Published in final edited form as:

Am J Med Genet A. 2012 August ; 0(8): 1815–1822. doi:10.1002/ajmg.a.35445.

A Newly Recognized Syndrome With Characteristic Facial Features, Skeletal Dysplasia, and Developmental Delay

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Abstract

We describe a series of seven male patients from six different families with skeletal dysplasia, characteristic facial features, and developmental delay. Skeletal findings include patellar dislocation, short tubular bones, mild metaphyseal changes, brachymetacarpalia with stub thumbs, short femoral necks, shallow acetabular roofs, and platyspondyly. Facial features include: a flattened midface with broad nasal bridge, cleft palate or bifid uvula and synophrys. All of the patients demonstrated pre-school onset of a cognitive developmental delay with a shortened attention span. Some of the cognitive delay was masked by a warm and engaging personality. We posit that these individuals have a newly recognized syndrome characterized by the described features. There is some phenotypic overlap between these patients and Desbuquois dysplasia; however molecular testing demonstrated that this is a distinct disorder. Given the family information available for each patient, we are suspicious that the constellation of findings reported herein could be an X-linked recessive syndrome.

Keywords

skeletal dysplasia; patellar dislocation; developmental delay

INTRODUCTION

We describe what we consider to be a novel syndrome in seven male patients from six different families, with skeletal dysplasia, characteristic facial features, and developmental delay. The osseous findings include patellar dislocation, short tubular bones, mild metaphyseal changes, brachymetacarpalia with stub thumbs, short femoral necks, shallow acetabular roofs and platyspondyly. The facial features comprise a flattened midface with broad nasal bridge, cleft palate or bifid uvula, and synophrys. All of the patients demonstrated pre-school onset of a cognitive developmental delay with a shortened attention span. Some of the cognitive delay was masked by a warm and engaging personality (see Figs. 1–4).

The first four patients have been followed in the A. I. duPont Hospital for Children Skeletal Dysplasia Program. Two siblings, Patients 5 and 6, are followed in Oakland (Kaiser Permanente Hospital), and Patient 7 is followed in Los Angeles (Kaiser Permanente Hospital). Skeletal surveys were obtained from all of the patients and carefully examined by the senior authors (RL, CS).

Patient 1 (26 Years of Age)

Patient 1 was the first pregnancy for his nonconsanguineous, then 15-year-old father and 17-year-old mother. The young couple was healthy, average statured, without learning disability, from English/Irish/Italian ancestry, and with no family history of dwarfism. He was delivered by caesarian due to breech presentation, at term gestation, with APGAR score of 9 (see Fig. 1; Tables I and II). He was recognized to be disproportionately small for his age at the time of birth, receiving a diagnosis of an unusual achondroplasia. He walked at 22 months, and expressive language delay was noted at 3 years. He underwent tonsillectomy and adenoidectomy with pressure equalization tube (PET) placement at 5 years. At 9 years a WISC-III full scale IQ was 53 and verbal IQ was 58. He is noted to have an engaging, outgoing personality. Left genu valgum with patellar tracking dysfunction developed and at age 16 and a patellartibial realignment was done. The following year, realignment osteotomies were necessary. Minimally nearsighted with astigmatism, he wears glasses. There is currently mild bilateral conductive hearing loss. He has hypodontia with only 3–4 secondary teeth present. Tooth quality appears to be average. Puberty began at 16 years of age and progressed normally. Other noted features on most recent examination include (see Tables I and II): a low posterior hairline, and neck webbing. Mild genu varum was present on the right with patella dislocation. The right knee lacked 50–60° from full extension and the left knee lacked 40° from full extension. Bilateral pronated pes planus was present. The elbows lacked full extension, flexion, pronation, and supination. The proximal IP joints had decreased flexion. Chromosome analysis and *CANT1* sequencing were normal.

