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# New Lethal Skeletal Dysplasia with Dandy-Walker Malformation, Congenital Heart Defects, Abnormal Thumbs, Hypoplastic Genitalia, and Distinctive Facies

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## Abstract

We report on two sibs with a lethal form of bone dysplasia with distinctive skeletal findings including rhizomelic and mesomelic limb shortening, hooked clavicles, dumbbell femurs, and absence of talus and calcaneus ossification. Other clinical features include Dandy-Walker malformation, congenital heart defects, joint contractures, genital hypoplasia, and distinctive facial features. These sibs appear to have a previously undescribed skeletal dysplasia, which is most likely inherited in an autosomal recessive fashion.

### Keywords

Skeletal dysplasia; bone dysplasia; lethal dysplasia; dwarfism; Dandy-Walker malformation; radial ray abnormality

## INTRODUCTION

There are more than 380 types of skeletal dysplasias which have been clearly delineated. Of those dysplasias which present at birth, approximately 50% are stillborn or die shortly after birth. We report two sibs with a previously undescribed skeletal dysplasia including multiple congenital anomalies, which was lethal in the perinatal period.

## CLINICAL REPORTS

Sib 1 was a male who was stillborn to a 25-year-old G4 P2 AB1 Guatemalan woman and her 31-year-old nonconsanguineous Guatemalan husband. Both parents are healthy and of normal stature for ethnic background. They have a healthy son and a history of a previous miscarriage. Another son died in Mexico at 40 days of age, possibly secondary to a congenital heart defect. He was said to have no skeletal abnormalities. Prenatal ultrasound in this pregnancy noted polyhydramnios, short limbs, Dandy-Walker malformation, pericardial effusion, and pulmonary stenosis. Chromosomes at 500–650 band resolution performed on amniocytes were normal 46,XY. Preterm labor at 27 weeks gestation led to the birth of the infant whose difficult resuscitation suggested pulmonary hypoplasia.

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Birth weight was 1170 g (25–50$^{th}$ centile) and birth length 34.5 cm (10$^{th}$ centile). He was generally hirsute with a low anterior hairline. He had brachycephaly, hypertelorism, short upturned nose, high nasal bridge, thin lips, posterior cleft palate, and low set ears (Fig. 1A). The chest was mildly narrow and the genitalia were small. There was rhizomelic and mesomelic shortening of the limbs (Fig. 1B). There was shortening of the distal phalanx of each thumb, adducted thumbs, marked fifth finger clinodactyly, flexion contractures of the knees, and flared toes (Fig. 1C). Radiographs demonstrated severe mesomelia, milder rhizomelia, occipital ossification defect, narrow chest, eleven pairs of ribs, butterfly vertebra at T7, laterally displaced and hooked clavicles, rounded ilia with flat acetabular roofs, absent pubic bone ossification, dumbbell femurs, absent talus and calcaneus ossification, and proportionately normal sized hands with short/hypoplastic first metacarpals and phalanges (Fig. 2).

Sib 2 was a female of 31 weeks gestation born one year later to the same parents. Prenatal ultrasound revealed short limbs, Dandy-Walker malformation, and tetralogy of Fallot. She required intubation in the delivery room and was difficult to oxygenate and ventilate, suggesting pulmonary hypoplasia. Apgar scores were 1, 2, and 3 at 1, 5, and 10 minutes.

Birth weight was 1877 g (75–90$^{th}$ centile), length 39.5 cm (25$^{th}$ centile), and occipital-frontal circumference 27.5 cm (10–25$^{th}$ centile). She had generalized hirsutism, brachycephaly, large anterior fontanelle, hypertelorism, right preauricular pit, low set ears, and narrow palate (Fig. 3A). The chest was mildly narrow and the external genitalia were hypoplastic (Fig. 3B). She had limb shortening, joint contractures, adducted thumbs, unusual finger positioning (Fig. 3C), ulnar deviation of the wrists, and long first toes (Fig. 3D).

