

## Case Report

### Congenital Knee Dislocation in a Patient with Larsen Syndrome and a Novel Filamin B Mutation

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**Abstract** We treated a patient with multiple congenital joint dislocations and facial dysmorphisms consistent with Larsen syndrome. Sequencing of the FLNB gene resulted in identification of a novel, de novo 508G>C point mutation resulting in substitution of proline for a highly conserved alanine (A170P). This mutation has not been described previously but is likely causative because this alanine is highly conserved and is located in the calponin homology domain where other mutations have been described. We also report the successful use of a minimally invasive technique in achieving initial correction of bilateral congenital knee dislocations in this patient. The technique consists of serial manipulations and castings followed by an open quadriceps tenotomy. Longer

followup is needed to ensure maintenance of correction and to avoid the need for more extensive surgery, which has been the traditional treatment for congenital knee dislocation associated with Larsen syndrome.

#### Introduction

Larsen syndrome (OMIM 150250) was first described in 1950 as the combination of multiple joint dislocations and characteristic craniofacial abnormalities [16]. The incidence is estimated to be one in 100,000 live births with many cases now having an identifiable genetic etiology [27]. Craniofacial anomalies include flat facies with a prominent forehead, hearing loss, a depressed nasal bridge, and widely spaced eyes. The presence of accessory calcaneal or carpal ossification centers seen radiographically is a useful diagnostic feature in early childhood. A spatulate-shaped thumb is often present as well as short metacarpals. The feet commonly have either rigid equinovalgus or equinovarus deformities. Progressive cervical kyphosis from hypoplasia of the posterior vertebral bodies with resultant myelopathy is the most serious orthopaedic manifestation and occurs in a minority of patients with Larsen syndrome.

Perhaps the most common and difficult to treat orthopaedic manifestation of Larsen syndrome is congenital dislocation of the knee. Most patients are unresponsive to serial manipulation and casting [13, 18, 20]. Instead, open reduction with VY quadricepsplasty, anterior capsulotomy, and release of the anterior portions of the collateral ligaments is the most common treatment offered [6]. This treatment, however, is fraught with complications, including incomplete reduction, recurrent knee dislocations, or stiffness resulting in poor knee function [12]. We report a

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successful short-term result using serial manipulations and castings followed by an open quadriceps tenotomy for congenital knee dislocation in a patient with Larsen syndrome.

The autosomal-dominant and sporadic forms of Larsen syndrome (LRS1; MIM 150250) have been associated with missense mutations in the filamin B (FLNB) gene, which encodes an actin-binding cytoskeletal protein, filamin B [14, 26]. Filamin B is one of three known human filamin proteins, all of which have important roles in cytoskeletal development. Four distinct conditions other than Larsen syndrome have been attributed to mutations in FLNB: perinatal lethal atelosteogenesis type I (AOI; MIM 108720) [14], atelosteogenesis type III (AOIII; MIM 108721) [14], boomerang dysplasia (MIM 112310) [4], and spondylo-carpotarsal synostosis syndrome (MIM 272460) [14]. The distribution of all currently known mutations is not random. There are two clusters of mutations: those in exons 2 to 4, encoding a calponin homology domain (CH2), and in exons 25 to 33 encoding filamin repeats 13 to 17. We describe the treatment of a patient with Larsen syndrome who has a novel mutation in FLNB.

### Case Report

The patient was a male newborn of Arabian descent with clinical characteristics of Larsen syndrome. The patient was a 3030-g product of a 37-week gestation born by cesarean section because of breech presentation. The pregnancy was complicated by gestational diabetes requiring insulin, polyhydramnios, advanced maternal age (40 years), paternal age of 45 years, and a high maternal serum alpha-fetoprotein. The patient was evaluated by a geneticist at 1 week of age at which time the diagnosis of Larsen syndrome was confirmed.