Patient 2 (21 Years of Age)

Patient 2 was the third pregnancy for his nonconsanguineous, average-statured, 30-year-old mother and 38-year-old father. The family is from German/Polish/Irish/Dutch ancestry. Pregnancy was complicated by polyhydramnios and shortened limbs on prenatal ultrasound examination. He was delivered vaginally at term with APGAR score of 8 and 9 (see Fig. 1;

Tables I and II). He underwent PET placement for chronic otitis media at 17 months; a small soft palate cleft was diagnosed later in life and required surgical closure. All initial developmental milestones through the first 17 months were age appropriate, but speech delay was noted and therapy initiated at 27 months. At eight years, the WISC-III full scale IQ was 49, verbal scale IQ 58, and performance scale IQ 47. Right-sided patellofemoral tracking abnormality with internal tibial torsion, distal tibial valgus and in toeing prompted a lateral release, medial reefing and Roux-Goldthwait patellar procedure. At 13 years, left patellar realignment with ilio-tibial band lengthening and biceps femoris lengthening was performed, as well as right lateral patellar release with ilio-tibial band lengthening and biceps femoris lengthening. Bilateral distal tibial and fibular realignment derotational osteotomies were also performed. Pubertal development onset was at 12 years of age and progressed normally. Class III malocclusion was present; formal ophthalmologic evaluations revealed no abnormalities. Laboratory investigations, including chromosome analysis, 7-dehydrocholesterol, and *CANT1* sequencing were normal.

Patient 3 (8 Years of Age)

Patient 3 was the first term pregnancy for his 26-year-old mother and 39-year-old father, both from Russia. APGAR scores were 5 and 7. An inguinal hernia repair was performed in Russia. He was adopted into his current family at 22 months of age (see Fig. 1; Tables I and II). Initially, all developmental milestones were age-appropriate and he rapidly learned English. At the age of 6, formal developmental assessments found delays in all areas, including fine and gross motor, pre-academic, and language. Physical and occupational therapy, and educational services have been implemented. Due to bilateral patellar dislocation, patellar realignment with lateral release, medial plication and ilio-tibial band lengthening was performed on the right at age 5 and on the left at age 6. Dentition is thus far normal, and formal ophthalmologic evaluations have not revealed any abnormalities. There is rhizomelic shortening in the upper extremities with normal ranges of motion at the elbows. The hands and wrist showed marked ligamentous laxity. *RMRP* sequencing, *CANT1* sequencing and BAC Array CGH were normal.

Patient 4 (19 Years of Age)

Patient 4 was the second pregnancy for his nonconsanguineous, average-statured, 19-year-old mother and 18-year-old father. Family is from Russian/Latvian/German origin. Prenatal ultrasound at 5 months of gestation showed short limbs. He was born at term via cesarean (see Fig. 1; Tables I and II). Inguinal hernia surgery was performed at 16 months of age. At 5 years of age the Desbuquois syndrome was considered. Developmental motor skills were slightly delayed; cognitive delay and attention span issues were recognized at 9 years of age, and special education has been required. At ages 16 and 17 patient has had, respectively, left and right patellar reconstruction, soft tissue and Fulkerson osteotomy, plus distal femur osteotomy with EBI rail. Physical examination at age 17 years showed a high pitched voice, a warm outgoing personality and disproportionate short stature, predominantly rhizomelic, with a short and broad neck, stocky habitus and truncal obesity. Dental crowding with a supernumerary conical tooth is present. Elbow supination was deficient due to a subluxed radial heads. Lower extremities showed flexible flat feet. Chromosome analysis and *CANT1* sequencing was normal.

Patient 5 (23 Years of Age)

Patient 5 was the first pregnancy for his nonconsanguineous, average statured parents of Dominican/West Indian/African American ancestry. His mother was 20 years old. Long bones, below the 5th centile, were seen in prenatal ultrasounds at 25 and 37 weeks. Delivery was by cesarean due to failure to progress at term. APGAR scores were 8 and 9 (see Fig. 1; Tables I and II). Delayed motor milestones, ongoing difficulties with fine motor skills, and speech delay have been present and by age 10, he was receiving special education; currently he is socially immature, yet has an outgoing personality. Hearing and vision exams have been normal. The patellae are dislocating and he is noted to have mild genu valgum. He is morbidly obese. Negative genetic testing included chromosome analysis, fragile X syndrome molecular testing, subtelomere probes, *GNAS1* sequencing for Albright hereditary osteodystrophy and *CANT1* sequencing were normal.

