Arch Argent Pediatr. 2026;e202510995

Geleophysical dysplasia associated with *FBN1* variants and phenotypic variability: A case series in Argentine children

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ABSTRACT

Geleophysical skeletal dysplasia is an extremely rare condition characterized by predominantly acral skeletal involvement with a progressive course, associated with short stature and short limbs. Skin, joint, and organ involvement have been described; cardiorespiratory involvement is fatal. It is inherited in an autosomal dominant or recessive manner and is associated with variants in genes encoding extracellular matrix proteins: *ADAMTSL2*, *LTBP3,* and *FBN1*.

This article describes a series of children with *FBN1*-associated geleophysical dysplasia who were followed up at a pediatric hospital. All presented with severe short stature and short limbs. Radiological findings were consistent in the hands (brachymetacarpal and brachyphalangeal features, notches in the metacarpals, and delayed ossification of the carpus). There was variability in severity and organ involvement indicators. Given the complexity of the condition and the multiple systems involved, there is a need for recommendations regarding a multidisciplinary approach throughout life and the importance of genetic counseling.

Keywords: *bone development disorders; geleophysical dysplasia; fibrillin-1; growth disorders; acromelia.*

doi: http://dx.doi.org/10.5546/aap.2025-10995.eng

To cite: Melgarejo SL,Ramos Mejía R, Arbelo M, Huckstadt V, del Pino M. Geleophysical dysplasia associated with *FBN1* variants and phenotypic variability: A case series in Argentine children. *Arch Argent Pediatr.* 2026;e202510995. Online ahead of print 11-JUN-2026.

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Funding*: None.*

Conflict of interest: *None.*

Received*: 12-17-2025*
Accepted*: 4-7-2026*

INTRODUCTION

Geleophysical dysplasia is a rare skeletal dysplasia (SD), with approximately 100 cases reported to date.[1] It is characterized by predominantly acral skeletal involvement, with a progressive course similar to that of a lysosomal storage disorder.[1]

Growth retardation and short stature are present from the prenatal period or early childhood, with short limbs, hands, and feet. Final adult height may range from 3 to 6 standard deviations below the mean. It is accompanied by thickening of the skin, progressive joint stiffness, and contractures that interfere with function and gait (toe-walking), facial dysmorphisms, and progressive organ involvement (cardiac valvular disease, upper airway and pulmonary involvement, and hearing loss). Early death (average at 30 months) is reported in approximately 33% of affected children, secondary to cardiorespiratory compromise, with heart disease being a key determinant of prognosis.[1-3]

The most significant radiographic findings are observed in the hands: delayed ossification of the carpus, short metacarpals and phalanges, an internal notch in the second metacarpal, an external notch in the fifth metacarpal, and, in some cases, conical epiphyses in the phalanges. The long bones are shortened, and an internal notch and narrowing of the femoral heads may be observed.[1,4]

There is phenotypic and genotypic overlap with other conditions involving achromelic involvement, such as achromic SD, Weil-Marchesani, and Myhre syndromes; one of the distinguishing features is the presence of organ involvement.[5]

These genetically inherited conditions affecting the musculoskeletal system follow autosomal dominant or recessive inheritance patterns and share a common pathogenic mechanism.[4,6] The responsible genes encode proteins that cooperate within the same biological pathway in the extracellular matrix (ECM). Most of the affected proteins interact directly with fibrillin microfibrils in the ECM of the musculoskeletal system's connective tissue (*FBN1*, *ADAMTSL2*, *ADAMTS10*, *ADAMTS17*, *LTBP2*, and *LTBP3*) or have been linked to the regulation of transforming growth factor-β (TGF-β) signaling (*SMAD4*).[6-11]

About geophysical SD, pathogenic variants were identified in three genes encoding ECM proteins: *ADAMTSL2* and *FBN1*, each accounting for 50% of cases, and *LTBP3*, which accounts for less than 1%.[1] Attempts have been made to establish a phenotype-genotype correlation: the absence of cardiac involvement is described in children carrying variants in *LTBP3*, a higher frequency of pulmonary valvular disease, facial dysmorphisms, and gait abnormalities in children with variants in *ADAMTSL2*, and mitral valvular disease in those with variants in *FBN1.*[2,12]

The *FBN1* gene is located on the long arm of chromosome 15 and comprises 68 exons. It encodes a member of the fibrillin protein family, fibrillin-1, a calcium-binding protein consisting of 2871 amino acids. This ECM glycoprotein is a structural component of microfibrils that provide support in connective tissue; it is essential for the structural integrity of organs such as the aortic wall and the suspensory ligament of the lens.[13,14]

