related neuropathies. In clinical diagnosis and genetic counseling, the extensive phenotypic variability and reduced penetrance of neurologic phenotype of TRPV4-pathy should be taken into account.

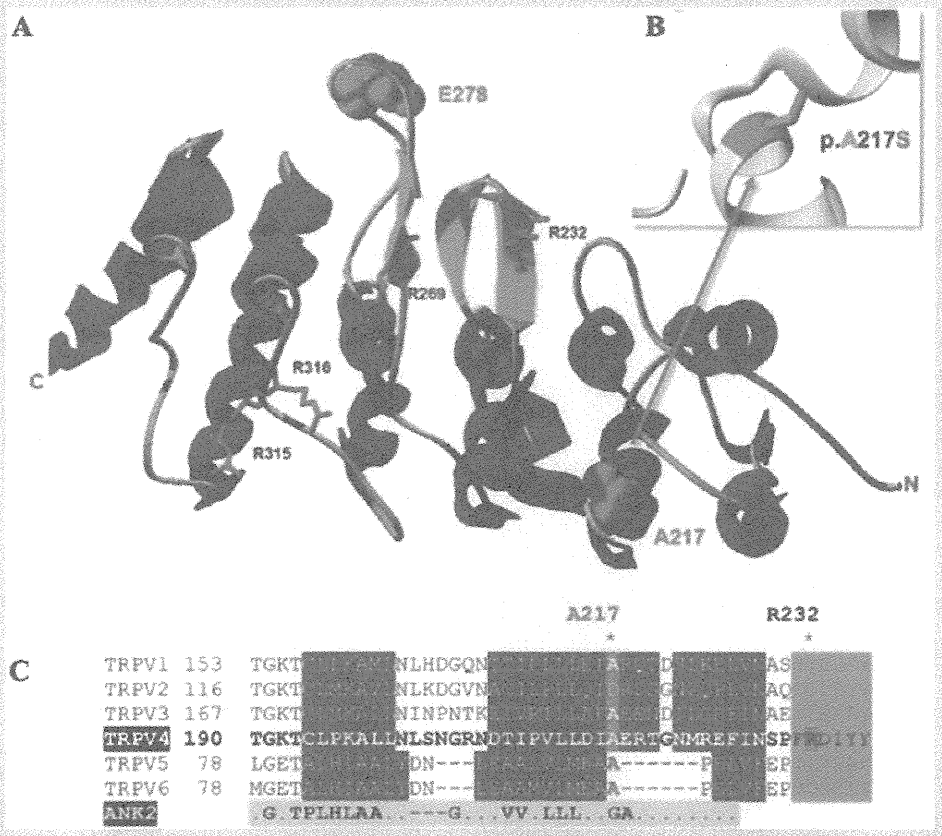

FIG. 6. A: A Ribbon diagram of the modeled ankyrin repeat region of human TRPV4. Residues E278and A217 mutated in Patients 1 and 3, respectively, are depicted as red spheres, all other previously reported ankyrin repeat region residues affected by arginine substitutions in dominant neuropathies (R232, R269, R315, and R316) are represented as sticks. B: A close-up view of position 217 from a different angle. The non-polar to polar substitution p.A217S changes helical winding in the second ankyrin repeat region of TRPV4. The overlays of wild type alanine (green) and the substituted serine (red) are superposed in the ribbon and stick model to illustrate molecular dimensions of the respective amino acids. C: Alignment of the second ankyrin repeat region of human TRPVs, corresponding to amino acids 190–226 in TRPV4; ankyrin consensus residues conserved in TRPVs are included in yellow shading at the bottom. Blue shading indicates helical stretches confirmed in chicken Trpv4 and rat Trpv6 crystal structure, green shading indicates β-sheets; A217 (red) is conserved in all but one of TRPVs.

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CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A

Axial Spondylometaphyseal Dysplasia: Additional Reports

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Axial spondylometaphyseal dysplasia (SMD) (OMIM 602271) is an uncommon skeletal dysplasia characterized by metaphyseal changes of truncal-juxtatruncal bones, including the proximal femora, and retinal abnormalities. The disorder has not attracted much attention since initially reported; however, it has been included in the nosology of genetic skeletal disorders [Warman et al. (2011); Am J Med Genet Part A 155A:943–968] in part because of a recent publication of two additional cases [Isidor et al. (2010); Am J Med Genet Part A 152A:1550–1554]. We report here on the clinical and radiological manifestations in seven affected individuals from five families (three sporadic cases and two familial cases). Based on our observations and Isidor's report, the clinical and radiological hallmarks of axial SMD can be defined: The main clinical findings are postnatal growth failure, rhizomelic short stature in early childhood evolving into short trunk in late childhood, and thoracic hypoplasia that may cause mild to moderate respiratory problems in the neonatal period and later susceptibility to airway infection. Impaired visual acuity comes to medical attention in early life and function rapidly deteriorates. Retinal changes are diagnosed as retinitis pigmentosa or pigmentary retinal degeneration on fundoscopic examination and cone-rod dystrophy on electroretinogram. The radiological hallmarks include short ribs with flared, cupped anterior ends, mild spondylar dysplasia, lacy iliac crests, and metaphyseal irregularities essentially confined to the proximal femora. Equally affected sibling pairs of opposite gender and parental consanguinity are strongly suggestive of autosomal recessive inheritance. © 2011 Wiley-Liss, Inc.

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INTRODUCTION

The term spondylometaphyseal dysplasia (SMD) encompasses a heterogeneous group of disorders characterized by dysplastic changes in the metaphyses of tubular bones and metaphyseal equivalents of the spine and flat bones. Amongst the SMDs, the most common is SMD Kozlowski type (OMIM 184252), followed by SMD Sutcliffe (corner fracture) type (OMIM 184255), but there are also other rare types [Wirth, 2008]. Aside from SMD Kozlowski type, which is caused by heterozygous mutations in the transient receptor potential cation channel, subfamily V, member 4 gene (*TRPV4*) [Nishimura et al., 2010], the etiologies of the SMDs remain unknown. It is intriguing that certain types of SMDs present as a multi-system disorder, as exemplified by SMD with cone-rod dystrophy (OMIM 608940) [Sousa et al., 2008; Turell et al., 2010].

We previously reported on a new type of SMD, based on the clinical and radiologic observations in three children (a Japanese girl and two Korean siblings) [Ehara et al., 1997]. The disorder was termed "axial SMD", because the metaphyseal changes were confined to the truncal and juxtatruncal bones. The disorder was seen in association with ocular abnormalities, including retinitis pigmentosa (RP) and/or optic atrophy. Very recently, two additional cases have been reported confirming the axial SMD as a distinct entity [Isidor et al., 2010]. The Nosology Group of the International Skeletal Dysplasia Society included the disorder in "Nosology and classification of genetic skeletal disorders: 2010 version", and the group termed the entity SMD with retinal degeneration, axial type (OMIM 602271) [Warman et al., 2011]. With the addition of five newly identified cases (three sporadic patients and two siblings) and follow-up our previously reported sibling case, we are able to delineate the key clinical and radiographic features of this condition and hopefully facilitate the diagnosis of further individuals.

CLINICAL REPORTS

Patient 1

Patient 1 is a Japanese girl born to healthy, nonconsanguineous parents. Birth length was 47.6 cm (−1.0 SD). At birth, she had mild respiratory distress and a narrow thorax was noted. A tentative radiological diagnosis of Shwachman-Diamond syndrome was made. Ophthalmological screening at age 3 weeks disclosed RP (Fig. 1A), and no electrical activities were detectable by electroretinogram (ERG) at 4 months (Fig. 1B). Length at age 11 months was 64.3 cm (−3.4 SD).

Patient 2 and 3 (siblings)

Patients 2 and 3 have consanguineous parents (first cousins) of Saudi Arabian origin who also have four healthy children.

Patient 2, a girl, was born by vaginal delivery at 40 weeks' gestation after an unremarkable pregnancy. Apgar scores were 9 and 10 at 1 and 5 min, respectively. Birth length was 51 cm, and weight 3,440 g (both at 50th centile). At age 4 months, she was noted to have micromelic short stature (<3rd centile) with rhizomelic shortening of the upper limbs and a narrow thorax with Harrison's grooves. At age $4\ ^{7/12}$ years, height was 93.5 cm (−4.0 SD), and weight was 13.1 kg (−3.0 SD). Ophthalmological examination at age 1 year showed early signs of RP. She underwent ERG examinations twice at age 3 and 4 years, which showed no response to light flash stimulation indicative of advanced retinal dysfunction, and visually evoked response study showed delayed P100. At last examination, she had low visual acuity and no night vision but she was able to walk independently. Her visual acuity has deteriorated faster than her brother's.

Patient 3, the older brother of Patient 2, was born by vaginal delivery at 40 weeks' gestation after an unremarkable pregnancy. Apgar scores were 9 at 1 and at 5 min. Birth weight was 3,480 g, length was 51 cm, and OFC was 35 cm (all at 50th centile). He sat at age 6 months and walked at 10 months. His development was unremarkable except for visual dysfunction. He was noted to have RP at age 9 months. Mild hyperopia and astigmatism were found bilaterally at age 3 years. He had ERG three times at age $2\ ^{9/12}$ years, 6 years, and 7 years, all of which showed abnormal response to light flash stimulation. However, visually evoked response study was not significantly affected. At age $3\ ^{7/12}$ years, he was referred for genetic consultation because of failure to thrive, short stature, small chest, and visual problems. He showed micromelic short stature (<3rd centile) with rhizomelic shortening of the upper limbs and a narrow thorax with Harrison grooves. At age 7 years, height was 106.5 cm (−5.5 SD), weight was 18.5 kg (−2.5 SD), and OFC was 52.6 cm (−2.5 SD).

At last review, he had low visual acuity and no night vision but he was able to walk independently and could read with difficulty during daytime.

Patient 4

Patient 4 is a Korean boy, who was the second child of nonconsanguineous, healthy parents. He came to medical attention at age 5 years because of short stature; 102.7 cm (−1.6 SD). He had mild bowlegs and pectus excavatum. At that time, inward gaze of the eyes and impaired visual acuity were also noted. At age 6 years, mild RP was diagnosed on fundoscopic examination. Then, visual acuity progressively worsened. At age 9 years, vision was severely impaired (V.d. = 0.06; V.s. = 0.125). On last examination, at 10 years of age, he had proportionate short stature with a height of 125.8 cm (−2.0 SD). In addition, modest narrow thorax, mild thoracic scoliosis, and rhizomelic shortening of the upper limbs were seen (Fig. 2A).