Patient 6 (19 Years of Age)

Patient 6 is the younger brother of Patient 5. He was his parents' second pregnancy. Short limbs were seen on prenatal ultrasound and he was delivered at term by cesarean (see Fig. 1; Tables I and II). A submucous cleft palate was present. Early on, he was recognized as having the same syndromic condition as his brother. Delayed development is present and necessitated special education programs. Dislocating patellae are present as is significant genua vara and a limb length discrepancy. Abnormal progression of digital lengths was noted with shortened 4th and relatively elongated 3rd digits noted on the right side. Additionally, he has esotropia with left hypertropia and strabismus, a high pitched voice, and sleep apnea. Chronic joint pain and morbid obesity were also a concern. *CANT1* sequencing was normal.

Patient 7 (15 Years of Age)

Patient 7 was the first pregnancy for his consanguineous (first cousin) 23-year-old short (145 cm) mother and 19-year-old father, both of Mexican ancestry. Family history includes a 12-year-old brother mildly short, and a great aunt with short stature. He was born without complications at term in Mexico. Short stature was noted at birth (see Fig. 1; Tables I and II). He had respiratory complications in the first 2 weeks of life. He has had a delayed motor development, walked with 18 months and has always needed special education. At present age, 13 years, he is unable to read or write, although receptive language skills are good. His patellae are bilaterally dislocated. Restriction of elbow motion, with incomplete extension and incomplete forearm supination are present. He has a cauliflower ear deformity on the right and bilateral palmar transverse creases with a single finger flexion crease on 2nd and 5th fingers on the right and 2nd, 4th, and 5th fingers on the left. Mild tibial bowing was present. Chromosome analysis and *CANT1* sequencing were normal.

DISCUSSION

We present seven male patients from six families of different ethnic backgrounds, with skeletal dysplasia, characteristic facial features, and developmental delay. Craniofacial and skeletal findings are summarized in Tables I and II. The fact that all seven of our patients are males raises the possibility that this syndrome may be X-linked. Although the mother of

Patient 7 is mildly short, it does not appear that the biological mothers share a phenotype with these boys, further suggesting possible X-linked recessive. Certainly, autosomal recessive inheritance also remains a possibility. Each patient had normal chromosomal analyses and a single patient had a normal BAC Array CGH. All patients had normal *CANT1* sequencing.

Body habitus was similar in all the patients: mildly disproportionate short stature with shortened limbs of predominantly rhizomelic type and a short supple neck. The most important skeletal finding was patellar tracking abnormalities, present in all cases. Patellar dislocation was bilateral and chronic although in Patients 5 and 6 the patellae were at times, in place clinically and at other times were dislocated. Patellar realignment procedures were required in Patients 1, 2, 3, and 4. Small thorax, pectus carinatum, and antero-lateral rib flaring was found in five of seven (71%) patients. Increased ligamentous laxity of the extremities hands with brachydactyly was present in all and cutaneous syndactyly appeared in three of seven (43%) of the individuals. Patients 1, 4, and 7, showed lack of extension, pronation, and supination of the forearms, in addition, Patient 4 had bilateral subluxed radial head.

All seven patients have strikingly similar craniofacial features including a flattened midface and depressed nasal bridge. Bifid uvula and/or cleft palate were found in four of seven (57%) patients. Three of seven (43%) patients had microcephaly. Although minor ophthalmologic problems were present in Patient 1 (astigmatism) and Patient 6 (esotropia, hypertropia, and strabismus), there did not appear to be a pattern of involvement; Patient 1 had also mild bilateral conductive hearing deficit. None of the patients had cardiac issues. As additional dysmorphic facial features, Patient 7 had upturned nares and a left “cauliflower ear.” Patient 1 was noted to have a low posterior hair line with a webbed neck. Patients 1, 4, 5, 6, and 7 had epicanthal folds present at a younger age and over time, these gradually resolved. Patients 1, 2, 4, and 7 were noted to have synophrys on at least one examination although several families report shaving this feature.

