Bone 123 (2019) 18–22

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Case Report

KBG syndrome presenting with brachydactyly type E

Renata Libianto[a,b,c,*], Kathy HC Wu[d,e,f,g], Sophie Devery[d], John A Eisman[a,b,f,h], Jackie R Center[a,b,f,h]

[a] Bone Division, Garvan Institute of Medical Research, Sydney, Australia
[b] Department of Endocrinology, St Vincent's Hospital Sydney, Australia
[c] Department of Medicine, The University of Melbourne, Australia
[d] Clinical Genomics Unit, St Vincent's Hospital Sydney, Australia
[e] Discipline of Genetic Medicine, University of Sydney, Australia
[f] School of Medicine, UNSW, Sydney, Australia
[g] Genomics and Epigenetics Division, Garvan Institute of Medical Research, Sydney, Australia
[h] School of Medicine Sydney, University of Notre Dame, Australia

ARTICLE INFO

Keywords:
KBG syndrome
ANKRD11 gene
Skeletal disorder
Brachydactyly type E

ABSTRACT

We report the case of a young woman who presented at age 10 years with height on the tenth centile, brachydactyly type E and mild developmental delay. Biochemistry and hormonal profiles were normal. Differential diagnoses considered included Albright hereditary osteodystrophy without hormone resistance (a.k.a pseudopseudohypoparathyroidism), 2q37 microdeletion syndrome and acrodysostosis. She had a normal karyotype and normal FISH of 2q37. Whole genome sequencing (WGS) identified a mutation in the *ANKRD11* gene associated with KBG syndrome. We review the clinical features of the genetic syndromes considered, and suggest KBG syndrome be considered in patients presenting with syndromic brachydactyly type E, especially if short stature and developmental delay are also present.

1. Case

The patient initially presented at age 10 years with brachydactyly and mild developmental delay. Investigations at the time revealed general shortening of metacarpals and metatarsals, especially of the 4th and 5th digits, as well as advanced bone age (12 years at chronological age of 10.5 years). No specific diagnosis was made and she was lost to follow-up.

She represented at age 24 years to an Endocrinologist and subsequently to a Clinical Geneticist, due to ongoing uncertainty regarding the diagnosis and a renewed interest by the patient. Her medical history was reviewed and included a clavicular fracture after falling off a mattress as a toddler; childhood jaw surgery to correct mandibular protrusion; lower limb length discrepancy requiring the use of orthotics since late-teens, and depression. She underwent menarche at the age of 10 years and continued to have regular menstrual cycles. She was taking citalopram for anxiety/depression and an oral contraceptive pill for dysmenorrhoea.

She was born after a normal pregnancy and delivery, with birth weight, length and head circumference all within the average range. She was delayed in her developmental milestones and required extra support in a mainstream school for specific learning difficulties. She completed high school and went on to obtain a nursing certificate.

Her parents are non-consanguineous and of Caucasian background. An older sister had a short distal phalanx of the thumb and a repaired atrial septal defect. Two other siblings are apparently normal. There is a strong family history of osteoporosis affecting her mother, two maternal aunts and maternal grandmother. On the paternal side, her father, two uncles and a grandfather all had a history of learning difficulties/dyslexia.

On examination, she had a height of 155 cm (10th percentile) and body mass index of 30.8 kg/m^2. Several distinctive facial features were identified including a round face, low anterior hairline, a short philtrum, unusual-looking ears, and prominent upper central incisors (Fig. 1). She had noticeably short 4th and 5th fingers and toes (Fig. 2). She also had leg length difference with her right femur being 1 cm shorter than the left. Two faint, irregularly shaped café-au-lait macules were noted on her right inner arm and back.

Investigations revealed a low 25-hydroxy-vitamin D level of 22 nmol/L and she was advised to take vitamin D supplements. Other biochemistry and hormonal profiles were normal (Table 1). Her bone mineral density was within normal limits. X-ray confirmed variably

* Corresponding author at: Bone Division, Garvan Institute of Medical Research, 384 Victoria St, Darlinghurst, NSW 2010, Australia.
E-mail address: renata.libianto@monash.edu (R. Libianto).

https://doi.org/10.1016/j.bone.2019.03.012
Received 19 December 2018; Received in revised form 5 March 2019; Accepted 11 March 2019
Available online 12 March 2019

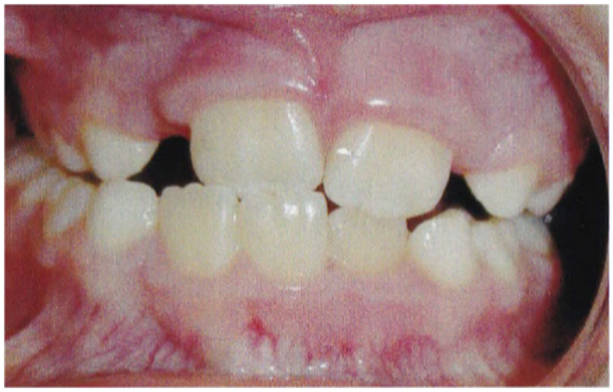

Fig. 1. Photograph taken at age 8.5 years revealed macrodontia of the upper central incisors.