Radiographs (Fig. 4) demonstrated severe mesomelia, milder rhizomelia especially in the lower extremities, eleven pairs of ribs, laterally hooked clavicles, rounded ilia with almost absent sacrosciatic notches, dumbbell femurs, absent/delayed talus and calcaneus ossification, and proportionately normal sized hands with short first metacarpals. Postnatal head ultrasound confirmed Dandy-Walker malformation. Echocardiogram revealed severe tetralogy of Fallot. Chromosome analysis at 650–850 band resolution was normal 46,XX and FISH studies of 22q11.2 did not reveal a deletion. 7-dehydrocholesterol was normal. Because of the severe anomalies and poor prognosis, the baby was removed from the ventilator at 7 days of age. Autopsy was refused.

## DISCUSSION

We report two sibs with a lethal condition characterized by Dandy-Walker malformation, congenital heart defects, palatal abnormalities, distinctive facial features, short limbs, and numerous skeletal abnormalities. The clinical and radiographic features were remarkably similar in both sibs (Tables I and II). Extensive review of the literature did not identify a skeletal dysplasia nor a syndrome with similar anomalies. Dandy-Walker malformation can occur as an isolated anomaly or as a feature of numerous syndromes, chromosome disorders, and teratogenic conditions. At least nine skeletal disorders have been reported with Dandy-Walker malformation. These disorders are Ellis-van Creveld [Zangwill et al., 1988], Klippel-Feil syndrome [Asai et al., 1989], asphyxiating thoracic dystrophy [Silengo et al., 2000], Beemer-Langer short rib polydactyly [Lin et al., 1991], chondrodysplasia punctata-multiple anomalies [Mortier et al., 1998], Dandy-Walker cyst-osteopetrosis [Ben Hamouda et al., 2001], Guschmann mesomelic campomeliapolydactyly [Guschmann et al., 2001], Moerman lethal dysplasia [Moerman et al., 1985], and Ritscher-Schinzel syndrome [Ritscher et al., 1987]. However, none of these dysplasias resembles our patients. The sibs we report most likely represent a previously undescribed autosomal recessive lethal skeletal

dysplasia. It is also possible that this condition could be due to a microdeletion or duplication and therefore array CGH should be performed in the next recognized case.

## REFERENCES


Asai A, Hoffman HJ, Hendrick EB, Humphreys RP. Dandy-Walker syndrome: experience at the Hospital for Sick Children, Toronto. Pediatr Neurosci. 1989; 15:66–73. [PubMed: 2635298]

Ben Hamouda H, Sfar MN, Braham R, Ben Salah M, Ayadi A, Soua H, Hamza H, Sfar MT. Association of severe autosomal recessive osteopetrosis and Dandy-Walker syndrome with agenesis of the corpus callosum. Acta Orthop Belg. 2001; 67:528–532. [PubMed: 11822087]

Guschmann M, Horn D, Entezami M, Urban M, Hänal S, Kunze J, Vogel M. Mesomelic campomelia, polydactyly and Dandy-Walker cyst in siblings. Prenat Diagn. 2001; 21:378–382. [PubMed: 11360278]

Lin AE, Doshi N, Flom L, Tenenholz B, Filkins KL. Beemer-Langer syndrome with manifestations of orofaciodigital syndrome. Am J Med Genet. 1991; 39:247–251. [PubMed: 1867273]

Moerman P, Vandenberghe K, Fryns JP, Haspeslagh M, Lauweryns JM. A new lethal chondrodysplasia with spondylocostal dysostosis, multiple internal anomalies and Dandy-Walker cyst. Clin Genet. 1985; 27:160–164. [PubMed: 3884191]

Mortier GR, Messiaen L, Espeel M, Smets KJ, Vanzieleghem BD, Roels F, De Paepe AM. Chondrodysplasia punctata with multiple congenital anomalies: a new syndrome? Pediatr Radiol. 1998; 28:790–793. [PubMed: 9799302]

Ritscher D, Schinzel E, Bolthauser E, Briner J, Arbenz U, Sigg P. Dandy-Walker (like) malformation, atrioventricular septal defect and a similar pattern of minor anomalies in 2 sisters: a new syndrome? Am J Med Genet. 1987; 26:481–491. [PubMed: 3812597]

Silengo M, Gianino P, Longo P, Battistoni G, Defilippi C. Dandy-Walker complex in a child with Jeune's asphyxiating thoracic dystrophy. Pediatr Radiol. 2000; 30:430. [PubMed: 10876833]

