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NLM Citation: Turnpenny PD, Sloman M, Dunwoodie S. Spondylocostal Dysostosis, Autosomal Recessive. 2009 Aug 25 [Updated 2023 Aug 17]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
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Spondylocostal Dysostosis, Autosomal Recessive

Synonyms: Costovertebral Dysplasia, Spondylocostal Dysplasia

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Created: August 25, 2009; Updated: August 17, 2023.

Summary

Clinical characteristics

Spondylocostal dysostosis (SCDO), defined radiographically as multiple segmentation defects of the vertebrae in combination with abnormalities of the ribs, is characterized clinically by a short trunk in proportion to height; short neck; and non-progressive mild scoliosis in most affected individuals – rarely, more significant scoliosis occurs. Respiratory function in neonates with severe disease may be compromised by reduced size of the thorax. By age two years lung growth may improve sufficiently to support relatively normal growth and development. In severely affected individuals with restricted pulmonary capacity, there is a possibility that pulmonary hypertension may eventually impact cardiac function. Males with SCDO appear to be at increased risk for inguinal hernia.

Diagnosis/testing

The diagnosis of SCDO is based on radiographic features. Identification of biallelic pathogenic variants in *DLL3*, *HES7*, *LFNG*, *MESP2*, *RIPPLY2*, or *TBX6* can confirm the diagnosis of autosomal recessive SCDO.

Management

Treatment of manifestations: Surgical intervention may be necessary when scoliosis is significant; external bracing (e.g., by use of a vertical expandable prosthetic titanium rib) may be considered, as well as growing rods and other devices as appropriate. Respiratory support, including intensive care, is provided as needed for the small proportion of individuals with acute respiratory distress and chronic respiratory failure. Expert management is indicated for chronic respiratory failure, which can result in pulmonary hypertension and

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cardiac failure. Standard treatment of neurologic problems associated with *LFNG*-related SCDO. Inguinal hernias are treated per routine.

Surveillance: Growth, spinal curvature, respiratory function, neurologic and motor function, and development should be monitored. The parents / care providers of young males need to be alert for the signs of inguinal hernia and its potential complications.

Genetic counseling

SCDO caused by biallelic pathogenic variants in *DLL3*, *HES7*, *LFNG*, *MESP2*, *RIPPLY2*, or *TBX6* is inherited in an autosomal recessive manner. (Autosomal dominant inheritance of *TBX6*-related SCDO has been reported in a three-generation family.) If both parents are known to be heterozygous for an autosomal recessive SCDO-causing pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the autosomal recessive SCDO-related pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible. In experienced hands, detailed fetal ultrasound scanning is sensitive enough to detect multiple segmentation defects of the vertebrae as early as 13 weeks' gestation, especially when the malformation is anticipated and looked for specifically. However, molecular genetic testing of an at-risk pregnancy is considered the gold standard for accurate prenatal diagnosis.

Diagnosis

Suggestive Findings

Spondylocostal dysostosis (SCDO) **should be suspected** in individuals with the following radiographic features and family history:

- **Multiple segmentation defects of the vertebrae (M-SDV)** most evident on anteroposterior radiograph of the whole spine. Abnormal segmentation of at least ten contiguous vertebrae. In the affected fetus or young child each vertebra is round or ovoid with smooth boundaries; the appearance of the vertebral column has been referred to as the "pebble beach" sign [Turnpenny et al 2003] (see Figure 1), especially in *DLL3*-related SCDO. As ossification proceeds after mid- to late childhood, the "pebble beach" appearance gives way to multiple irregularly shaped vertebral bodies and hemivertebrae that may be difficult to distinguish individually on plain x-ray.
- **Mild scoliosis**
- **Rib abnormalities.** Malalignment of at least some ribs with a variable number of intercostal rib fusions, and sometimes a reduction in rib number
- No major asymmetry to the shape of the thorax
- **Family history consistent with autosomal recessive inheritance** (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of autosomal recessive SCDO **is established** in a proband with suggestive radiographic features and biallelic pathogenic (or likely pathogenic) variants identified by molecular genetic testing in one of the genes listed in Table 1.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants. (2) Identification of biallelic variants of uncertain significance

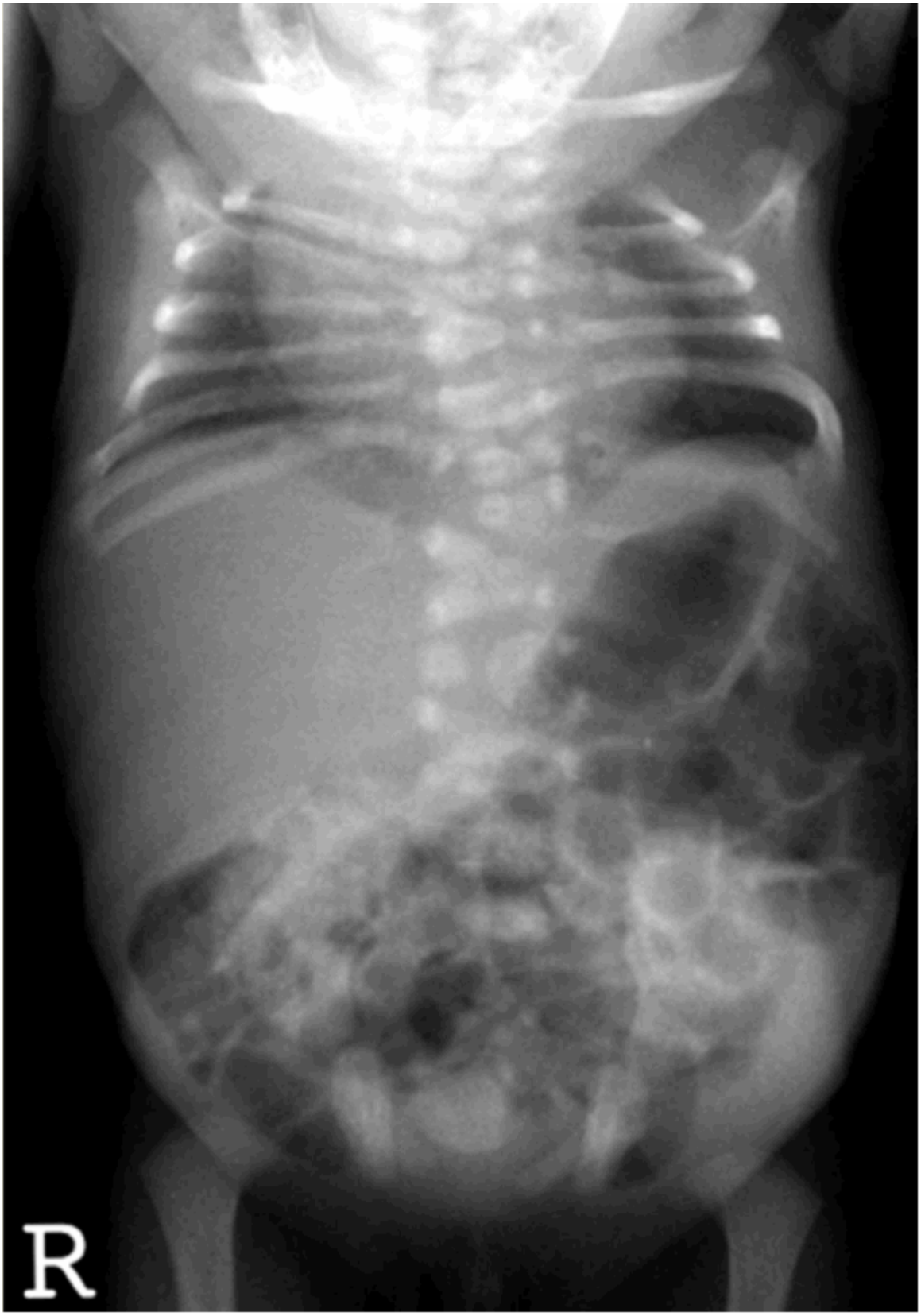

Figure 1. Typical axial skeletal features in an infant with *DLL3*-related SCDO. All vertebrae are abnormal: the vertebral bodies are ovoid and vary in size and shape ("pebble beach" sign). Ribs show occasional fusion distal to the costovertebral articulation. The overall shape of the thoracic cage is symmetric.

(or of one known pathogenic variant and one variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel, serial single-gene testing), and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

A multigene panel that includes *DLL3*, *HES7*, *LFNG*, *MESP2*, *RIPPLY2*, *TBX6*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Serial single-gene testing. Prioritized genetic testing may be pursued as single-gene testing based on clinical features:

- Sequence analysis of ***LFNG*** can be performed first in individuals with severe truncal shortening observed on radiographs.
- Sequence analysis of ***MESP2*** can be performed first in individuals with radiographic features more typical of spondylothoracic dysplasia (or dysostosis) (STD); the ribs tend to be straight and more regularly aligned than in the other forms of SCDO (i.e., demonstrating fewer points of fusion), resulting in a "crab-like" appearance.

Option 2

When the phenotype is indistinguishable from many other skeletal dysplasias, c**omprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Autosomal Recessive Spondylocostal Dysostosis

Gene [1, 2]	Proportion of AR SCDO Attributed to Pathogenic Variants in Gene [3]	Proportion of Pathogenic Variants [4] Detectable by Method	
		Sequence analysis [5]	Gene-targeted deletion/ duplication analysis [6]
DLL3	~60% [7]	95%	2 individuals [8]
HES7	~5% [9]	100%	None reported [10]
LFNG	~5%	100%	None reported [10]
MESP2	~5% [11]	100%	None reported [10]
RIPPLY2	~5%	100%	None reported [10]

Table 1. continued from previous page.

Gene [1, 2]	Proportion of AR SCDO Attributed to Pathogenic Variants in Gene [3]	Proportion of Pathogenic Variants [4] Detectable by Method	
		Sequence analysis [5]	Gene-targeted deletion/ duplication analysis [6]
TBX6	~20% [12]	100%	See footnote 13.
Unknown	See footnote 14.		

AR = autosomal recessive; SCDO = spondylocostal dysostosis
1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. The percentages in column two are estimates based on published reports [Authors, personal communication].
4. See Molecular Genetics for information on variants detected in these genes.
5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Bulman et al [2000], Bonafé et al [2003], Turnpenny et al [2003]
8. One individual with a deletion of exons 2-4 (detected by an in-house-designed MLPA kit) and one individual with a whole-gene deletion (detected by array CGH and confirmed by in-house-designed MLPA) [Authors, personal communication]
9. Three reported families and an additional four unreported individuals [P Turnpenny, personal communication]
10. No deletions or duplications involving *HES7*, *LFNG*, *MESP2*, or *RIPPLY2* have been identified in individuals with autosomal recessive SCDO [Authors, personal communication].
11. Three known families with *MESP2*-related SCDO [Whittock et al 2004b; Authors, unpublished data]
12. Six families with *TBX6*-related SCDO have been reported [Lefebvre et al 2017; P Turnpenny, personal communication].
13. Large *TBX6* deletions/duplications have not been reported in individuals with autosomal recessive SCDO. Heterozygous *TBX6* deletions, sometimes in *trans* with a hypomorphic allele, have been reported in individuals with congenital scoliosis and müllerian aplasia or renal malformations (see Genetically Related Disorders) [Sandbacka et al 2013, Wu et al 2015, Li et al 2022].
14. One individual with an SCDO-like phenotype including multiple regional segmentation defects of the vertebrae and multiple intervertebral fusions of laminae, in addition to dysmorphic features and cleft palate, was homozygous for a *DMRT2* start-loss variant [Bouman et al 2018]. With severe left-sided rib cage deficiency, the infant died at age nine days; to date, it is not known whether *DMRT2*-related SCDO is a distinct entity.

