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Robinow syndrome: a diagnosis at the fingertips

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Short clinical summary

A 1-month-old full-term female was transferred to our facility from an outside hospital for further evaluation. Pregnancy was complicated by maternal diabetes, and birth weight was 4.1 kg. She was prenatally diagnosed with hypoplastic left heart syndrome and omphalocele. Postnatally, she was found to have cleft lip and palate, two natal teeth, choanal atresia, bilateral clubfeet, and imperforate anus. Physical examination was notable for short limbs and broad, apparently duplicated distal phalanx of digits 1–2 of both hands (Fig. 1). Her facial dys-morphology included frontal bossing, malar hypoplasia, flat nasal bridge, hypertelorism, anteverted nares, and full cheeks (Fig. 2). Imaging was notable for normal-appearing uterus but no gonadal tissue on pelvic ultra-sound, as well as bifid distal phalanges of the bilateral first and second digits on hand radiographs (Fig. 3). Of her various dysmorphic features, we found her duplicated distal phalanges to be the most unique and striking feature, and searched the literature extensively for reports of similar cases, but found none at the time. Her clinical course was marked by cardiorespiratory failure requiring chronic mechanical ventilation, and she ultimately underwent tracheostomy. Throughout her life, she was dependent on tube feeding, ultimately requiring gastrostomy placement. The course was further complicated by pulmonary hypertension and apnea. She expired at 7 months of age because of apnea of unclear etiology. Family history was unremarkable.

Keywords

Bifid distal phalanges; Hypertelorism; Malar hypoplasia; Frontal bossing; Anteverted nares; Wide nasal bridge; Flat nasal bridge; Cleft lip and palate

Investigations

Initial genetic testing, including microarray, FISH 22q11, and *CHD7* sequencing, were normal. Initial results of whole exome sequencing revealed heterozygous inherited variants in *DYNC2H1*, *MKS1*, and *WDR35*. Homozygous or compound heterozygous pathogenic variants in these genes cause short rib polydactyly syndrome type III, Bardet-Biedl syndrome type 13, and cranioectodermal dysplasia type 2, respectively. None of these phenotypes matched our patient. Exome reanalysis was performed in 2017, and revealed a de novo 1-bp deletion in *DVL3*: c.1592delC. As reported by White *et al.* (2016), frameshift

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Conflicts of interest

There are no conflicts of interest.

variants such as this one, located in the penultimate exon of *DVL3*, are a cause of autosomal dominant Robinow syndrome.

Discussion

Robinow syndrome is a genetically heterogeneous disorder characterized by facial dysmorphisms, genital hypoplasia, and mesomelic limb shortening. The auto-somal recessive form is caused by biallelic loss-of-function variants in *ROR2*. The autosomal dominant form has three known etiologies: hypomorphic mutations in *WNT5A*, and frameshift mutations in the penultimate exon of *DVLI*, or the penultimate or last exon of *DVL3*.

Characteristic facial features include prominent eyes, flat nasal bridge, and frontal bossing. In addition, affected individuals can exhibit hypertelorism, short noses, ante-verted nares, cleft lip and palate, dental anomalies, and malar hypoplasia. Other associated malformations include syndactyly, broad thumb and first toe, heart defects, and omphalocele (Saraiva *et al.*, 1999; Kargi *et al.*, 2004; White *et al.*, 2016).

In one of the earliest reports of Robinow syndrome, a radiograph showed bifid distal phalanges (Fig. 3; Kelly *et al.*, 1975). Another paper described a patient with broad fingers and thumbs (Kargi *et al.*, 2004). In a 2016 case series of *DVL3*-associated Robinow syndrome patients, at least one exhibited bifid first and second phalanges, which confirmed that bifid distal phalanges are a feature of Robinow syndrome (White *et al.*, 2016).

Some of our patient's features have been previously reported, including cleft lip and palate, dysmorphic features, and digital anomalies (Kargi *et al.*, 2004; White *et al.*, 2016). However, some features have heretofore never been described in a case of Robinow syndrome, including imperforate anus and choanal atresia. In addition, although two reported patients have had respiratory infections leading to death, our patient's cause of death, apnea, was unique (Vera-Roman, 1973; Wadlington *et al.*, 1973). Although her dysmorphic facies were notable, they were nonspecific, as were her anatomic malformations of the heart, anus, and umbilicus. Our case highlights that bifid distal phalanges should be regarded as a common finding in autosomal dominant Robinow syndrome, and possibly expands the phenotype to include imperforate anus, choanal atresia, and death due to apnea. We propose that bifid distal phalanges of the hands are a hallmark feature of all types of Robinow syndrome, and attention to them will aid in the clinical diagnosis.

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Fig. 1. Patient's left hand. Note bifid distal phalanx of digit 2, broad digits 3 and 4, and short digit 5 with clinodactyly.

Fig. 2.
Patient's face. Note the hypertelorism, wide flat nasal bridge, malar hypoplasia, anteverted nares, and repaired cleft lip.

Fig. 3.

(a) Patient's radiograph (Kelly *et al.*, 1975). (b) Our patient's left hand radiograph. Note the bifid distal phalanges of digits 1 and 2. (c) Our patient's right hand radiograph. Note the bifid distal phalanges of digits 1 and 2.