

## Clinical Report

# Two Patients With Monomelic Ulnar Duplication With Mirror Hand Polydactyly: Segmental Laurin–Sandrow Syndrome

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**We have studied two unrelated boys with isolated left mirror hand and ulnar duplication. Neither had facial anomalies and family histories were unremarkable. We suggest that these boys have segmental Laurin–Sandrow syndrome, or mirror-image duplication, due to somatic mutation involving precursor cells of the left upper limb and that the facial and digital abnormalities in Laurin–Sandrow syndrome are consistent with ectopic anterior hedgehog signaling in the developing limb bud and in the maxillary processes of the face, which closely resemble findings in the *Doublefoot (Dbf)* mouse mutant.**

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**KEY WORDS:** ulnar duplication; Laurin–Sandrow; doublefoot; hedgehog

### INTRODUCTION

The Laurin–Sandrow syndrome (LSS) comprises duplication of ulna and fibula with absence of radius and tibia and preaxial poly/syndactyly of hands and feet, frequently in a mirror-like configuration [MIM #135750; Laurin et al., 1964; Sandrow et al., 1970]. Cleft nares and/or short, grooved columella or grooved philtrum are part of the proposed diagnostic criteria for this entity. While triphalangeal preaxial polydactyly or mirror-image polydactyly are always present in these patients considerable variability in the proximal limb defects is observed. Shortness of the tibia and fibula or normal radius and ulna may occur with typical digital and facial anomalies. Autosomal dominant inheritance has been described based on rare instances of vertical transmission. Overall, LSS is quite rare and only ten cases have been reported to date [Laurin et al., 1964; Sandrow et al., 1970; Kogekar et al., 1993; Martin et al., 1993; Martínez-Frías et al., 1994; Hatchwell and Dennis, 1996; Pilkington et al., 2000; Kantaputra, 2001].

At least 16 cases of single limb ulnar duplication and mirror-image polydactyly have been reported [Santero, 1936; Buettner, 1938; Stroer, 1938; Mukerji, 1956; Entin, 1959; Harrison et al., 1960; Pintilie et al., 1964; Burman, 1968;

Hussl et al., 1985]. Here, we describe two additional boys with isolated left mirror hand and ulnar duplication. We suggest consideration of somatic mosaicism for a mutation in lateral plate mesoderm sufficient to induce ectopic anterior hedgehog activity early in limb bud morphogenesis leading to a segmental form of LSS.

We also speculate that the *Doublefoot* mutation in the mouse [Lyon et al., 1996; Hayes et al., 1998; Yang et al., 1998; Hayes et al., 2001] is the LSS homolog and that molecular characterization in both will enhance our understanding of the regulation of ectopic hedgehog activity and will provide a useful tool for molecular segregation of the different forms of preaxial polydactyly in humans.

### CLINICAL REPORTS

#### Patient 1

When first seen, the proband was a 4-month-old boy born with preaxial polydactyly of his left hand. He was born at term after an uneventful pregnancy. Prenatal ultrasonography failed to visualize the left thumb, but other findings were otherwise normal. He was growing normally. Results of abdominal ultrasonography and 2-dimensional echocardiography were normal. He was the first child born to a 29-year-old mother and 31-year-old father; there was no apparent consanguinity. Both parents were normal and did not have limb abnormalities. Family history was unremarkable.

The patient's height, length, and head circumference were at the 25th centile for age. There were no nasal or auricular abnormalities. All physical findings were normal except for the left upper limb. The left forearm was 1 cm shorter than the right; there were no differences in the upper arm lengths. Left shoulder mobility and configuration were normal. There was severely limited flexion and extension at the left elbow; pronation and supination was possible by only 10° at most in both directions. The patient held his left wrist in 90° flexion, and passive movements showed extension only up to the neutral position; passive dorsiflexion of the left wrist was not possible. Left hand had eight fingers and no thumb. Fingers two to five were normally developed with full passive and active mobility; four additional digits were present preaxial to the index finger. These fingers were about one third smaller than the normally developed fingers two to five. The first three fingers immediately radial to the index finger were developed normally with full passive and active flexion and extension. The fourth most radial finger was hypoplastic with limited passive flexion and extension; active flexion of this finger was limited to approximately 30° total range of motion.