Learning disability with speech delay are common intellectual impairments among these individuals and cognitive delays became evident at pre-school ages. Except Patients 2 and 3, all had variable motor delays. All of the subjects had speech therapy and special education programs. Despite their intellectual limitations, all seven patients have a warm, easy going and engaging personality. Their social and engaging nature tends to mask their intellectual disabilities. The patients have a rather low, gravelly voice.

Skeletal radiographic surveys were carefully examined and non-specific brachymetacarpalia was universal (see Fig. 2). Most had stub thumbs. Long bones presented mild metaphyseal widening, and relatively normal to minimally flattened epiphyses. The pelvis had a Desbuquois-like appearance, especially in the younger patients, showing short femoral necks and flat acetabular roofs. Valgus and windswept deformities in the knees were frequently seen. Laterally displaced patellae appeared upon weight bearing (see Figs. 3 and 4). The two brothers, Patients 5 and 6, had vertebral end plates indentations on thoracic spine radiographs (see Fig. 4). None had cervical spine instability or odontoid hypoplasia. The skeletal findings in our patients, such as the metaphyseal widening, epiphyseal

flattening, and platyspondyly, are suggestive of a mild spondylo-epi-metaphyseal dysplasias (SEMD).

Taken together we do not consider this constellation of features matches with any described syndrome. There are two major skeletal dislocation syndromes in the differential, Desbuquois dysplasia (DBD) and Larsen syndrome [Lachman, 2007; Warman et al., 2011]. Desbuquois et al. [1966] and later other authors have described a unique form of micromelic chondrodysplasia with multiple joint dislocations, round face, midface hypoplasia, glaucoma, and cardiac defects. Among the skeletal findings of DBD were: advanced carpal and tarsal bone ages, supernumerary carpal bones, short tubular bones with delayed epiphyseal ossification, wide metaphyses, prominence of the lesser trochanters, flat acetabular roofs, and osteoporosis [Desbuquois et al., 1966; Piussan et al., 1975; Gillesen-Kaesbach et al., 1995]. This condition was later proved to be autosomal recessive, and to be clinically and genetically heterogeneous [Le Merrer et al., 1991; Faivre et al., 2004a,b]. Specifically the classic radiographic hand profile with phalangeal dislocation, a supernumerary bone distal to the second metacarpal, delta shape phalanges, and bifid thumb phalange was absent in 16 out of 35 patients, leading to the distinction between DBD, Type I or classic type and DBD, Type II with normal hands [Faivre et al., 2004a]. Kim et al. [2010] have subsequently broadened the clinical spectrum, adding a third type of DBD with distinct hand/feet anomalies from groups 1 and 2, advanced carpal age, short metacarpals, elongated phalanges, and normal intelligence [2010]. Recently, mutations in the calcium-activated nucleotidase 1 gene (*CANT1*) that encodes, an extracellular protein expressed in chondrocytes and implicated in endoplasmic reticulum metabolism have been determined to cause DBD types 1, 2, and Kim [Huber et al., 2009; Faden et al., 2010; Furuichi et al., 2011].

Some of the clinical and radiographic findings in our patients, such as the short femoral necks and flat acetabular roofs, advanced bone age and patellar dislocations do resemble DBD, or a Desbuquois-like phenotype. In fact, Patient 4 had carried a diagnosis of DBD during infancy and early childhood. Early bone age surveys reported advanced bone age in carpals, osteoporosis, and prominent lesser trochanters. Patient 3 showed advanced carpal bone age, and “monkey wrench” appearance of proximal femurs. We have not found the typical hand anomalies of Desbuquois including supernumerary carpal and tarsal bones, extra center of ossification distal to the second metacarpal bone, bifid distal or proximal thumb phalanges, delta phalanges, nor fingers dislocations. None of our patients had coronal vertebral clefts or clubfoot. Heart defects or glaucoma were not seen (see Table III). All of our patients were screened for mutations in the *CANT1* gene which have been previously described to cause DBD. Sequencing of the coding regions of exons 3, 4, and 5 were normal, and no deletions were identified in the 5'-UTR-exon 1 region of the gene. Interestingly, Faivre et al. [2004b] described three patients with DBD in whom linkage to the 17q25.3 *CANT1* region was excluded and Furuichi et al. [2011] described one patient with DBD and normal hands in whom *CANT1* sequencing failed to demonstrate any mutations. It is possible that these individuals, whom were each described to have DBD with normal hands, may have the syndrome which we are describing in this cohort.

