Spondylocostal Dysostosis

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Spondylocostal dysostosis is a group of conditions characterized by abnormal development of bones in the spine and ribs. The bones of the spine (vertebrae) are misshapen and abnormally joined together (fused). Many people with this condition have abnormal side-to-side curvature of the spine (scoliosis) due to malformation of the vertebrae. In addition to spinal abnormalities, some of the rib bones may be fused together or missing. Affected individuals have short, rigid necks and short torsos because of the bone malformations. As a result, people with spondylocostal dysostosis have short bodies but normal-length arms and legs, called short-trunk dwarfism.

genetic conditions

1. Introduction

The spine and rib abnormalities, which are present from birth, cause other signs and symptoms of spondylocostal dysostosis. Infants with this condition have small chests that cannot expand adequately, often leading to life-threatening breathing problems. As the lungs expand in the narrow chest, the muscle that separates the abdomen from the chest cavity (the diaphragm) is forced down and the abdomen is pushed out. The increased pressure in the abdomen can cause a soft out-pouching around the lower abdomen (inguinal hernia), particularly in males with spondylocostal dysostosis.

Some people with spondylocostal dysostosis also have a type of birth defect known as a neural tube defect. Neural tube defects occur when a structure called the neural tube, a layer of cells that ultimately develops into the brain and spinal cord, fails to close completely during the first few weeks of embryonic development. Examples of neural tube defects that occur in people with spondylocostal dysostosis include a spinal cord abnormality known as spina bifida and a brain abnormality called a Chiari malformation.

Although breathing problems can be fatal early in life, many affected individuals live into adulthood.

Spondylocostal dysostosis has often been grouped with a similar condition called spondylothoracic dysostosis, and both are sometimes called Jarcho-Levin syndrome; however, they are now considered distinct conditions.

2. Frequency

Spondylocostal dysostosis is a rare condition, although its exact prevalence is unknown.

3. Causes

Mutations in several genes are known to cause spondylocostal dysostosis. The most common form of the condition, spondylocostal dysostosis type 1, is caused by mutations in the *DLL3* gene. Mutations in other identified genes each account for a small number of cases of the condition.

The *DLL3* gene and other genes involved in spondylocostal dysostosis play roles in the Notch signaling pathway, which is important in embryonic development. One of the functions of Notch signaling is directing the separation of future vertebrae and ribs from one another during early development, a process called somite segmentation. When the Notch signaling pathway is disrupted, somite segmentation does not occur properly, resulting in the malformation and fusion of the bones of the spine and ribs seen in spondylocostal dysostosis.

Mutations in the identified genes account for approximately 25 percent of cases of spondylocostal dysostosis. Researchers suggest that additional genes involved in the Notch signaling pathway might also be associated with the condition.

3.1 The genes associated with Spondylocostal dysostosis

- DLL3
- MESP2

4. Inheritance

Spondylocostal dysostosis can have different inheritance patterns. Most types, including type 1, are inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition. Other types of spondylocostal dysostosis are inherited in an autosomal dominant pattern. Autosomal dominant inheritance means that one copy of an altered gene in each cell is sufficient to cause the disorder. The signs and symptoms of spondylocostal dysostosis are typically more severe with autosomal recessive inheritance.

5. Other Names for This Condition

- Jarcho-Levin syndrome
- SCDO

References

1. Alatas I, Canaz H, Akkoyun N, Er A, Demirhan O, Kizilay D, Emel E. Neural tubedefects in Jarcho-Levin syndrome: study of twenty-eight cases. Pediatr Neurosurg.2015;50(2):57-62. doi:

10.1159/000380770.

2. Berdon WE, Lampl BS, Cornier AS, Ramirez N, Turnpenny PD, Vitale MG, SeimonLP, Cowles RA. Clinical and radiological distinction between spondylothoracicdysostosis (Lavy-Moseley syndrome) and spondylocostal dysostosis (Jarcho-Levinsyndrome). Pediatr Radiol. 2011 Mar;41(3):384-8. doi: 10.1007/s00247-010-1928-8.
3. Bulman MP, Kusumi K, Frayling TM, McKeown C, Garrett C, Lander ES, Krumlauf R,Hattersley AT, Ellard S, Turnpenny PD. Mutations in the human delta homologue,DLL3, cause axial skeletal defects in spondylocostal dysostosis. Nat Genet. 2000 Apr;24(4):438-41.
4. Dunwoodie SL. Reprint of mutation of the fucose-specific beta1,3N-acetylglucosaminyltransferase LFNG results in abnormal formation of the spine. Biochim Biophys Acta. 2009 Sep;1792(9):862-73.
5. Gucev ZS, Tasic V, Pop-Jordanova N, Sparrow DB, Dunwoodie SL, Ellard S, Young E, Turnpenny PD. Autosomal dominant spondylocostal dysostosis in threegenerations of a Macedonian family: Negative mutation analysis of DLL3, MESP2,HES7, and LFNG. Am J Med Genet A. 2010 Jun;152A(6):1378-82. doi:10.1002/ajmg.a.33471.
6. McInerney-Leo AM, Sparrow DB, Harris JE, Gardiner BB, Marshall MS, O'ReillyVC, Shi H, Brown MA, Leo PJ, Zankl A, Dunwoodie SL, Duncan EL. Compoundheterozygous mutations in RIPPLY2 associated with vertebral segmentation defects.Hum Mol Genet. 2015 Mar 1;24(5):1234-42. doi: 10.1093/hmg/ddu534.
7. Sparrow DB, Chapman G, Turnpenny PD, Dunwoodie SL. Disruption of the somiticmolecular clock causes abnormal vertebral segmentation. Birth Defects Res CEmbryo Today. 2007 Jun;81(2):93-110. Review.
8. Sparrow DB, Guillén-Navarro E, Fatkin D, Dunwoodie SL. Mutation ofHairy-and-Enhancer-of-Split-7 in humans causes spondylocostal dysostosis. Hum MolGenet. 2008 Dec 1;17(23):3761-6. doi: 10.1093/hmg/ddn272.
9. Sparrow DB, McInerney-Leo A, Gucev ZS, Gardiner B, Marshall M, Leo PJ, ChapmanDL, Tasic V, Shishko A, Brown MA, Duncan EL, Dunwoodie SL. Autosomal dominantspondylocostal dysostosis is caused by mutation in TBX6. Hum Mol Genet. 2013 Apr 15;22(8):1625-31. doi: 10.1093/hmg/ddt012.
10. Whittock NV, Sparrow DB, Wouters MA, Sillence D, Ellard S, Dunwoodie SL,Turnpenny PD. Mutated MESP2 causes spondylocostal dysostosis in humans. Am J Hum Genet. 2004 Jun;74(6):1249-54.