Patient 5

Patient 5 is a Japanese boy born to healthy, nonconsanguineous parents. He was delivered at 41 weeks' gestation. Birth length was 48.5 cm (−0.9 SD), weight was 3,052 g (−0.2 SD), and OFC was 34.0 cm (+0.1 SD). A narrow thorax was noted at birth. Apgar scores were 7 at 1 min and 5 at 5 min. He had moderate respiratory distress with laryngomalacia necessitating oxygen therapy in the neonatal period. The laryngomalacia improved gradually over the course of the first year. He was given a radiological diagnosis of

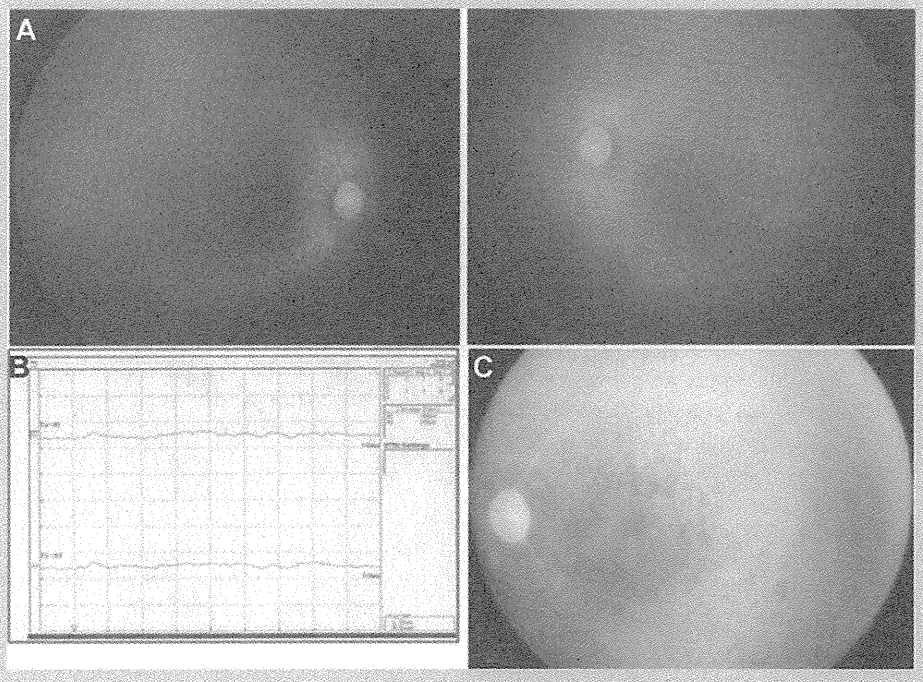

FIG. 1. Ophthalmological findings. A: in Patient 1, fundoscopy showed RP at age 2 months. B: in Patient 1, ERG did not trace electric activities at age 4 months. C: in Patient 5, fundoscopic findings were advanced RP with reduced retinal blood flow and optic nerve atrophy at age 12 years.

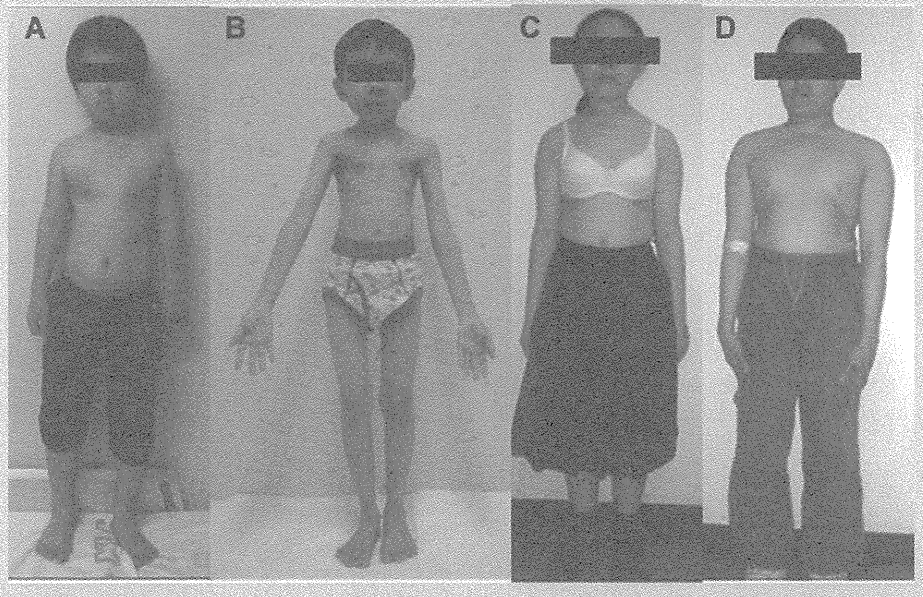

FIG. 2. Clinical photographs. A: Patient 4 at age 10 years. A mild narrow thorax and rhizomelic shortening of the upper limbs are noted. B: Patient 5 at age 12 years. Short trunk is striking with a mild narrow thorax. C: Patient 6 at age 15 years, (D) Patient 7 at age 23 years. Mild short trunk is evident, and the thorax is mildly narrow.

Jeune asphyxiating thoracic dysplasia in infancy. He had recurrent episodes of pneumonia until age 5 years. At age 6 years, severe short stature was recorded (−6.5 SD). Visual problems were suspected at an early age as he never showed any light response or the ability to track moving objects. Nystagmus was identified in early infancy. He was diagnosed as having macular RP at age 2 months. Visual evoked potential test showed no response. Severe hyperopia with disturbed visual acuity (V.d. = 0.01, V.s. = 0.01) was documented at age 5 years. Visual acuity gradually declined. He suffered from bilateral cataracts of the posterior subcapsular lense at 11 years. At age 12 years, fundoscopic findings showed advanced RP with reduced retinal blood flow and optic nerve atrophy (Fig. 1C). Clinical examination at that age demonstrated a height of 107.2 cm (−6.2 SD), arm span of 111.7 cm, and upper segment of 51 cm. He had a mild narrow thorax, mild scoliosis, rhizomelic shortening of the limbs, and markedly short trunk (Fig. 2D). Some permanent teeth had not yet erupted. Pulmonary function tests showed restrictive impairment with 38% forced vital capacity and 114.5% forced expiratory volume in 1 sec.

Patient 6 & 7 (siblings)

Patients 6 and 7 are Korean siblings, whose manifestations in childhood were previously reported [Ehara et al., 1997]. They were born to healthy, nonconsanguineous parents. Birth weight was normal. Short stature was noted in early childhood, as well as thoracic hypoplasia with susceptibility to airway infections. Height was 76 cm (−5.5 SD) at age 3 years in the younger sister, and 108 cm (−5.1 SD) at age 10 years in the older brother. The younger sister was diagnosed as having optic atrophy with nystagmus at age 3 years. Impaired visual acuity of the older brother came to attention at age 6 months, and he was diagnosed as having optic atrophy and retinal degeneration associated with nystagmus at age 8 years. At the most recent examination, the sister was 15 years, and the brother was 23 years old. Their heights were 131 cm (−5.1 SD) and 144 cm (−4.9 SD), respectively. They presented with a narrow thorax, short-trunk, and rhizomelic shortening of the upper limbs (Fig. 2C,D). They were functionally blind at that time.

RADIOLOGICAL FINDINGS

The radiographic findings in all patients were similar but with a variable degree of severity. The phenotype evolved with age.

Chest

Short ribs with flared, cupped anterior ends were evident in the neonatal period (Fig. 3A). This finding became prominent in childhood, most striking in late childhood (Fig. 3B–I), and then less conspicuous in adolescence and adulthood (Fig. 3J,K).

Spine

Spondylar changes were mild in infancy and early childhood (Fig. 4A–D). Platyspondyly became more apparent in late childhood (Fig. 4E–H). Vertebral height increased in adolescence and normalized in adulthood (Fig. 4I,J).

Pelvis

Lacy ilia were discernible in the neonatal period and became overt in childhood. Metaphyseal irregularities of the proximal femora became manifest in infancy and then progressed. Coxa vara devel-

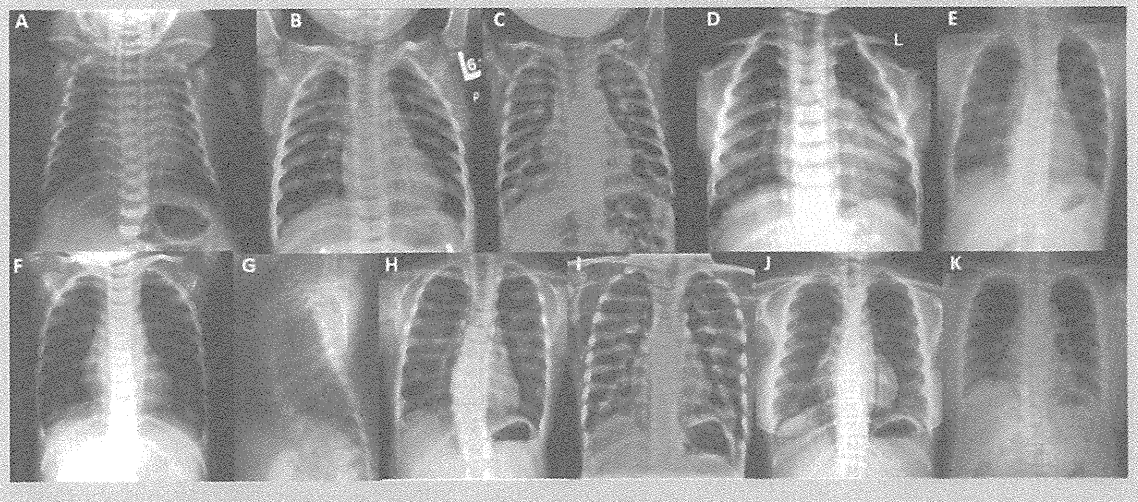

FIG. 3. Radiographs of the chest. A: Patient 1 at age 2 days, (B) Patient 2 at age $1^{4/12}$ years, (C) Patient 5 at age 2 years, (D) Patient 3 at age 4 years, (E) Patient 4 at age 5 years, (F) and (G) Patient 6 at age 8 years. Note a narrow thorax in (A), (C–E), and short ribs with cupped, flared anterior ends in all. Thoracic narrowing is modest in (B) and (F). Mild irregularities of the proximal humeral metaphyses are seen in (A,B) and (C). H: Patient 4 at age 10 years, (I) Patient 5 at age 12 years. Cupping and flaring of the anterior ends of the ribs are most conspicuous in late childhood. Thoracic narrowing is modest. J: Patient 6 at age 15 years, (K) Patient 7 at 23 age years. A narrow thorax is persistent, but cupping and flaring of the anterior ends of the ribs are less conspicuous than those at younger ages.