The patient was first seen in our orthopaedic clinic at the age of 22 months. We performed an extensive pedigree analysis, which revealed no other cases of Larsen syndrome or other heritable orthopaedic anomalies in the family. Abnormal findings on physical examination included hypertelorism and a flat nasal profile with a flat nasal bridge (Fig. 1). The philtrum measured 1.5 cm ( $> 2$  SD above the mean) [20]. Specific facial feature measurements performed included the outer canthal distance [9.1 cm,  $> 3$  SD above the mean] [20], the inner canthal distance [3.5 cm,  $> 3$  SD above the mean] [15], the interpupillary distance [5.4 cm,  $> 2$  SD above the mean] [8], and the palpebral fissure lengths [2.8 cm,  $> 2$  SD above the mean] [15]. No evidence of cleft palate was found. The legs were extended with the feet over the shoulders at rest. The hips and knees could not be passively manipulated into normal position. The feet had mild equinovagis deformities that



**Fig. 1** A photograph of the index patient shows the typical facial features of Larsen syndrome, including hypertelorism, a flat nasal profile, and a flat nasal bridge.



**Fig. 2** A radiograph of the foot of the index patient shows an accessory calcaneal ossification center.

were passively correctable. The hands were clinically normal, but the elbows had fixed  $20^\circ$  flexion contractures. Skeletal survey confirmed bilateral knee and hip dislocations. Accessory calcaneal ossification centers were present on radiographs taken at 18 months of age (Fig. 2). Typical findings of shortened metacarpals and wide distal phalanges were not present. Dysraphism involving the cervical and upper thoracic vertebral bodies were present with mild cervical kyphosis and scoliosis.

The patient underwent serial casting for the bilateral knee dislocations starting at 22 months of age (Fig. 3). Sixty degrees of knee flexion was obtained bilaterally after application of six casts changed weekly. The decision was



**Fig. 3** A lateral radiograph of the patient's knee was obtained at the time of initiation of serial casting.



**Fig. 4** A lateral radiograph of the patient's knee obtained after casting and open quadriceps tenotomy shows correction of the knee dislocation.

made at that time to proceed with a miniopen quadriceps tenotomy. After a complete quadriceps tenotomy, the knees reduced and greater than 90° flexion was obtained (Fig. 4). Clinical evaluation 1 year after surgery revealed excellent maintenance of knee range of motion with flexion greater than 90° (Fig. 5).

We performed FLNB gene testing (Connective Tissue Gene Tests, Allentown, PA) to confirm the diagnosis of Larsen syndrome. Exons 1 to 46 of the FLNB gene were amplified by polymerase chain reaction. We then sequenced the amplified products using ABI 3730 sequencers (Applied Biosystems, Foster City, CA) and



**Fig. 5** A clinical photograph of the patient's knee 1 year after the quadriceps tenotomy shows full knee flexion.

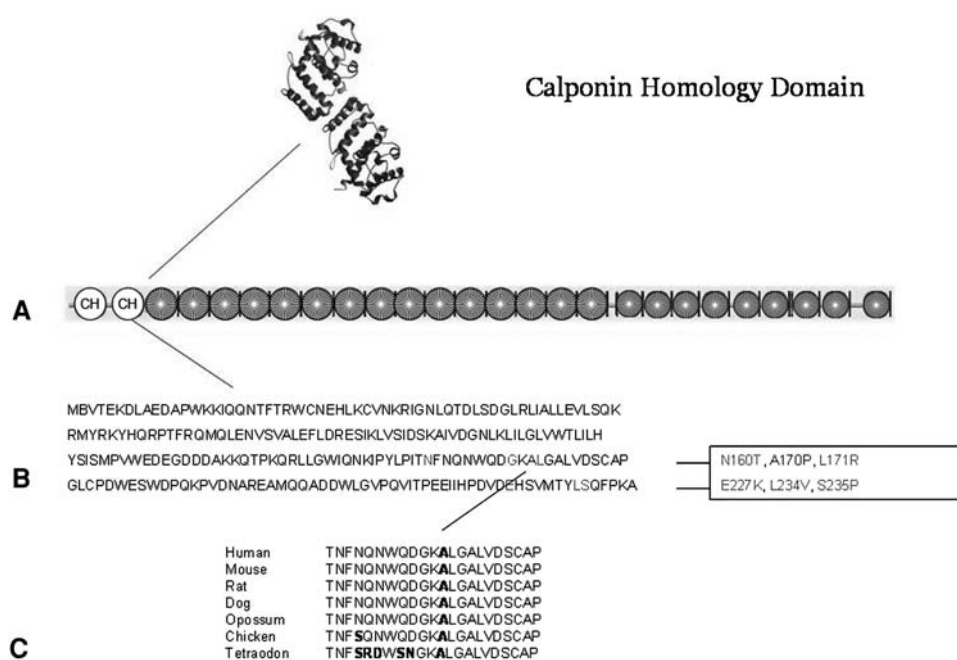
analyzed them for sequence variations. The clinical importance of the variations was determined by comparison with wild-type sequences, previously reported mutations, and correlation with the structure of filamin B.