Zangwill KM, Boal DK, Ladda RL. Dandy-Walker malformation in Ellis-van Creveld syndrome. Am J Med Genet. 1988; 31:123–129. [PubMed: 3223493]

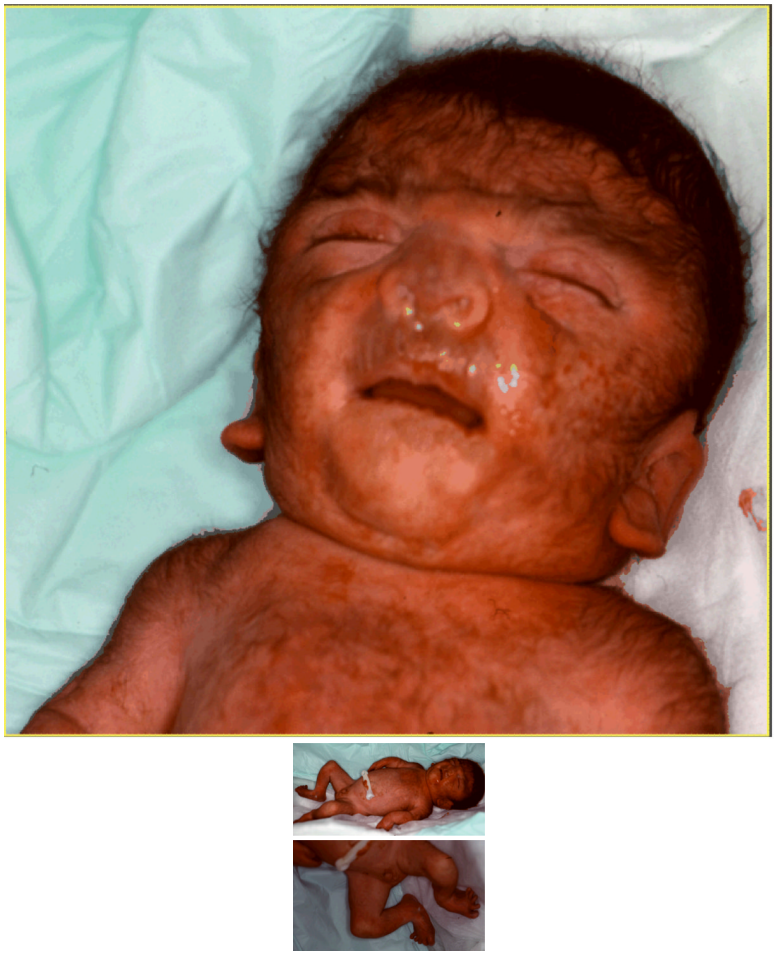


**Fig. 1.**
Sib1. A: Facial features including hypertelorism, short upturned nose, low set ears. B: Short limbs and small genitalia. C: Flexion contractures and flared toes. [Color figure and be viewed in the online issue, which is available at www.interscience.wiley.com]