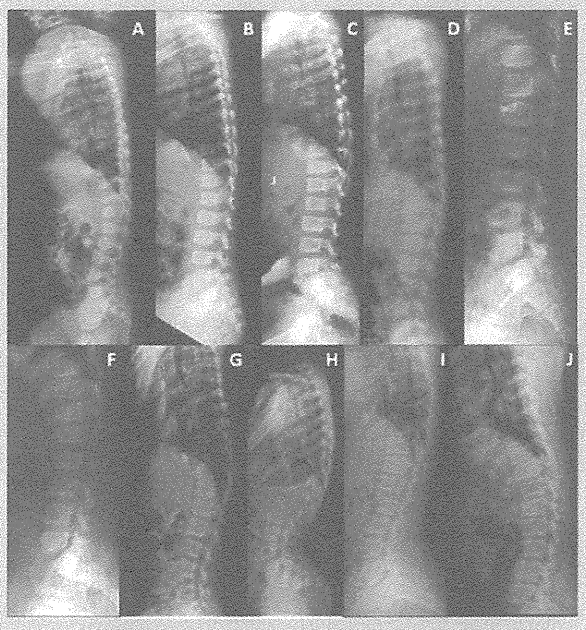

FIG. 4. Radiographs of spine. A: Patient 1 at age 6 months. The vertebral bodies are somewhat ovoid, but platyspondyly is not evident. B: Patient 2 at age 1 $^{4/12}$ years, (C) Patient 3 at age 4 years, (D) Patient 4 at age 5 years. Mild platyspondyly is evident. E: Patient 6 at 8 age years, (F) Patient 7 at age 10 years, (G) Patient 4 at age 10 years, (H) Patient 5 at age 12 years. Platyspondyly is most conspicuous in late childhood. I: Patient 6 at age 15 years, (J) Patient 7 at age 23 years. Platyspondyly is discernible but milder than that in childhood.

oped in late childhood (Fig. 5A–I). The iliac and metaphyseal changes diminished during adolescence, leaving only coxa vara (Fig. 5J,K).

Limbs

The proximal humeri showed mild metaphyseal irregularities (Fig. 3 A–C). Metaphyseal changes were absent or very mild in the knee (Fig. 6A–G).

Hands

Hands were unremarkable in all patients (data not shown).

DISCUSSION

Based on our experiences and the observations reported by Isidor et al. [2010], it is clear that axial SMD is a distinctive disease entity with recognizable clinical and radiographic features. "A new form of oculoskeletal syndrome" reported by Megarbane et al. [2004] may represent the same disorder. The clinical manifestations of the present and previously reported patients are summarized in Table I. The clinical hallmarks include postnatal growth deficiency, thoracic hypoplasia, and retinal abnormalities. Equally affected siblings of opposite gender and the presence of consanguinity in some parents are strongly suggestive of an autosomal recessive pattern of inheritance.

Although birth length is in the normal range, short stature with rhizomelic limb shortening becomes apparent during childhood. Short stature is mild to moderate during childhood; however, growth failure is progressive, and final height may be less than −5 SD. Progressive shortening of the trunk over time results in the ultimately short-trunk body proportion. Thoracic hypoplasia with mild to moderate respiratory distress in the neonatal period is apparent in some cases, while it may be asymptomatic in others. The narrow thorax occasionally gives rise to Harrison grooves and susceptibility to airway infection in infancy and early childhood. Laryngotracheomalacia may contribute to the respiratory problems.

RP or pigmentary retinal degeneration is detectable during childhood and retinal changes may even be observed in the neonatal period. Electroretinography reveals cone-rod dystrophy [Isidor et al., 2010]. Secondary optic atrophy may ensue, and one child (Patient 5) presented cataracts that might be secondary to RP [Jackson et al., 2001]. The prognosis for vision is unfavorable.

As discussed by Isidor et al. [2010], the differential diagnosis includes Shwachman-Bodian-Diamond syndrome (OMIM 260400), Jeune asphyxiating thoracic dysplasia (OMIM 208500), Saldino-Mainzer syndrome (OMIM 266920), Dyggve-Melchior-Clausen (DMC) dysplasia (OMIM 223800), and SMD with cone-rod dystrophy (OMIM 608940). Shwachman-Diamond syndrome causes thoracic hypoplasia and metaphyseal dysplasia most conspicuously in the proximal femora. However, Shwachman-Bodian-Diamond syndrome, unlike axial SMD, is associated with neutropenia and pancreatic exocrine dysfunction but not retinal and spondylar changes. Both Jeune asphyxiating thoracic dysplasia and Saldino-Mainzer syndrome manifest thoracic hypoplasia and retinopathy. Nevertheless, progressive nephropathy and brachydactyly are seen in these disorders and are conspicuously absent in axial SMD. Lacy ilia and spondylar dysplasia in axial SMD may raise a suspicion of DMC. However, DMC shows more severe platyspondyly and epimetaphyseal dysplasia but not retinal changes. SMD with cone-rod dystrophy is a recently identified skeletal dysplasia associated with retinal cone-rod dystrophy. The clinical and radiological pattern in SMD with cone rod dystrophy is similar to that of axial SMD. However, there are clinical and radiological differences between both disorders. Visual impairment is milder in SMD with cone rod dystrophy. Affected individuals do not show complete loss of visual acuity. On the other hand, the skeletal changes of SMD with cone rod dystrophy are much more severe than those in axial SMD. Generalized metaphyseal dysplasia and more severe platyspondyly in SMD with cone rod dystrophy contrast with metaphyseal dysplasia confined to the juxtatruncal bones and mild platyspondyly in axial SMD.

In the neonatal period, axial SMD should be differentiated from SMD Sedaghatian type (OMIM 250220), a perinatally lethal osteochondrodysplasia comprising minor facial, cardiac and cerebral anomalies [Elçioglu and Hall, 1998]. Unlike axial SMD, SMD Sedaghatian type manifests overt metaphyseal dysplasia and lacy ilia in the neonatal period.

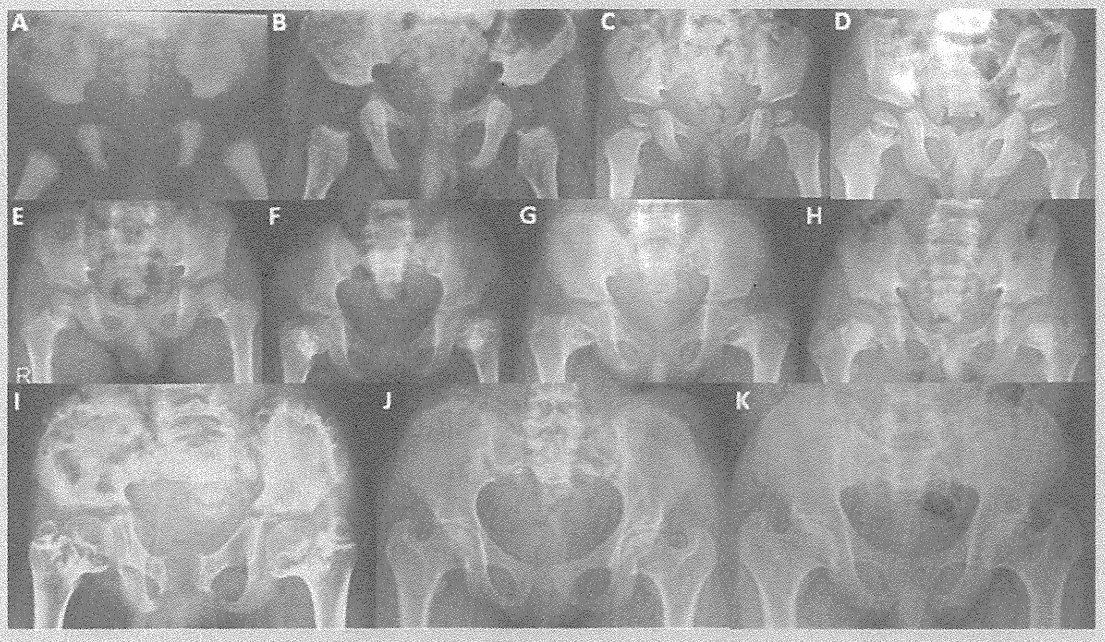

FIG. 5. Radiographs of pelvis. A: Patient 1 at 2 days. The ilia are somewhat hypoplastic but lacy ilia are not evident. B: Patient 1 at age 6 months. The iliac crests are somewhat irregular. C: Patient 2 at age $1^{4/12}$ years. The iliac crests and proximal femoral metaphyses are irregular. D: Patient 3 at age 4 years, (E) Patient 4 at age 5 years. Lacy ilia and metaphyseal irregularities of the proximal femora are apparent. F: Patient 6 at age 8 years, (G) Patient 7 at age 10 years, (H) Patient 4 at age 10 years, (I) Patient 5 at age 12 years. Proximal femoral metaphyseal irregularities with coxa vara are conspicuous in all patients. Lacy ilia are varied among the patients. J: Patient 6 at age 15 years, (K) Patient 7 at age 23 years. Lacy ilia and metaphyseal irregularities already diminish, but coxa vara is persistent.

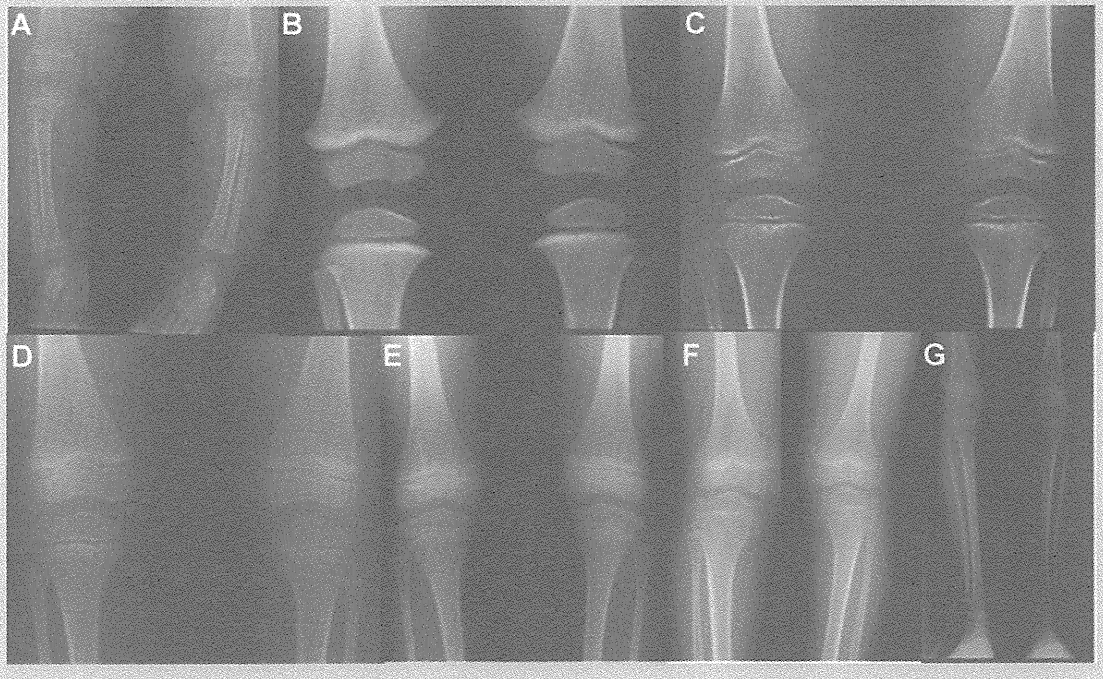

FIG. 6. Radiographs of lower limbs. A: Patient 1 at age 6 months, (B) Patient 2 at age $1^{4/12}$ years, (C) Patient 3 at age 4 years, (D) Patient 6 at age 8 years, (E) Patient 7 at age 10 years, (F) Patient 4 at 10 years, (G) Patient 5 at 12 years. Metaphyseal changes are absent or very mild in the knee but the knee epiphyses are slightly flattened, notably in (B) and (C).