DNA sequencing analysis revealed two potential mutations in FLNB. In exon 2, a 508G>C transversion resulted in the substitution of proline for alanine at amino acid 170 (A170P). This mutation was de novo and not present in either of the unaffected parents. In addition, this alanine is highly conserved in 12 of 13 species (Fig. 6) and is located within one of the two regions where nearly all mutations in dominantly inherited FLNB disorders have been described (exons 2–4 and 27–29). A second potential mutation was identified in exon 36, a previously undescribed 6028C>T transition that converts a codon for arginine (CGC) to a codon for cysteine (TGC) (R2010C). However, the patient's unaffected mother also has the R2010C variant. A comparison was made between our patient and five other published cases of patients with Larsen syndrome [3] in terms of location of mutation in FLNB, amino acid change, and clinical features (Table 1).

## Discussion

In 1950, Larsen et al. [16] described multiple congenital large joint dislocations with facial abnormalities in six genetically independent patients. Many sporadic cases have been described in addition to an autosomal-dominant form [17, 24, 25]. The autosomal-dominant form has been associated with mutations in FLNB, a cytoskeletal structural protein [14]. There are three filamin genes in mammals, FLNA, FLNB, and FLNC, all of which are important in cytoskeletal development. FLNA and FLNB are expressed ubiquitously in contrast to FLNC, which is predominantly expressed in muscle. Mutations in FLNA are known to cause five X-linked disorders with developmental anomalies in the brain, skeleton, and cardiovascular

**Fig. 6A–C** (A) A schematic is shown of filamin B with two calponin homology domains, and repeats 1–24 with hinges between 15 and 16, and 23 and 24. (B) The newly found mutation A170P lies in the calponin homology domain near other mutations described in Larsen syndrome. (C) The mutation reported here is in a highly conserved region across many species.



**Table 1.** Phenotypic features of Larsen syndrome attributable to mutations in the calponin homology domain of FLNB

Patient	Mutation	Amino acid change	Midface hypoplasia	Cleft palate	Scoliosis	Myelopathy	Accessory ossification center	Spatulate fingers
1 <sup>3</sup>	482T>G	F161C	+	–	+	–	+	+
2 <sup>3</sup>	502G>A	G168S	+	–	+	–	+	+
3 <sup>3</sup>	700G>A	L234V	+	–	+	–	N/A	–
4 <sup>3</sup>	679G>A	E227K	+	–	–	–	+	+
5 <sup>3</sup>	679G>A	E227K	+	+	+	–	+	+
6*	508G>C	A170P	+	–	+	–	+	–

\*Patient in current manuscript; <sup>3</sup> = patients from Bicknell et al. [3]; Mutation column (T = thymine; G = guanine; A = alanine; C = cytosine); Amino acid change column (F = phenylalanine; C = cysteine; G = glycine; S = serine; L = leucine; V = valine; E = glutamine; K = lysine).

system [9, 10]. FLNB is suspected to play a role in vertebral segmentation, joint formation, and enchondral ossification [14].

Almost all mutations in dominantly inherited Larsen syndrome have been reported in just five of the total 46 coding exons of FLNB (exon 2, two patients; exon 4, two patients; exon 27, two patients; exon 28, two patients; and exon 29, three patients) [13, 27]. We identified two potential disease-causing variants in FLNB in our patient with Larsen syndrome, although it is likely the exon 2, de novo mutation at nucleotide position 508 resulting in amino acid substitution (A170P) is causative. The variant identified in exon 36, 6028 C>T transition (R2010C), also was identified in the patient's mother, who is not affected. To the best of our knowledge, neither has been reported previously as a mutation or a polymorphism.