Clinical Characteristics

Clinical Description

Spondylocostal dysostosis (SCDO), defined radiographically as multiple segmentation defects of the vertebrae that is usually generalized throughout the spine, is characterized clinically by a short trunk in proportion to height, short neck, and non-progressive mild scoliosis in most affected individuals. To date, nearly 100 individuals have been identified and/or reported with SCDO and biallelic pathogenic variants in one of the genes listed in Table 1. The following description of the phenotypic features associated with this condition is based on the cited reports.

Skeletal. Multiple segmentation defects of the vertebrae, which is usually generalized throughout the spine, results in:

- A short trunk in proportion to height. The extent varies and the data is very limited, but based on leg length measurements, individuals with SCDO are 10% shorter than projected adult height. Some individuals have severe short stature, with height up to four standard deviations below the mean [Sparrow et al 2006; Schuhmann et al 2021; P Turnpenny, personal communication]. *LNFG*-related SCDO appears to be associated with shorter stature compared to other causes of SCDO (see Figure 2). The reason(s) for this variability is not well understood.

- Short neck. The extent varies, and the data is limited, but – similar to the decrease in overall spine length – the neck is likely to be shortened by approximately 10%. The range of limitation in neck mobility has not been formally assessed.
- Non-progressive, or mildly progressive but self-limiting, scoliosis occurs in most affected individuals, usually apparent radiographically in infancy. More significant scoliosis, with a greater degree of progression, especially at the thoracolumbar region, is apparent in individuals with *LFNG*-related SCDO [Sparrow et al 2006, Takeda et al 2018, Schuhmann et al 2021]. Severe scoliosis, including the need for scoliosis surgery, appears to be relatively rare [A Cornier, personal communication; P Turnpenny, personal communication].

Respiratory. The most important consideration in neonates diagnosed with SCDO is impaired respiratory function, which may be compromised by reduced size of the thorax. In these infants, respiratory insufficiency may be the presenting clinical problem. Life-threatening respiratory insufficiency requiring neonatal intensive care appears to be rare but anecdotally has been known to occur. One individual died in infancy from respiratory insufficiency and at postmortem was found to have a membranous left hemidiaphragm [Turnpenny et al 1999]. This has not been reported in any other individuals with SCDO. The most significant potential secondary complication is chronic respiratory failure caused by reduced lung capacity in individuals with severe disease.

In children requiring early respiratory support, lung growth may improve sufficiently to support relatively normal growth and development by age two years. However, life-threatening complications can occur, especially pulmonary hypertension and cardiac failure in individuals with severely restricted lung capacity from birth. There is no systematic review concerning susceptibility to pulmonary infection and pneumonia or incidence of pulmonary hypertension.

Inguinal hernia. Males with SCDO appear to be at increased risk for inguinal hernia, which has been noted in the neonatal period [Turnpenny et al 1999, Turnpenny et al 2003, Otomo et al 2019].

Neurologic complications appear to be rare. Lumbosacral meningomyelocele was reported in one individual [Sparrow et al 2008] and a neural tube defect occurred in a second individual [Authors, personal communication] with *HES7*-related SCDO. Syringomyelia was identified at age seven years in one individual with *LFNG*-related SCDO on spine MRI performed due to new balance problems. By age ten years this individual had urinary incontinence; he was intellectually normal [E Fryssira and M Christodoulou, personal communication]. Distal arthrogryposis was reported in one individual with *LFNG*-related SCDO; it was not clear whether this was a primary abnormality or secondary to impingement of neural pathways in the cervical vertebrae [Sparrow et al 2006].

Other

- Cosegregation of dextrocardia was reported in a large consanguineous Middle Eastern kindred with *HES7*-related SCDO (see Figure 3) [Sparrow et al 2013a]; whether this was due to *HES7*-related SCDO or a separate genetic cause has not been established.
- Solitary pelvic kidney, uterine dysgenesis, absence epilepsy, and inner ear (presumed sensorineural) deafness were reported in one individual with *LFNG*-related SCDO [Schuhmann et al 2021].

Prognosis. In the absence of restricted lung capacity, individuals with SCDO have normal life expectancy. The risk of pulmonary hypertension and associated complications is unknown.

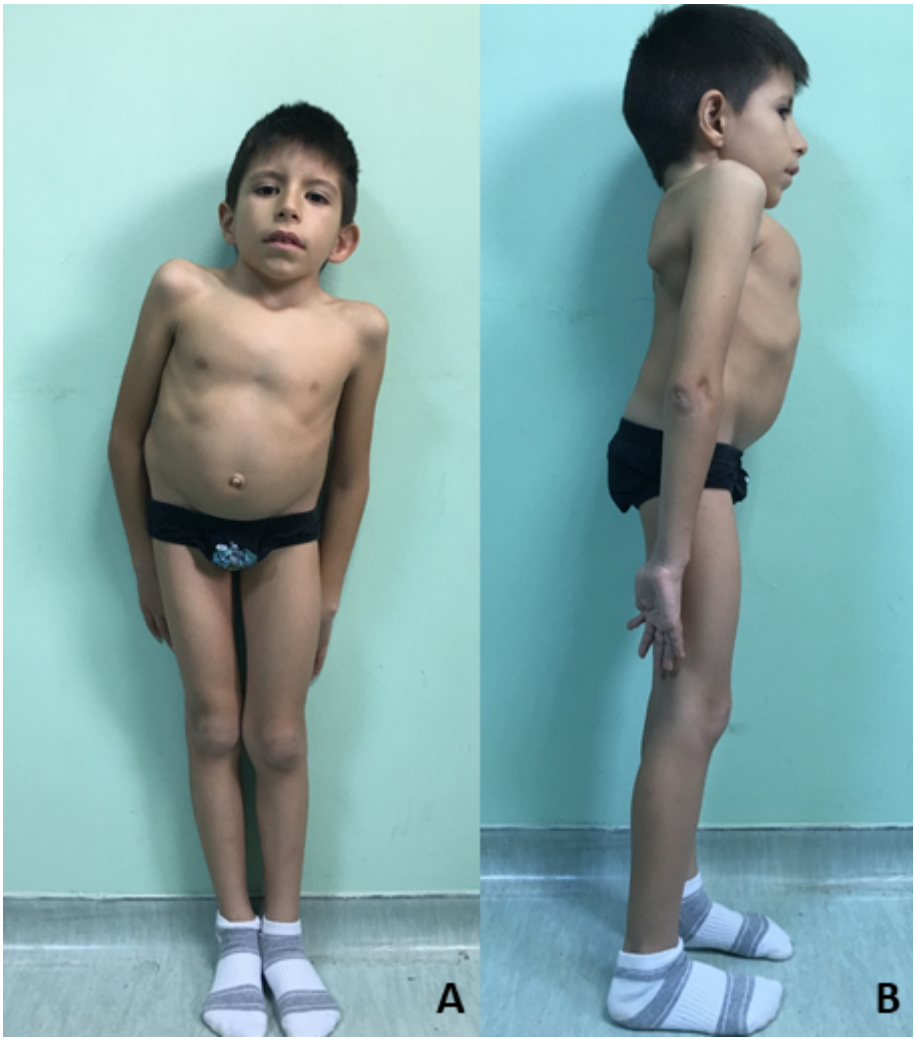

Figure 2. Individual with *LFNG*-related SCDO at age seven years nine months showing marked truncal shortening
Courtesy of Prof Eleni Fryssira, Athens, Greece. *LFNG* analysis performed in Lausanne, Switzerland.

Phenotype Correlations by Gene

DLL3. Scoliosis is generally mild and non-progressive, and the need for surgical intervention to stabilize the spine is rare. However, more significant scoliosis has been observed in some individuals (see Figure 4) [A Cornier, personal communication].

HES7. Radiographic features in the limited number of published individuals have ranged from resembling spondylothoracic dysostosis (STD) [Sparrow et al 2008] (see Figure 5) to those typical in *DLL3*-related SCDO; all vertebrae display abnormal segmentation.

LFNG. Shortening of the spine and scoliosis appear to be more severe in individuals with *LFNG*-related SCDO compared to that seen in *DLL3*-, *HES7*-, and *MESP2*-related SCDO, because all vertebral bodies appear to show more severe segmentation defects (see Figure 2, Figure 6, and Figure 7) [Lefebvre et al 2018]. Rib anomalies are similar to those seen in *DLL3*- and *MESP2*-related SCDO.

MESP2. Spine radiographs in individuals with *MESP2*-related SCDO show at least some disruption of all vertebral segments. However, lumbar vertebrae are relatively mildly affected compared to thoracic vertebrae (see

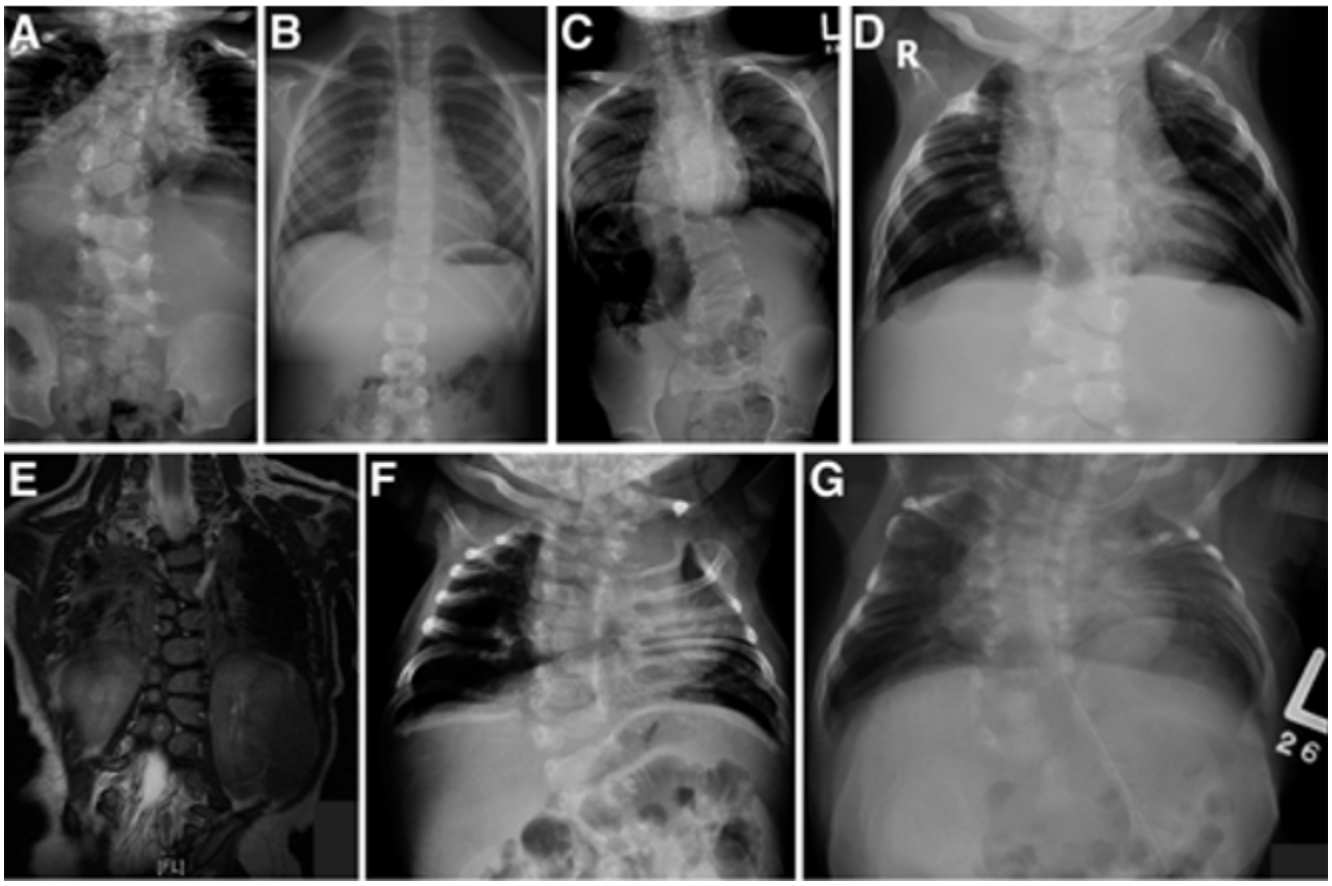

Figure 3. individuals with *HES7*-related SCDO compared to an unaffected individual. X-ray and MRI images showing vertebral and rib malformations and dextrocardia. Seven affected individuals from three families, all with the same homozygous pathogenic *HES7* variant, were reported. Two of the seven individuals had neural tube defects.