In addition, together with other fibrillins, it plays a role in growth regulation by interacting with transforming growth factors (TGF-β).[6,14] Signals transduced by members of the TGF-β superfamily regulate the establishment of skeletal differentiation through their effects on the proliferation, differentiation, and migration of osteoprogenitor cells.[15,16]

Pathogenic variants in *FBN1* associated with the geleophysical phenotype encode TGF-β-binding protein-like domain 5 (TB5), which contains eight cysteine residues and contributes to fibrillin-1 folding through intradomain disulfide bonds. Variants that delete a cysteine are associated with a severe phenotype.[1]

Other variants in *FBN1* have been associated with phenotypes of tall stature, ophthalmopathy, and aortic abnormalities.[17,18]

OBJECTIVES

Description of the clinical, growth-related, radiological, and molecular variability in children with *FBN1*-associated skeletal dysplasia caused by pathogenic variants in the *FBN1* gene, from a case series of children with rare skeletal disorders at a high-complexity pediatric hospital.

Summarize a guideline for monitoring and screening for complications in affected patients.

POPULATION AND METHODS

Four patients with acral involvement under follow-up and confirmed *FBN1*-related geleophysical dysplasia were included in the analysis. For each case, anthropometric data (weight, height, sitting height, head circumference, and hand length) were collected from medical records. Measurements were performed by

trained personnel using a standardized technique,[19] with a stadiometer and Harpenden® long-arm caliper, with measurement errors of 0.47 cm for height and 0.49 cm for sitting height. The standard deviation score (SDs) was calculated using local references in LMS Growth® software. Following the signing of an informed consent form, DNA was extracted from peripheral blood lymphocytes. A panel of genes associated with SD was analyzed using next-generation sequencing (NGS). For the proposed follow-up protocol, the existing literature was reviewed and summarized, and recommendations were developed based on local experience.

This study has been approved by the center's Ethics and Research Review Committee (CRIE, by its Spanish acronym), under number 1780.

RESULTS

The clinical characteristics and molecular findings of the children are described in *Tables 1* and *2*. *Figure 1* summarizes the growth data; all children were born with a birth weight appropriate for gestational age. During follow-up, they presented with severe short stature, short limbs, achromia, and relative macrocephaly. The radiological findings are shown in *Figure 2*. The findings in the hands were consistent: brachymetacarpalism, brachyphalangism, metacarpal notching, and delayed ossification of the carpus. In the hips, narrow femoral epiphyses were observed.

Table 1. Clinical characteristics of the cases evaluated

	Case 1	Case 2	Case 3	Case 4
Sex	**Male**	**Female**	**Male**	**Female**
Birth anthropometry				
Weight (SD)	0.06	0.6	0.79	0.1
Body length (SD)	-0.9	NE	NE	0.49
Last recorded anthropometric measurement				
Age (years)	10.7	1.8	6.9	16.1
Height (SD)	-4.4	-4.9	-5.9	-8.6
SH/height (SD)	5.2	2.3	7.1	7.1
HC/height (SD)	6.2	2.5	5.2	10.6
Skin thickening	+	+	+	+
Toe-walking	+	NE	+	-
Cardiovascular	No abnormalities	Severe mitral stenosis and moderate insufficiency	Severe mitral stenosis and moderate regurgitation	Small muscular ventricular septal defect. Mild mitral regurgitation. Subaortic membrane and moderate aortic stenosis.
Respiratory	Bronchial obstruction Severe restrictive ventilatory failure Non-invasive ventilation during sleep	Laryngeal synechiae Laryngitis Respiratory failure	Secondary pulmonary hypertension	Snoring disorder
Ophtalmological	NE	Severe myopia	NE	Asymptomatic conductive hearing loss
Other organs	-	-	-	Serous otitis media

