INTRODUCTION

Larsen syndrome is a hereditary disorder that impacts the development of bones in the body. One in 100,000 babies is born with Larsen syndrome each year (Sajnani, Yiu, & King, 2013). Symptoms can vary, even within members of the same family; however, the condition is typically characterized by large-joint dislocations and craniofacial anomalies. The hallmark feature of this condition is dislocations of the knee, hip, elbow, and wrist joints. Craniofacial abnormalities include

1 | CLINICAL REPORT

A case study of atypical Larsen syndrome with absent hallmark joint dislocations

Neslida Kodra | Callie Diamonstein | Natalie S. Hauser

Inova Translational Medicine Institute, Inova Fairfax Hospital, Virginia

Correspondence
Neslida Kodra, Inova Translational Medicine Institute, Falls Church, VA. Email: Neslida.Kodra@inova.org

Abstract

**Background:** A family with skeletal and craniofacial anomalies is presented. Whole-exome sequencing (WES) analysis indicated a diagnosis of Larsen syndrome, although their clinical presentation does not include the hallmark joint dislocations typically observed in Larsen syndrome.

**Methods:** Patient consent for the sharing of de-identified clinical and genetic information, along with use of photographs for publication, was obtained. WES and variant segregation analysis by WES were performed by commercial laboratory, GeneDx (Gaithersburg, MD), on peripheral blood samples from the proband, her brother, and her parents using methods detailed on their website for test XomeDx Whole Exome Sequencing Trio (https://www.genedx.com/test-catalog/available-tests/xomedx-whole-exome-sequencing-trio/). WES uses next-generation sequencing (NGS) technology to assess for variants within the coding regions, or exons, of approximately 23,000 genes. For the FLNB gene (NM_001457.3), 100% of the coding region was covered at a minimum of 10x. GeneDx uses Sanger sequencing to confirm NGS variants.

**Results:** WES revealed a heterozygous pathogenic variant, p.Glu227Lys (c.679G>A), in the FLNB gene in three out of the four family members tested. This variant is associated with Larsen syndrome, a skeletal dysplasia condition with a wide range of phenotypic variability that usually includes congenital joint dislocations.

**Conclusion:** This is a highly unusual presentation of Larsen syndrome in which the identifying hallmark trait is absent in the patients’ phenotypes.

**KEYWORDS**
FLNB, joint dislocations, Larsen syndrome, phenotypic variability, skeletal dysplasia, whole-exome sequencing
hypertelorism, prominent forehead, depressed nasal bridge, and a flattened midface. Cleft palate, clubfoot, short stature, and spinal anomalies such as scoliosis and kyphosis are also very common.

Larsen syndrome is caused by mutations in the FLNB gene (OMIM 603381), which encodes the connective tissue protein, filamin B. This protein is thought to be involved in vertebral segmentation, joint formation, and endochondral ossification (Kраков, 2004). Five disorders have been described from pathogenic variants in the FLNB gene: spondylocarpotarsal syndrome (SCT), Larsen syndrome, type I atelosteogenesis (AO1), type III atelosteogenesis (AO3), and boomerang dysplasia (Robertson, 2008; Farrington-Rock et al., 2006). However, as with many traditionally described gene-disease associations, FLNB-related disorders may represent an overall spectrum of disorders (Xу et al., 2018). In this spectrum of skeletal dysplasia conditions, Larsen syndrome is generally mildest, although within Larsen syndrome itself there is a range in phenotype.

While pathogenic variants in FLNB are typically inherited in an autosomal dominant fashion, autosomal recessive inheritance is also possible (Bicknell et al., 2006; Краков et al., 2004; Robertson, 2008; Zhang et al., 2006). Autosomal recessive inheritance of FLNB variants is associated with SCT by causing a lack of expression in the FLNB protein (Robertson, 2008). The other four disorders, Larsen syndrome, AO1, AO3, and boomerang dysplasia, are associated with autosomal dominant or de novo variants in a gain-of-function manner (Farrington-Rock et al., 2006). Heterozygous pathogenic variants in FLNB account for the majority of patients with Larsen syndrome; however, recently discovered homozygous pathogenic variants in CHST3 (OMIM 603799) and B4GALT7 (OMIM 604327) confirm the existence of recessive forms (Cartault et al., 2015; Hermanns et al., 2008). This case study will examine an atypical presentation of Larsen syndrome in which a family has a classic pathogenic FLNB variant with an autosomal dominant mode of inheritance, but is lacking the typical associated hallmark joint dislocations.