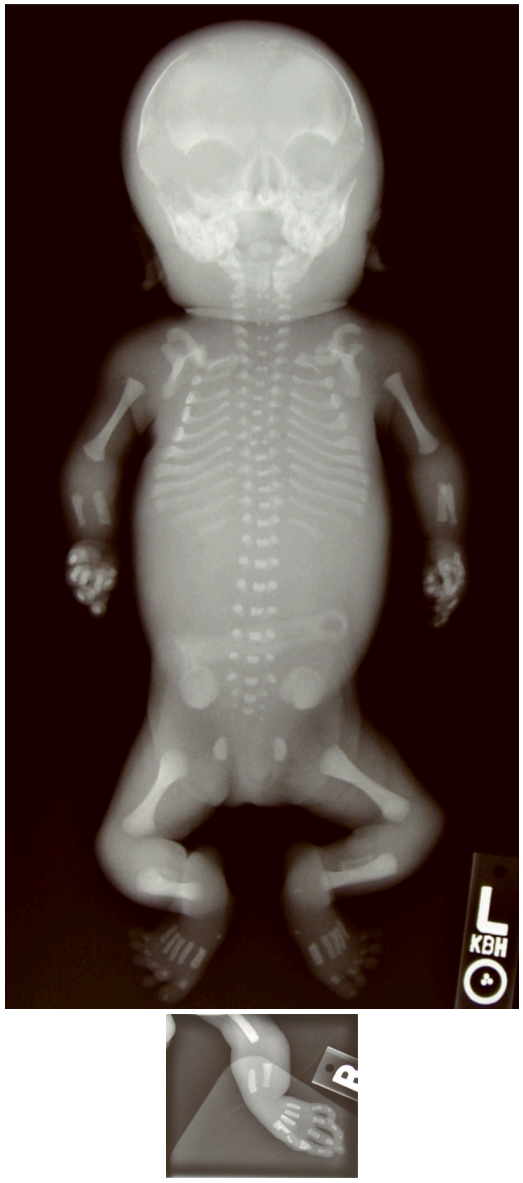
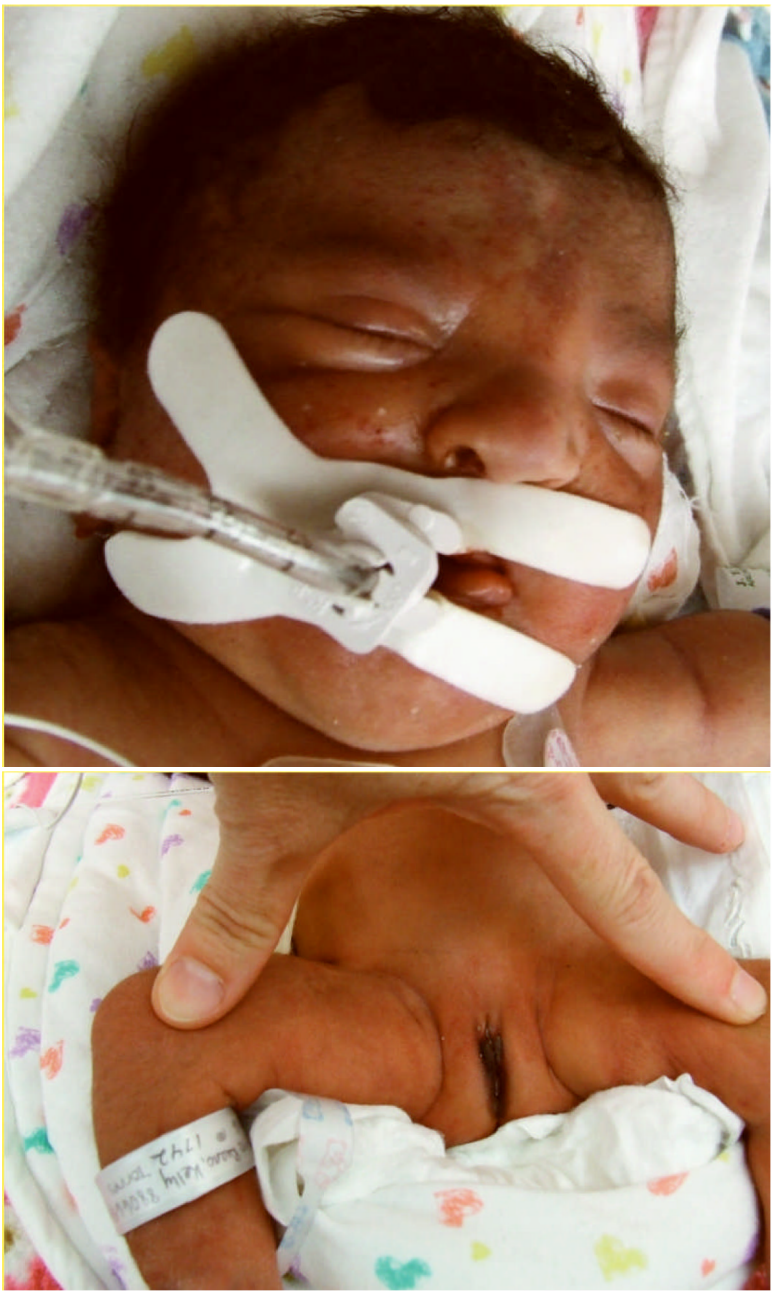



**Fig. 2.**

Radiographs of sib 1. A: Severe mesomelia, milder rhizomelia, 11 pairs of ribs, butterfly vertebra at T7, laterally displaced/ hooked clavicles, rounded ilia, dumbbell femurs, absent talus and calcaneus ossification. B: short first metacarpal and phalanges.