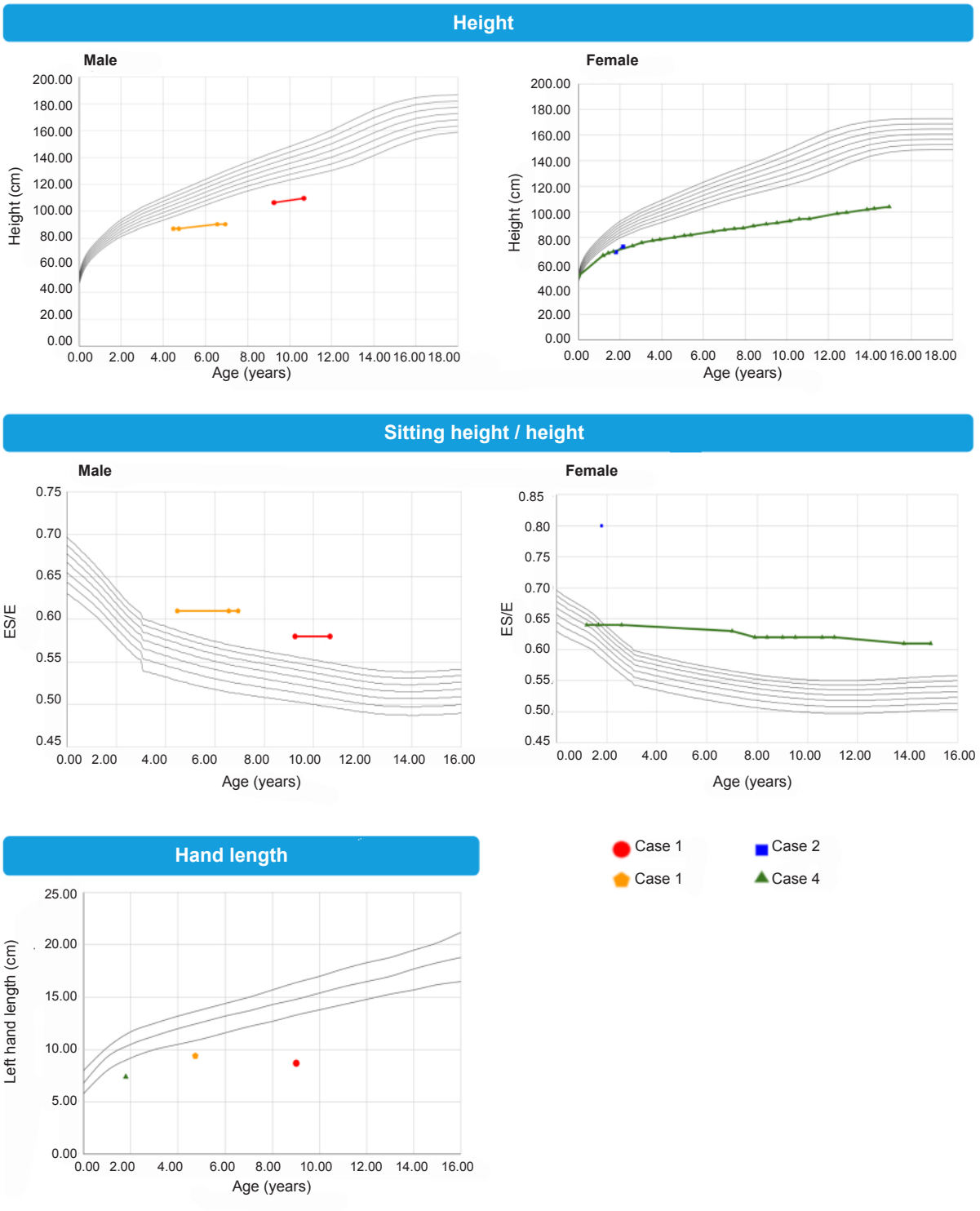
SD: standard deviation; SH: sitting height; HC: head circumference; NE: not evaluated.

Table 2. Genetic variants in the children evaluated

Case	Genetic variant	Exon	Protein hange	Molecular consequence	Interpretation
1	*FBN1*:c.5244T>G	43/66	p.Cys148Trp	Missense	LPV
2	*FBN1*:c.5087A>G	42/66	p.Tyr1696Cys	Missense	PV
3	*FBN1*:c.5096A>G	42/66	p.Tyr1699Cys	Missense	PV
4	*FBN1*:c.5285G>T	43/66	p.Gly1762Val	Missense	LPV

LPV: likely pathogenic variant; PV: pathogenic variant.

Figure 1. Clinical data of the patients



The height growth curves indicate a severe height deficit in both males and females. The sitting height-to-standing height ratios indicate short limbs in both males and females. Acromyria (shortened hand length) is observed in both sexes. Argentine references were used to assess height, and the sitting height-to-standing height ratio,[19] and data collected by Feingold in 1974 were used for hand length.[25]

In all cases, the families received genetic counseling before and after the molecular testing was performed.