Another congenital dislocation syndrome is Larsen syndrome. Larsen syndrome is characterized by multiple congenital dislocations of the large joints and typical facial features. Some common findings are shared with our patients, such as the stub thumb, and midline defects, like cleft palate and bifid uvula [Larsen et al., 1950; Latta et al., 1971]. Patient 4 presented with bilateral radial head subluxation. However none of our patients had the “dish face” appearance, nor the typical congenital femora and tibiae anterior dislocation, or congenital hip dislocation. Cervical kyphosis and thoracolumbar scoliosis were not found in our series either [Sakaura et al., 1976]. Furthermore, patients with Larsen syndrome do not have marked learning disabilities.

The differential diagnosis for our patients includes variants of SEMD [Cormier-Daire, 2008]. Although the clinical entity of SEMD with joint laxity has been well characterized [OMIM 271640; Tsirikos et al., 2003], those patients often have congenital heart disease, progressive kyphoscoliosis, and skin hyperelasticity, and do not demonstrate intellectual disability. Furthermore, the entity SEMD with multiple dislocations [OMIM 603546; Hall et al., 2002] also appears distinct from our cases in that those patients have different facial features, do not demonstrate intellectual disability, and have characteristic long metacarpal bones and phalanges (“leptodactyly”) [Kim et al., 2009]. It appears that SEMD with joint laxity is an autosomal recessive disorder, whereas clinical evidence supports an autosomal dominant pattern of inheritance for SEMD with multiple dislocations.

CONCLUSION

We present a series of seven male patients from six families of different ethnic backgrounds with skeletal dysplasia, characteristic facial features, and developmental delay. We posit that these individuals have a newly recognized syndrome characterized by the described features. It appears possible that several other patients with a similar phenotype have been described in the literature as having a *CANT1* negative form of DBD or a Desbuquois-like phenotype. Given the family information available for each patient, we are suspicious that the constellation of findings reported herein could be an X-linked recessive syndrome. Further studies to identify the molecular basis of this condition are ongoing.

Acknowledgments

The authors would like to thank all of the families for their support and participation in this work. Financial support for this work was provided by the Nemours Clinical Cluster Grant and the sequencing facility from the COBRE-funded Biomolecular Core Laboratory.

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FIG. 1.

First row: A: Patient 3 at 2 years and 10 months; B: Patient 2 at 2 years and 10 months; C: Patient 2 at 15 years and 11 months; D: Patient 1 at 24 years and 7 months. Second row: E: Patients 6 (left) and 5 (right) at 17 years and 21 years, respectively; F: Patient 7 at 13 years; and G: Patient 4 at 17 years old.

FIG. 2. Hand radiographs; A: Patient 3 at 2 years and 11 months; B: Patient 2 at 17 years. Note stub thumbs, brachydactyly type E, and brachymetacarpalia.

FIG. 3.

Lower extremity radiographs; A: Patient 3 at 3 years; B: Patient 2 at 20 years. Note significant diaphyseal shortening, mild metaphyseal widening, and short femoral necks, with flat acetabular roofs; C: Patient 4. Note knees showing bilateral patellae dislocation.

FIG. 4.

A: Cervico-thoracic spine of Patient 5 at 17 years; B: Thoraco-lumbar spine of Patient 7 at 13 years; Note mild platyspondyly and presence of indentations on vertebrae endplates in 4A; C: Patient 3 at 3 years. Note Short femoral necks with flat acetabular roofs and “monkey wrench” appearance of proximal femurs.