TABLE I. Clinical Characteristics of Patients With Axial SMD

	Present patients							Ehara et al. [1997]	Isidor et al. [2010]		Megarbane et al. [2004]
Patient	**1**	**2**	**3**	**4**	**5**	**6[a]**	**7[a]**	**Case1**	**Patient 1**	**Patient 2**	**Single case**
Race	Japanese	Saudi Arabian	Saudi Arabian	Korean	Japanese	Korean	Korean	Japanese	NA	NA	Lebanese
Sex	Female	Female	Male	Male	Male	Female	Male	Female	Male	Male	Female
Age at last visit (yrs)	0.9	4.5	7	10	12	15	23	5	14	15	4
Family history	Sporadic	Sib	Sib	Sporadic	Sporadic	Sib	Sib	Sporadic	Sporadic	Sporadic	Sporadic
Short stature	−3.4 SD	−4.0 SD	−5.5 SD	−2.0 SD	−6.2 SD	−5.1 SD	−4.7 SD	−3.6 SD	−3.2 SD	−3.6 SD	<3% tile
Small thorax	+	+	+	+	+	+	+	+	+	+	−
Short trunk	−	−	−	+	+	+	+	−	NA	NA	NA
Rhizomelic shortness	+	+	+	+	+	+	+	+	+	+	+
Respiratory disturbance at birth	+	NA	NA	NA	+	NA	NA	−	−	−	NA
Respiratory infection in childhood	NA	NA	NA	NA	+	+	+	+	NA	NA	NA
RP/optic atrophy	+	+	+	+	+	+	+	+	+	+	+
Age of Dx of RP (years)	0	1	0.9	6[b]	0.1	3	8[c]	0.1	5	6.5	3
Scoliosis	−	−	−	+	+	−	−	−	−	−	−

NA, not available; RP, retinitis pigmentosa.

[a]Follow-up study of cases previously described as Case 3 and 2, respectively by Ehara et al. [1997].
[b]Impaired visual acuity was noticed at 5 years of age.
[c]Impaired visual acuity was noticed at 6 months of age.

The molecular basis of axial SMD remains elusive; however, homozygosity mapping and whole genome sequencing techniques should elucidate the disease-causing gene in the near future. Further case reports, sample registration, and investigations will be invaluable in order to thoroughly understand this entity.

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ORIGINAL ARTICLE

A founder mutation of *CANT1* common in Korean and Japanese Desbuquois dysplasia

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Desbuquois dysplasia (DBQD) is a severe skeletal dysplasia of autosomal recessive inheritance. DBQD is classified into types 1 and 2 based on presence or absence of hand anomalies. In a previous study, we found a *CANT1* (for calcium-activated nucleotidase 1) mutation, c.676G>A in five DBQD families. They were all East Asians (Japanese or Korean). The high prevalence of the same mutation among Japanese and Korean suggested that it is a common founder mutation in the two populations. To examine a possible common founder, we examined the region around *CANT1* in chromosomes with c.676G>A mutation by genotyping polymorphic markers in the region for the families. We examined their haplotypes using the family data. We identified in all families a common haplotype containing the *CANT1* mutation that ranged up to 550 kb. The two unrelated carriers of the mutation in general populations in Korea and Japan could also have the haplotype. We estimated the age of the founder mutation as ~1420 years (95% CI=880–1940 years). The c.676G>A mutation of *CANT1* commonly seen in Japanese and Korean DBQD should be derived from a common founder.
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Keywords: calcium-activated nucleotidase 1; common founder; common haplotype; desbuquois dysplasia

INTRODUCTION

Desbuquois dysplasia (DBQD; MIM #251450) is a severe skeletal dysplasia of autosomal recessive inheritance that belongs to 'multiple dislocation group'.[1] DBQD is clinically heterogeneous and classified into two types on the basis of presence (type 1) or absence (type 2) of characteristic hand anomalies, which consist of an extra ossification center distal to the second metacarpal, delta phalanx, bifid distal thumb phalanx and dislocation of the inter-phalangeal joints.[2] Type 2 DBQD contained a further clinical subtype, Kim variant,[3] which is characterized by short metacarpals with elongated phalanges that result in nearly normal length of the fingers.

Recently, Huber *et al.*[4] identified mutations in the gene encoding the calcium-activated nucleotidase 1 (CANT1) in DBQD type 1, which is followed by Faden *et al.*[5] We also found *CANT1* mutations in DBQD type 2 and Kim variant. In our series, we identified *CANT1* mutations in all seven patients from five unrelated families with DBQD Kim variant, and all patients had c.676G>A (p.V226M). The five families were Japanese or Korean. c.676G>A was also found in 1/754 Japanese and 1/187 Korean controls in a heterozygous state.[6] These results led us consider that the mutation may be inherited from a common founder(s) among Japanese and Korean. To test the hypotheisis, we examined haplotypes of the patients around *CANT1* and found that the mutation was on a common haplotype background of ~500 kb.

MATERIALS AND METHODS

Subjects

Seven DBQD patients from five families (four Japanese and three Korean) and their parents were examined. One Japanese family (DB1) was consanguineous (1st cousin marriage) and two sib patients from the family had c.676G>A in a homozygous state. The other patients were of non-consanguineous and compound heterozygotes of the mutations.[6] Their phenotypes were all diagnosed as DBQD Kim variant as previously reported.[3] One Japanese (CT1) and one Korean (CT2) subject from general populations who were found to have c.676G>A in a heterozygous state in the previous study were also examined.[3]

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Genotyping

Genomic DNA was extracted from blood by standard procedures or from saliva using Oragene DNA Self-Collection kit (DNA Genotek, Ottawa, Ontario, Canada). Affymetrix 10K Gene-Chip microarray (Affymetrix, Santa Clara, CA, USA) was used for family DB1 to determine homozygous regions containing *CANT1* inherited from a common ancestor in the consanguineous family. Single nucleotide polymorphisms (SNPs) for the founder haplotype determination were genotyped by direct sequencing. The regions containing targeted SNPs were amplified by PCR from genomic DNA, and then PCR products were diluted and sequenced by using an ABI Prism 3730 automated sequencer (PE Biosystems, Tokyo, Japan). We separated 5′-FAM–labeled PCR products containing microsatellites by sizes on an ABI Prism 3730 automated sequencer (PE Biosystems) against the Genescan-500LIZ size standard. PCR primers for the polymorphisms are listed in Supplementary Table 1.

Haplotype analysis

We determined the mutation-containing haplotype of patients according to the genotypes of the trio (the patient and parents). We determined the homozygous region of DB1 using the microarray data of the family members. All the patients were genotyped for the markers selected from the homozygous region of DB1. The genotyping of the makers for their parents were examined only when the patients were heterozygotes. The boundaries of the common haplotype were determined by sequential genotyping of SNPs in flanking regions. The SNPs were selected from the HapMap database (Phase II+ III, release 27).

Estimation of the mutation age

We estimated the age of the founder mutation by the method previously described.[7,8] We used the following equation:

$$g = \log[(p_d - p_n)/(1 - p_n)]/\log(1 - \theta),$$

where p_d and p_n denote frequencies of the ancestral allele at the marker locus on the chromosomes with A and G alleles at the disease locus. θ denotes the recombination fraction between the marker and the disease locus. The age of the mutation was corrected by taking the population growth into account using the following equations:

$$g_c = g + g_0,$$

$$g_0 = -(1/d)\ln[\theta \times e^d/(e^d - 1)],$$

where d denotes the population growth rate. Physical and genetic map positions in bp and cM for SNP loci were obtained from the HapMap database (Phase II, release 21).

RESULTS

Genotyping and identification of a common haplotype

Using the SNP microarray data, we first determined a homozygous region of the genome that contained *CANT1* in the consanguineous family, DB1. The family had a stretch of SNPs that was homozygous in the patients and heterozygous in the parents. The homozygous stretch flanked by rs2934226 and rs2306755 extended up to ~9.8 Mb. Of 48 SNPs that composed the stretch in the microarray data, we selected 10 SNPs around *CANT1*; six were at the 3′ to *CANT1* and four were at the 5′ to *CANT1*. We genotyped them for the five families. A possible common haplotype was restricted in the region between rs6501224 and rs2377402.

To confirm the common haplotype and define its more detailed boundary, we selected 13 SNPs in the boundary regions from a database and genotyped them for the five families. In the SNPs we could get a definite haplotype result, all in a region from rs10512617 to rs2045660 showed a common haplotype. The nearest SNPs to rs10512617 and rs2045660 that defined the different haplotypes in any of the five families were rs11077391 and rs2377309, respectively. At the SNPs between rs10512617 and rs2045660, the two carriers of the mutation (CT1 and CT2) had all the alleles that composed the common haplotype. Therefore, they could also have the same haplotype (Table 1).

Table 1 Haplotypes of markers with the c.676G>A mutation in the Desbuquois dysplasia (DBQD) families and control subjects

		Subject						
		DBQD Family					Control	
Marker	Distance[a]	DB1	DB2	DB3	DB4	DB5	CT1	CT2
rs7405591	1712736	C	T	T	T	C	T	T
rs4789523	978405	T	T	T/C[b]	T	T	T/C	T/C
rs4129767	587275	C	C	C	C	T	C	C/T
rs6501224	488804	G	G	C	G	G	G	G
rs16971539	434643	A	G	G/A[b]	G	G	G	G
rs9899295	402575	A	G	A	G	G	A/G	G
rs9896451	347233	G	G	A	G	G	G	G/A
rs11077391	330052	G	A	A	G	A	G	G
rs10512617	297708	G	G	G	G	G	G	G
rs4103047	254069	C	C	C	C	C	C	C/G
rs3744801	197531	C	C	C	C	C	C/T	C
rs2889529	93784	C	C	C	C	C	C/T	C/T
c.676G>A	0							
rs8077024	2287	C	C	C	C	C	C/T	C
D17S1847	33602	185	185	185	185	185	185/191	185/189
rs2707047	132355	G	G	G	G	G	G/A	G/A
rs2612787	132449	T	T	T	T	T	T/C	T/C
rs9302889	168892	T	T	T	T	T	T/A	T
rs12600665	180703	G	G	G	G	G	G/A	G
rs2045660	185092	C	C	C	C	C	C	C
rs2377309	201821	C	C	C	C	C/T[b]	C	C/T
rs2612753	220795	G	G	G	G	T	G/T	G
rs1000791	274619	T	A	T	T	T	T	T/C
rs2377402	340187	A	C	C	A	C	C	C

[a]Base number between the marker and the disease locus.
[b]Equivocal because of the double heterozygosity of the parents.