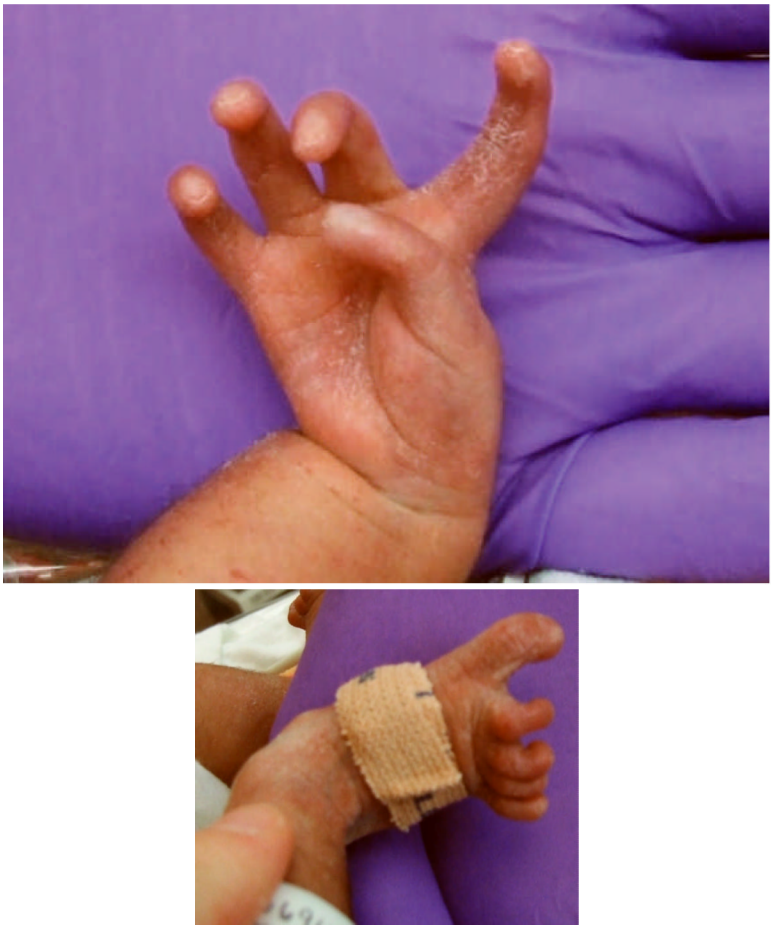


**Fig. 3.**

Sib 2. A: Facial features including hypertelorism and low set ears. B: Hypoplastic genitalia. C: Ulnar deviation of wrist and unusual finger positioning. D: Long first toe. [Color figure and be viewed in the online issue, which is available at www.interscience.wiley.com]