A & C. Individuals with *HES7*-related SCDO and dextrocardia

B. Unaffected individual

E, F, and G. Imaging of individuals with *HES7*-related SCDO

Reproduced from Sparrow et al [2013a]

Figure 8). In the limited reports thus far, the ribs tend to be straight and more regularly aligned than in other forms of SCDO (i.e., demonstrating fewer points of fusion).

RIPPLY2. Two brothers with *RIPPLY2*-related SCDO had vertebral segmentation defects affecting the posterior elements of C1-C4 and hemivertebrae and butterfly vertebrae of T2-T7 (see Figure 9). Marked cervical kyphosis at C2-C3 was associated with cord compression, and mild thoracic scoliosis was present [McInerney-Leo et al 2015]. Three individuals from two families, with the same pathogenic variant [Serey-Gaut et al 2020], had agenesis of the posterior and lateral elements of most cervical vertebrae, with limited and variable involvement of some thoracic vertebrae. The radiologic pattern was distinct from other forms of SCDO, and *RIPPLY2*-related *SCDO* may be better categorized as a form of Klippel-Feil anomaly.

TBX6. Although the number of reported individuals with *TBX6*-related SCDO is limited, this phenotype resembles that of *DLL3*-related SCDO. Radiologically it is almost indistinguishable (see Figure 10) [C Shaw-Smith, personal communication].

See Figure 11 for radiographic comparison of *DLL3*-, *LFNG*-, *HES7*-, and *TBX6*-related SCDO and *MESP2*-related STD.

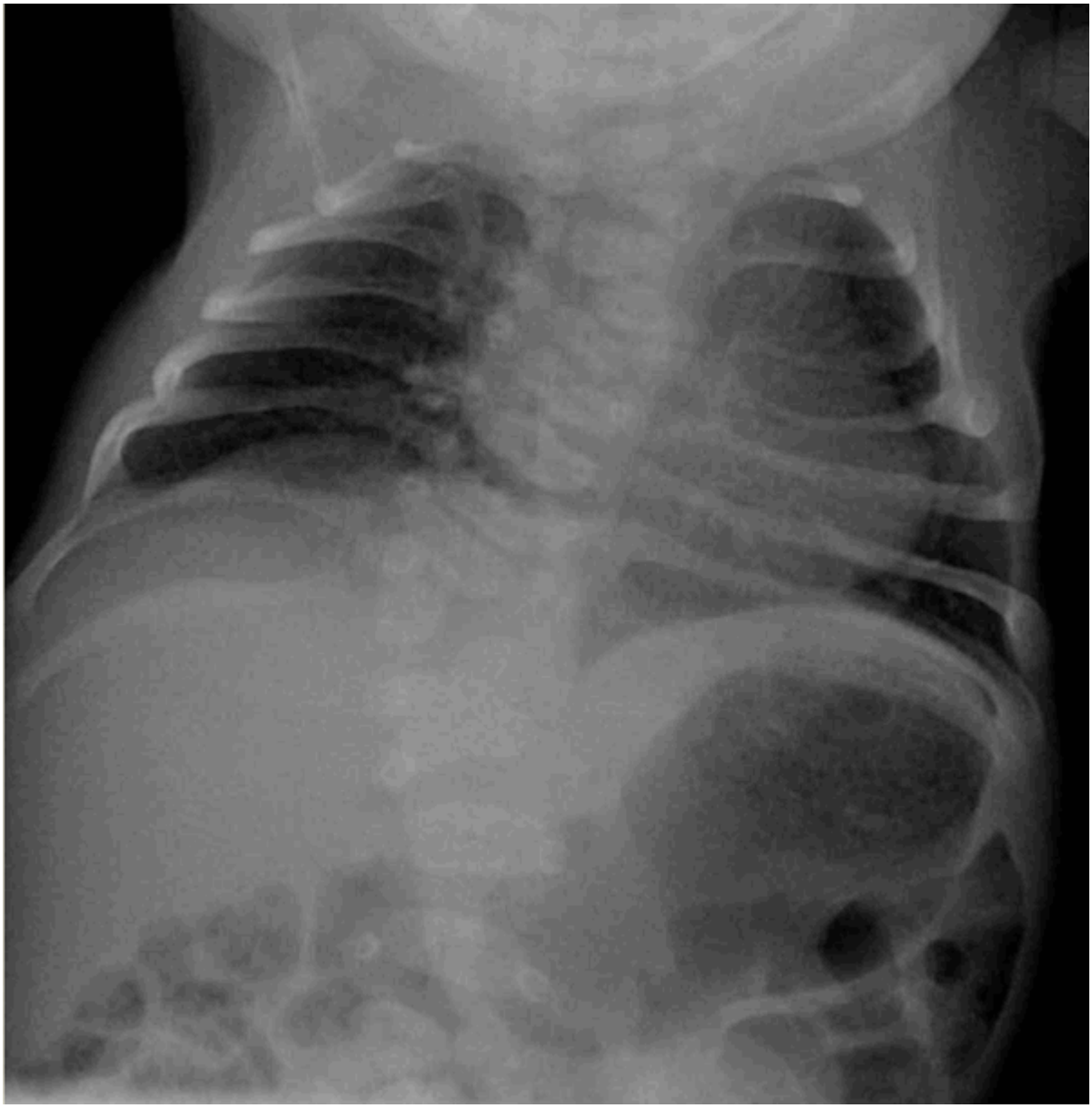

Figure 4. Radiograph of infant with *DLL3*-related SCDO and unusually severe scoliosis

Genotype-Phenotype Correlations

DLL3. The radiographic features of *DLL3*-related SCDO appear to be very consistent (see Figure 1). However, two individuals homozygous for *DLL3* pathogenic missense variants in the region encoding the EGF domain had slightly milder phenotypes (see Figure 12). Some evidence suggests that these pathogenic missense variants would allow the EGF domains to adopt the correct fold in the DLL3 protein but perhaps be thermodynamically less stable than the wild type protein [Authors, unpublished data]. However, some of the pathogenic missense variants identified in affected individuals cause a phenotype that is indistinguishable from that caused by *DLL3* pathogenic truncating variants. This probably results from the different effects conferred upon protein folding compared to those pathogenic missense variants associated with the slightly milder phenotype.

MESP2. The 4-bp duplication c.500_503dup occurs after the basic helix-loop-helix (bHLH) domain and causes a frameshift resulting in a premature stop codon within the second (and final) *MESP2* exon [Whittock et al 2004b]. Transcripts with this pathogenic variant would not be subject to nonsense-mediated decay. Individuals

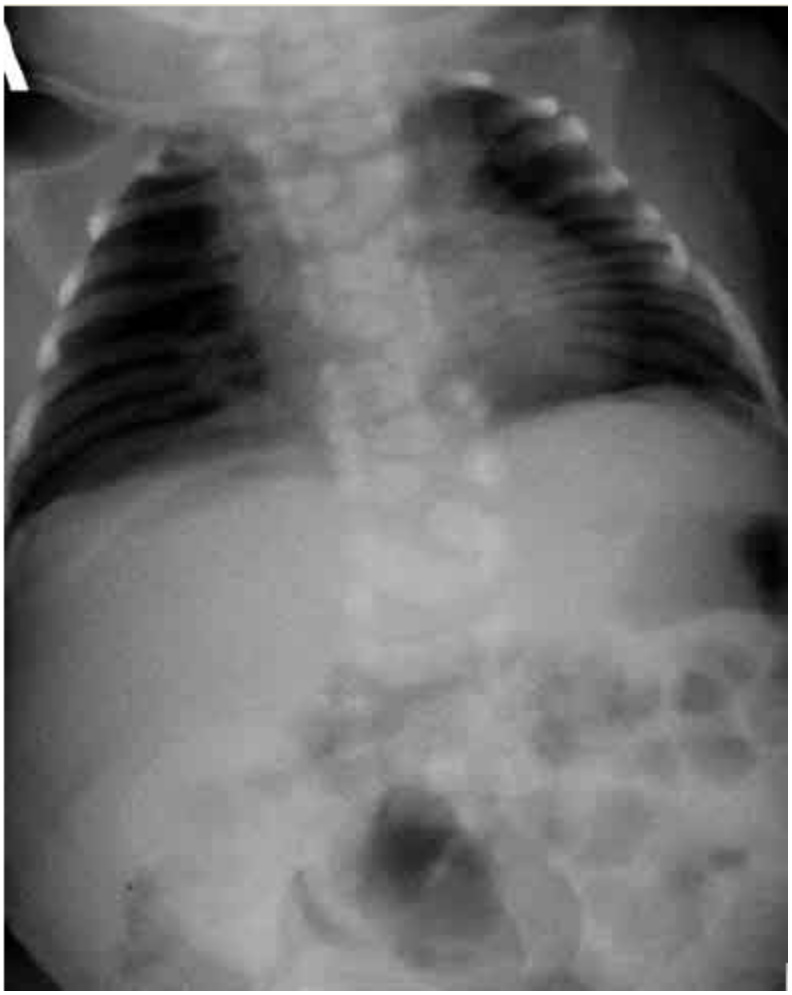

Figure 5. Radiograph of child with *HES7*-related SCDO. Segmentation anomalies of all vertebrae are severe. The vertebral pedicles are relatively prominent ("tramline" sign) compared with those of *DLL3*-related SCDO. These radiographic findings resemble those of spondylothoracic dysostosis (STD) (see Figure 11).

Reproduced from Sparrow et al [2008] with permission from Oxford University Press

with this pathogenic variant are predicted to have a truncated protein containing an intact bHLH domain, which may retain some function. In contrast, the pathogenic nonsense variants identified in spondylothoracic dysostosis (STD) (see Genetically Related Disorders) are located within the first exon, and the resulting mutated mRNA transcripts are predicted to be susceptible to nonsense-mediated decay. Therefore, persons homozygous or compound heterozygous for these pathogenic nonsense variants are likely to have reduced or absent levels of MESP2 protein, which may account for the difference in severity between the *MESP2*-related SCDO and STD phenotypes.

TBX6. See Genetically Related Disorders for genotype-phenotype correlations observed in allelic disorders.

No genotype-phenotype correlations for *HES7*, *LFNG*, or *RIPPLY2* have been identified.

Penetrance

To date, penetrance appears to be complete for the pathogenic variants implicated in autosomal recessive SCDO.