Estimation of the mutation age

The markers that defined the haplotype of the families were used for estimation of the mutation age. The disease chromosomes of DB1 were counted as one because of its consanguinity. p_d was calculated in five chromosomes with A allele at the disease locus from the five DBQD families. As frequency of the mutation (A allele) was quite low in control subjects, we regarded the allele frequency of markers in the general Japanese population as p_n, and the allele frequencies were obtained from NCBI dbSNP database. The population growth rate, d was set to 0.08 as previously described.[7] The allele, frequency of which was higher in the five chromosomes than that in the general population was regarded as the ancestral allele. We excluded the markers in the region less than 60 kb from the disease locus.[9] The estimated ages by different markers ranged from 30 to 246 generations (mean=71; 95% CI=44–97; median=41; standard deviation=58) (Table 2). If we assumed an intergenerational time of 20 years, the age of the mutation was estimated to be 1420 years (95% CI=880–1940 years; median=820 years; standard deviation=1160 years).

DISCUSSION

We have demonstrated that the c.676G>A mutation in Japanese and Korean had a common founder because all five chromosomes with

Table 2 Estimated age of the c.676G>A mutation

Marker	*Pd*	*Pn*	*θ*	*g*	*gO*	*gc*
rs7405591	0.4	0.295	0.0545	34.0	4.3	38.3
rs4129767	0.8	0.488	0.0191	25.7	17.4	43.1
rs6501224	0.8	0.698	0.0145	74.5	20.9	95.4
rs9899295	0.6	0.430	0.00998	120.6	25.5	146.1
rs9896451	0.8	0.488	0.00432	114.3	36.0	150.3
rs11077391	0.6	0.295	0.00401	208.6	37.0	245.6
rs10512617	1	0.400	0.00394	0	37.1	37.1
rs4103047	1	0.659	0.00391	0	37.2	37.2
rs3744801	1	0.523	0.00385	0	37.4	37.4
rs2889529	1	0.233	0.00187	0	46.5	46.5
c.676G>A			0			
rs2707047	1	0.145	0.00407	0	36.7	36.7
rs2612787	1	0.024	0.00408	0	36.7	36.7
rs9302889	1	0.727	0.00691	0	30.1	30.1
rs12600665	1	0.500	0.00722	0	29.6	29.6
rs2045660	1	0.576	0.00727	0	29.5	29.5
rs2612753	0.8	0.589	0.0106	62.8	24.8	87.6
rs1000791	0.8	0.625	0.0159	47.6	19.7	67.3
rs2377402	0.4	0.157	0.0201	61.3	16.8	78.1

c.676A in DBQD patients had a common haplotype composed of nine markers around this disease locus. In addition, the genotype of the two unrelated normal subjects with this mutation contained all the alleles that composed the common haplotype, suggesting that the founder mutation has widely spread among Korean and Japanese populations. The haplotype region ranged 480–550 kb. We estimated the age of this mutation at ~1400 years (95% CI=880–1940 years). Although the calculated CI is quite wide, we can estimate the c.676G>A mutation dates back to a time around the late Kofun era. Because the allele frequency of c.676G>A in Korean controls is much higher than that in Japanese controls, we speculated that the common founder was a Korean, and this mutation spread from Korea to Japan. This speculation is not contradictory to migration from Korea to Japan in the ancient history.

Although the exact prevalence of DBQD is difficult to determine, DBQD is generally considered as a very rare disease. However, the carrier frequency of the common mutation is considerably high in Korean. From our experience,[6] the frequency of the *CANT1* mutation is speculated as about double of that of the common mutation. Thereafter, prevalence of DBQD is ~1/35000 in Korean and ~1/600000 in Japanese; the former is far higher than our impression in daily practice. Many DBQD patients caused by *CANT1* mutations may be pre- or peri-natally lethal, although all the East Asian cases of DBQD with *CANT1* mutations so far reported had good prognosis. Alternatively, many DBQD may be undiagnosed and/or be put into the waste box of diagnosis as unknown 'multiple dislocation group' of skeletal dysplasia. Diagnosis of DBQD based on clinical and/or radiographic information is sometimes very difficult because of the overlapping phenotype with other diseases.[10]

In DBQD patients, the founder mutation was identified in all the seven Kim variant patients, and only in the Kim variant patients to our knowledge. Therefore, this mutation may be closely related with specific phenotypes of the Kim variant; that is , accelerated carpal bone ages in childhood, short metacarpals, elongated appearance of phalanges and absence of accessory ossification center distal to the second metacarpal and thumb anomalies.[3] Further accumulation of Korean and Japanese DBQD patients and examination of their *CANT1* mutations are necessary to conclude relation of the founder mutation and the specific phenotype. The founder mutation may present with other phenotype. Moreover, further collection of DBQD patients and screening of *CANT1* mutations in other populations would help confirming the phenotype–genotype relation. Other mutation (s) may present with the Kim-type DBQD phenotype. The diagnosis of DBQD is sometimes very difficult at present; however, we think identification of the specific phenotypes of hands followed by examination of the founder mutation in *CANT1* would efficiently led us to definite diagnosis in Japanese and Korean patients suspected for having DBQD.

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Name of Disorder	疾患名	遺伝子*	ONJ	Gendia	GeneTests	国内コマーシャルベース	研究ベース
1. FGFR3 group	1. FGFR3グループ						
Thanatophoric dysplasia type 1 (TD1)	致死性骨異形成症1型(TD1)	FGFR3		○	○		可能(応相談)
Thanatophoric dysplasia type 2 (TD2)	致死性骨異形成症2型(TD2)	FGFR3		○	○		可能(応相談)
Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN)	SADDAN(重症軟骨無形成症, 発達遅滞, 黒色表皮腫)	FGFR3		○	○		可能(応相談)
Achondroplasia	軟骨無形成症	FGFR3		○	○		可能(応相談)
Hypochondroplasia	軟骨低形成症	FGFR3		○	○		可能(応相談)
Hypochondroplasia-like dysplasia	軟骨低形成症様異形成症						
2. Type 2 collagen Group and similar disorders	2. 2型コラーゲングループと類似疾患						
Achondrogenesis type 2 (ACG2; Langer-Saldino)	軟骨無発生症2型(ACG2: Langer-Saldino型)	COL2A1		○	○		可能(応相談)
Platyspondylic dysplasia, Torrance type	扁平椎異形成症, Torrance型	COL2A1			○		可能(応相談)
Hypochondrogenesis	軟骨低発生症	COL2A1		○	○		可能(応相談)
Spondyloepiphyseal dysplasia congenital (SEDC)	先天性脊椎骨端異形成症(SEDC)	COL2A1		○	○		可能(応相談)
Spondyloepimetaphyseal dysplasia (SEMD) Strudwick type	脊椎骨端骨幹端異形成症(SEMD), Strudwick型	COL2A1			○		可能(応相談)
Kniest dysplasia	Kniest骨異形成症	COL2A1		○	○		可能(応相談)
Spondyloperipheral dysplasia	脊椎末梢異形成症	COL2A1			○		可能(応相談)
Mild SED with premature onset arthrosis	早発性関節症を伴う軽症型脊椎骨端異形成症						
SED with metatarsal shortening (formerly Czech dysplasia)	中足骨短縮を伴う脊椎骨端異形成症(前Czech異形成						
Stickler syndrome type 1	Stickler症候群1型	COL2A1		○	○		可能(応相談)
Stickler-like syndrome(s)	Stickler様症候群						
3. Type 11 collagen Group	3. 11型コラーゲングループ						
Stickler syndrome type 2	Stickler症候群2型	COL11A1		○	○		可能(応相談)
Marshall syndrome	Marshall症候群	COL11A1		○	○		可能(応相談)
Fibrochondrogenesis	線維性軟骨発生症	COL11A1			○		可能(応相談)
Otospondylomegaepiphyseal dysplasia (OSMED), recessive type	耳脊椎巨大骨端異形成症(OSMED), 劣性遺伝型	COL11A2		○	○		可能(応相談)
Otospondylomegaepiphyseal dysplasia (OSMED), dominant type (Weissenbacher-Zweymuller syndrome, Stickler syndrome type 3)	耳脊椎巨大骨端異形成症(OSMED), 優性遺伝型(Weissenbacher-Zweymuller症候群3型)	COL11A2		○	○		可能(応相談)
4. Sulphation disorders group	4. 硫酸化障害グループ						
Achondrogenesis type 1B (ACG1B)	軟骨無発生症1B型(ACG1B)	SLC26A2 (DTDST)		○	○		可能(応相談)
Atelosteogenesis type 2 (AO2)	骨発生不全症2型(AO2)	SLC26A2 (DTDST)		○	○		可能(応相談)
Diastrophic dysplasia (DTD)	捻曲性骨異形成症(DTD)	SLC26A2 (DTDST)		○	○		可能(応相談)
MED, autosomal recessive type (rMED; EDM4)	MED, 常染色体劣性遺伝型(rMED, EDM4)	SLC26A2 (DTDST)		○	○		可能(応相談)
SEMD, PAPSS2 type	SEMD PAPSS2型	PAPPSS2					
Chondrodysplasia with congenital joint dislocations, CHST3 type (recessive Larsen syndrome)	先天性関節脱臼を伴う軟骨異形成症, CHST3型(劣性Larsen症候群)	CHST3			○		
Ehlers-Danlos syndrome, CHST14 type ("musculo-skeletal variant")	Ehlers-Danlos症候群, CHST14型 ("筋骨格変異")	CHST14		○	○		可能(応相談)
5. Perlecan group	5. Perlecanグループ						
Dyssegmental dysplasia, Silverman-Handmaker type	分節異常骨異形成症, Silverman-Handmaker型	HSPG2		○	○		可能(応相談)
Dyssegmental dysplasia, Rolland-Desbuquois type	分節異常骨異形成症, Rolland-Desbuquois	HSPG2		○	○		可能(応相談)
Schwartz-Jampel syndrome (myotonic chondrodystrophy)	Schwartz-Jampel症候群(筋ミオトニー軟骨異栄養症)	HSPG2		○	○		可能(応相談)
6. Aggrecan group	6. Aggrecanグループ						
SED (Spondyloepiphyseal Dysplasia), Kimberley type	SED, Kimberley型	ACAN					可能(応相談)
SEMD (Spondyloepimetaphyseal Dysplasia), Aggrecan type	SEMD, Aggrecan型	ACAN					可能(応相談)
Familial osteochondritis dissecans	家族性離断性骨軟骨症	ACAN					可能(応相談)
7. Filamin group and related disorders	7. Filaminグループと関連異常						
Frontometaphyseal dysplasia	全頭骨幹端異形成症	FLNA		○	○		可能(応相談)
Osteodysplasty Melnick-Needles	異形成骨症Melnick-Needles型	FLNA		○	○		可能(応相談)
Otopalatodigital syndrome type 1 (OPD1)	耳口蓋指症候群1型(OPD1)	FLNA		○	○		可能(応相談)
Otopalatodigital syndrome type 2 (OPD2)	耳口蓋指症候群2型(OPD2)	FLNA		○	○		可能(応相談)
Terminal Osseous Dysplasia with Pigmentary Defects (TODPD)	色素異常を伴う末端骨形成異常症(TODPD)	FLNA			○		可能(応相談)
Atelosteogenesis type 1 (AO1)	骨発生不全症1型(AO1)	FLNB		○	○		可能(応相談)
Atelosteogenesis type 3 (AO3)	骨発生不全症3型(AO3)	FLNB		○	○		可能(応相談)