A radiograph of the left forearm and hand (Fig. 1A,B) showed absence of the radius and ulnar duplication. Carpal bones were not ossified. Seven metacarpal bones were normally developed and only the most radial finger lacked a metacarpal. All eight fingers had three phalanges (Fig. 1B: one flexed digit hides a

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Fig. 1. **A, B:** Radiographs of the left arm of case 1 showing duplicated ulna and hand showing eight-finger triphalangeal polydactyly.

terminal phalanx seen in other views). Radiography of the left shoulder and arm were normal (not shown).

#### Patient 2

This 6-year-old boy was the 7-pound, 8-ounce product of an uncomplicated pregnancy. Father had a unilateral clubfoot

and mother had a mild hallux valgus. His full sister was normal on exam. There is no consanguinity. His psychomotor development was normal. Left wrist was markedly flexed with a total of seven left digits and no thumb. Nasal columella, nares, and philtrum were normal. No chromosome analysis was performed. He has had four surgical procedures on his hands and elbow. Inflexibility and normal nasal morphology is shown in Figure 2A, and radiographs are shown in Figure 2B–D. These showed two ulnae and seven triphalangeal digits.

#### DISCUSSION

Preaxial polydactyly with absent thumb and supernumerary digits arranged in a descending order from the index finger medially is designated “mirror hand polydactyly” and, in combination with absent radius and tibia and ulnar and/or fibular duplication, is designated LSS. Numerous examples are known of preaxial or mirror-image polydactyly with or without radial and/or tibial shortness [Lettice et al., 2003; Wechsler et al., 2004], and there likely is genetic heterogeneity [Vargas et al., 1995; Kim et al., 1997; Matsumoto et al., 1997; Borg et al., 1999; Kondoh et al., 2002]. The simultaneous presence of nasal clefts, short columella, hypoplastic alae nasi, or a crease in the philtrum is distinctive and would be diagnostic of LSS [Martínez-Frias et al., 1994]. A review of the abnormalities of nine reported patients with LSS is presented in Kantaputra [2001]; Pilkington et al. [2000], reported an additional patient. All reported cases of LSS have had normal humeri and femora with abnormalities limited to the forearm/foreleg and hand/foot. Interestingly, no case of LSS has had a duplicated humerus. The development of a duplicated ulna and/or fibula indicates that the signals promoting altered patterning occur early during limb bud outgrowth.

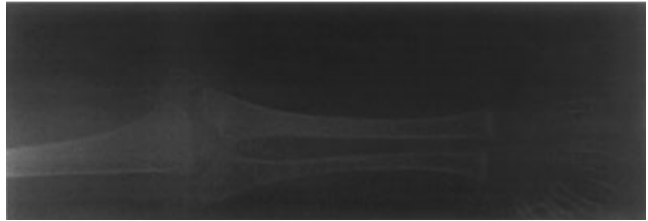
Our patients are different from those reported above in having unilateral, upper limb preaxial polydactyly, and ulnar duplication without any nasal changes, and may not be attributable to the genetic mutation causing LSS. Our two cases and 14 other patients with unilateral upper limb involvement in the reported cases of Stroer [1938, one case, right side], Santero [1936, five cases: three left-sided, two right sided], Buettner [1938, one case, left side], Mukerji [1956, one case, left side], Entin [1959, one case, left side], Harrison et al. [1960, three cases: one left-sided, two right-sided involvement], Pintilie et al. [1964, one case, left side], Hussl et al. [1985, one case, left side], indicate that either side can be affected; however, in this small sample there is a slight preponderance of left involvement (11:5). The single-limb involvement in our patients could result from the unique characteristics of the specific mutations or natural variability among patients with LSS. The latter is attractive given that very few patients have been described with LSS. However, somatic mosaicism for new dominant mutations arising postzygotically could also explain these findings.