shortened fifth metacarpal and fourth metatarsal bones bilaterally with no subcutaneous calcifications (Fig. 3). Apart from the initial suggestion of advanced bone age at a chronological age of 10 years, subsequent skeletal survey performed at age 12 years was reported to be normal, with no ectopic ossifications. She had a normal karyotype and normal FISH of 2q37.2 chromosomal region.

Her pattern of bony anomalies fell into the classification of Brachydactyly Type E and the syndromic causes of which, in association with short stature and developmental delay, were considered and summarised in Table 2. Due to the wide differentials and the lack of a commercial gene panel that would cover all differential diagnoses, whole genome sequencing (WGS) was arranged. WGS with genome-wide analysis identified a heterozygous frameshift mutation in the *ANKRD11* gene (c.3045del, p.(Asp1016Ilefs*302)). This was confirmed to be a de novo mutation, as neither parent carried the mutation. This variant is associated with KBG syndrome (OMIM #148050) and has been classified as a pathogenic (class 5) variant based on the ACMG criteria [1]. The patient provided consent for the publication of her case.

2. Discussion

This young woman presented with brachydactyly type E, distinctive facies, leg length discrepancy, and mild intellectual impairment. The skeletal anomalies provided important clues, based on which the differential diagnoses were derived.

Table 1
Biochemistry and hormonal profiles.

	Result	Reference range
Serum calcium	2.51 mmol/L	2.10–2.60
Serum phosphorus	0.75 mmol/L	0.75–1.50
Thyroid stimulating hormone	1.8 mIU/L	0.5–4.0
Intact parathyroid hormone	3.1 pmol/L	1.5–9.9
25(OH) vitamin D	22 nmol/L	51–200
Type 1 procollagen (P1NP)	44 ng/mL	15–90
Prolactin	145 mIU/L	40–570
Cortisol (AM)	254 nmol/L	AM 120–620, PM 100–400
Adrenocorticotrophic hormone	5.0 pmol/L	< 11
Growth hormone	2.7 mIU/L	< 18
Insulin-like growth factor-1	30 nmol/L	13–41

Brachydactyly is classified into several types, depending on the affected digit and the topography of the shortened bone within the digit [2]. Based on Temtamy's classification in 1978, our patient demonstrated brachydactyly type E, which is characterised by shortened metacarpals +/− metatarsals. Brachydactyly type E may be an isolated occurrence, or could be part of a syndrome such as Turner syndrome, 2q37 microdeletion syndrome (a.k.a brachydactyly with mental retardation syndrome), or Albright Hereditary Osteodystrophy (AHO) with/without hormone resistance [3]. Pseudopseudohypoparathyroidism (PPHP) was considered based on her AHO features, including short stature, shortened 4th/5th metacarpals/metatarsals, a round face, and mild intellectual impairment, with absence of hormone resistance. Other less likely differential diagnoses were considered, including acrodysostosis type 2, due to its overlapping features of short stature, elevated body mass index, brachydactyly (albeit being more generalised in acrodysostosis), advanced bone age, and developmental delay. McCune-Albright syndrome was considered in light of the café-au-lait macules albeit in atypical distribution, and lower limb asymmetry, the latter thought to be reminiscent of somatic mosaicism that is known to be the pathogenic mechanism of this condition. Although our patient does not have the characteristic fibrous dysplasia, the presentation of McCune-Albright syndrome can vary widely, depending on the stage at which post-zygotic mutations occur [4]. Table 2 summarises the shared features of these conditions.