Nomenclature

The term **Jarcho-Levin syndrome (JLS)** [Jarcho & Levin 1938] has been used (confusingly) to refer to:

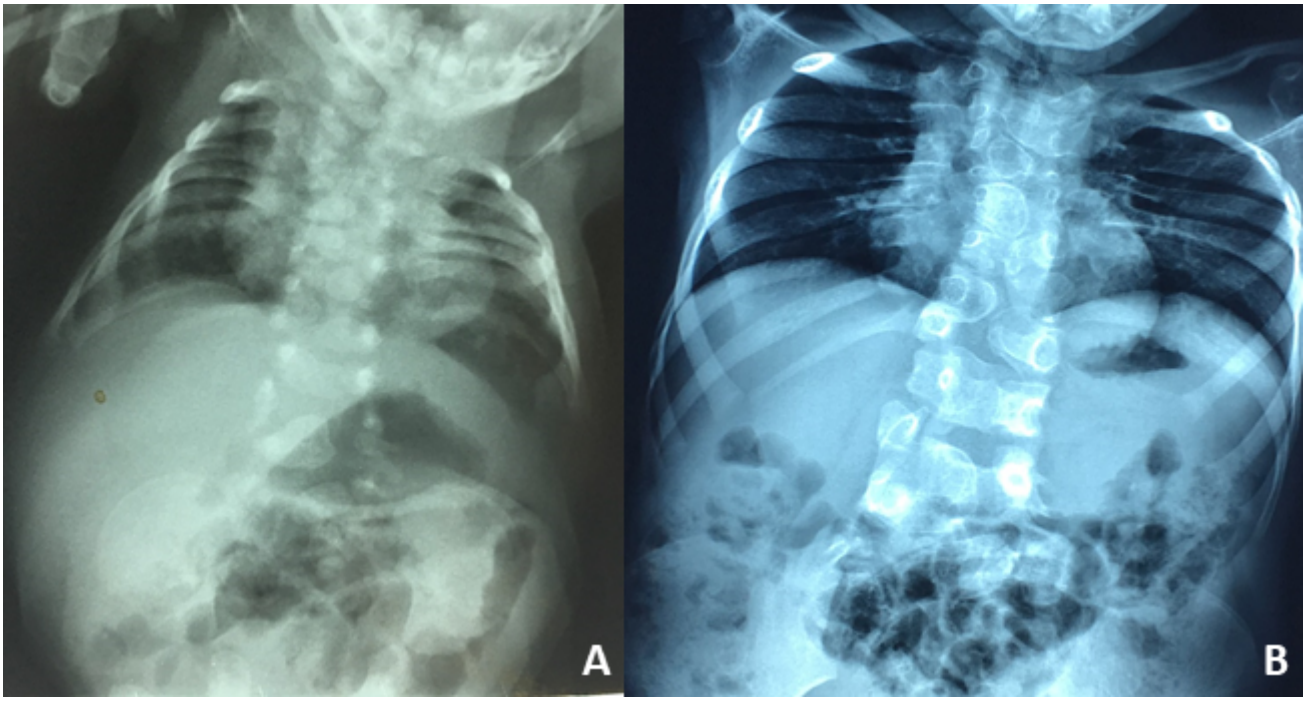

Figure 6. Radiographs of a child with *LFNG*-related SCDO

A. Spine radiograph as a neonate. The pattern of malsegmentation is not clearly distinguishable from typical findings in *DLL3*-related SCDO.

B. Spine of same individual age six years nine months. The block-like appearance of the lumbar vertebrae is seen in this form of SCDO.

- All radiologic phenotypes that include segmentation defects of the vertebrae (SDV) and abnormal rib alignment, including reports of phenotypes that are neither similar to the case description of Jarcho & Levin [1938] nor consistent with spondylothoracic dysostosis (STD);
- STD in Puerto Ricans of Spanish descent (see Genetically Related Disorders).

Use of the terms **costovertebral dysplasia** and **spondylothoracic dysostosis/dysplasia** for segmentation abnormalities of the spine and ribs has led to great confusion. Note: These disorders are dysostoses rather than dysplasias:

- "Costovertebral dysplasia" is now used less frequently.
- "Spondylothoracic dysostosis/dysplasia" (STD) is recognized as being distinct from SCDO (see Differential Diagnosis).
- Note: Spondylothoracic dysostosis is referred to as "vertebral segmentation defect (congenital scoliosis) with variable penetrance" in the 2023 revision of the Nosology of Genetic Skeletal Disorders [Unger et al 2023]. It is the authors' judgment that STD does not fit within the broad category of "congenital scoliosis." Congenital scoliosis is usually caused by segmentation defects in a single vertebra (or segmentation defects in a limited number of vertebrae within one region of the spine), whereas STD is a generalized form of SDV, and scoliosis is not a major feature.

The wide range of radiologic phenotypes with multiple segmentation defects of the vertebrae (M-SDV) within SCDO has highlighted the need to rationalize nomenclature for these diverse and poorly understood disorders. The International Consortium for Vertebral Anomalies and Scoliosis (ICVAS), now subsumed into the International Consortium for Scoliosis Genetics Development and Disease (ICSGDD), proposed two algorithms:

- The clinical algorithm, used for routine reporting of SDV, identifies seven broad categories (see Figure 13). For the purposes of clinical reporting, additional comments can describe SDV findings in more detail.

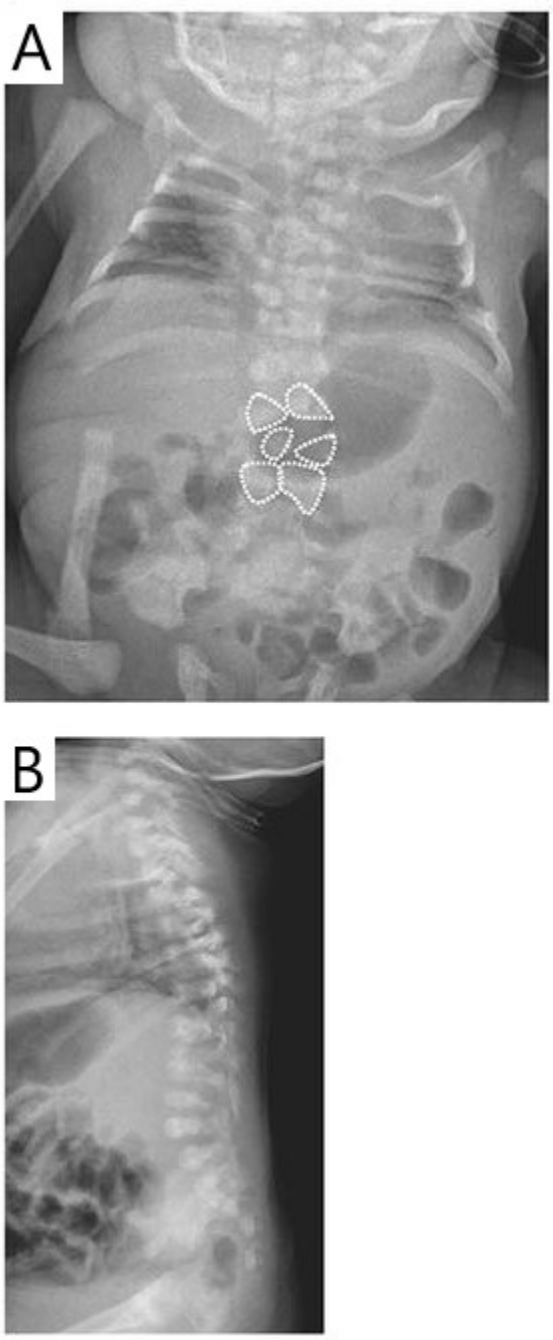

Figure 7. Segmentation defects of the vertebrae of the entire spine with angulated vertebral bodies (dotted lines) at birth in an individual with *LNFG*-related SCDO (patient 18 of Lefebvre et al [2018])

Reprinted with permission from Lefebvre et al [2018]

- The research algorithm, used for more detailed documentation of SDV, employs ontology applicable to humans and animal models (see Figure 14).

Note: In the classification system proposed by the ICVAS, SCDO is the preferred term for generalized segmentation defects of the vertebrae (G-SDV) with rib involvement [Turnpenny et al 2007, Offiah et al 2010].

Klippel-Feil anomaly (KFA) refers to cervical vertebral fusion anomalies. The term "KFA" is used broadly for a number of phenotypes.

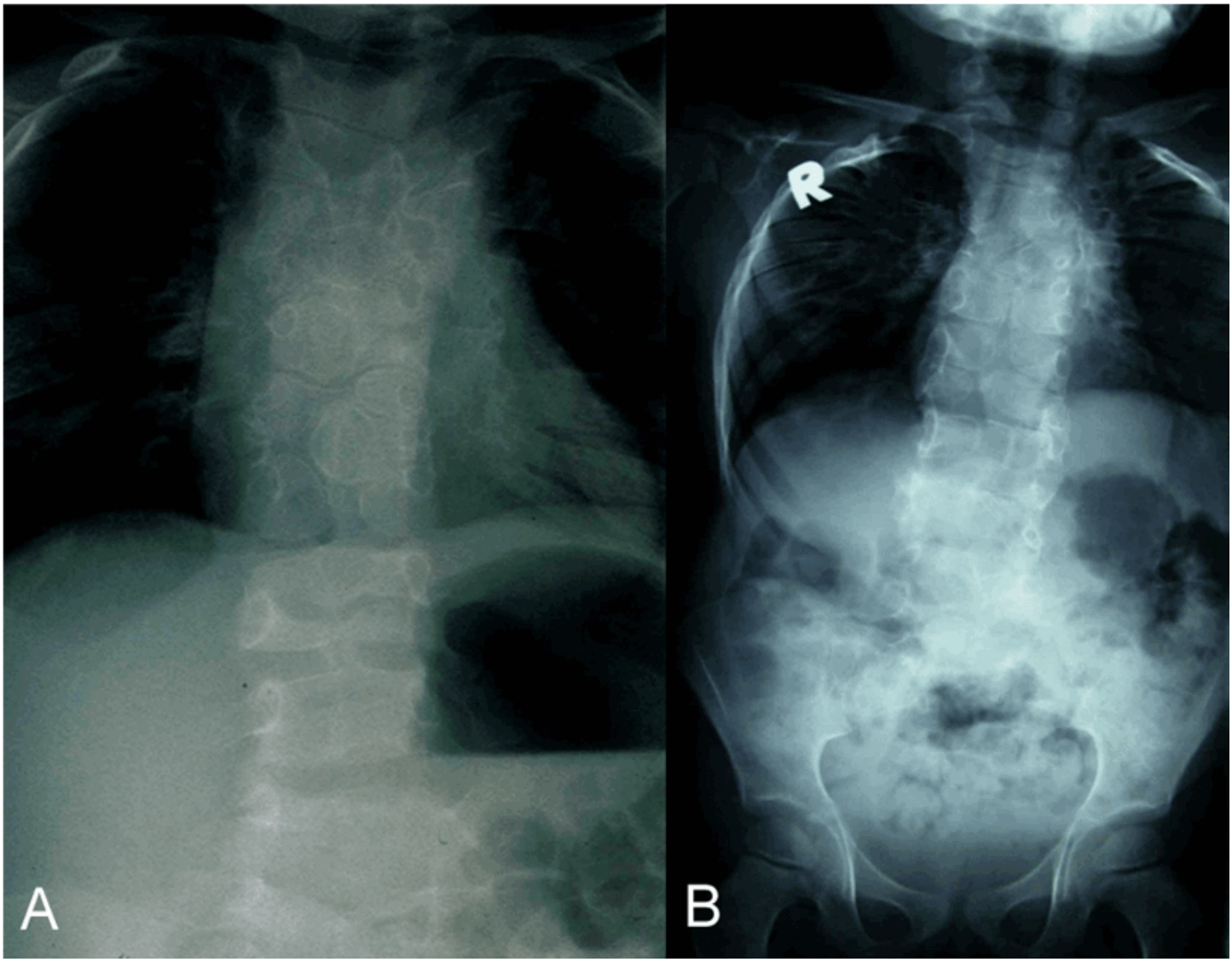

Figure 8. Radiographs of a child with *MESP2*-related SCDO. The generalized segmentation defects of the vertebrae show more angular features than is typical of *DLL3*-related SCDO.

Prevalence

***DLL3*-related SCDO.** Seventy-five percent of individuals have been the offspring of consanguineous unions (Exeter Laboratory experience), mostly of Middle Eastern or Pakistani origin, and occasionally of European origin and elsewhere. A small number of individuals from northern Europe (England, Wales, the Netherlands, and Switzerland) have been shown to be compound heterozygotes [Bonafé et al 2003, Whittock et al 2004a]. Assuming a period of time during which approximately one million births occurred, the carrier frequency in the European population in the UK would be approximately 1:350.

HES7-, *LFNG*-, *MESP2*-, and *RIPPLY2*-related SCDO have been reported in only a small number of individuals [Whittock et al 2004b, Bonafé & Superti-Furga 2005, Sparrow et al 2006, Sparrow et al 2008, Sparrow et al 2010, Sparrow et al 2013a, Lefebvre et al 2017]. *TBX6*-related SCDO has been reported more often, suggesting it is the second most common form of SCDO after *DLL3*-related SCDO.

