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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

50 Years Ago Today: The Expanding Phenotype of Larsen Syndrome

Latta RJ, Graham CB, Aase J, Scham SM, Smith DW. Larsen's Syndrome: A Skeletal Dysplasia with Multiple Joint Dislocations and Unusual Facies. J Pediatr 1971;78:291-8.

Fifty years ago, Latta et al reported a 6-month-old male infant with multiple joint dislocations including the knee, hip, and elbow joints, as well as bilateral clubfoot deformities. The child had mid facial flattening and a low nasal bridge. Skeletal radiographs were significant for shortening of the proximal fibula; bilateral heel valgus with forefoot varus; shortening of the metatarsals, metacarpals, and phalanges; and hypoplasia of the distal half of the humerus. Spinal radiographs were significant for flattened hypoplastic vertebrae. The patient's radiographic features were very similar to those reported among 6 children, representing sporadic occurrences in their families, 21 years prior in *The Journal* by Larsen et al.[1] Inheritance for Larsen syndrome was postulated to be autosomal dominant or autosomal recessive. Other features associated with Larsen syndrome include short stature, hypertelorism, flattened nasal bridge, cleft palate, hearing loss, and accessory carpal bones.

Monoallelic missense mutations in filamin B were subsequently identified in 5 families with affected individuals affected by Larsen syndrome.[2] Filamins are cytoplasmic localized proteins that stabilize actin filament networks through their linkage to the cellular membrane and forming a platform for cell signaling to take place.

Larsen syndrome is a clinically and genetically heterogeneous syndrome. Homozygous or compound heterozygous mutations in *CHST3* have been associated with autosomal recessive Larsen syndrome, which is characterized by multiple joint dislocations in the neonatal period and evolves into spondyloepiphyseal dysplasia Omani type associated with kyphoscoliosis, disc degeneration, arthritis involving the spine hand hips, and dysplastic heart valves. Additional autosomal recessive forms of Larsen syndrome are characterized by mutations in *B4GALT7*and *GZF1*, which encodes GDNF-inducible zinc finger protein 1, a transcription factor with unknown function.[3] *GZF1*-mediated Larsen syndrome is associated with severe myopia and milder skeletal involvement.

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