TABLE 1

Anthropometric Data and Craniofacial Features

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Current age (years)	26	21	8	19	23	19	15
Birth weight (g; %ile)	2,600; 5th	3,218; 25th	3,800; 75th	2,537; 5th	3,270; 25th	2,324; 3rd	NA
Birth length (cm; %ile)	42.0; <3rd	44.1; <3rd	42.0; <3rd	38.7; <3rd	43.0; <3rd	43.0; <3rd	34.2; <3rd
Birth OFC (cm; %ile)	33.7; 10th	33.0; 10th	NA	35.0; 25th	NA	NA	NA
Age at most recent exam (years)	22	20	7	16	22	18	14
Height (cm; height age in years)	114.0; 5.7	116.0; 6.1	94.0; 3	130.0; 8.4	120.0; 6.8	114.0; 5.7	97.0; 3.3
Weight (kg)	36.7	46.8	18.0	52.3	59.0	51.0	19.0
OFC (cm; %ile)	53.0; <3rd	51.5; <3rd	49.5; 3rd	55.3; 50th	55.7; 25th	57.2; 75th	47.0; <3rd
Arm span/height ratio	1.027	0.956	0.951	0.992	0.94	1.15	NA
Upper/lower segment ratio	1.32	1.4	1.45	1.34	1.08	1.07	1.24
Developmental delay/learning disability	+	+	+	+	+	+	+
Craniofacial features							
Flat midface	+	+	+	+	+	+	+
Depressed nasal bridge	+	+	+	+	+	+	+
Cleft palate/bifid uvula	-	+	-	+	+	+	-
Epicanthal folds	+	-	-	+	+	+	+
Synophrys	+	+	-	+	-	-	+

NA, not available.

TABLE II

Skeletal, Limb, and Connective Tissue Features

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Patellae dislocation/lateral displacement	+	+	+	+	+	+	+
Ligamentous laxity	+	+	+	+	+	+	+
Small thorax	+	+	+	+	+	+	+
Pectus carinatum	+	—	+	+	+	+	—
Rib flare	+	—	+	+	+	+	—
Brachydactyly	+	+	+	+	+	+	+
Brachymetacarpalia	+	+	+	+	—	—	—
Stub thumb	+	+	+	+	+	+	+
Cutaneous syndactyly	+	+	—	+	—	—	—
Short femoral necks/flat acetabular roofs	+	+	+	+	+	+	+
Increased lumbar lordosis	+	+	+	—	+	+	+
Vertebral endplate indentations	—	—	—	—	+	+	—

TABLE III

Desbuquois Dysplasia Types 1, 2, and Kim, Major Features Compared to the Present Study

	DBD type 1	DBD type 2	DBD type Kim	Present study
Major criteria				
"Monkey wrench" appearance of pelvis	+	+	+	+
Flat acetabular roof	+	+	+	+
Elevated greater trochanter (age related)	+	+	+	+
Proximal fibular overgrowth	+	+	+	–
Advanced carpal/tarsal bone age	+	+	+	+
Hands/feet				
Accessory ossification proximal phalanx, second digit	+	–	–	–
Bifid distal phalanx of the thumb	+	–	–	–
Delta phalanx/delta-like phalanx	+	–	–	–
Phalangeal dislocation	+	–	+	–
Elongated appearance of fingers/toes	–	–	+	–
Other criteria				
Brachydactyly with "stub thumbs"	+	+	–	+
Brachymetacarpalia	+	+	+	+
Wide metaphyses	+	+	+	+
Flat epiphyses	+	+	+	+
Vertebral body indentations/coronal or sagittal clefts	+	+	+	–
Wide anterior ribs	+	+	–	+
Enlarged first metatarsal	+	+	+	–
Coxa valga	+	+	+	–
Medial deviation of the foot	+	+	+	–
Present study major features				
Developmental delay/learning disability	+/-	+/-	–	+
Ligamentous laxity	+	+	+	+
Patellae dislocation/lateral displacement	–	–	+	+
<i>CANT1</i> mutation	+	+	+	–