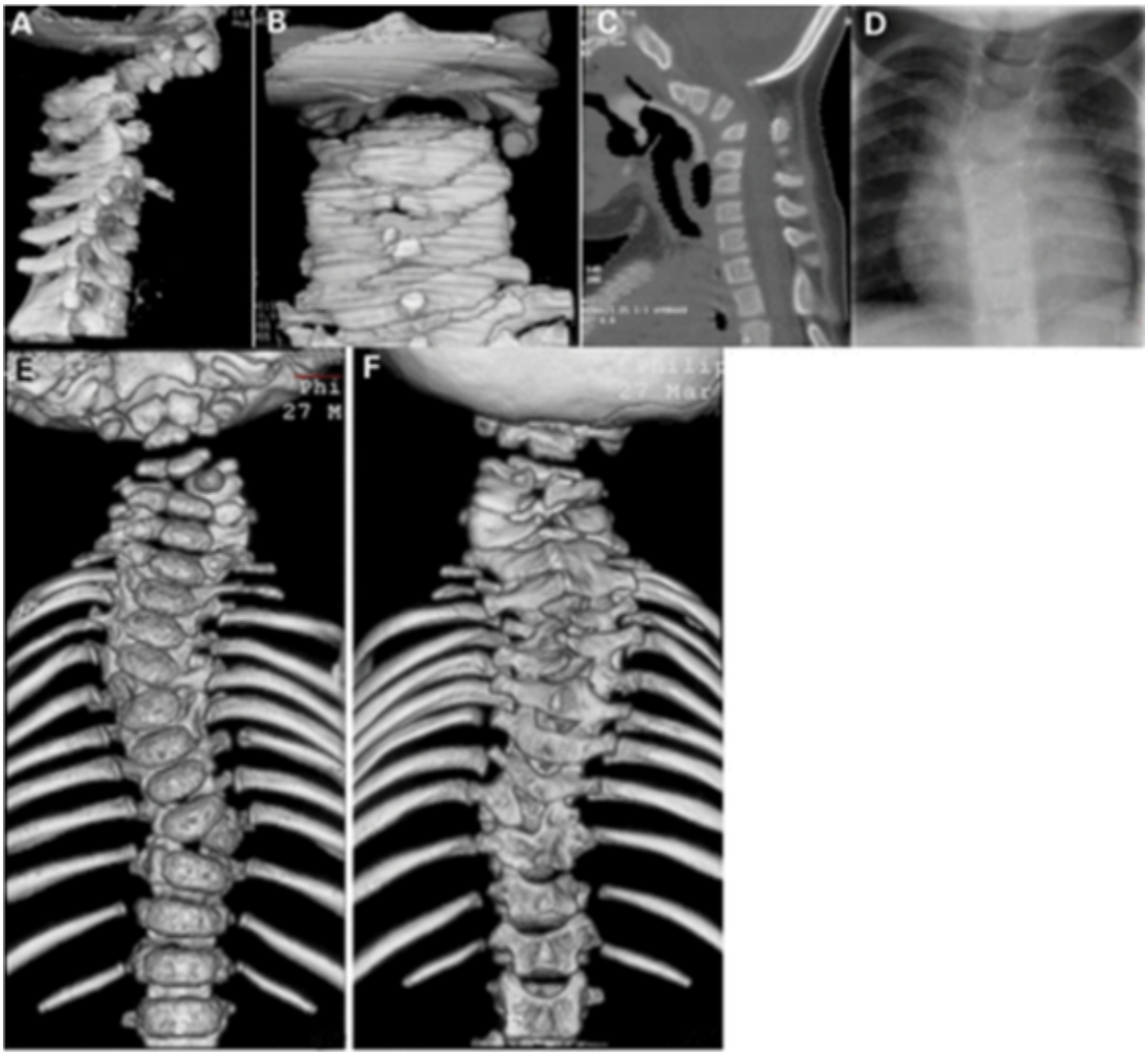

Figure 9. Imaging of individuals with *RIPPLY*-related SCDO

A-C. 3D CT of male age 15 months with *RIPPLY*-related SCDO, showing failure of formation of the posterior elements of C1-C4 with descent of the occipital bone, resulting in canal stenosis and cord compression

D. AP radiograph of same male age 12 months, showing hemivertebrae and butterfly vertebrae situated between T2 and T7, resulting in a mild thoracic scoliosis

E & F. 3D CT of affected brother of A-D, age three years, showing complex craniocervical anomaly with deficiency of the posterior elements of C1-C3, left hemivertebrae at C4 and T9, and right hemivertebra at T4.

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Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *DLL3*, *HES7*, *LFNG*, or *RIPPLY2*.

***MESP2*-related spondylothoracic dysostosis (*MESP2*-STD).** To date, most individuals reported with *MESP2*-related STD have had pathogenic nonsense variants in exon 1 of *MESP2*, which are predicted to result in nonsense-mediated decay; however, several affected individuals have been reported who are heterozygous for a pathogenic nonsense variant and a pathogenic missense variant [Cornier et al 2008]. STD occurs most frequently in Puerto Ricans of Spanish descent [A Cornier, personal communication], presumably as a result of the *MESP2* founder variant p.Glu103Ter (see Figure 15).

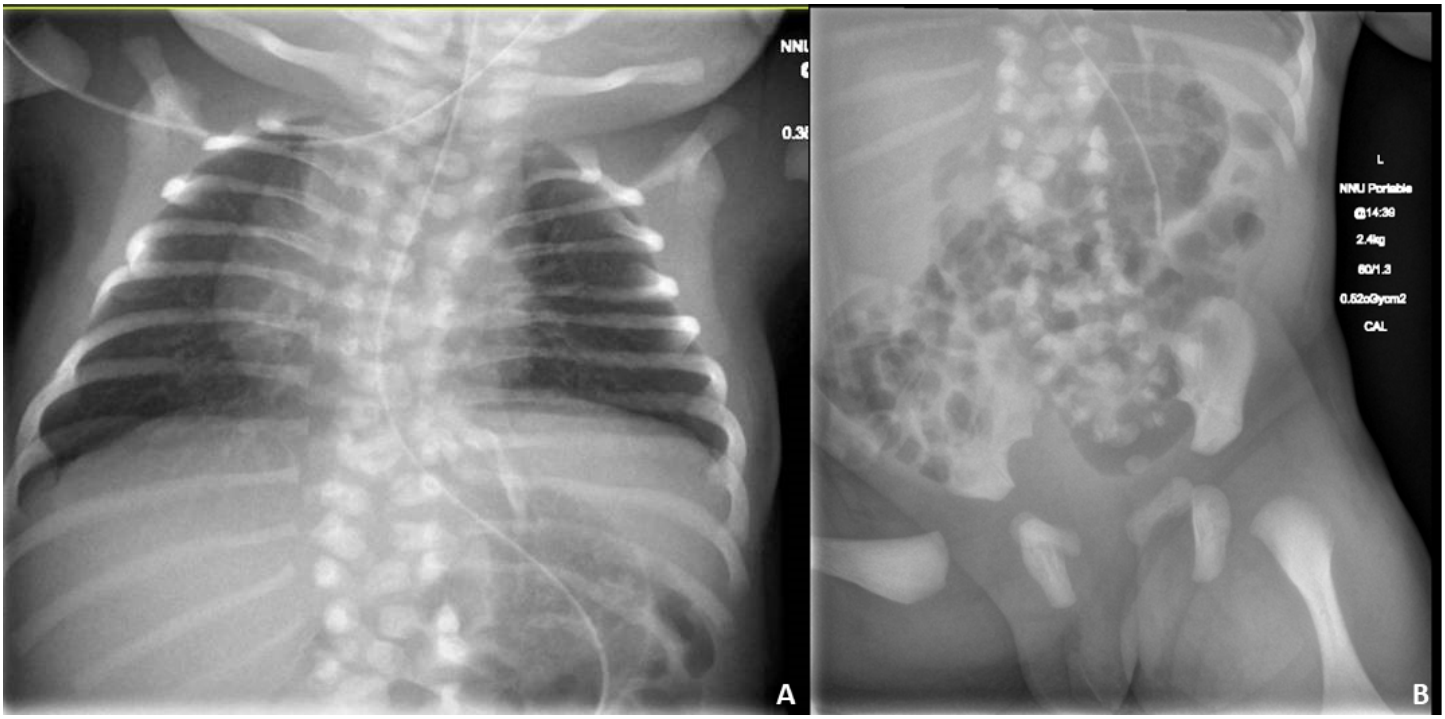

Figure 10. Thoracic (A) and lumbar spine (B) radiographs of an infant with *TBX6*-related SCDO

Courtesy of Charles Shaw-Smith, Exeter, UK

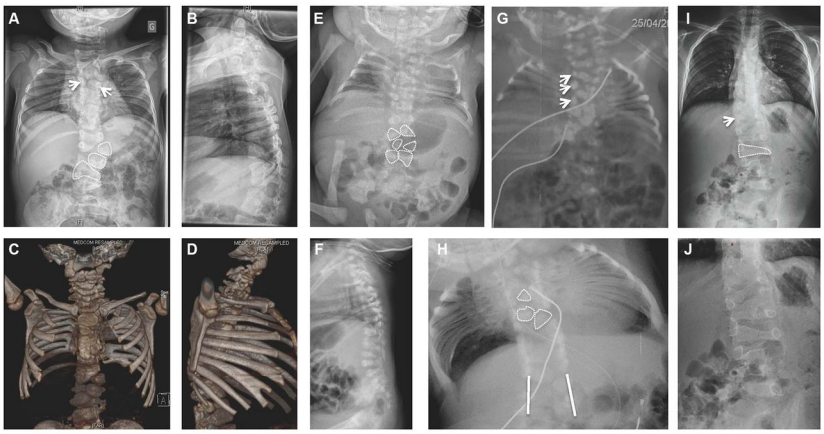

Figure 11. Radiologic features for the different genes identified in a cohort of individuals with regional multiple segmentation defects of the vertebrae

A-D. An individual with *DLL3*-related SCDO

E & F. An individual with *LFNG*-related SCDO

G. An individual with *HES7*-related SCDO

H. An individual with spondylothoracic dysostosis (STD) due to biallelic pathogenic variants in *MESP2*

I & J. An individual with *TBX6*-related SCDO

Reprinted with permission from Lefebvre et al [2018]

TBX6. To date, *TBX6* pathogenic variants have been associated with the following:

