Novel Insights from Clinical Practice

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Novel Clinical and Radiological Findings in a Family with Autosomal Recessive Omodysplasia

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Established Facts

- The skeletal hallmarks in autosomal recessive omodysplasia comprise severe shortening and distal tapering of the humeri and femora resulting in a club-like appearance and proximal radioulnar diastasis.

Novel Insights

- We identified a recurrent and not previously described type of abnormal patterning in all long bones.

Keywords
GPC6 · Omodysplasia · Radiological feature · Recessive omodysplasia · Skeletal dysplasia

Abstract
Autosomal recessive omodysplasia (*GPC6*-related) is a rare short-limb skeletal dysplasia caused by biallelic mutations in the *GPC6* gene. Affected individuals manifest with rhizomelic short stature, decreased mobility of elbow and knee joints as well as craniofacial anomalies. Both upper and lower limbs are severely affected. These manifestations contrast with normal height and limb shortening restricted to the arms in autosomal dominant omodysplasia (*FZD2*-related). Here, we report 2 affected brothers of Pakistani descent from Denmark with *GPC6*-related omodysplasia, aiming to highlight the clinical and radiological findings. A homozygous deletion of exon 6 in the *GPC6* gene was detected. The pathognomonic radiological findings were distally tapered humeri and femora as well as severe proximal radioulnar diastasis. On close observations, we identified a recurrent and not previously described type of abnormal patterning in all long bones.

Omodysplasia is a rare short-limb skeletal dysplasia with predominant shortening of the upper arms. It was first applied to a series of 5 patients with similar phenotypes by Maroteaux et al. [1989]. The authors also mentioned previous cases described by Barrow and Fitzsim-

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mons, [1984] and Viljoen et al. [1987]. Later, omodysplasia was divided into an autosomal recessive (AR) form (*GPC6*-related, OMIM 258315) and an autosomal dominant (AD) form (*FZD2*-related, OMIM 164745). Both forms share common craniofacial dysmorphism as well as common skeletal abnormalities of the upper arms. However, AR omodysplasia manifests with severe rhizomelic short stature and both upper and lower limb involvement, while AD omodysplasia presents with normal height or mild short stature and only the upper limb involvement with distinctively associated shortening of the first metacarpals [Borochowitz et al., 1995; Campos-Xavier et al., 2009]. Recently, however, some experts prefer to put *FZD2*-related AD omodysplasia into a group of Robinow syndrome and to apply the term omodysplasia only to *GPC6*-related AR omodysplasia.

The skeletal hallmarks in AR omodysplasia comprise severe congenital shortening and distal tapering of the humeri and femora, resulting in a club-like appearance and proximal radioulnar diastasis. The elbow and knee joints are restricted. The facial features include frontal bossing, frontal capillary hemangiomas, low-set ears, a flat nasal bridge, anteverted nostrils, and a long prominent philtrum. There have been few reports on associated congenital heart defects, pterygia, craniosynostosis, cryptorchidism, hernias, and cognitive delay [Barrow and Fitzsimmons, 1984; Maroteaux et al., 1989; Borochowitz et al., 1991; Baxova et al., 1994; al Gazali and Abou al-Asaad, 1995; Stoll et al., 1995; Masel et al., 1998; Elcioglu et al., 2004; Tan et al., 2005]. To date, approximately 25 cases of AR omodysplasia are known [Maroteaux et al., 1989; al Gazali and Abou al-Asaad, 1995; Borochowitz et al., 1995; Stoll et al., 1995; Masel et al., 1998; Elcioglu et al., 2004; Tan et al., 2005; Albano et al., 2007; Campos-Xavier et al., 2009]; however, all patients had been described prior to the causal gene discovery [Campos-Xavier et al., 2009]. We report on 2 siblings with AR omodysplasia caused by a homozygous deletion of exon 6 in *GPC6*. They are the first cases to be published after the clarification of the molecular basis. The aim of this study is to highlight the clinical and radiological findings of these patients.