Turner syndrome and 2q37 microdeletion syndrome were excluded

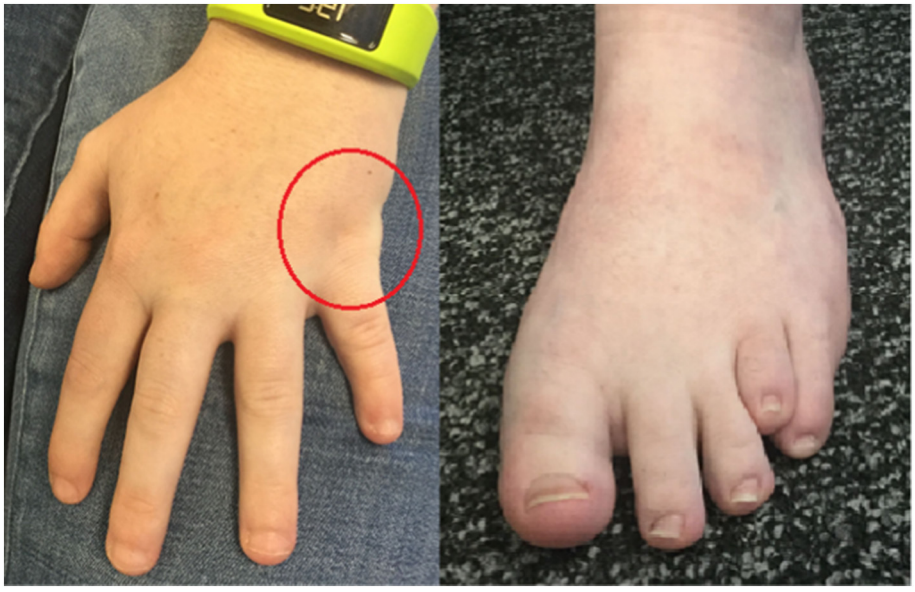

Fig. 2. Brachydactyly, with a short left 5th metacarpal and a short left 4th metatarsal. A “dimple” sign can be seen due to the shortened metacarpal.

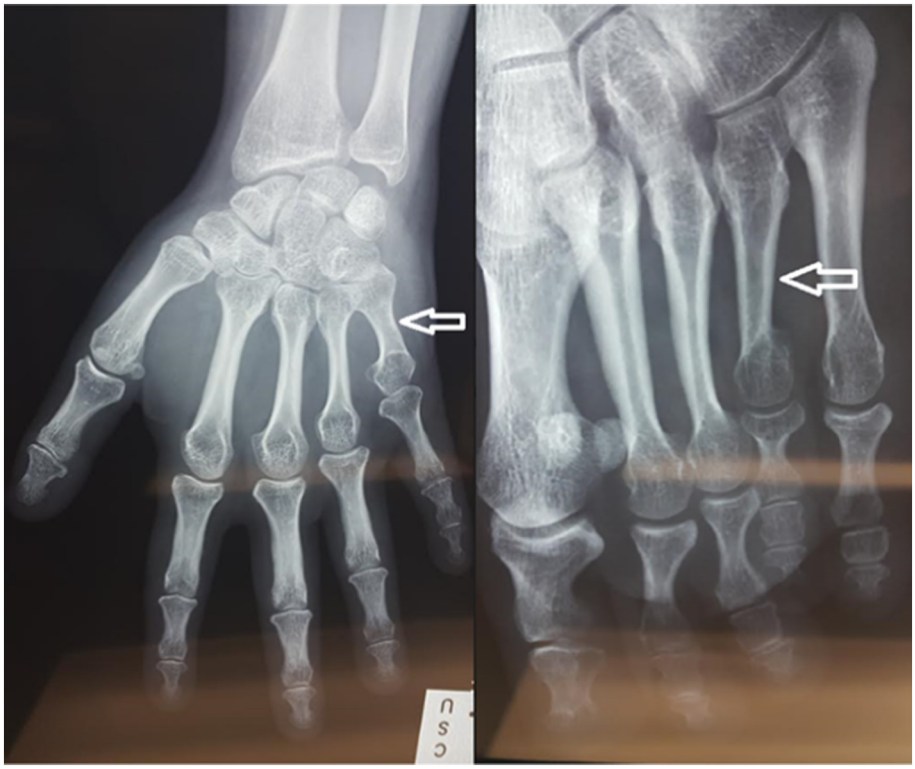

Fig. 3. X-ray showing the shortened metacarpal and metatarsal bones.

based on the normal karyotype and normal 2q37.2 FISH results, respectively. WGS did not identify any clinically significant variant in the *GNAS, PRKAR1A*, or *PDE4D* genes. The patient was found to have a heterozygous loss-of-function mutation in exon 10 of the *ANKRD11* gene, associated with KBG syndrome.

ANKRD11 gene is located on chromosome 16 and encodes for the protein Ankyrin repeat domain-containing protein 11, which functions as a nuclear co-regulator and regulates neurogenesis in the embryonic brain [5]. It recruits histone deacetylases (HDACs), resulting in the inhibition of ligand-dependent transcriptional activation [6]. One of these HDACs, HDAC4, regulates genes involved in bone, muscle, and neurological development. Indeed, haploinsufficiency of HDAC4 has been identified to be the critical mechanism that determines the AHO-like phenotype of 2q37 microdeletion syndrome [7]. The association between *ANKRD11* and HDAC4 may explain some of the shared features between 2q37 microdeletion syndrome and KBG syndrome, such as short stature, brachydactyly, and developmental delay.