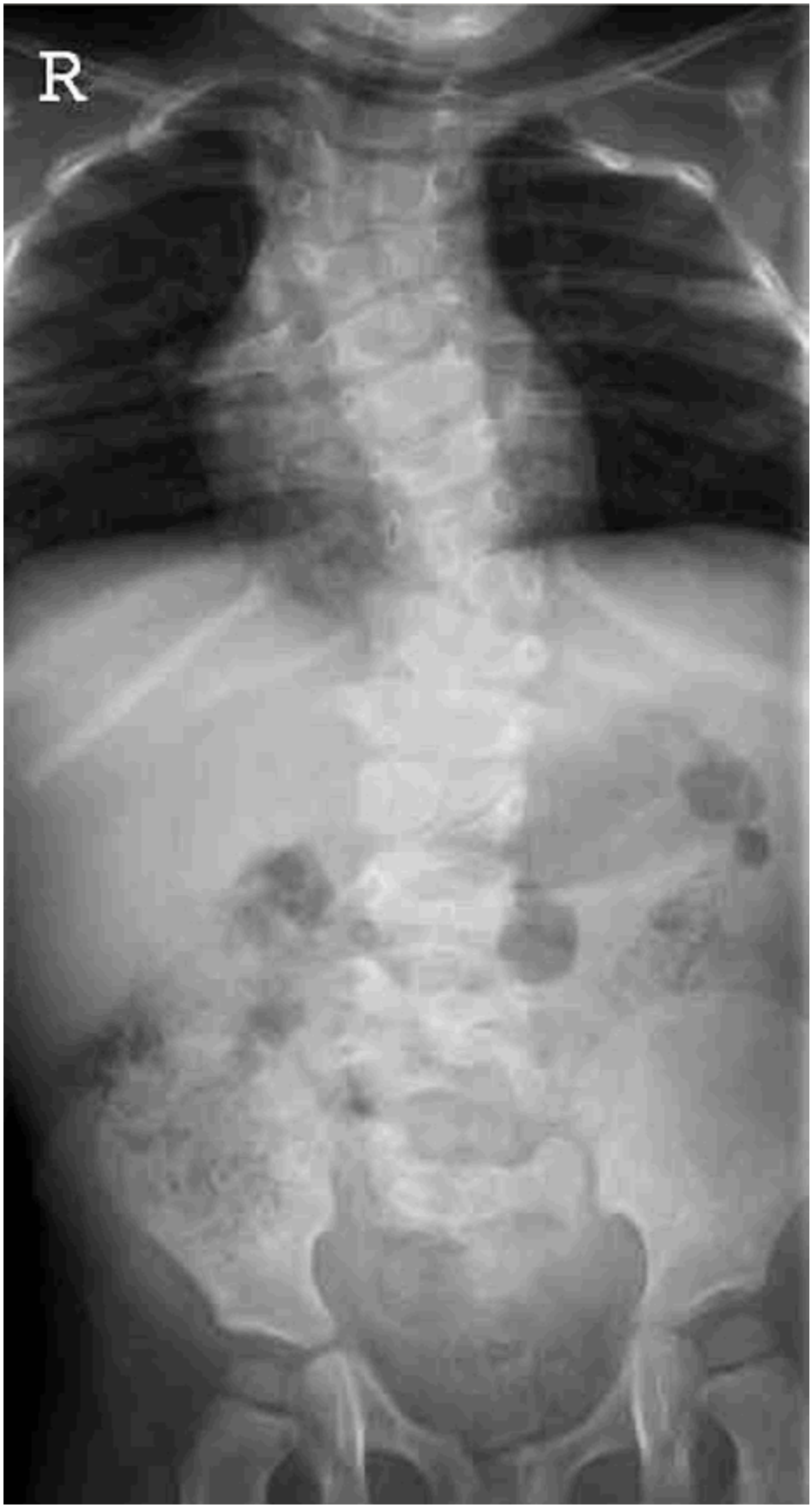

Figure 12. Radiograph of a child with a mild form of *DLL3*-related SCDO. All vertebrae show at least some relatively mild segmentation abnormality.

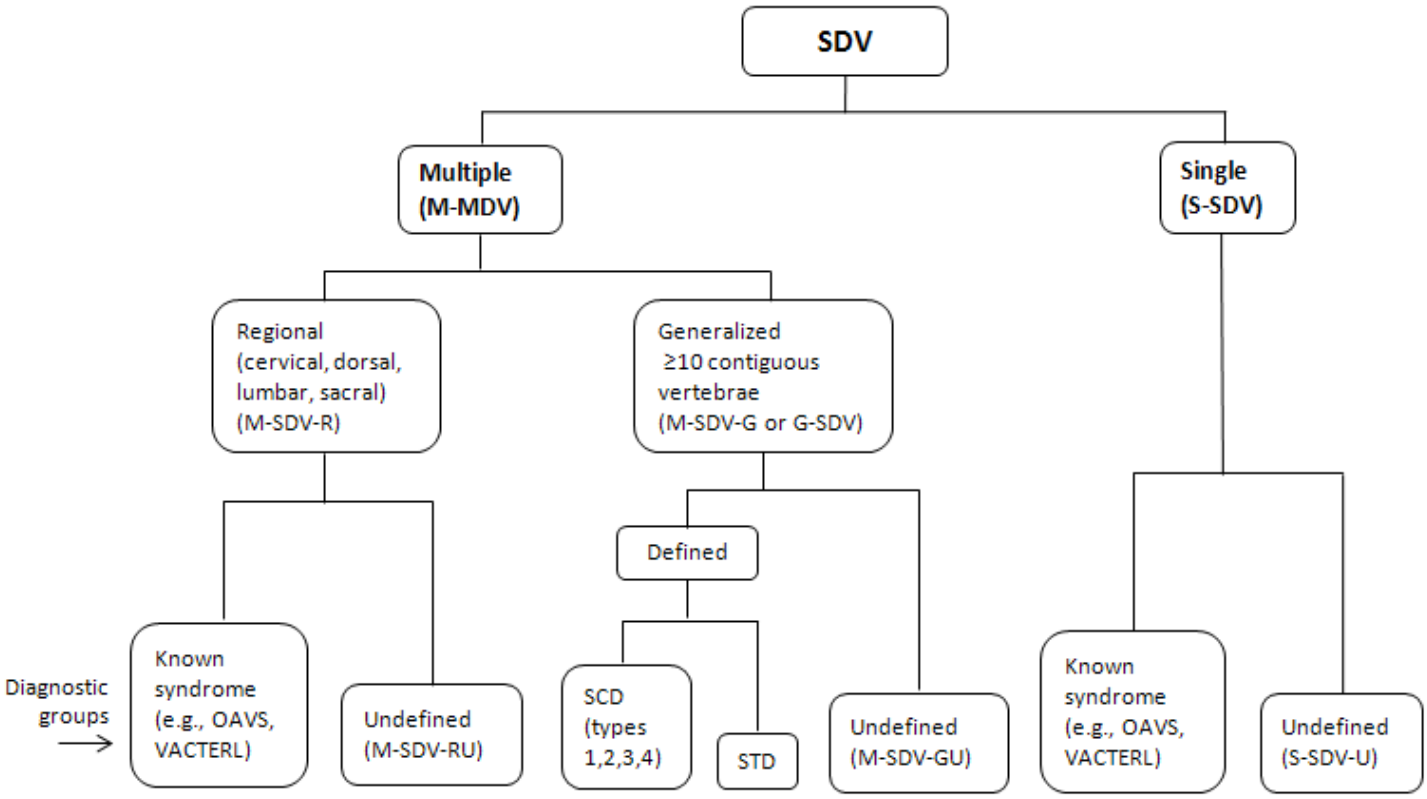

Figure 13. ICVAS clinical classification algorithm

All forms of SDV can be placed in one of seven broad categories. The classification combines a descriptive approach for the diverse radiologic phenotypes encountered in clinical practice with specific diagnoses where the genotype and/or syndrome is clearly established. For any given case a radiologic report also includes a specific description of the site and nature of the vertebral anomalies.

G = generalized; M = multiple; R = regional; S = single; SDV = segmentation defect(s) of the vertebrae; U = undefined

- Heterozygous *TBX6* deletions, sometimes in *trans* with a hypomorphic allele, have been reported in individuals with congenital scoliosis and müllerian aplasia or renal malformations [Sandbacka et al 2013, Wu et al 2015, Li et al 2022]. The most commonly reported hypomorphic allele is the T-C-A permissive haplotype, defined by single-nucleotide polymorphisms at the positions of rs2289292, rs3809624, and rs38090627 [Chen et al 2020].
- Autosomal dominant spondylocostal dysostosis (SCDO) was identified in a three-generation family. The widespread vertebral malformations consisted of a mixture of hemivertebrae and blocks of fused segments. There was relative sparing of rib involvement. Mild scoliosis was centered on the mid-thoracic region. No other anomalies were identified, and neurodevelopment was normal. A heterozygous *TBX6* pathogenic variant (p.Ter437CextTer81), disrupting the natural stop codon, segregated with the condition, and functional studies demonstrated approximately half the wild type transcriptional activation activity [Gucev et al 2010, Sparrow et al 2013b] (see Figure 8). Subsequent analysis showed that this *TBX6* stop-lost variant was located within the T-C-A permissive haplotype. The combined reduction in *TBX6* expression and transcriptional activation might therefore account for the SCDO phenotype or, possibly, the 81 amino acids added to the C-terminal may affect the ability of TBX6 to interact with other proteins that are critical in vertebral formation [Wu et al 2015].
- Variable segmentation anomalies, most commonly affecting the lower thoracic or upper lumbar regions and usually presenting as congenital scoliosis, have been reported. This may be due to deletion of *TBX6* on one allele and a high-risk haplotype of polymorphisms on the other allele [Wu et al 2015, Takeda et al 2017].

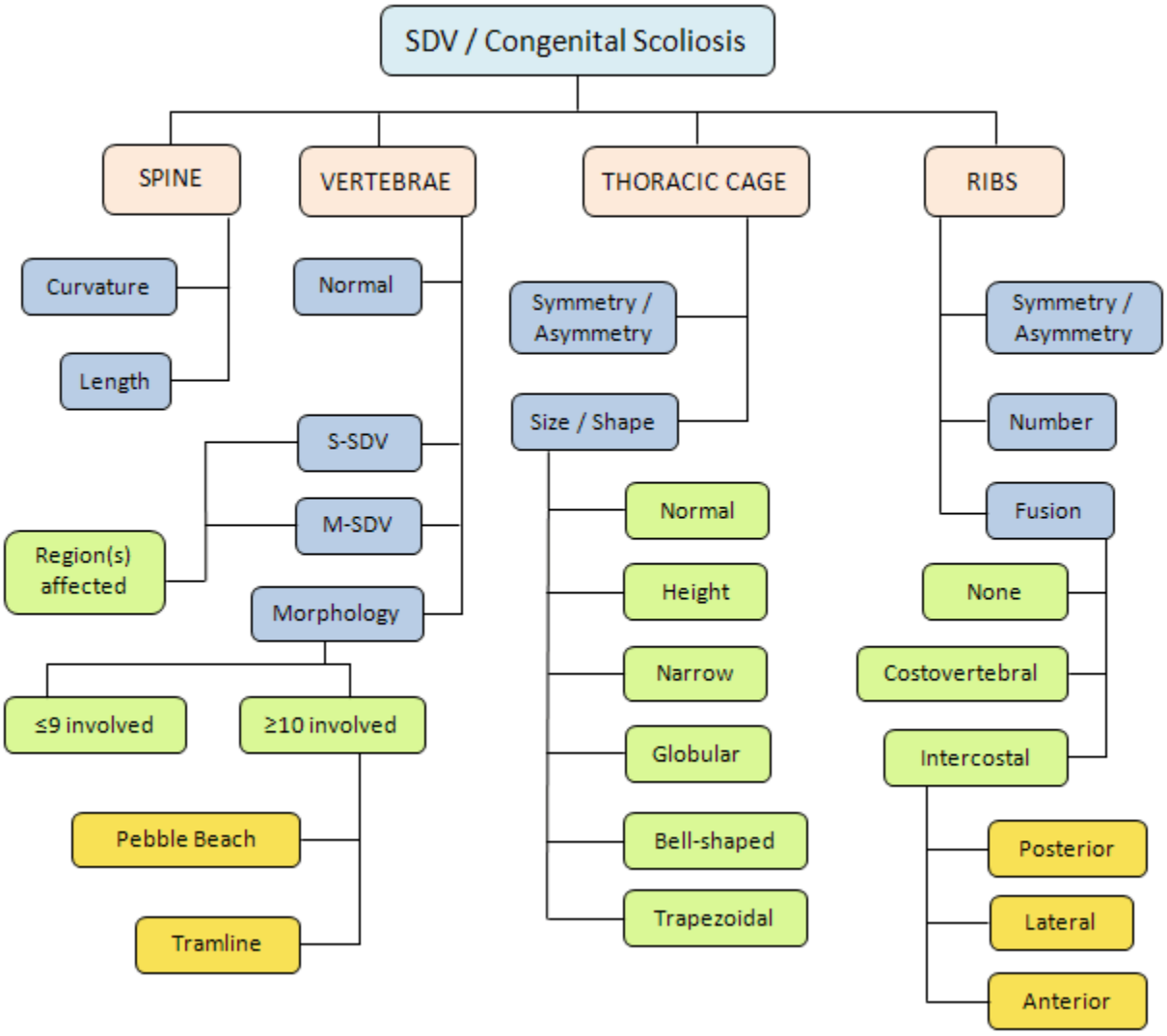

Figure 14. ICVAS research classification algorithm: a more detailed, systematic analysis of radiographic anatomic features. Documentation of phenotypes in a systematic ontology facilitates direct interspecies comparison and stratification of patient cohorts for research.