Case Presentation

The 2 brothers were born to consanguineous parents (cousins) from Pakistan. The family history was not noteworthy except for the consanguinity. The first child of the couple is a healthy girl. The proband is the second child and was diagnosed clinically with omodysplasia after birth. During the second pregnancy, a routine prenatal ultrasound at 21 weeks' gestation revealed severe rhizomelic shortening of the limbs. The parents were offered a prenatal chromosomal microarray analysis, direct testing for potential mutation in the *FGFR3* gene and a gene panel for osteogenesis imperfecta, all of which were performed on a chorionic villus sampling, and no pathogenic abnormalities were identified. The parents did not want an abortion, and at 41 weeks' gestation, the mother gave birth to a boy. Birth weight was 3,300 g (29th centile) and his birth length was 45 cm (<0.4th centile). His facial features included frontal bossing, a flat nasal bridge, low-set ears, anteverted nostrils, and a long philtrum, but no frontal capillary hemangioma (parental permission to publish pictures was not available). Our patient did not have short first metacarpal bones, which is a feature seen in AD omodysplasia. He had bilateral cryptorchidism that was eventually corrected surgically at the age of 12 months. He showed no signs of congenital heart defects or craniosynostosis. He learned to sit at the age of 7 months and walk unaided at the age of 15 months. He is currently 3½ years old and shows no signs of intellectual disability or developmental delay. His height is 74 cm (<0.4th centile) and the weight is 10 kg (<0.4th centile). Joint movement of the elbow and knee was restricted.

A skeletal survey was performed shortly after birth and at the age of 3 years. The radiological examination in the neonatal period

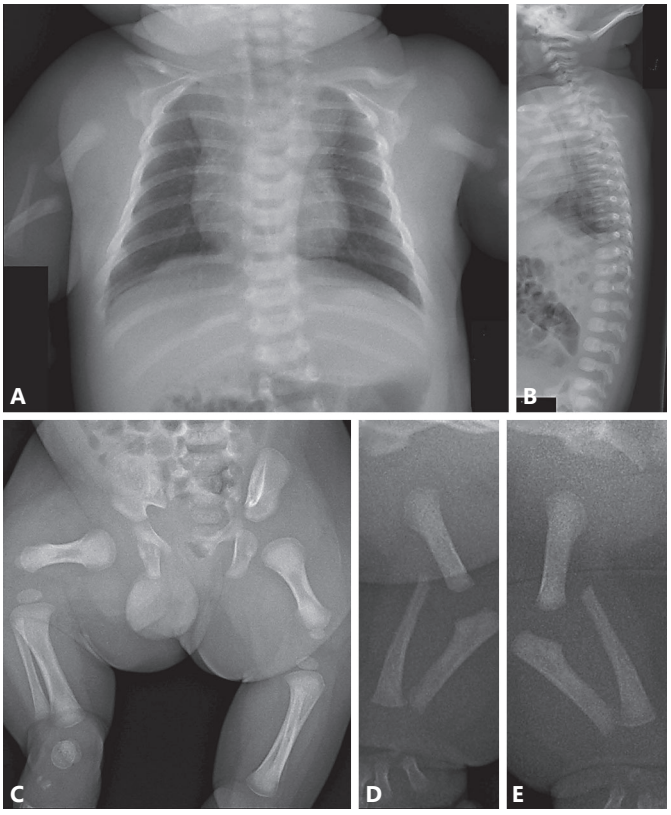

Fig. 1. A–E Skeletal survey of patient 1 after birth showing characteristic features of AR omodysplasia. Features include a broad and short diaphysis and either a distal or a proximal tapering of all long bones. The spine and pelvis were unremarkable (**C**).

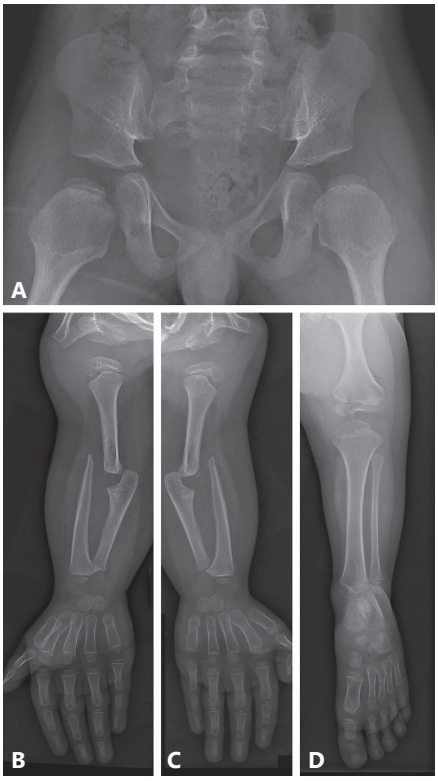

Fig. 2. A–D Skeletal survey of patient 1 at 3 years of age showing the same radiological pattern as that previously seen after birth.

showed short and broad diaphysis in all long bones. The humeri and femora were most severely affected, the ulnae and radii were lesser affected, and the tibiae and fibulae were least affected. The long bones were club shaped varying in appearance due to broadening of one bone end and tapering of the other. The humeri and femora showed distal tapering, the radii and fibulae proximal tapering, while the ulnae and tibiae showed distal tapering. Severe radioulnar diastasis was seen. The proximal tibial epiphyses were larger than normally seen. The acrominal processes of the scapulae were prominent, while the scapular wings were small. The spine, pelvis, hands, and feet were unremarkable (Fig. 1). The follow-up skeletal survey performed at the age of 3 years showed the same radiological pattern as that previously seen (Fig. 2). It was noticeable that the epiphyses of the proximal humeri, proximal femora, and distal femora were flat, while those of the proximal tibiae and distal fibulae were not. The iliac wings were somewhat small along with mild shortening of the greater sciatic notches.