Compared with five other patients with Larsen syndrome with mutations in the calponin homology domain

(CH2) of FLNB (CH2, mutations: 482T>G, 502G>A, 700G>A, 679G>A) [3], our patient had similar facial and spinal deformities but lacked the characteristic hand deformities (spatulate fingers) typically seen in this patient population (Table 1). Spatulate fingers were described in all cases of the initial paper by Larsen et al. [16] and in 19 of 20 cases (95%) of Larsen syndrome with FLNB mutations reported by Bicknell et al. [3]. Another hand anomaly, an accessory distal thumb phalanx, recently was reported in a patient with Larsen syndrome and a specific mutation in FLNB, but outside the calponin homology domain, causing the amino acid substitution G1691S [1]. Additional patients with Larsen syndrome will need to be genotyped to determine whether there are specific phenotypes predicted by specific mutations in the calponin homology domain.

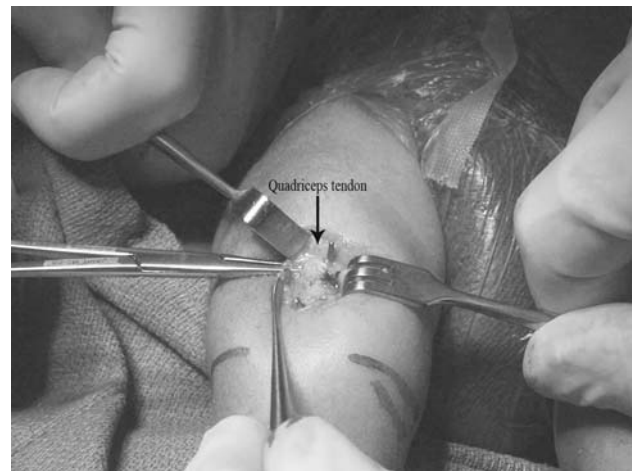
Current treatment of a congenital knee dislocation begins with gentle stretching and serial casting. This

method reportedly is successful for mild hyperextension deformities that are addressed soon after birth [2, 11, 22]. A Pavlik harness is useful for maintaining knee flexion achieved by serial casting. These milder deformities typically occur in otherwise normal children and often are associated with breech presentation [12]. Complete congenital knee dislocation, however, usually occurs in the presence of muscle imbalance and/or ligamentous laxity such as that occurring in myelodysplasia, arthrogyposis, and Larsen syndrome and are reportedly unresponsive to traditional cast correction techniques in most cases [6, 12, 23]. Serially casting the knees in these severe cases can place the proximal tibial epiphysis and metaphysis at risk for plastic deformation.

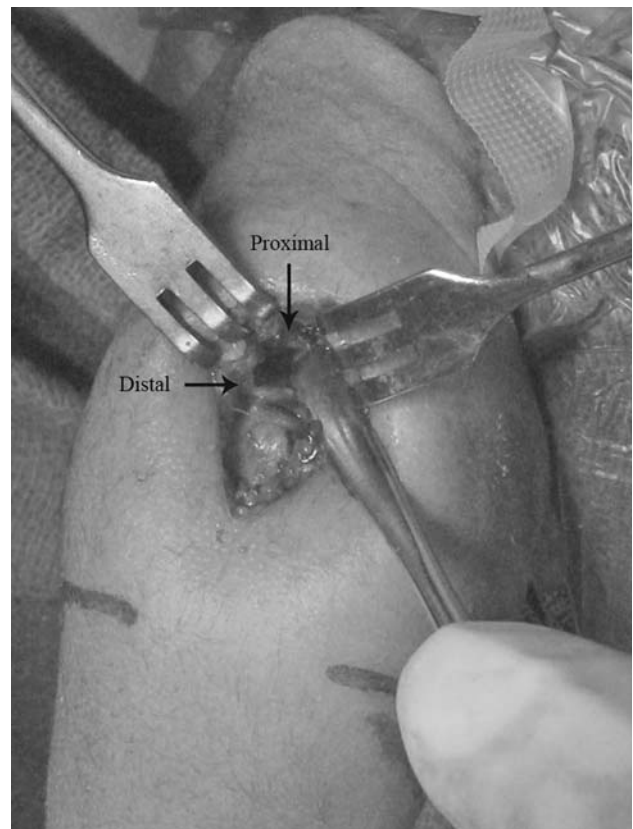
We begin serial long-leg casting to treat the congenital knee dislocation as soon as the children are medically stable. With the patient relaxed with a bottle of milk, gentle traction is applied to the tibia to stretch the contracted quadriceps muscle. After several minutes of stretching, we apply a long-leg plaster cast from the toes to the top of the thigh. The cast is applied in one section and is carefully molded to maintain the position achieved with stretching and to avoid skin sores. We change casts on a weekly basis in the clinic. Once the tibia reaches the distal femur with traction, flexion of the knee was started with pressure applied directly to the proximal tibia.