- A distinct, very severe, lethal form of STD with müllerian duct anomalies was reported [P Turnpenny, unpublished data], more severe than the individual with severe *TBX6*-related SCDO reported by Errichiello et al [2020].
- Müllerian aplasia / MURCS association / Mayer-Rokitansky-Küster-Hauser syndrome has been reported [Sandbacka et al 2013].

Contiguous gene deletions. It has been determined that vertebral abnormalities and scoliosis observed in some individuals with the 16p11.2 recurrent deletion result from a combination of a *TBX6* null allele (i.e., the recurrent deletion that encompasses *TBX6* as well as multiple adjacent genes) and a hypomorphic *TBX6* allele [Wu et al 2015]. The 16p11.2 recurrent deletion phenotype is characterized by motor speech disorder, language disorder, motor coordination difficulties, psychiatric conditions, and autistic features.

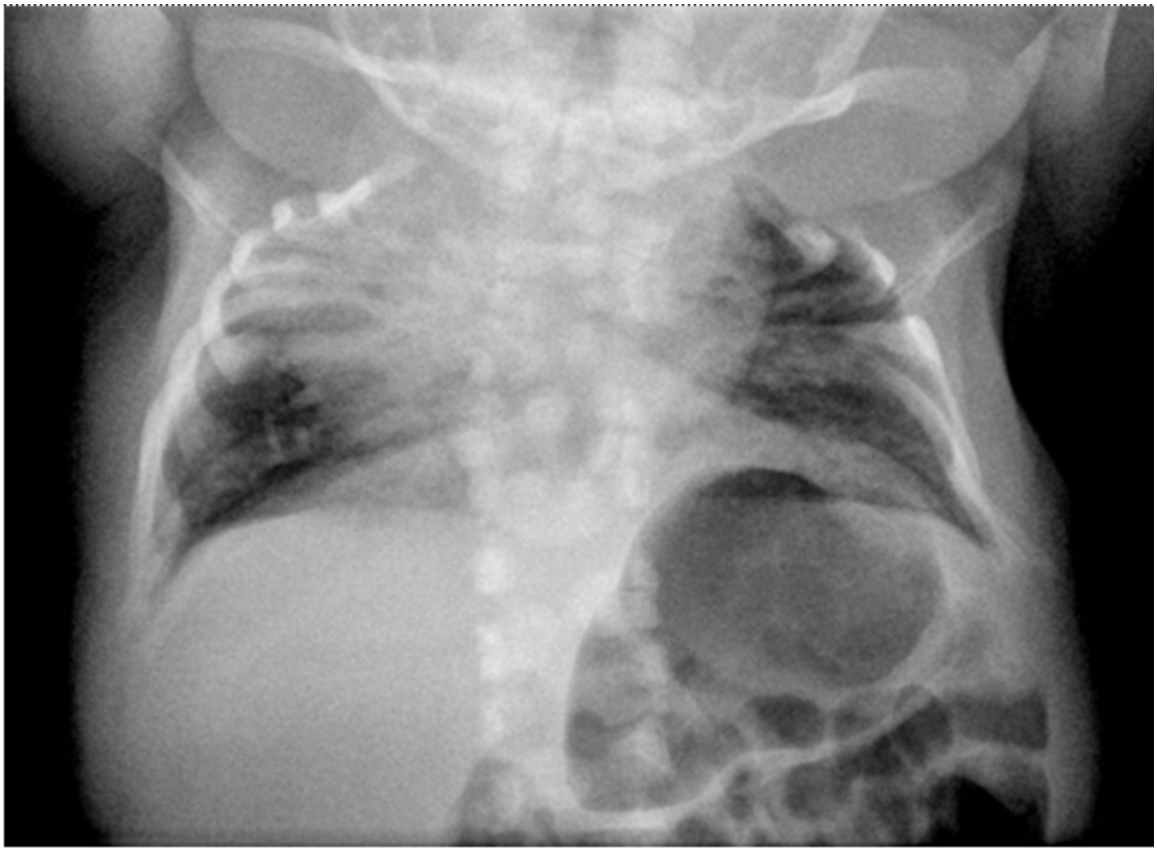

Figure 15. Radiograph of an infant with *MESP2*-related STD. The spine is severely shortened with fusion of the ribs posteriorly at the costovertebral junctions. The ribs fan out in a "crab-like" manner, and in many individuals the ribs show no points of intercostal fusion distal to their posterior origins.

Differential Diagnosis

Rarely, spondylocostal dysostosis (SCDO) occurs in association with chromosome abnormalities; however, apart from trisomy 8 mosaicism, no consistent genomic region has been involved, and the significance of these associations is unknown.

Autosomal dominant SCDO. One family with autosomal dominant SCDO due to a heterozygous *TBX6* pathogenic variant has been reported (OMIM 122600). Additional families with autosomal dominant SCDO without an identified gene have also been reported; in these families the extent of segmentation defects of the vertebrae is quite variable [Rimoin et al 1968, Kubryk & Borde 1981, Temple et al 1988, Lorenz & Rupprecht 1990].

Spondylothoracic dysostosis (STD), despite similarities to autosomal recessive SCDO, has distinctive phenotypic features that warrant this separate designation. Infants with STD are at the highest risk for respiratory insufficiency and have a nearly 50% mortality rate by the end of infancy [Cornier et al 2004]. To date, most individuals reported with STD have had pathogenic nonsense variants in exon 1 of *MESP2* (see Genetically Related Disorders). The differences in the radiographic findings in STD that distinguish it from SCDO include the following (see Figure 11):

- More severe shortening of the spine (all vertebral segments affected), especially the thoracic spine, leading to impaired respiratory function in infancy
- Rib fusions typically occurring posteriorly at the costovertebral origins, where the spinal shortening is most severe. The ribs usually appear straight and neatly aligned without points of fusion along their

length. On anteroposterior x-ray the ribs characteristically "fan out" from their costovertebral origins in a "crab-like" fashion.
- A distinctive radiographic appearance called the "tramline sign" that results from early radiographic prominence of the vertebral pedicles, in contrast to the vertebral bodies, which have no regular form or layout [Turnpenny et al 2007].

Segmentation defects of the vertebrae (SDV) are estimated to occur in 0.5-1.0 in 1,000 live births, but in clinical practice the radiologic phenotypes and syndromic associations are extremely diverse. Syndromic forms of multiple segmentation defects of the vertebrae (M-SDV) should be considered if the diagnostic criteria for SCDO or STD are not met. For most individuals the underlying cause is not known, but an increasing number of genes are being identified. Some of the M-SDV syndromes to consider are listed in Tables 2a and 2b.

Table 2a. Selected Genes Associated With M-SDV (SCDO and STD excluded)

Gene(s)	MOI	Syndrome/Disorder
ACVR1	AD	Fibrodysplasia ossificans progressiva
ANKRD11 [1]	See footnote 1.	KBG syndrome
CHD7	AD	*CHD7* disorder (incl CHARGE syndrome)
CHRNG	AR	Multiple pterygium syndrome, Escobar variant (OMIM 265000)
DHODH	AR	Postaxial acrofacial dysostosis (OMIM 263750)
FLNB	AD	Atelosteogenesis type III (See *FLNB* Disorders.)
	AD	Larsen syndrome (See *FLNB* Disorders.)
	AR	Spondylocarpotarsal synostosis syndrome (See *FLNB* Disorders.)
GDF3	AD	Klippel-Feil syndrome/anomaly (OMIM PS118100)
GDF6	AD	
MEOX1	AR	
GPC3	XL	Simpson-Golabi-Behmel syndrome type 1
GPC4	XL	
HSPG2	AR	Dyssegmental dysplasia, Silverman-Handmaker type (OMIM 224410)
IKBKG	XL	Incontinentia pigmenti
JAG1	AD	Alagille syndrome
NOTCH2	AD	
KMT2D	AD	Kabuki syndrome
KDM6A	XL	
MKKS	AR	McKusick-Kaufman syndrome
MNX1	AD	Currarino syndrome (OMIM 176450)
PUF60	AD	Verheij syndrome (OMIM 615583)
RECQL4	AR	RAPADILINO syndrome (OMIM 266280)
ROR2	AR	*ROR2*-related Robinow syndrome
SF3B2	AD	Goldenhar syndrome / oculo-auriculo-vertebral spectrum (OMIM 164210)

Table 2a. continued from previous page.

Gene(s)	MOI	Syndrome/Disorder
SLC26A2	AR	Atelosteogenesis type II (de la Chapelle dysplasia)
SOX9	AD	Campomelic dysplasia
TBX6	AD	Müllerian aplasia / MURCS association / Mayer-Rokitansky-Kuster-Hauser syndrome (See Genetically Related Disorders.)
WNT9B [2]	AD	Mayer-Rokitansky-Kuster-Hauser syndrome
TMCO1	AR	Cerebro-facio-thoracic dysplasia (OMIM 213980)
VANGL1	AD	Caudal dysgenesis syndrome
WNT5A	AD	Autosomal dominant Robinow syndrome

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; M-SDV = multiple segmentation defects of the vertebrae; RAPADILINO = radial ray defect, patellae hypoplasia or aplasia and cleft or highly arched palate, diarrhea and dislocated joints, little size and limb malformation, nose slender and normal intelligence; SCDO = spondylocostal dysostosis; STD = spondylothoracic dysostosis; XL = X-linked

1. KBG syndrome is caused by either a heterozygous pathogenic variant in *ANKRD11* or deletion of 16q24.3 that includes *ANKRD11*. Recurrence risk for sibs of a proband with KBG syndrome depends on the genetic alteration.

2. Waschk et al [2016]

Table 2b. Other Syndromes/Conditions That Include M-SDV (SCDO and STD excluded)

Syndrome/Condition	
22q11.2 deletion syndrome (DiGeorge syndrome / velocardiofacial syndrome)	
Chromosome abnormalities	
Maternal diabetes mellitus	
Syndromes of unknown genetic cause	Casamassima-Morton-Nance syndrome (OMIM 271520) (SDV & urogenital anomalies)
	Cleft-limb-heart malformation syndrome (OMIM 215850)
	Dyssegmental dysplasia, Rolland-Desbuquois type (OMIM 224400)
	Facial dysmorphism with multiple malformations (OMIM 227255)
	Femoral hypoplasia-unusual facies syndrome (OMIM 134780)
	Lower mesodermal agenesis
	OEIS complex (OMIM 258040)
	Phaver syndrome (OMIM 261575)
	Spinal dysplasia, Anhalt type (OMIM 601344)
	Limb deficiency-vertebral hypersegmentation-absent thymus [1]
	VATER/VACTERL (OMIM 192350)
	Wildervanck syndrome (OMIM 314600)

M-SDV = multiple segmentation defects of the vertebrae; SCDO = spondylocostal dysostosis; STD = spondylothoracic dysostosis

1. Urioste et al [1996]

Note: A single individual with an SCDO-like phenotype with multiple regional segmentation defects of the vertebrae, multiple intervertebral fusions of laminae, dysmorphic features, and cleft palate has been reported in association with homozygosity for a start-loss variant in *DMRT2* [Bouman et al 2018]. With severe left-sided rib cage deficiency, the infant died at age nine days. It is not yet known if *DMRT2*-related SCDO is a distinct entity.

Neural tube defects are also frequently associated with adjacent severe segmentation anomalies of one or more vertebrae. However, current consensus is that the diagnosis of SCDO should be reserved for individuals with abnormal segmentation of at least ten contiguous vertebrae.

