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A report of three families with *FBN1*-related acromelic dysplasias and review of literature for genotype-phenotype correlation in gelophysic dysplasia

S.W. Cheng[a,1], Ho-Ming Luk[a,1], YoYo W.Y. Chu[b], Yuet-Ling Tung[b], Elanie Yin-Wah Kwan[c], Ivan Fai-Man Lo[a], Brian Hon-Yin Chung[b,*]

[a] Clinical Genetic Service, Department of Health, HKSAR, Hong Kong
[b] Department of Paediatrics and Adolescent Medicine, University of Hong Kong, HKSAR, Hong Kong
[c] Department of Paediatrics and Adolescent Medicine, Pamela Youde Nethersole Eastern Hospital, HKSAR, Hong Kong

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ABSTRACT:

Acromelic dysplasia is a heterogeneous group of rare skeletal dysplasias characterized by distal limb shortening. Weill-Marchesani syndrome (WMS), Geleophysic dysplasia (GD) and Acromicric dysplasia (AD) are clinically distinct entities within this group of disorders and are characterized by short stature, short hands, stiff joints, skin thickening, facial anomalies, normal intelligence and skeletal abnormalities. Mutations of the Fibrillin-1 (*FBN1*) gene have been reported to cause AD, GD and related phenotypes. We reported three families with acromelic short stature. *FBN1* analysis showed that all affected individuals carry a heterozygous missense mutation c.5284G > A (p.Gly1762Ser) in exon 42 of the *FBN1* gene. This mutation was previously reported to be associated with GD. We reviewed the literature and compared the clinical features of the patients with *FBN1* mutations to those with A Distintegrin And Metalloproteinase with Thrombospondin repeats-like 2 gene (*ADAMTSL2*) mutations. We found that tip-toeing gait, long flat philtrum and thin upper upper lip were more consistently found in GD patients with *ADAMTSL2* mutations than in those with *FBN1* mutations. The results have shed some light on the phenotype-genotype correlation in this group of skeletal disorders. A large scale study involving multidisciplinary collaboration would be needed to consolidate our findings.

1. Introduction

Acromelic dysplasia is a heterogeneous group of rare skeletal dysplasias characterized by disproportionate short stature with distal limb shortening. In the 2015 Nosology and Classification of Skeletal Disorders, the acromelic dysplasia group consists of 10 conditions, including, among others, Weill-Marchesani syndrome (WMS), Geleophysic dysplasia (GD) and Acromicric dysplasia (AD). These three disorders share common features of short stature, short hands, stiff joints, skin thickening, facial anomalies, normal intelligence and abnormal skeletal symptoms. Nevertheless, they are distinct entities due to their unique features. For instance, WMS can be differentiated from GD and AD by the presence of lens dislocation or microspherophakia which may lead to severe myopia, cataract and glaucoma (Le Goff and Cormier-Daire, 2012), whereas GD has features of progressive cardiac valvular abnormalities, characteristics 'happy' face, hepatomegaly, tracheal stenosis and tip-toeing gait (Scott et al., 2005). Specific mutations in Fibrillin-1 (*FBN1*) gene have been identified in AD, GD and WMS patients (Le Goff and Cormier-Daire, 2012). As opposed to Marfan syndrome, in which mutations of FBN1 are found throughout the entire length of the gene, mutations in *FBN1* that underlie the acromelic dysplasias are predominantly limited to the hot spot which is located in exon 41 and exon 42 (Sakai et al., 2016). Exons 41 and 42 encode the 5th 8-cysteine domain in fibrillin-1 (the heparin binding TGFβ-binding protein-like domain 5 (TB5) of fibrillin-1). *FBN1* is the only gene implicated in AD, which is inherited in autosomal dominant manner (Le Goff et al., 2011). In contrast, both GD and WMS are genetically heterogeneous. GD can be caused by mutations of two genes, namely A Distintegrin And Metalloproteinase with Thrombospondin repeats-like 2 gene (*ADAMTSL2*) and *FBN1*, with autosomal recessive and autosomal dominant inheritance, respectively (Le Goff et al., 2011). For WMS, three genes including *ADAMTS10, ADAMTS17* and *LTBP2* cause the autosomal recessive form, while *FBN1* causes the autosomal dominant form (Wang et al., 2014). *FBN1* mutations that cause WMS, AD and GD were shown to be associated with disrupted heparin binding to TB5 that maybe related to fibrillin biology and pathogenesis of