1.2 Genetic analysis

A postnatal chromosome microarray analysis on patient 2 was normal. When patient 1 was born, whole-exome sequencing (WES) was recommended, and the family agreed to a WES quad, including patient 1 (as proband), patient 2, the father (patient 3) and the mother. A heterozygous pathogenic variant, p.Glu227Lys (c.679G>A), was found in the FLNB gene in patient 1, patient 2, and patient 3 (Table 1). The mother was negative for this variant.

The E227K variant in the FLNB gene has been reported in association with Larsen syndrome, as both a de novo variant and an inherited variant (Bicknell et al., 2006; Krakow et al., 2004; Zhang et al., 2006). This variant is located within a critical region, the actin-binding region, where multiple other common pathogenic variants can be found (Daniel et al., 2012). Because this variant is a nonconservative amino acid substitution, it can change the secondary structure of the filamen B protein. Zhao, Shapiro, and Eto (2015) conducted
Functional studies that found that pathogenic variants in this region, including the E227K variant, can induce binding of the filament B protein to F-actin. This interaction causes F-actin accumulation in the cell which can prevent normal skeletal development (Zhao et al., 2015). Therefore, the E227K variant meets the American College of Medical Genetics and Genomics criteria for pathogenicity.

2 | DISCUSSION

This case highlights the variability in phenotypic expression of Larsen syndrome, even in regards to its hallmark feature of multiple joint dislocations. Dislocations of major joints are the most prominent clinical feature of Larsen syndrome and can be present soon after birth. Affected individuals may have several surgical procedures to stabilize the hip and knee joints. Later in adolescence, progressive degenerative arthritis of the joints can lead to painful contractures. Therefore, it

### FIGURE 1
Notable physical features of patient 3. (a) Arachnodactyly observed in patient 3, noting long and slender fingers. (b) Bilaterally laterally deviated great toes and arachnodactyly of toes on patient 3. (c) Dysmorphic facial features of patient 3. He has mild hypertelorism along with anteverted nares.

### FIGURE 2
Pedigree of the affected family. Symptomatic individuals are in black. A pattern of autosomal dominant inheritance is visualized.

### TABLE 1
Whole-exome sequencing results for patients 1–3: autosomal dominant inheritance of a pathogenic variant in the FLNB gene

| Patient | Gene | Variant | Coding DNA | Zygosity  | Inherited from | Classification |
|---------|------|---------|------------|-----------|----------------|----------------|
| 1 (proband) | FLNB | p.Glu227Lys | c.679G>A | Heterozygous | Father | Pathogenic |
| 2 (brother of proband) | FLNB | p.Glu227Lys | c.679G>A | Heterozygous | Father | Pathogenic |
| 3 (father of proband) | FLNB | p.Glu227Lys | c.679G>A | Heterozygous | Unknown | Pathogenic |

Note. The mother of the proband tested negative for this variant, indicating that patients 1 and 2 inherited the pathogenic variant from their father (patient 3).
is significant that none of the family members presented here had any dislocations, which is atypical of Larsen syndrome and many of the skeletal dysplasias similar to it.

Phenotypic variability in Larsen syndrome and similar skeletal dysplasias is very common. Tanteles, Dixit, and Dhar (2013) detailed a case of a CHST3 autosomal recessive Larsen syndrome where the proband was not born with any joint dislocations but went on to develop hip, elbow, and wrist arthritis during later childhood. Her maternal half-brother on the other hand, was born with knee dislocations that resolved spontaneously (Tanteles et al., 2013). Indeed, much of the literature has focused on expanding the phenotypic range for this condition by detailing how unusual features may be present in a Larsen patient or typical features may be absent. Although uncommon, at least four nonrelated cases of dental issues have been reported in patients with this condition (Sajnani et al., 2013). Both conductive and sensorineural hearing loss are also uncommon features of Larsen syndrome, however, there have been a handful of reports of an association between the two (Herrmann, Kelly, Fried, & Strome, 1981; Nash, Majithia, Ujam, & Singh, 2012). Our proband had mixed hearing loss while both her father and brother had normal hearing. The proband also had skeletal and facial anomalies but had no dislocations or short stature. On the contrary, she was in the 99th percentile for height. Patient 3 had anomalies in the fingers and toes but he had no issues with walking. At 5 ft 9 in., he was also unaffected by short stature.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

ORCID
Nesilda Kodra https://orcid.org/0000-0001-8140-5373
Natalie S. Hauser https://orcid.org/0000-0001-7663-1851