CLINICAL CASE 1

A 10.7-year-old boy on his last visit, the second child of healthy, normal-height parents (mother 172.0 cm, father 184.0 cm) who are not consanguineous. He was born via emergency cesarean section due to maternal hypertension and abnormal Doppler findings at 38 weeks. He has had growth retardation since age 2, which is why he began undergoing evaluations. He has respiratory involvement, but no cardiac involvement. On physical examination, he presented with indurated skin on the face and abdomen, camptodactyly of the hands, and a tiptoe gait.

CLINICAL CASE 2

The only child of healthy, separated, non-consanguineous parents. She was diagnosed with mitral valve disease at 3 months of age, which required mechanical valve replacement at 18 months of age. She also had laryngeal synechiae, which required surgical correction, and high myopia. She died at age 7 due to severe respiratory failure. On physical examination, she presented with soft-tissue infiltration of the face, hands, and feet, as well as camptodactyly.

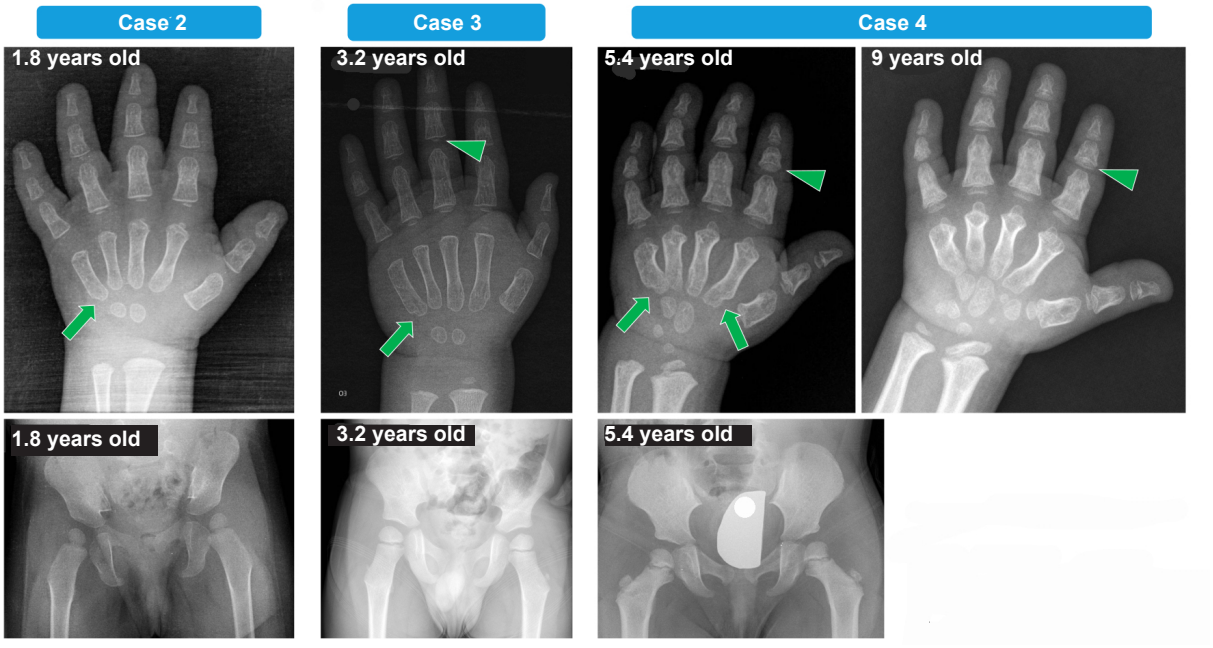
CLINICAL CASE 3

A 6.9-year-old boy on the last visit, the only child of a healthy couple, of normal height (mother's height 157.0 cm, father's height 165.0 cm), not consanguineous. He was born following a monitored pregnancy. He required admission to the Neonatal Intensive Care Unit due to amniotic fluid aspiration syndrome and suspected sepsis. Diagnosed with mitral valve disease at 3 years of age with pulmonary hypertension. He required repair and subsequent biological and mechanical mitral valve replacement (at 3.5 and 6 years of age) and developed severe prosthetic valve dysfunction. On physical examination, he presented with facial, hand, and foot skin thickening and a toe-walking gait.