Sometimes in patients with complete dislocation of the knee, flexion of the knee often cannot be started for several weeks until the quadriceps muscle is adequately stretched. It is important not to put flexion force on the distal tibia and/or ankle when flexing the knee because this creates a long lever arm that can result in iatrogenic physal separation of the distal femur or plastic deformation of the proximal tibia. In general we obtain a lateral radiograph of the knee once knee flexion reaches 45° and again if 90° flexion is reached during serial casting to confirm correction is being obtained. Closed treatment should be stopped if anatomic reduction of the tibia cannot be confirmed. If 90° flexion is obtained and normal restoration of the femoral-tibial articulation is seen on a lateral radiograph, it is unlikely any surgical intervention will be necessary.

If 90° flexion cannot be achieved with an average of six to seven casts, we believe a miniopen quadriceps tenotomy is indicated. We position the patient supine on a radiolucent table. No tourniquet is used because this interferes with the location of the surgical incision. The entire leg is prepped into the field from the hip to the tip of the toes to allow easy manipulation of the knee. We make a 2-cm vertical midline incision just above the superior pole of the patella. Dissection is carried down to the patella and the quadriceps tendon. We isolate the quadriceps tendon using a right-angled hemostat (Fig. 7). The quadriceps tendon is transected completely approximately 1 cm proximal to its



**Fig. 7** An intraoperative photograph shows isolation of the quadriceps tendon with a right angle clamp before sectioning.



**Fig. 8** An intraoperative photograph shows the proximal and distal cut ends of the quadriceps tendon after sectioning 1 cm proximal to the patellar insertion.

insertion on the superior pole of the patella (Fig. 8). We then gently flex the knee until greater than 90° flexion is obtained. If 90° flexion cannot be obtained after the quadriceps tenotomy, the anterior knee capsule is released as well as the lateral retinaculum until 90° flexion is obtained.

We obtain an intraoperative lateral knee radiograph to ensure anatomic reduction of the tibia on the distal femur. After wound closure and dressing application, a long-leg plaster cast is placed with the knee in 90° flexion. We change the cast in the operating room 3 weeks postoperatively to stretch the knee into extension and assess range of motion. Another long-leg cast is applied with the knee in 70° flexion for 2 weeks. The last cast is removed in the clinic and formal physical therapy is started on an outpatient basis to maintain knee flexion and extension. Splints also are used for 4 to 6 weeks alternating between flexed and extended positions at the knee.

An extensile surgical release operation has been described for correcting most complete congenital knee dislocations associated with Larsen syndrome [5, 19]. The quadriceps mechanism requires considerable lengthening, although it must remain attached proximally and distally. The anterior knee capsule is released to the collateral ligaments. If 90° knee flexion is not achieved with this release, the medial hamstrings, iliotibial band, and lateral intermuscular septum are lengthened as well [7]. A spica cast is used postoperatively to maintain reduction [7, 12]. Physical therapy and splinting are necessary after the spica cast to maintain flexion and minimize loss of extension. Although early surgical reconstruction provides a more satisfactory functional result than late reconstruction in patients with Larsen syndrome [2, 6, 12, 19, 21], it is fraught with potential complications, including loss of knee flexion and development of a knee flexion contracture.

There is one published report on the use of step-cut quadriceps tendon lengthening in three patients with congenital knee dislocation associated with various neurologic conditions [23]. The authors reported good initial correction of the deformity, but the treatment in all three patients was started at an average of 18 days of life. We report the successful initial correction of a 22-month-old patient with Larsen syndrome with congenital knee dislocation using serial casting and a miniopen quadriceps tenotomy. The technique is simple in concept but does require attention to detail to avoid plastic deformation of the proximal tibia with casting. Longer followup is necessary to ensure maintenance of correction.

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