A postnatal chromosomal microarray analysis of a peripheral blood sample of the patient identified an approximately 6-kb homozygous intragenic deletion of exon 6 in *GPC6* (NM_005708.5): arr[hg19] 13q31.3(94953093_94958981)×0. This confirmed the diagnosis of *GPC6*-related AR omodysplasia. Chromosomal microarray was performed using the Agilent SurePrint G3 Human CGH Microarray kit 2×400K (Agilent Technologies, Santa Clara, CA, USA) as previously described [Schejbel et al., 2011].

The second boy (patient 2) with AR dysplasia was born at 39 weeks' gestation. Birth weight was 3,500 g (50th centile), and his

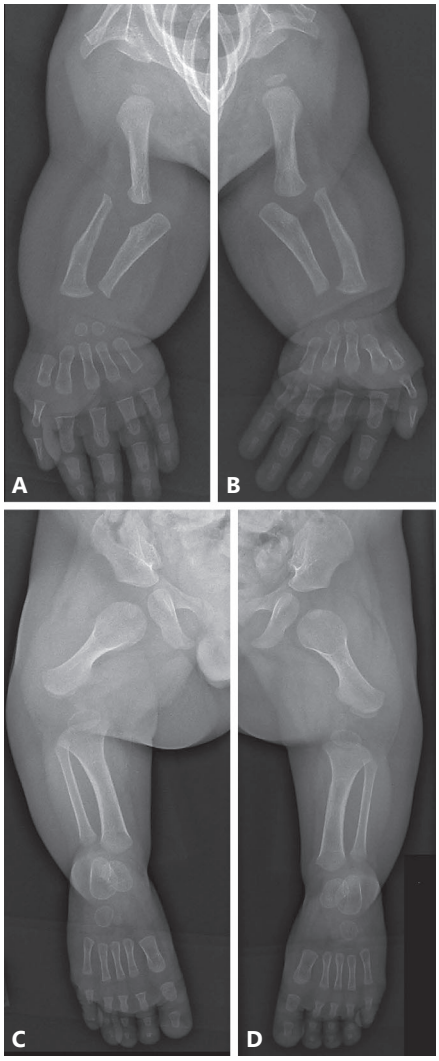

Fig. 3. A–D Skeletal survey of patient 2 at 6 months of age showing the same pattern as that of patient 1. The proximal tibia showed megaepiphyses at this age (**C**, **D**).

birth length was 47 cm (2nd–9th centile). Prenatal ultrasound had revealed severe short limbs. His facial features also included frontal bossing, a flat nasal bridge, low-set ears, anteverted nostrils, and a long philtrum, but no frontal capillary hemangioma. He had unilateral cryptorchidism that has not yet been operated. Like his brother, he showed no signs of congenital heart defects or craniosynostosis. He is currently 12 months old and has a minor developmental delay in gross motor achievements. His height is 55 cm (<0.4th centile) and he weighs 5 kg (<0.4th centile). The elbow and knee joint movement was restricted. A skeletal survey performed at the age of 6 months showed the same pattern as that of patient 1. The proximal tibia showed megaepiphyses at this age (Fig. 3). Postnatal chromosomal microarray analysis of patient 2 showed the same homozygous intragenic deletion in the *GPC6* gene as in the older brother (clinical and radiological findings summarized in Table 1).

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Table 1. Clinical and radiological manifestations in novel and previously published cases with autosomal recessive omodysplasia (*GPC6*-related)