* Corresponding author.
E-mail address: Bhychung@hku.hk (B.H.-Y. Chung).
[1] co- first author.

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acromelic dysplasia. (Cain et al., 2012). Further studies were needed to investigate the dysregulation of FBN1/ADAMTS/TGFβ interrelationship that leads to such opposite phenotypes.

Acromelic dysplasia is an extremely rare condition and only six Chinese cases had been reported in literature (Wang et al., 2014). Here we report the clinical and genetic findings of another six patients from three Chinese families. The genotype-phenotype correlation of these patients is also studied.

2. Patient information

2.1. Family 1

2.1.1. Patient 1

Patient 1 was the second child of non-consanguineous Chinese couple. She was 9 years and 6 months. She was born by normal spontaneous delivery at 37 + 6 weeks. The perinatal history was unremarkable with birth weight of 2.925 kg (25th centile), body length of 48.5 cm (10–25th centile) and occipitofrontal circumference (OFC) of 33 cm (10th centile). She was referred to the genetic clinic for short stature at the age of 6 years and 7-month-old. She was then noted to have short limbs and short stature, with a height of 104.4 cm («3rd centile, Ht < -4SDS), arm span of 95 cm, and upper-to-lower segment ratio of 1.78. Her body weight was 22 kg (25th centile) and head circumference was 49.5 cm (10th centile). She also had narrow and upward slanting palpebral fissures, an impression of hypotelorism, mild mid-face hypoplasia, depressed nasal bridge, acromelic shortening of limbs and increased lumbar lordosis (Fig. 1a–b, 1d and 1g-h). She had normal development. There was no organomegaly and neurological examination was normal. A soft ejection systolic murmur was noted on cardiovascular examination and was confirmed by echocardiography to be due to mild dysplastic pulmonary valve with stenosis and a tiny PDA. Skeletal survey at the age of 8 years and 6 months showed shortened phalanges. A subsequent skeletal survey at the age of 9 years and 4 months showed left femoral head notching (Fig. 1c), left 2nd metacarpal notching, and shortened phalanges without cone shaped epiphysis. Bone age was estimated to be 6 years and 10 months at the chronological age of 8 years and 6 months. Other baseline investigations, including thyroid function test and IGF1 levels, were normal. She had strong family history of short stature on the paternal side. Her father and younger sister were similarly affected (Fig. 1a–b). Her mother was 145 cm in height. Apart from short stature, she also complained of progressive joint stiffness particularly involving the interphalangeal joints (Fig. 1e).

2.1.2. Patient 2

He was a 59 years-old Chinese gentleman and was the father of patient 1. He had similar short limbs and short stature with a height of 131.6 cm (Ht SDS -5.4) and body weight of 49.1 kg (3rd centile) (Fig. 1a–b). He had upper segment-to-lower segment ratio of 1.38. His arm span was 128 cm. He had an impression of hypotelorism, depressed nasal bridge, mild mid-face hypoplasia, and acromelic shortening of limbs. Cardiovascular examination and abdominal examination were unremarkable. He had hypertension on anti-hypertensive treatment. His intelligence was normal.