Larsen syndrome (dominant)	Larsen症候群(優性)	FLNB		○	○	可能(応相談)
Spondylo-carpal-tarsal dysplasia	脊椎・手根骨・足根骨異形成症	FLNB			○	可能(応相談)
Spondylo-carpal-tarsal dysplasia	脊椎・手根骨・足根骨異形成症	FLNBと非連鎖				
Franck - ter Haar syndrome	Franck - ter Haar症候群					
Serpentine fibula - polycystic kidney syndrome	蛇行腓骨・多嚢胞腎症候群					
8. TRPV4 group	TRPV4 group					
Metatropic dysplasia	変容性骨異形成症	TRPV4		○	○	可能(応相談)
Spondyloepimetaphyseal dysplasia, Maroteaux type (Pseudo-Morquio syndrome type 2)	脊椎骨端骨幹端異形成症, Maroteaux型 (偽性Morquio症候群2型)	TRPV4			○	可能(応相談)
Spondylometaphyseal dysplasia Kozlowski type	脊椎骨端異形成症Kozlowski型	TRPV4		○	○	可能(応相談)
Brachyolmia, autosomal dominant type	短体幹症, 常染色体優性遺伝型	TRPV4		○	○	可能(応相談)
Familial digital arthropathy with brachydactyly	短指症を伴う家族性指関節症					
9. Short-rib dysplasias (with or without polydactyly) Group	9. 短肋骨異形成症(多指症を伴う/伴わない)グループ					
Chondroectodermal dysplasia (Ellis-van Creveld)	軟骨外胚葉性異形成症 (Ellis-van Creveld)	EVC, EVC2		○	○	
SRP type 1/3 (Saldino-Noonan/Verma-Naumoff)	SRP 1/3型 (Saldino-Noonan/Verma-Naumoff)	DYNC2H1		○	○	
SRP type 1/3 (Saldino-Noonan/Verma-Naumoff)	SRP 1/3型 (Saldino-Noonan/Verma-Naumoff)	IFT80			○	
SRP type 1/3 (Saldino-Noonan/Verma-Naumoff)	SRP 1/3型 (Saldino-Noonan/Verma-Naumoff)	DYNC2H, IFT80と非連鎖				
SRP type 2 (Majewski)	SRP 2型 (Majewski)	DYNC2H1		○		
SRP type 4 (Beemer)	SRP 4型 (Beemer)					
Oral-Facial-Digital syndrome type 4 (Mohr-Majewski)	口・顔面・指症候群4型 (Mohr-Majewski)					
Asphyxiating thoracic dysplasia (ATD; Jeune)	窒息性胸郭異形成症 (ATD; Jeune)	IFT80			○	
Asphyxiating thoracic dysplasia (ATD; Jeune)	窒息性胸郭異形成症 (ATD; Jeune)	DYNC2H1		○	○	
Asphyxiating thoracic dysplasia (ATD; Jeune)	窒息性胸郭異形成症 (ATD; Jeune)	DYNC2H, IFT80と非連鎖				
Thoracolaryngopelvic dysplasia (Barnes)	胸郭咽頭骨盤異形成症 (Barnes)					
10. Multiple epiphyseal dysplasia and pseudoachondroplasia Group	10. 多発性骨端異形成症および偽性軟骨無形成症グループ					
Pseudoachondroplasia (PSACH)	偽性軟骨無形成症(PSACH)	COMP			○	可能(応相談)
Multiple epiphyseal dysplasia (MED) type 1 (EDM1)	多発性骨端異形成症 (MED) 1型 (EDM1)	COMP			○	可能(応相談)
Multiple epiphyseal dysplasia (MED) type 2 (EDM2)	多発性骨端異形成症 (MED) 2型 (EDM2)	COL9A2		○	○	可能(応相談)
Multiple epiphyseal dysplasia (MED) type 3 (EDM3)	多発性骨端異形成症 (MED) 3型 (EDM3)	COL9A3	○		○	可能(応相談)
Multiple epiphyseal dysplasia (MED) type 5 (EDM5)	多発性骨端異形成症 (MED) 5型 (EDM5)	MATN3			○	可能(応相談)
Multiple epiphyseal dysplasia (MED) type 6 (EDM6)	多発性骨端異形成症 (MED) 6型 (EDM6)	COL9A1	○	○	○	可能(応相談)
Multiple epiphyseal dysplasia (MED), other types	多発性骨端異形成症 (MED), 他の型					
Stickler syndrome, recessive type	Stickler症候群, 劣性遺伝型	COL9A1	○		○	可能(応相談)
Familial hip dysplasia (Beukes)	家族性臼蓋形成不全症 (Beukes)					
Multiple epiphyseal dysplasia with microcephaly and nystagmus (Lowry-Wood)	小頭症と眼振を伴う多発性骨端異形成症 (Lowry-Wood)					
11. Metaphyseal dysplasias	11. 骨幹端異形成症					可能(応相談)
Metaphyseal dysplasia, Schmid type (MCS)	骨幹端異形成症, Schmid型(MCS)	COL10A1			○	可能(応相談)
Cartilage-Hair-Hypoplasia (CHH; metaphyseal dysplasia, McKusick type)	軟骨・毛髪低形成症(CHH; 骨幹端異形成症, McKusick型)	RMRP		○	○	可能(応相談)
Metaphyseal dysplasia, Jansen type	骨幹端異形成症, Jansen型	PTH1R [PTHR1]			○	
Eiken dysplasia	Eiken異形成症					
Metaphyseal dysplasia with pancreatic insufficiency and cyclic neutropenia (Shwachman-Bodian-Diamond syndrome, SBDS)	膵不全, 周期性好中球減少を伴う骨幹端異形成症 (Shwachman-Bodian-Diamond症候群, SBDS)	SBDS			○	
Metaphyseal anadysplasia type 1	回復性骨幹端異形成症1型	MMP13				可能(応相談)
Metaphyseal anadysplasia type 2	回復性骨幹端異形成症2型	MMP9				可能(応相談)
Metaphyseal dysplasia, Spahr type	骨幹端異形成症, Spahr型					
Metaphyseal Acroscyphodysplasia (various types)	骨幹端先端杯状異形成症(種々の型)					
Genochondromatosis (type 1/type 2)	生殖器軟骨腫症(1型/2型)					
Metaphyseal chondromatosis with D-2-hydroxyglutaric aciduria	D-2-水酸化グルタール酸尿症を伴う骨幹端軟骨腫症	IDH1				可能(応相談)
12. Spondylometaphyseal dysplasias (SMD)	12. 脊椎骨幹端異形成症(SMD)					
Odontochondrodysplasia (ODCD)	歯牙軟骨形成不全症(ODCD)					
Spondylometaphyseal dysplasia, Sutcliffe/corner fracture type	脊椎骨幹端異形成症, Sutcliffe/corner fracture型					
SMD with severe genu valgum	高度外反膝を伴うSMD					