CLINICAL CASE 4

A 16-year-old adolescent, the only child of healthy parents. An athlete with preserved function, currently in the final stage of growth. With a history of mitral regurgitation

Figure 2. Radiological findings



Anterior hand X-rays. Brachymetacarpal and brachyphalangeal features are observed in all cases; additionally, in cases 2, 3, and 4 at 5.4 years of age, a notch is observed in the proximal metacarpal (arrow). In cases 3 and 4, delayed ossification of the carpus and conical epiphyses in the phalanges are observed (arrowhead).
Anterior hip X-rays. Narrow femoral epiphyses are observed in all cases. In addition, cases 2 and 3 show coxa valga.

and ventricular septal defect, she underwent subaortic membrane resection at age 7. Due to her respiratory and audiological disorders, she required tympanostomy and adenoidectomy. She presented with infiltrated, thickened skin and brachydactyly, with limited mobility in the metacarpophalangeal and interphalangeal joints, elbows, hips, and knees. *Figure 3* shows the clinical characteristics of the girl at 15 months and 14 years of age.

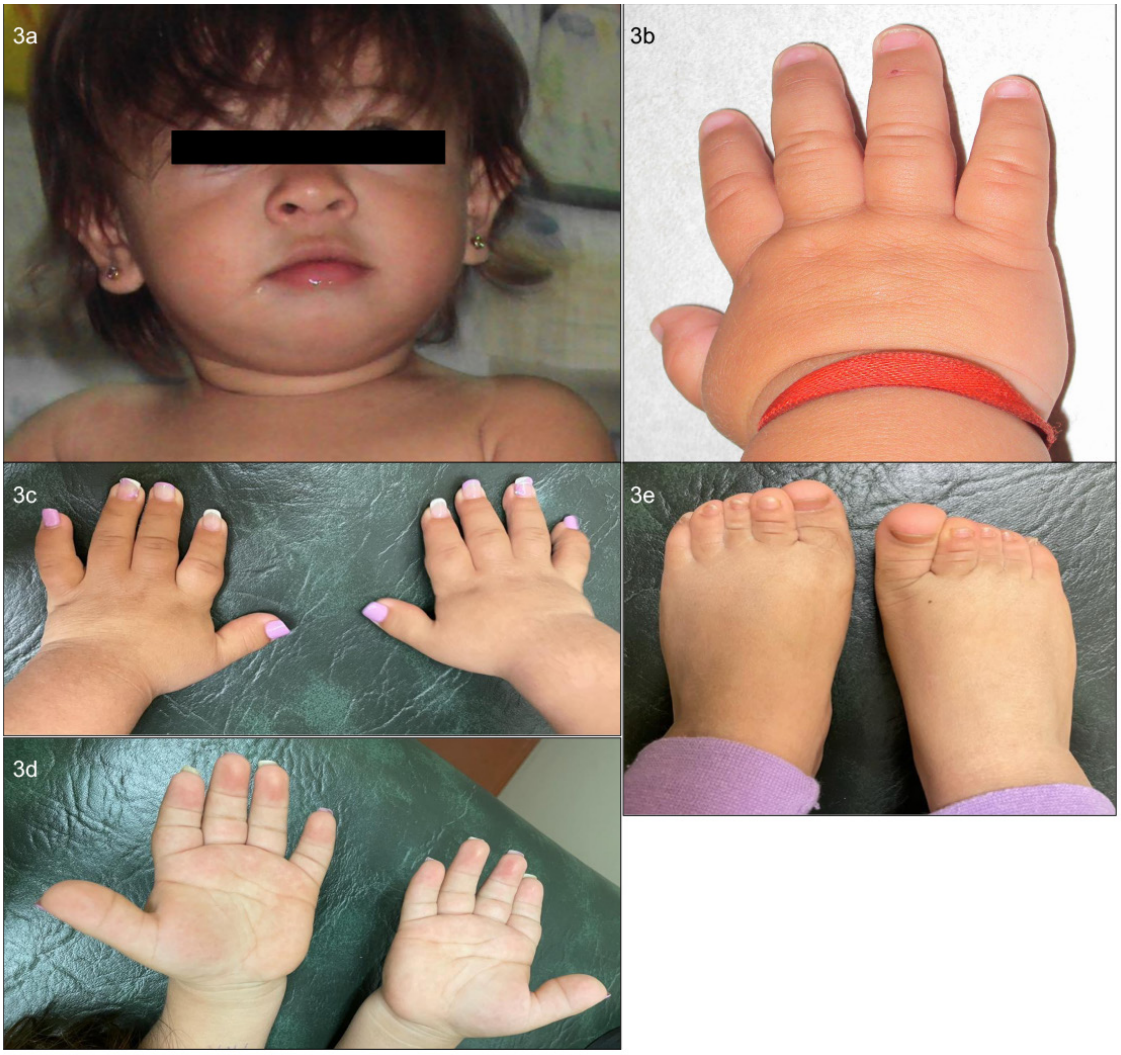
DISCUSSION

Skeletal dysplasias are rare disorders characterized by significant skeletal involvement, high phenotypic variability, and genetic heterogeneity,[5,20] with geleophysical dysplasia being a very rare condition.