REFERENCES
Bicknell, L. S., Farrington-Rock, C., Shafeghati, Y., Rump, P., Alanay, Y., Alembik, Y., … Robertson, S. P. (2006). A molecular and clinical study of Larsen syndrome caused by mutations in FLNB. Journal of Medical Genetics, 44(2), 89–98. https://doi.org/10.1136/jmg.2006.043687
Cartault, F., Munier, P., Jacquemont, M.-L., Vellayoudom, J., Doray, B., Payet, C., … Cormier-Daire, V. (2015). Expanding the clinical spectrum of B4GALT7 deficiency: Homozygous p.R270C mutation with founder effect causes Larsen of Reunion Island syndrome. European Journal of Human Genetics, 23, 49–53. https://doi.org/10.1038/ejhg.2014.60
Daniel, P. B., Morgan, T., Alanay, Y., Bijlsma, E., Cho, T. J., Cole, T., … Robertson, S. (2012). Disease-associated mutations in the actin-binding domain of filamin B cause cytoplasmic focal accumulations correlating with disease severity. Human Mutation, 33, 665–673. https://doi.org/10.1002/humu.22012
Farrington-Rock, C., Firestein, M. H., Bicknell, L. S., Superti-Furga, A., Bacino, C. A., Cormier-Daire, V., … Krakow, D. (2006). Mutations in two regions of FLNB result in atelosteogenesis I and III. Human Mutation, 27, 705–710. https://doi.org/10.1002/humu.20348
Herrmanns, P., Unger, S., Rossi, A., Perez-Aytes, A., Cortina, H., Bonafé, L., … Superti-Furga, A. (2008). Congenital joint dislocations caused by carbohydrate sulfotransferase 3 deficiency in recessive Larsen syndrome and humero-spinal dysostosis. American Journal of Human Genetics, 82, 1368–1374. https://doi.org/10.1016/j.ajhg.2008.05.006
Herrmann, H. C., Kelly, J. H., Fried, M. P., & Strome, M. P. (1981). The association of a hearing deficit with Larsen’s syndrome. Journal of Otolaryngology, 10, 45–48.
Krakov, D., Robertson, S. P., King, L. M., Morgan, T., Sebald, E. T., Bertolotto, C., … Cohn, D. H. (2004). Mutations in the gene encoding filamin B disrupt vertebral segmentation, joint formation and skeletogenesis. Nature Genetics, 36, 405–410. https://doi.org/10.1038/ng1319
Nash, R., Majithia, A., Ujam, A., & Singh, A. (2012). Ossicular malposition in Larsen syndrome: A case report. Journal of Surgical Case Reports, 11, rjs007–rjs007. https://doi.org/10.1093/jscr/rjs007
Robertson, S. (2008). [Updated 2013]. FLNB-RELATED disorders. In M. P. Adam, H. H. Ardinger, R. A. Pagon, & S. E. Wallace (Eds.), GeneReviews® [Internet]. Seattle, WA: University of Washington. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK2534/
Sajnani, A. K., Yu, C. K., & King, N. M. (2013). Larsen syndrome: A review of the literature and case report. Special Care in Dentistry, 30(6), 255–260. https://doi.org/10.1111/j.1754-4505.2010.00163.x
Tanteles, G. A., Dixit, A., & Dhar, S. (2013). Two Somali half-siblings with CHST3-related chondrodysplasia illustrating the phenotypic spectrum

ACKNOWLEDGMENT
We thank the reported family.

ACKNOWLEDGMENTS
We thank the reported family.
and intrafamilial variability. *American Journal of Medical Genetics. Part A*, 161A, 2588–2593. https://doi.org/10.1002/ajmg.a.36094

Xu, Q., Wu, N., Cui, L., Lin, M., Thirumal Kumar, D., Doss, G. P., … G. (2018). Comparative analysis of the two extremes of FLNB-mutated autosomal dominant disease spectrum: From clinical phenotypes to cellular and molecular findings. *American Journal of Translational Research, 10*(5), 1400–1412.

Zhang, D., Herring, J. A., Swaney, S. S., McClendon, T. B., Gao, X., Browne, R. H., … Wise, C. A. (2006). Mutations responsible for Larsen syndrome cluster in the FLNB protein. *Journal of Medical Genetics, 43*(5), e24. https://doi.org/10.1136/jmg.2005.038695

Zhao, Y., Shapiro, S. S., & Eto, M. (2015). F-actin clustering and cell dysmotility induced by the pathological W148R missense mutation of filamin B at the actin-binding domain. *American Journal of Physiology. Cell Physiology, 310*(1), C89–98. https://doi.org/10.1152/ajpcell.00274.2015

**How to cite this article:** Kodra N, Diamonstein C, Hauser NS. A case study of atypical Larsen syndrome with absent hallmark joint dislocations. *Mol Genet Genomic Med*. 2019;7:e648. https://doi.org/10.1002/mgg3.648