Case No.	Patient												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Reference	Barrow and Fitzsimmons [1984]	Viljoen et al. [1987]	Maroteaux et al. [1989]		Borochowitz et al. [1991] Campos-Xavier et al. [2009]	Borochowitz et al. [1991] Campos-Xavier et al. [2009]	Borochowitz et al. [1991]	Borochowitz et al. [1991]	Kiss et al. [1991]	Gugliantini et al. [1991]	Di Lucca and Mitchell [2001] Campos-Xavier et al. [2009]	Baxova et al. [1994] Campos-Xavier et al. [2009]	Baxova et al. [1994] Campos-Xavier et al. [2009]
Case No. of original report	NA	NA	4	5	1	2	3	4	NA	NA	4	1	2
Case No. by Campos-Xavier et al. [2009]	–	–	–	–	7	8	–	–	–	–	4	1	2
GPC6 variants detected	NA	NA	NA	NA	Deletion (exon 3)	Deletion (exon 3)	NA	NA	NA	NA	Deletion (exon 5+6)	c.778delC (p.Leu260PhefsX4)	c.778delC (p.Leu260PhefsX4)
Parental consanguinity	NA	NA	NA	NA	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes
Sex	M	M	M	M	M	M	F	M	M	M	F	F	M
Age	Newborn	16 years	1.2 years	Newborn	1 year	1 year	Newborn	0.9 years	0.1 years	0.5 years	NA	1.9 years	Unknown
Clinical features													
Craniofacial dysmorphism	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes
Facial hemangioma	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes
Cryptorchidism	Yes	Yes	Yes	NA	Yes	Yes	No	Yes	NA	Yes	NA	No	NA
Cognitive delay	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	No	NA	Yes
Motor delay	NA	NA	NA	NA	Yes	Yes	NA	Yes	NA	NA	Yes	Yes	NA
Skeletal features													
Short, distally tapered femora	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes
Short, distally tapered humeri	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		NA	Yes	Yes
Dislocated elbows	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes
Short radii and ulnae	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	NA	NA	Yes	Yes
Short tibiae and fibulae	Yes	No	NA	NA	Yes	Yes	Yes	NA	Yes	NA	NA	Yes	Yes
Limited extension elbows and knees	NA	NA	Yes	NA	NA	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes

Table 1 (continued)

Case No.	Patient													
	14	15	16	17	18	19	20	21	22	23	24	25	1	2
Reference	al Gazali and Abou al-Asaad [1995]	Stoll et al. [1995]	Masel et al. [1998]		Elçioglu et al. [2004]		Elçioglu et al. [2004] Campos-Xavier et al. [2009]	Elçioglu et al. [2004] Campos-Xavier et al. [2009]	Elçioglu et al. [2004]	Tan et al. [2005] Campos-Xavier et al. [2009]	Albano et al. [2007]	Campos-Xavier et al. [2009]	Our patient	Our patient
Case No. of original report	NA	NA	1	3	1	2	3	4	5	3	NA	9	1	2
Case No. by Campos-Xavier et al. [2009]	–	–	–	–	–	–	5	6	–	3	–	9	–	–
GPC6 variants detected	NA	NA	NA	NA	NA	NA	Duplication (exon 4)	Duplication (exon 4)	NA	Deletion (exon 4)	NA	Deletion (exon 3)	Deletion (exon 6)	Deletion (exon 6)
Parental consanguinity	Yes	Yes	NA	Yes	Yes	No	No	No	NA	Yes	Yes	NA	Yes	Yes
Sex	M	F	M	F	F	M	M	M	F	F	M	M	M	M
Age	3 years	3 years	0.1 years	1.9 years	2.5 years	4 years	15 years	9 years	Newborn	NA	9 years	5 years	3.5 years	1 years
Clinical features														
Craniofacial dysmorphism	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Facial hemangioma	Yes	Yes	No	Yes	Yes	No	No	No	Yes	NA	No	Yes	Yes	Yes
Cryptorchidism	Yes	No	NA	No	No	Yes	Yes	Yes	No	No	NA	No	Yes	Yes
Cognitive delay	NA	NA	NA	NA	Yes	NA	NA	Yes	NA	No	No	No	No	No
Motor delay	NA	NA	NA	NA	Yes	NA	NA	NA	NA	Yes	No	Yes	No	Yes
Skeletal features														
Short, distally tapered femora	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Short, distally tapered humeri	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dislocated elbows	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Short radii and ulnae	Yes	Yes	NA	Yes	Yes	NA	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes
Short tibiae and fibulae	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Limited extension elbows and knees	Yes	NA	NA	NA	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes

GPC6, heparan-sulfate proteoglycan Gly; NA, not available.