	錐体・杆体ジストロフィを伴うSMD					
SMD with retinal degeneration, axial type	網膜変性を伴うSMD, 脊柱型					可能(応相談)
Spondyloenchondrodysplasia (SPENCD)	脊椎軟骨内異形成症(SPENCD)	ACP5				可能(応相談)
Dysspondyloenchondromatosis	異常脊椎軟骨内腫症					
Cheiro-spondyloenchondromatosis	手・脊椎軟骨内腫症					
13. Spondylo-epi-(meta)-physeal dysplasias (SE(M)D)	脊椎・骨端(・骨幹端)異形成症(SE(M)D)					
Dyggve-Melchior-Clausen dysplasia (DMC)	Dyggve-Melchior-Clausen骨異形成症(DMC)	DYM		○		
Immuno-osseous dysplasia (Schimke), (Schimke Immunoosseous Dysplas	免疫不全性骨異形成症 (Schimke)	SMARCAL1		○(prenatalなし)		
SED Wolcott-Rallison type (Multiple Epiphyseal Dysplasia with Early-Ons	SED Wolcott-Rallison型	EIF2AK3	○	○		
SEMD Matrilin type	SEMD Matrilin型	MATN3		○		
SEMD short limb - abnormal calcification type	SEMD短肢・異常石灰化型	DDR2		○		
SED tarda, X-linked (SED-XL)	X連鎖性遅発性SED(SED-XL)	TRAPPC2	○	○		
Spondylo-Megaepiphyseal-Metaphyseal Dysplasia (SMMD)	脊椎・巨大骨端・骨幹端異形成症(SMMD)	NKX3-2				
Spondylodysplastic Ehlers-Danlos syndrome	脊椎異形成Ehlers-Danlos症候群	SLC39A13				可能(応相談)
SPONASTRIME dysplasia	SPONASTRIME骨異形成症					
SEMD with joint laxity (SEMD-JL) leptodactylic or Hall type	関節弛緩を伴うSEMD (SEMD-JL) leptodactylic型/Hall					可能(応相談)
SEMD with joint laxity (SEMD-JL) Beighton type	関節弛緩を伴うSEMD (SEMD-JL) Beighton型					
Platyspondyly (brachyolmia) with amelogenesis imperfecta	エナメル質形成不全を伴う扁平椎症(短体幹症)					
Late onset SED, autosomal recessive type	遅発性SED, 常染色体劣性遺伝型					
Brachyolmia, Hobaek / Toledo types	短体幹症, Hobaek型 / Toledo型					
14. Severe spondylodysplastic dysplasias	14. 重症脊椎異形成症					
Achondrogenesis type 1A (ACG1A)	軟骨無発生症1A型(ACG1A)	TRIP11		○		可能(応相談)
Schneckenbecken dysplasia	蝸牛様骨盤異形成症	SLC35D1				可能(応相談)
Spondylometaphyseal dysplasia, Sedaghatian type	脊椎骨幹端異形成症, Sedaghatian型	SBDS				可能(応相談)
Severe spondylometaphyseal dysplasia (SMD Sedaghatian-like)	重症脊椎骨幹端異形成症 (SMD Sedaghatian型類似)	SBDS				可能(応相談)
Opsismodysplasia	成熟遅延骨異形成症					
15. Acromelic dysplasia	15. 遠位肢異形成症					
Trichorhinophalangeal dysplasia types 1/3	毛髪鼻指節異形成症1型/3型	TRPS1	○	○		可能(応相談)
Trichorhinophalangeal dysplasia type 2 (Langer-Giedion)	毛髪鼻指節異形成症2型(Langer-Giedion)	TRPS1, EXT1		○		可能(応相談)
Acrocapitofemoral dysplasia	先端大腿骨頭異形成症	IHH	○			
Cranioectodermal dysplasia (Levin-Sensenbrenner) type 1	頭蓋外胚葉異形成症 (Levin-Sensenbrenner) 1型					
Cranioectodermal dysplasia (Levin-Sensenbrenner) type 2	頭蓋外胚葉異形成症 (Levin-Sensenbrenner) 2型					
Geleophysic dysplasia	幸福顔貌骨異形成症	ADAMTSL2		○		
Geleophysic dysplasia, other types	幸福顔貌骨異形成症, 他の型					
Acromicric dysplasia	先端短肢異形成症					
Acrodysostosis	先端異骨症					
Angel-shaped phalango-epiphyseal dysplasia (ASPED)	天使形指節骨骨端異形成症(ASPED)					
Saldino-Mainzer dysplasia	Saldino-Mainzer骨異形成症					
16. Acromesomelic dysplasias	16. 遠位中間肢異形成症					
Acromesomelic dysplasia type Maroteaux (AMDM)	遠位中間肢異形成症 Maroteaux型 (AMDM)	NPR2	○	○		
Grebe dysplasia	Grebe骨異形成症	GDF5		○		可能(応相談)
Fibular hypoplasia and complex brachydactyly (Du Pan)	腓骨低形成複雑短指症 (Du Pan)	GDF5	○	○		可能(応相談)
Acromesomelic dysplasia with genital anomalies	性器異常を伴う遠位中間肢異形成症	BMPR1B				
Acromesomelic dysplasia, Osebold-Remondini type	遠位中間肢異形成症, Osebold-Remondini型					
17. Mesomelic and rhizo-mesomelic dysplasias	17. 中間肢・近位肢中間肢異形成症					
Dyschondrosteosis (Leri-Weill)	異軟骨骨症 (Leri-Weill)	SHOX, SHOXY	○	○	三菱化学実施	可能(応相談)
Langer type (homozygous dyschondrosteosis)	Langer型 (ホモ接合型異軟骨骨症)	SHOX, SHOXY	○	○		可能(応相談)
Omodysplasia	肩骨異形成症	GPC6		○		
Robinow syndrome, recessive type	Robinow症候群, 劣性遺伝型	ROR2	○	○		可能(応相談)
Robinow syndrome, dominant type	Robinow症候群, 優性遺伝型					
Mesomelic dysplasia, Korean type	中間肢異形成症, Korean型					
Mesomelic dysplasia, Kantaputra type	中間肢異形成症, Kantaputra型					
Mesomelic dysplasia, Nievergelt type	中間肢異形成症, Nievergelt型					
Mesomelic dysplasia, Kozlowski-Reardon type	中間肢異形成症, Kozlowski-Reardon型					

Mesomelic dysplasia with acral synostoses (Verloes-David-Pfeiffer type)	先端癒合症を伴う中間肢異形成症 (Verloes-David-Pfeiffer type)				
Mesomelic dysplasia, Savarirayan type (Triangular Tibia-Fibular Aplasia)	中間肢異形成症, Savarirayan型 (三角形脛骨・腓骨無形成症)				
18. Bent bones dysplasias	18. 彎曲骨異形成症				
Campomelic dysplasia (CD)	屈曲肢異形成症(CD)	SOX9	○	○	可能(応相談)
Stüve-Wiedemann dysplasia	Stüve-Wiedemann骨異形成症	LIFR	○	○	
Kyphomelic dysplasia, several forms	後彎肢異形成症, 各型				
19. Slender bone dysplasia Group	19. 狭細骨異形成症グループ				
3-M syndrome (3M1)	3-M症候群(3M1)	CUL7		○	
3-M syndrome (3M2)	3-M症候群(3M2)	OBSL1		○	
Kenny-Caffey dysplasia type 1	Kenny-Caffey骨異形成症1型	TBCE	○		
Kenny-Caffey dysplasia type 2	Kenny-Caffey骨異形成症2型				
Microcephalic osteodysplastic primordial dwarfism type 1/3 (MOPD1)	小頭型骨異形成性原発小人症1型/3型(MOPD1)	RNU4ATAC			
Microcephalic osteodysplastic primordial dwarfism type 2 (MOPD2; Majewski type)	小頭型骨異形成性原発小人症1型/3型(MOPD2; Majewski型)	PCNT		○(prenatalなし)	
Microcephalic osteodysplastic dysplasia, Saul-Wilson type	小頭型骨異形成性異形成症, Saul-Wilson型				
IMAGE syndrome (Intrauterine Growth Retardation, Metaphyseal Dysplasia, Adrenal Hypoplasia, and Genital Anomalies)	IMAGE症候群 (子宮内胎児発育遅延, 骨幹端異形成, 副腎低形成, 性器異常)				
Osteocraniostenosis	骨頭蓋狭窄症				
Hallermann-Streiff syndrome	Hallermann-Streiff症候群	GJA1			
20. Dysplasias with multiple joint dislocations	20. 多発性脱臼を伴う骨異形成症				
Desbuquois dysplasia (with accessory ossification centre in digit 2)	Desbuquois骨異形成症 (第2指の副骨化中心を伴う)	CANT1		○	可能(応相談)
Desbuquois dysplasia with short metacarpals and elongated phalanges (Kim type)	短い中手骨と長い指骨を伴うDesbuquois骨異形成症(Kim 型)	CANT1			可能(応相談)
Desbuquois dysplasia (other variants with or without accessory ossification centre)	Desbuquois骨異形成症 (副骨化中心を伴う/伴わない他の亜型)				可能(応相談)
Pseudodiastrophic dysplasia	偽性捻曲性骨異形成症				
21. Chondrodysplasia punctata (CDP) Group	21. 点状軟骨異形成症(CDP)グループ				
CDP, X-linked dominant, Conradi-Hünermann type (CDPX2)	CDP, X連鎖性優性遺伝型, Conradi-Hünermann型 (CDPX2)	EBP	○	○	
CDP, X-linked recessive, brachytelephalangic type (CDPX1)	CDP, X連鎖性劣性遺伝型, 末梢骨短縮型 (CDPX1)		○		可能(応相談)
CHILD (congenital hemidysplasia, ichthyosis, limb defects)	CHILD症候群 (先天性片側異形成, 魚鱗癬様紅皮症, 四肢欠損)	NSDHL	○	○	
CHILD (congenital hemidysplasia, ichthyosis, limb defects)	CHILD症候群 (先天性片側異形成, 魚鱗癬様紅皮症, 四肢欠損)	EBP		○	
Greenberg dysplasia	Greenberg骨異形成症	LBR		○	
Rhizomelic CDP type 1	近位肢型CDP 1型	PEX7	○	○	
Rhizomelic CDP type 2	近位肢型CDP 2型	GNPAT		○	
Rhizomelic CDP type 3	近位肢型CDP 3型	AGPS		○	
CDP tibial-metacarpal type	CDP脛骨・中手骨型				可能(応相談)
Astley-Kendall dysplasia	Astley-Kendall骨異形成症				
22. Neonatal osteosclerotic dysplasias	新生児骨硬化性異形成症				
Blomstrand dysplasia	Blomstrand骨異形成症	PTHR1		○	
Desmosterolosis	デスモステロール症	DHCR24		○	
Caffey disease (including infantile and attenuated forms)	Caffey病 (乳児型・寛解型を含む)	COL1A1		○	可能(応相談)
Caffey disease (severe variants with prenatal onset)	Caffey病 (出生前発症の重症型)	COL1A1		○	可能(応相談)
Raine dysplasia (lethal and non-lethal forms)	Raine骨異形成症 (致死型および非致死型)	FAM20C			
23. Increased bone density group (without modification of bone shape)	骨変形を伴わない骨硬化性疾患グループ				
Osteopetrosis, severe neonatal or infantile forms (OPTB1)	大理石骨病, 重症新生児型/乳児型 (OPTB1)	TCIRG1		○	可能(応相談)
Osteopetrosis, severe neonatal or infantile forms (OPTB4)	大理石骨病, 重症新生児型/乳児型 (OPTB4)	CLCN7	○	○	可能(応相談)
Osteopetrosis, infantile form, with nervous system involvement (OPTB5)	神経系罹患を伴う大理石骨病, 乳児型, (OPTB5)	OSTM1		○	