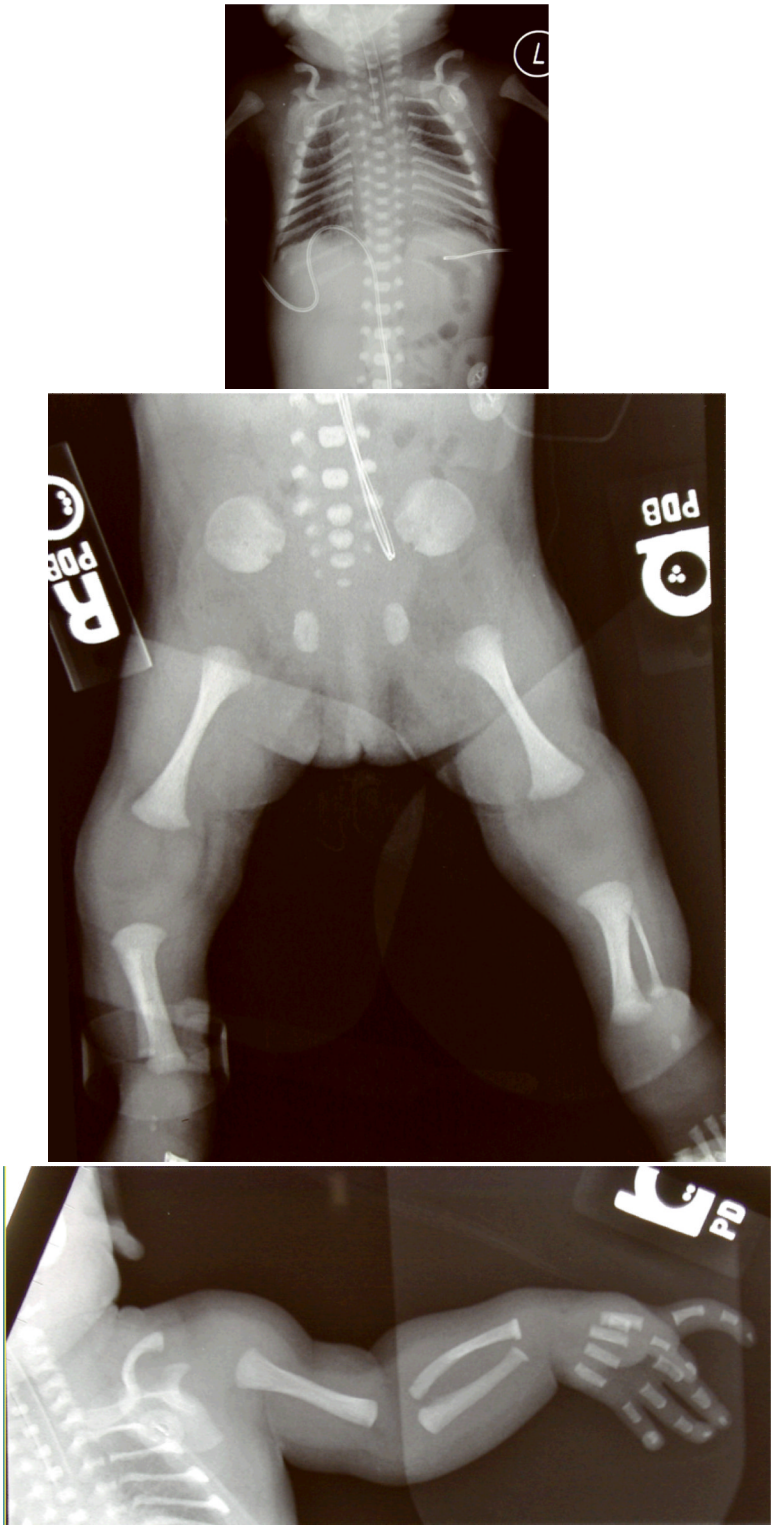



**Fig. 4.**

Radiographs of sib 2. A: 11 pairs of ribs, laterally hooked clavicles. B: Rounded ilia, dumbbell femurs, mesomelia, rhizomelia. C: Mesomelia, rhizomelia, short first metacarpal and infolded thumb. D: Absent/delayed talus and calcaneus ossification.

**Table I**

Clinical Features

| | Sib 1 | Sib 2 | Total |
|---|---|---|---|
| Neonatal lethality | + | + | 2/2 |
| Dandy Walker malformation | + | + | 2/2 |
| Cleft palate | + | − | 1/2 |
| Congenital heart defect | + | + | 2/2 |
| Pulmonary hypoplasia | + | + | 2/2 |
| Hypertelorism | + | + | 2/2 |
| Short nose | + | + | 2/2 |
| Preauricular pit | − | + | 1/2 |
| Low set ears | + | + | 2/2 |
| Thin lips | + | + | 2/2 |
| Mesomelic limb shortening | + | + | 2/2 |
| Joint contractures | + | + | 2/2 |
| Narrow chest | + | + | 2/2 |
| Genital hypoplasia | + | + | 2/2 |
| Adducted thumbs | + | + | 2/2 |

**Table II**

Radiographic Features

| | Sib 1 | Sib 2 | Total |
|---|---|---|---|
| Severe mesomelia | + | + | 2/2 |
| Mild rhizomelia | + | + | 2/2 |
| Butterfly vertebra | + | − | 1/2 |
| 11 pairs ribs | + | + | 2/2 |
| Laterally hooked clavicles | + | + | 2/2 |
| Rounded ilea | + | + | 2/2 |
| Dumbbell femurs | + | + | 2/2 |
| Absent talus/calcaneus/pubic ossification | + | + | 2/2 |
| Short 1$^{st}$ metacarpals | + | + | 2/2 |