KBG syndrome is named after the initials of the last names of three original families reported in 1975. There have been over 100 patients reported in the literature, but the actual prevalence is not known, and perhaps under-reported because of the variable presentation that can often be mild [8]. It is an autosomal dominant condition characterised by short-stature (height < 3rd percentile), macrodontia of the central upper incisors, distinctive facial features and learning difficulties [9]. In a series of 32 KBG patients from 27 families, the most universal findings were speech delay and learning difficulties [10]. Macrodontia of the upper central incisors was seen in 85%, and 43% had seizures with onset varying between infancy and mid-teens [10]. Short stature (< 3rd percentile) was a feature in 40% of the patients and brachydactyly, especially of the 5th finger with striking clinodactyly, were the most consistent features. Delayed bone age was also a feature of KBG syndrome. Since the initial clinical description in 1975 and the subsequent identification of the *ANKRD11* gene in association with KBG syndrome in 2011 [12], several diagnostic criteria have been proposed [13,14] and subsequent revisions to the criteria have been suggested [10,15].

The diagnosis of KBG syndrome was unexpected in our patient, as her facial phenotype was different, and she had advanced, rather than delayed, bone age. In retrospect, this diagnosis explains many of her other features, including a shorter height (on the 10th percentile), brachydactyly, prominent upper central incisors which was retrospectively appreciated, and mild learning difficulties. Indeed, a recent Australian study of 18 KBG syndrome cases (16 with confirmed *ANKRD11* gene mutation), whilst reporting a lower incidence of seizures (16.7%), supported the removal of the bone age criteria, and proposed potential revisions to account for stature which can range from short (< 10th percentile) to normal stature [15]. Furthermore, it has been suggested that KBG syndrome is more common than is recognised, as adult relatives are increasingly diagnosed retrospectively after their children's diagnosis, especially as the use of whole exome/genome sequencing becomes more prevalent.

3. Conclusion

We present the case of a young woman with brachydactyly type E and other features resembling AHO. WGS, that excluded syndromes associated with AHO, identified a de novo heterozygous pathogenic mutation in the *ANKRD11* gene, associated with KBG syndrome. Had targeted genetic testing been undertaken, the definitive diagnosis may not have been reached. KBG syndrome is likely to be more common than is recognised due to the variable and often mild phenotype. We suggest that KBG syndrome should be considered in the differential diagnosis of syndromic brachydactyly type E, especially if short stature and developmental delay are also present.

Conflict of interest

The authors declare no conflict of interest.

Table 2
Differential diagnoses of syndromes associated with brachydactyly type E.

	Brachydactyly	Short stature	Obesity	Developmental delay	Facial dysmorphism	Bone age	Hormone resistance	Other features	Genetic basis
Patient	+ (type E)	10th centile (postnatal onset)	+	+ (mild)	Round facies, short philtrum, low anterior hairline	Advanced/ normal	−	Leg length discrepancy, two faint café-au-lait macules	
KBG syndrome	+ (type E reported); more consistently 5th finger clinodactyly	+ (postnatal onset)	−	+ (mild-moderate)	Triangular face, long philtrum, hypertelorism, low anterior hairline, macrodontia	Delayed	−	Macrodontia of the upper central incisor, congenital cardiac anomaly	Heterozygous LOF mutation in *ANKRD11* gene
PPHP [11]	+ (type E)	+ (prenatal onset)	+ (less common)	+ (moderate)	Round facies	Advanced	−	Subcutaneous ossification	LOF mutation in paternal *GNAS* gene
Acrodysostosis type 2	+ (generalised)	+	+ (variable)	+ (mild-moderate)	Maxillary and nasal hypoplasia, hypertelorism, low-set ears, epicanthic folds	Advanced	+ (type 1) −/mild (type 2)	Cone-shaped epiphyses, vertebral anomaly	Heterozygous GOF mutation in *PRKAR1A* (type 1); or missense mutation in *PDE4D* (type 2)
2q37 microdeletion syndrome	+ (type E)	+	+	+ (± autism)	Round facies, sparse hair/ eyebrow, upslanting palpebral fissures, midface hypoplasia	N/A	−	Hypotonia, joint hypermobility, scoliosis	Heterozygous deletion of chromosomal region 2q37 involving *HDAC4* gene
Turner syndrome	+	+	+	±	Posteriorly-rotated ears, webbed neck, low posterior hairline	Normal	−	Primary hypogonadism, congenital cardiac defect, skeletal/renal anomalies	Chromosomal aneuploidy 45,XO
McCune Albright syndrome	−	N/A	N/A	−	Craniofacial expansile deformities	N/A	−	Characteristic café-au-lait macules that respect the midline or follow Lines of Blaschko, precocious puberty, fibrous dysplasia, scoliosis, excessive production of endocrine hormones	Postzygotic somatic GOF mutation in *GNAS* gene

LOF – loss of function; GOF – gain of function.

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