2.1.3. Patient 3

Patient 3 was the younger sister of patient 1. She was a 2 year and 10 months Chinese girl. She was born at 32 weeks of gestation by Caesarean section. Her birth weight was 1.87 kg (< 3rd centile). She first came to the genetic clinic at 5 months of age. At that time, her body length was 58.5 cm (< 3rd centile, Ht −2.02 SDS), body weight was 6.6 kg (25-50thcentile) and her head circumference was 39 cm (< 3rd centile). She had an impression of hypotelorism, mild mid-face hypoplasia, depressed nasal bridge and relatively small hands and feet (Fig. 1f and i). Cardiovascular, respiratory and abdominal examinations were normal. Her development was appropriate for age. At the age of 2 years and 9 months, her height was 80 cm («3rd centile, Ht −3.42 SDS) and body weight was 10.4 kg (10th centile). She had upper segment-to-lower segment ratio of 1.67.

2.2. Family 2

2.2.1. Patient 4

Patient 4 was a 7 years and 6 months old boy. He was first known to the pediatric service at the age of 6 years due to short stature. He was born at 32 weeks of gestation by Caesarean section. His parents are non-consanguineous. Antenatal history was unremarkable. His birth weight was 1.59 kg (< 3rd centile) which was small for gestational age. His body height was all along below the 3rd centile and progressively deviated with age. His upper segment to lower segment ratio was 1.44 at the age of 5 years and 3 months. His latest body height at 7 years and 6 months was 100.5 cm («3rd centile, Ht −3.84 SDS) and his latest body weight was 15.5 kg (< 3rd centile). His head circumference was at the 25thcentile all along. He also had mild speech delay. He had mid-face hypoplasia, depressed nasal bridge, thick lips and small hands and feet (Fig. 1k1-1k6). He experienced progressive limitation of extension at the wrists, elbows, shoulders and hand joints (Fig. 1j3). He had increased lumbar lordosis (Fig. 1j1-1j2). He had no tiptoeing gait. Echocardiogram showed mildly thickened mitral valve with mitral regurgitation. Abdominal ultrasound demonstrated mild hepatomegaly at the age of 6 years. Eye examination was normal. In view of his dropping height centile, endocrine investigations including thyroid function test, insulin-growth-factor 1 and clonidine stimulation test were performed with normal results. Skeletal survey showed mild J-shaped sella, cone shaped epiphysis and mild proximal tapering of the 2nd to 5thmetacarpal bones (Fig. 1l).

2.3. Family 3

2.3.1. Patient 5

He was a 36-year-old gentleman. His antenatal and perinatal histories were unremarkable. He had a history of short stature with disproportionate limb shortening since early childhood. He suffered from reduced growth velocity at the age of 5 years and was put on growth hormone for 6 months in Queen Mary Hospital in Hong Kong. He then migrated to Australia and defaulted the follow-up. His body height was 146.8 cm (14 cm < 3rd centile, Ht < −4 SDS) and sitting height was 85.6 cm (3–10th centile) (Fig. 1s). He was also noted to have a heart murmur. His face and head were normal (Fig. 1q). He had short toes (Fig. 1r). He had no joint stiffness, organomegaly, eye problem, and respiratory problems all along.

2.3.2. Patient 6

Patient 6 was the son of patient 5. He was a 2 years and 10 months boy when he was referred to pediatric endocrine clinic for short stature. He was born full term with birth weight of 3.25 kg and body length of 49.5 cm (10–25th centile). His antenatal history was unremarkable. He had normal development and was noted to have reduced growth velocity at 1 year and 6-month-old. His current body height was 81 cm («3rd centile, Ht SDS -3.65). His upper to lower segment ratio was 1.67. His body weight was 11 kg (3rd centile). His arm span was 72.5 cm. He had bulbous nose, broad nasal bridge, mid-face hypoplasia, relatively big head (Fig. 1m–o). His echocardiogram showed thickened mitral valve with short chordae and mild mitral regurgitation. His skeletal survey was normal. He had no eye problem, joint stiffness or organomegaly.

3. Results

In view of the disproportionate short stature, acromelic shortening and facial features, acromelic dysplasia was suspected. We performed