Preaxial and/or mirror-image polydactyly along with malformation of the radius and/or ulna with or without other anomalies have been observed in the chick and mouse. Disruptions in the hedgehog pathway have been hypothesized for LSS. Usually ectopic *hedgehog* expression or activity in anterior limb domains is observed and may occur via several mechanisms: (1) primary misregulation leading to the anterior expression of Sonic hedgehog, *Shh*, (transgenic mouse mutant *Sasquatch* or *Hemimelic-extra toes*) or Indian hedgehog, *Ihh*, (as in the mouse mutant *Doublefoot*), (2) *Alx4* loss of function, (3) *Gli3* loss of function, and (4) *dHAND*, *Hoxd12*, or *Hoxb8* transgenic ectopic expression [Lettice et al., 2003; Wechsler et al., 2004]. Ectopic anterior expression of *dHAND* can induce anterior *Shh* expression giving rise to mirror-image (usually triphalangeal) digit duplications and duplicated ulna [Charité et al., 2000].

**A**



**C**



**B**



**D**



Fig. 2. **A:** Left arm and lateral face views of case 2 showing best attempt to flex elbow with help to touch nose; normal nasal configuration. **B–D:** Radiographs showing duplicated ulna and seven-finger triphalangeal polydactyly.

A case with monomelic foot mirror polydactyly associated with absent tibia and duplicated fibula was reported [Viljoen and Kidson, 1990]. This patient had also midline sacrococcygeal teratoma. The authors proposed that the tumor interfered with cellular migration and displaced the ZPA cells anteriorly. Kim et al. [1997] identified an apparently balanced de novo translocation involving 2p23 and 14q13 in a Japanese boy with tetramelic mirror-image polydactyly, but without long bone involvement or nasal defects. They suggested consideration of this case as a variant of LSS. Van Steensel [1997] suggested consideration of *Strong's luxoid* mutants (*lst*), which have preaxial polydactyly of all limbs and reductions of the radius and ulna, as the basis for LSS gene. *lst* and other luxoid mouse mutants have mutations within the *Alx4* gene, a homeobox containing gene, and have numerous defects [Qu et al., 1997, 1998]. Humans with *ALX4* deletion or mutation have parietal foramina and no preaxial polydactyly. The available model system literature and human molecular data suggest the likelihood that there is genetic heterogeneity in the basis for the occurrence of mirror-image polydactyly with or without tibial hemimelia or ulnar/fibular duplication.

### Proposal for the Etiology of LSS

The autosomal dominant *Doublefoot* mutation (*Dbf*) in the mouse occurred spontaneously; heterozygous mutant mice have preaxial polydactyly with six to eight digits on all four feet with partial syndactyly, usually lacking a thumb [Lyon et al., 1996; Yang et al., 1998; Hayes et al., 1998, 2001]. In these mutants, the tibiae and fibulae are either bowed or shortened, the tail is kinked, and the head is shortened and broad. Fertility is impaired and growth is retarded. Homozygotes often have a split or cleft face resulting from failure of the maxillae to fuse in the midline. Hayes et al. [2001] narrowed the mutation to a 0.4 cM interval on mouse chromosome 1 which included the *Ihh*, *Wnt6*, and *Wnt10a* genes, all of which are expressed in developing limbs and face. Ectopic activation of the Indian hedgehog (*Ihh*) gene in the distal limb buds between E10.5 and E11.5 gestation and in the branchial arches leads to broader and shorter facial processes [Yang et al., 1998; Hayes et al., 2001]. Hayes et al. [2001] proposed the possibility of a regulatory mutation affecting the expression of *Ihh* and of at least *Wnt6*. The shortened columellas with clefts, cleft nares, or philtrum clefts seen in humans with classic LSS are compellingly similar to *Doublefoot* murine facial anomalies, which result from failure of fusion of the maxillary processes. The similarity suggests that, at least for LSS with facial clefting, that one strong candidate is the *Doublefoot* 'homolog' in humans. Other cases of mirror image polydactyly with or without more proximal defects and without nasal/philtrum clefts may be genetically distinct. In these situations, ectopic hedgehog activity should be considered in the context of the outline above.

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