Management

No clinical practice guidelines for autosomal recessive spondylocostal dysostosis (SCDO) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with autosomal recessive SCDO, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Autosomal Recessive Spondylocostal Dysostosis: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Skeletal	Full spine x-rays, AP & lateral x-rays, & chest x-rays	
Respiratory	Assessment of respiratory function per pulmonologist, esp if tachypnea &/or feeding difficulties suggest possibility of respiratory insufficiency	
Gastrointestinal	• Assessment of feeding • Eval of male child for presence of inguinal hernia	
Kidneys / Urinary tract	Ultrasound eval of kidneys & urinary tract	In persons w/*LFNG*-related SCDO
Neurologic	MRI of full spinal cord to assess for assoc neurologic complications	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of AR SCDO to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

AR = autosomal recessive; MOI = mode of inheritance; SCDO = spondylocostal dysostosis
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

In the majority of individuals, treatment is conservative because the clinical manifestations of the vertebral and rib malformations do not increase with age.

Table 4. Autosomal Recessive Spondylocostal Dysostosis: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Growth	No specific nutritional needs to be considered other than maintaining appropriate weight for height	Persons w/SCDO all have variable short-trunk short stature.

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Scoliosis	Surgical intervention as needed if scoliosis is significant; severe scoliosis is unusual.	External bracing (e.g., using vertical expandable prosthetic titanium rib) [1] may be considered, as well as growing rods & other devices as appropriate.
Respiratory distress/ failure	• Respiratory support, depending on extent of pulmonary compromise (usually only necessary in severe disease) • Assessment for complications of respiratory disease, incl pulmonary hypertension & cardiac failure as indicated	
Neurologic	Standard treatment of neurologic problems assoc w/*LFNG*-related SCDO according to findings & symptoms	
Inguinal hernia	• Educate parents / care providers of young males of signs/ symptoms of inguinal hernia & potential complications. • Routine mgmt of inguinal hernia per general surgeon	

SCDO = spondylocostal dysostosis
1. Ramirez et al [2010], Parnell et al [2015], Pons-Odena et al [2017], Studer & Hasler [2020]

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 5 are recommended.

Table 5. Autosomal Recessive Spondylocostal Dysostosis: Recommended Surveillance

System/Concern	Evaluation	Frequency
Growth/Nutrition	Assess growth.	At each visit throughout childhood
Skeletal	Assessment for spinal curvature	Annually or as needed
Respiratory	Assessment of respiratory function	
Neurologic	Assessment of neurologic & motor function	Annually or as needed in those w/*LFNG*-related SCDO
Development	Developmental assessment	Annually or as needed
Gastrointestinal	The parents /care providers of young males need to be alert for signs of inguinal hernia & its potential complications.	Annually or as needed

SCDO = spondylocostal dysostosis

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Virtually all individuals with SCDO have relative truncal shortening, and some have generalized short stature. For affected women, pregnancy may give rise to exaggerated intra-abdominal pressure problems, though there is no published research on this issue. As the spine is distorted, there are likely to be concerns with offering spinal and/or epidural anesthesia. However, spinal anesthesia has been successfully administered [Dolak & Tartt 2009].

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Spondylocostal dysostosis (SCDO) caused by biallelic pathogenic variants in *DLL3*, *HES7*, *LFNG*, *MESP2*, *RIPPLY2*, or *TBX6* is inherited in an autosomal recessive manner.

Note: Autosomal dominant inheritance of *TBX6*-related SCDO has been reported in a three-generation family (all affected family members were male) [Sparrow et al 2013b]. Autosomal dominant inheritance is not discussed further in this section.

Pseudodominant inheritance. Although rare, there have been reports of SCDO appearing to be inherited in an autosomal dominant manner, although the extent of segmentation defects of the vertebrae (SDV) is variable [Temple et al 1988, Gucev et al 2010, Sparrow et al 2012]. In one such family [Floor et al 1989] the inheritance pattern was shown to be an example of pseudodominant inheritance (i.e., an autosomal recessive condition present in individuals in two or more generations of a family, thereby appearing to follow a dominant inheritance pattern) of *DLL3*-related SCDO in a highly consanguineous family [Turnpenny et al 1999, Whittock et al 2004a].

Risk to Family Members (Autosomal Recessive Inheritance)

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an autosomal recessive SCDO-causing pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an autosomal recessive SCDO-causing pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an autosomal recessive SCDO-causing pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an affected individual's reproductive partner* has heterozygous or biallelic pathogenic variants in the same autosomal recessive SCDO-related gene as that involved in the proband, offspring will be obligate heterozygotes (carriers) for an autosomal recessive SCDO-causing pathogenic variant.

* Molecular genetic testing for reproductive partners is appropriate, particularly if consanguinity is likely. Approximately 75% of individuals with autosomal recessive SCDO are from consanguineous families, usually from communities in which cousin partnerships are common.

Other family members. Each sib of the proband's parents is at 50% risk of being a carrier of an autosomal recessive SCDO-causing pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the autosomal recessive SCDO-causing pathogenic variants in the family. See Related Genetic Counseling Issues, **Family planning**.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.
- Molecular genetic carrier testing of individuals from high-risk families, in which one or more individuals has been diagnosed with SCDO, may be helpful in identifying at-risk couples.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the autosomal recessive SCDO-related pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Fetal ultrasound examination. In experienced hands, detailed fetal ultrasound scanning is sensitive enough to detect multiple segmentation defects of the vertebrae (M-SDV) as early as 13 weeks' gestation, especially when the malformation is anticipated and looked for specifically. However, molecular genetic testing of an at-risk pregnancy is considered the gold standard for accurate prenatal diagnosis. Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **UCLA International Skeletal Dysplasia Registry (ISDR)**
  Phone: 310-825-8998
  International Skeletal Dysplasia Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Spondylocostal Dysostosis, Autosomal Recessive: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
DLL3	19q13.2	Delta-like protein 3	DLL3 database	DLL3	DLL3
HES7	17p13.1	Transcription factor HES-7		HES7	HES7
LFNG	7p22.3	Beta-1,3-N-acetylglucosaminyltransferase lunatic fringe		LFNG	LFNG
MESP2	15q26.1	Mesoderm posterior protein 2	MESP2 database	MESP2	MESP2
RIPPLY2	6q14.2	Protein ripply2		RIPPLY2	RIPPLY2
TBX6	16p11.2	T-box transcription factor TBX6	TBX6 database	TBX6	TBX6

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Spondylocostal Dysostosis, Autosomal Recessive (View All in OMIM)

122600	SPONDYLOCOSTAL DYSOSTOSIS 5; SCDO5
277300	SPONDYLOCOSTAL DYSOSTOSIS 1, AUTOSOMAL RECESSIVE; SCDO1
602427	T-BOX TRANSCRIPTION FACTOR 6; TBX6
602576	LFNG O-FUCOSYLPEPTIDE 3-BETA-N-ACETYLGLUCOSAMINYLTRANSFERASE; LFNG
602768	DELTA-LIKE CANONICAL NOTCH LIGAND 3; DLL3
605195	MESODERM POSTERIOR BASIC HELIX-LOOP-HELIX TRANSCRIPTION FACTOR 2; MESP2
608059	HES FAMILY bHLH TRANSCRIPTION FACTOR 7; HES7
608681	SPONDYLOCOSTAL DYSOSTOSIS 2, AUTOSOMAL RECESSIVE; SCDO2
609813	SPONDYLOCOSTAL DYSOSTOSIS 3, AUTOSOMAL RECESSIVE; SCDO3
609891	RIPPLY TRANSCRIPTIONAL REPRESSOR 2; RIPPLY2
613686	SPONDYLOCOSTAL DYSOSTOSIS 4, AUTOSOMAL RECESSIVE; SCDO4
616566	SPONDYLOCOSTAL DYSOSTOSIS 6, AUTOSOMAL RECESSIVE; SCDO6

Molecular Pathogenesis

The six genes known to be associated with the six subtypes of autosomal recessive spondylocostal dysostosis (SCDO) encode proteins that are key components of the Notch signaling pathway, which (together with FGF and Wnt signaling) is one of the developmental pathways essential to normal somitogenesis [Dequéant et al 2006, Dequéant & Pourquié 2008].

- *DLL3* encodes a ligand of NOTCH1 that inhibits signaling.

- *HES7* encodes a basic helix-loop-helix (bHLH)-orange domain transcriptional repressor protein. *HES7* is a direct target of NOTCH1 receptor signaling and is also a cycling gene expressed in the presomitic mesoderm.
- *LFNG* encodes a glycosyltransferase that post-translationally modifies the Notch family of cell-surface receptors. *LFNG* is a direct target of NOTCH1 receptor signaling and is also a cycling gene expressed in the presomitic mesoderm.
- *MESP2* encodes a member of the bHLH family of transcriptional regulatory proteins. *MESP2* is a direct target of NOTCH1 receptor signaling.
- *RIPPLY2* is a negative regulator of TBX6 and is a direct transcriptional target of MESP2 and of TBX6.
- *TBX6* encodes a T-box transcription factor. TBX6 activates *DLL1* gene expression, which is an activating ligand of the NOTCH1 receptor; it also activates *MESP2* gene expression.

Mechanism of disease causation. Loss of function

Table 6. Autosomal Recessive Spondylocostal Dysostosis: Gene-Specific Laboratory Considerations

Gene [1]	Special Consideration
DLL3	Exon 8 is GC rich. PCR additives may be required.
HES7	Exon 4 is GC rich. PCR additives may be required.
MESP2	• Exon 1 contains a GQ poly tract consisting of 12 nucleotide repeats of type A, B, or C beginning at nucleotide 535. Repeat A: GGG CAG GGG CAA; repeat B: GGA CAG GGG CAA; repeat C: GGG CAG GGG CGC. • The reference sequence has an AABBC repeat. Bidirectional Sanger sequencing may be required.

1. Genes from Table 1 in alphabetic order.

Table 7. Pathogenic Variants Referenced in This *GeneReview* by Gene

Gene	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
MESP2	NM_001039958.2 NP_001035047.1	c.500_503dupACCG	p.Gly169ProfsTer199	See Genotype-Phenotype Correlations.

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

International Consortium for Spinal Genetics Development and Disease (ICSGDD)

Acknowledgments

Research on spondylocostal dysostosis (SCDO) in Exeter has been funded by Action Medical Research, British Scoliosis Research Foundation, and the Skeletal Dysplasia Group, to whom the authors are indebted. In the Exeter Molecular Genetics Laboratory the work was undertaken by Mike Bulman, June Duncan (deceased), Neil Whittock, and recently Melissa Sloman, all under the supervision of Sian Ellard. The work greatly benefited from collaboration with Kenro Kusumi, Sally Dunwoodie, and, more recently, Olivier Pourquié, Philip Giampietro, Alberto Cornier, Amaka Offiah, and Ben Alman, through the ICVAS consortium. Many clinicians have sent images of individuals with segmentation defects of the vertebrae (SDV), but for this review particular thanks are due to Dr Oivind Braaten, Oslo, Norway, and Drs Karin van Spaendonck-Zwarts and Mirjam M de Jong,

Groningen, the Netherlands, Professor Eleni Fryysira and Dr Michael Christadoulou, Athens, Greece, and Dr Charles Shaw-Smith, Exeter, UK. Sally Dunwoodie received SCDO research funds from the National Health and Medical Research Council (ID142006, 404804,1044543, 1042002, 1135886).

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Revision History

- 17 August 2023 (sw) Comprehensive update posted live
- 21 December 2017 (sw) Comprehensive update posted live
- 17 January 2013 (me) Comprehensive update posted live
- 25 August 2009 (et) Review posted live
- 6 February 2009 (pdt) Original submission

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Published Guidelines / Consensus Statements

The ICVAS classification system for congenital scoliosis and segmentation defects of the vertebrae has been published [Turnpenny et al 2007, Offiah et al 2010] and includes an algorithm that helps clinicians determine which individuals are most suitable for genetic testing.

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