Osteopetrosis, intermediate form, osteoclast-poor (OPTB2)	大理石骨病，中間型，低破骨細胞性 (OPTB2)	TNFSF11		○	可能(応相談)
Osteopetrosis, infantile form, osteoclast-poor with immunoglobulin deficiency (OPTB7)	免疫グロブリン欠損症を伴う低破骨細胞性大理石骨病，乳児型	TNFRSF11A		○	可能(応相談)
Osteopetrosis, intermediate form (OPTB6)	大理石骨病，中間型 (OPTB6)	PLEKHM1		○	
Osteopetrosis, intermediate form (OPTA2)	大理石骨病，中間型 (OPTA2)	CLCN7	○	○	可能(応相談)
Osteopetrosis with renal tubular acidosis (OPTB3)	腎尿細管アシドーシスを伴う大理石骨病 (OPTB3)	CA2		○	
Osteopetrosis, late-onset form type 1 (OPTA1)	大理石骨病，遅発型1型 (OPTA1)	LRP5		○	可能(応相談)
Osteopetrosis, late-onset form type 2 (OPTA2)	大理石骨病，遅発型2型 (OPTA2)	CLCN7	○	○	可能(応相談)
Osteopetrosis with ectodermal dysplasia and immune defect (OLEDAID)	外胚葉異形成と免疫不全を伴う大理石骨病 (OLEDAID)	IKBKG		○	
Osteopetrosis, moderate form with defective leucocyte adhesion (LAD3)	白血球付着不全を伴う大理石骨病，中間型 (LAD3)	FERMT3(KIND3)			
Osteopetrosis, moderate form with defective leucocyte adhesion	白血球付着不全を伴う大理石骨病，中間型	RASGRP2(CalDAGGEF1)			
Pyknodysostosis	濃化異骨症	CTSK		○	可能(応相談)
Osteopoikilosis	骨斑紋症	LEMD3	○	○(prenatalなし)	
Melorheostosis with osteopoikilosis	骨斑紋症を伴う流蝋骨症	LEMD3	○	○(prenatalなし)	
Osteopathia striata with cranial sclerosis (OSCS)	頭蓋骨硬化を伴う骨線状症)OSCS)				
Melorheostosis	メロレオストーシス，流蝋骨症	LEMD3	○	○(prenatalなし)	
Dysosteosclerosis	異骨性骨硬化症				
Osteomesopyknosis	骨中間濃化症				
Osteopetrosis with infantile neuroaxonal dysplasia	乳児神経軸索異形成症を伴う大理石骨病				
24. Increased bone density group with metaphyseal and/or diaphyseal involvement	24. 骨幹端・骨端罹患を伴う骨硬化性病変				
Craniometaphyseal dysplasia, autosomal dominant type	頭蓋骨幹端異形成症，常染色体優性遺伝型	ANKH			
Diaphyseal dysplasia Camurati-Engelmann	骨幹異形成症 Camurati-Engelmann型	TGFB1	○	○	可能(応相談)
Hematodiaphyseal dysplasia Ghosal	造血長管骨異形成症 Ghosal	TBXAS1			
Hypertrophic Osteoarthropathy	肥大性骨関節症	HPGD		○(prenatalなし)	
Pachydermoperiostosis (Hypertrophic osteoarthropathy, primary, autosomal dominant)	皮膚骨膜肥厚症 (肥大性骨関節症，原発性，常染色体優性遺伝型				
Oculodentoosseous dysplasia (ODOD) mild type	Oculodentoosseous dysplasia (ODOD) mild type	GJA1	○	○	
Oculodentoosseous dysplasia (ODOD) severe type	Oculodentoosseous dysplasia (ODOD) severe type	GJA1	○	○	
Osteoectasia with hyperphosphatasia (Juvenile Paget disease)	高アルカリフォスファターゼ症を伴う骨肥大症(若年性Paget病)	TNFRSF11B		○	可能(応相談)
Sclerosteosis	硬化性骨症	SOST		○(prenatalなし)	可能(応相談)
Endosteal hyperostosis, van Buchem type	骨内膜性骨増殖症，van Buchem型	SOST		○(prenatalなし)	可能(応相談)
Trichodentoosseous dysplasia	毛髪歯骨異形成症	DLX3			
Craniometaphyseal dysplasia, autosomal recessive type	頭蓋骨幹端異形成症，常染色体劣性遺伝型				
Diaphyseal medullary stenosis with bone malignancy	骨悪性腫瘍を伴う骨幹部骨髄腔狭窄症				
Craniodiaphyseal dysplasia	頭蓋骨幹異形成症	SOST			可能(応相談)
Craniometadiaphyseal dysplasia, Wormian bone type	頭蓋骨幹端異形成症，Worm骨型				
Endosteal sclerosis with cerebellar hypoplasia	Lenz-Majewski骨増殖異形成症				
Metaphyseal dysplasia, Braun-Tinschert type	Metaphyseal dysplasia, Braun-Tinschert type				
Pyle disease	Pyle病				
25. Osteogenesis Imperfecta and decreased bone density group	骨形成不全症と骨密度低下を示すグループ				
Osteogenesis imperfecta, non-deforming form (OI type 1)	骨形成不全症，非変形型(OI 1型)	COL1A1, COL1A2	○	○	可能(応相談)
Osteogenesis imperfecta, perinatal lethal form (OI type 2)	骨形成不全症，周産期致死型(OI 2型)	COL1A1, COL1A2, CRTAP	○	○	可能(応相談)
Osteogenesis imperfecta, progressively deforming type (OI type 3)	骨形成不全症，進行性変形型(OI 3型)	COL1A1, COL1A2	○	○	可能(応相談)
Osteogenesis imperfecta, moderate form (OI type 4)	骨形成不全症，中等症型(OI 4型)	COL1A1, COL1A2	○	○	可能(応相談)
Osteogenesis imperfecta with calcification of the interosseous membranes and/or hypertrophic callus (OI type 5)	骨内膜石灰化と肥大化骨を伴う骨形成不全症(OI 5型)				可能(応相談)
Osteogenesis imperfecta, other types	骨形成不全症，その他の型	CRTAP, FKBP10, LEPRE1, PPIB	○	○	可能(応相談)
Bruck syndrome type 1 (BS1)	Bruck症候群1型 (BS1)				
Bruck syndrome type 2 (BS2)	Bruck症候群2型 (BS2)	PLOD2	○	○	
Osteoporosis-pseudoglioma syndrome	骨粗鬆症・偽神経膠腫症候群	LRP5		○	可能(応相談)
Calvarial doughnut lesions with bone fragility	骨脆弱性を伴う頭蓋ドーナッツ様病変				
Idiopathic juvenile osteoporosis	特発性若年性骨粗鬆症				
Cole-Carpenter dysplasia (bone fragility with craniosynostosis)	Cole-Carpenter骨異形成症(頭蓋骨癒合症を伴う骨脆弱症)				

Spondylo-ocular dysplasia	脊椎・眼異形成症				
Osteopenia with radiolucent lesions of the mandible	下顎骨X線透過性病変を示す骨減少症				
Ehlers-Danlos syndrome, progeroid form	Ehlers-Danlos症候群，早老型	B4GALT7			
Geroderma osteodysplasticum	骨異形成性老人様皮膚症	GORAB			
Cutis laxa, autosomal recessive form, type 2B (ARCL2B)	皮膚弛緩症，常染色体劣性遺伝型，2B型 (ARCL2B)	PYCR1			
Cutis laxa, autosomal recessive form, type 2A (ARCL2A) (Wrinkly skin syndrome)	皮膚弛緩症，常染色体劣性遺伝型，2A型 (ARCL2A)，しわの多い皮膚症候群	ATP6V0A2	○	○	
Singleton-Merten dysplasia	Singleton-Merten症候群				
26. Defective mineralization group	26. 骨石灰化障害を示すグループ				
Hypophosphatasia, perinatal lethal and infantile forms	低フォスファターゼ症，周産期致死型・乳児型	ALPL(TNSALP)		○	可能(応相談)
Hypophosphatasia, adult form	低フォスファターゼ症，成人型	ALPL(TNSALP)		○	可能(応相談)
Hypophosphatemic rickets, X-linked dominant	低リン血症性くる病，X連鎖性優性遺伝型	PHEX	○	○	
Hypophosphatemic rickets, autosomal dominant	低リン血症性くる病，常染色体優性遺伝型	FGF23	○	○	
Hypophosphatemic rickets, autosomal recessive, type 1 (ARHR1)	低リン血症性くる病，常染色体劣性遺伝型，1型 (ARHR1)	DMP1	○	○	
Hypophosphatemic rickets, autosomal recessive, type 2 (ARHR2)	低リン血症性くる病，常染色体劣性遺伝型，2型 (ARHR2)	ENPP1	○	○	
Hypophosphatemic rickets with hypercalciuria, X-linked recessive	高Ca尿症を伴う低リン血症性くる病，X連鎖性劣性遺	CLCN5		○	
Hypophosphatemic rickets with hypercalciuria, autosomal recessive (HHRH)	高Ca尿症を伴う低リン血症性くる病，常染色体劣性遺伝型 (HHRH)	DMP1		○	
Neonatal hyperparathyroidism, severe form	新生児上皮小体機能亢進症，重症型	CASR		○	可能(応相談)
Familial hypocalciuric hypercalcemia with transient neonatal hyperparathyroidism	一過性新生児上皮小体機能亢進症を伴う家族性高Ca尿性高Ca血症	CASR		○	可能(応相談)
27. Lysosomal Storage Diseases with Skeletal Involvement (Dysostosis Multiplex Group)	27.骨変化を伴うリソソーム蓄積症(多発性異骨症グループ)				
Mucopolysaccharidosis type 1H / 1S	ムコ多糖症 1H/1S型	IDUA	○	○	
Mucopolysaccharidosis type 2	ムコ多糖症 2型	IDS	○	○	可能(応相談)
Mucopolysaccharidosis type 3A	ムコ多糖症 3A型	SGSH	○	○	
Mucopolysaccharidosis type 3B	ムコ多糖症 3B型	NAGLU	○	○	
Mucopolysaccharidosis type 3C	ムコ多糖症 3C型	HGSNAT	○	○	
Mucopolysaccharidosis type 3D	ムコ多糖症 3D型	GNS	○	○	
Mucopolysaccharidosis type 4A	ムコ多糖症 4A型	GALNS	○	○	
Mucopolysaccharidosis type 4B	ムコ多糖症 4B型	GLB1	○	○	
Mucopolysaccharidosis type 6	ムコ多糖症 6型	ARSB	○	○	
Mucopolysaccharidosis type 7	ムコ多糖症 7型	GUSB	○	○	
Fucosidosis	フコシドーシス	FUCA1	○	○	
alpha-Mannosidosis	アルファ-マンノーシス	MAN2B1	○	○	
beta-Mannosidosis	ベータ-マンノーシス	MANBA	○	○	
Aspartylglucosaminuria	アスパチルグルコサミン尿症	AGA		○	
GMI Gangliosidosis, several forms	GMIガングリオドーシス，各型	GLB1	○	○	
Sialidosis, several forms	シアリドーシス，各型	NEU1	○	○	
Sialic acid storage disease SIASD	シアル酸蓄積症 SIASD	SLC17A5		○	
Galactosialidosis, several forms	ガラクトシアリドーシス，各型	CTSA		○	
Multiple sulfatase deficiency	多種サルファターゼ欠損症	SUMF1	○	○	
Mucolipidosis II (I-cell disease), alpha/beta type	ムコ脂質症II型 (I-cell病)	GNPTAB	○	○	
Mucolipidosis III (Pseudo-Hurler polydystrophy), alpha/beta type	ムコ脂質症III型 (偽性Hurlerポリジストロフィー)，アルファ/ベータ型	GNPTAB	○	○	
Mucolipidosis III (Pseudo-Hurler polydystrophy), gamma type	ムコ脂質症III型 (偽性Hurlerポリジストロフィー)，ガンマ	GNPTAG (GNPTG)	○	○	
28. Osteolysis Group	29. 骨溶解症グループ				
Familial expansile osteolysis	家族性拡張性骨溶解症				
Mandibuloacral dysplasia type A	下顎先端異形成症 A型	LMNA	○	○	
Mandibuloacral dysplasia type B	下顎先端異形成症 B型	ZMPSTE24	○	○	
Progeria, Hutchinson-Gilford type	早老症，Hutchinson-Gilford型	LMNA	○	○	
Torg-Winchester syndrome	Torg-Winchester症候群	MMP2		○(prenatalなし)	
Hajdu-Cheney syndrome	Hajdu-Cheney症候群	NOTCH2		○	
Multicentric carpal-tarsal osteolysis with and without nephropathy	多中心性手根骨・足根骨溶解症(腎症を伴う/伴わな				可能(応相談)