Discussion

AR omodysplasia has been mapped to chromosome 13, and loss-of-function mutations in the *GPC6* gene (OMIM 604404) encoding glypican 6 (GPC6) were discovered in 2009 [Campos-Xavier et al., 2009]. So far, only genomic rearrangements affecting exons 3, 4, and 6, resulting in premature termination codons and a single base substitution (c.700C>T) leading to a nonsense mutation (p.Arg234*) in exon 3, have been shown to cause AR omodysplasia [Campos-Xavier et al., 2009]. A homozygous intragenic deletion of exon 6 as seen in our patients has not been described before. While *FZD2* is expressed in the developing face and skeleton and encodes the FRIZZLED2 protein that acts as a Wnt receptor, *GPC6* is both expressed in the developing skeleton and neurons [Allen et al., 2012; Saal et al., 2015]. In vitro studies have shown that *GPC6* stimulates the activity of various morphogens/growth factors, including Hedgehogs acting on bone growth [Capurro et al., 2017] *GPC6* is also expressed by astrocytes in vivo in the developing CNS, particularly in the cerebellum [Allen et al., 2012]. Allen et al. [2012] showed that GPC6 acts as astrocyte-secreted signals sufficient to induce functional synapses between purified retinal ganglion cell neurons. They also showed that depletion of these molecules from astrocyte-conditioned medium significantly reduces its ability to induce postsynaptic activity [Allen et al., 2012]. This potentially explains why a subset of patients with AR omodysplasia have been diagnosed with developmental delay [Nagasaki et al., 2018], while patients with AD omodysplasia tend to have a normal cognitive development. However, AD omodysplasia with intellectual disability has been reported by Warren et al. [2018]. In contrary, Campos-Xavier et al. [2009] argued that the presence of mental retardation could be a potential additional effect of consanguinity in these patients. While patient 1 did not show any signs of developmental delay, his younger brother showed minor developmental delay. These observations may suggest an incomplete penetrance of neurodevelopmental symptoms in *GPC6*-related AR omodysplasia.

The constellation of distinctive craniofacial dysmorphism, severe short stature, rhizomelic shortening of the limbs and restriction of the elbow and knee joints seen in our patients recapitulated the phenotypic spectrum of AR omodysplasia. The skeletal phenotype of AR omodysplasia was described in detail by Elcioglu et al. [2004]. They reported 5 novel patients, reviewed the literature on the disorder, and emphasized that the skeletal anomalies are confined to the limbs, while the skull, spine, thorax, and the bones of the hand and feet are normal [Elcioglu et al., 2004]. They also mentioned age-dependent evolution of the skeletal changes, i.e., the long bones show much better modeling and less severe shortening with age. The skeletal manifestations of the present cases mostly recapitulated those reported by Elcioglu et al. [2004]; yet, our siblings did not show flat tibial epiphyses, but large proximal tibial epiphyses in infancy, contrasting with their description (for an overview of the radiological findings in patients with AR omodysplasia, see Table 1).

The most striking skeletal change of AR omodysplasia is club-shaped humeri and femora due to hypoplasia of their distal ends and broadening of the proximal ends. Meticulous radiological observations disclosed that other long bones also have a club-like appearance, but to a lesser degree. This distinctive appearance probably represents abnormal pattern formation of the long bones at the early gestational age. Elcioglu et al. [2004] brought attention to the fact that club-like humeri and femora occur in *FLNB*-related skeletal dysplasias, including Larsen syndrome and atelosteogenesis type 1 and 3. Distal tapering of the humeri and femora can be seen in *DTDST*-related skeletal dysplasias, including diastrophic dysplasia and atelosteogenesis type 2. The phenotypic similarities among AR omodyplasia, *FLNB*-associated dysplasias, and *DTDST*-associated dysplasias may suggest that glypican 6, filamin B, and sulfated proteoglycans interact with each other at the early patterning of the long bones.

Finally, to the best of our knowledge, only 2 previous cases of prenatally diagnosed AR omodysplasia have been reported in the literature: Borochowitz et al. [1991] reported a prenatal diagnosis of AR omodysplasia made on an ultrasound scan at 17 week's gestation demonstrating short limbs, predominantly humeri and femora, dislocated elbows, and a normal skull and spine, and Tan et al. [2005] reported the earliest clinically diagnosed case of AR omodysplasia at 13 weeks and 3 days. The specific findings at this gestational age were a thickened nuchal translucency (6.0 mm) with abnormal long bones. Subsequent ultrasounds confirmed these findings, in addition to pronounced edema around the upper trunk [Tan et al., 2005]. In our case, bilateral rhizomelic shortening of the long bones in both pregnancies was helpful to raise a suspicion of skeletal dysplasia. However, due to maternal obesity in both pregnancies, we were unable to make the prenatal detection of proximal radial head dislocation and to delineate the facial profile in detail. With knowledge of the characteristic features of AR omodysplasia outlined in this study, the ultrasonographer may have

made a definitive prenatal diagnosis, if the circumstances for the ultrasound examination had been optimal.

Acknowledgment

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Statement of Ethics

Informed consent for genetic analysis was obtained from the family in compliance with the national ethics regulation.

Diclosure Statement

The authors have no conflicts of interest to disclose.

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