We have confirmed this condition associated with *FBN1* variants in four unrelated cases being followed at a pediatric hospital. All patients presented with *de novo* involvement, as described in the literature.[1] Their parents showed no signs suggestive of a skeletal condition. Given that complete penetrance is described for this condition, in the absence of clinical signs and radiological findings, no genetic testing was performed on the parents.[1]

Variants in *FBN1* associated with geleophysical dysplasia are primarily described in exons 41 and 42, and less frequently in

Figure 3. Case 4: clinical characteristics at 15 months of age and at 14 years of age



3a, 3b: 15 months of age; 3c-3e: 14 years of age. There is thickening of the skin on the face, hands, and feet. The nasal bridge is depressed, with anteverted nostrils and a prominent philtrum; the cheeks are full, and the upper lip is thin. The hands and feet are short, with brachydactyly.

exon 43—locations where changes have been detected in our patients.[21] In this condition, the pathogenic mechanism causing the disease is loss of function. Our patients had *missense* variants classified as disease-causing according to the criteria of the American College of Medical Genetics.[22]

Notably, other variants in *FBN1* have been associated with phenotypes characterized by tall stature, ophthalmopathy, and aortic abnormalities: Marfan syndrome, Marfan syndrome with lipodystrophy, familial *ectopia lentis*, MASS syndrome (MIM 154700, 616914, 129600, and 604308), and non-syndromic hereditary aortic disease.[17,18] In these conditions, characterized by tall stature, the variants are located throughout *FBN1* and do not specifically affect the TB5 domain, as they do in acromelic dysplasias. FBN1 orchestrates the TGFβ and BMP signaling pathways and regulates ECM maintenance. Although alterations in TGFβ signaling are described in patients with achromelic dysplasias, the pathomolecular mechanisms have not yet been fully elucidated; disorganization of ECM microfibrils, defects in growth plate organization, and tissue inflammation are common findings in these conditions. In tall phenotypes, increased TGFβ signaling has been observed, which could explain the dysregulated excessive growth.[23,24]

Geleophysical dysplasia is characterized by short stature with acral involvement. All children in this series presented with short stature, short limbs, and short hands, with varying degrees of severity. This condition overlaps clinically, radiologically, and genetically with other developmental disorders involving peripheral involvement, particularly achromic dysplasia. Organ, osteoarticular, and cutaneous involvement are among the distinguishing features.[5] Although in two of the cases (cases 1 and 4) amino acid changes at the same site have been reported in patients with achromic dysplasia,[2] the progressive organ and cutaneous involvement allowed for classification of the phenotype as geleophysical ED. Organ involvement was consistent in our patient series, demonstrating high variability in indicators of severity: heart disease, respiratory involvement, and natural history. Another consistent finding was skin thickening and joint stiffness, as described in the literature.[1,2]

A poor prognosis has been reported in association with cardiac valve thickening and upper airway obstruction, especially when detected at an early age.[1] Valvular heart disease detected within the first year of life progresses rapidly, leading to early heart failure, as seen in our patients. Close cardiac follow-up is recommended in cases of early detection, due to the risk of acute cardiorespiratory failure. In most of these cases, the need for valve replacement has been reported.[1,2]

Valvular disease developing somewhat later due to postnatal valve thickening is described in up to 70% of children under follow-up; the most common condition is pulmonary stenosis, followed by mitral and aortic involvement, and multivalvular involvement is possible.[2] Non-progressive valvular defects were detected in the literature at a mean age of 2.8 years (range 1 to 10 years).[2]

Another common finding that influences morbidity and mortality is the presence of respiratory and ventilatory disorders: pulmonary hypertension, restrictive and obstructive lung disease, airway obstruction, stenosis, and/or malacia.[1]

Given the complexity and diversity of the systems involved, it has been suggested that a multidisciplinary approach is needed for these children, along with organized long-term follow-up throughout childhood and into adulthood. In addition to a pediatrician or general practitioner, an integrated team is recommended, including geneticists, cardiologists, pulmonologists, an airway team, otolaryngologists, orthopedists, and ophthalmologists.[1]

The supplementary table summarizes the associated complications and recommended follow-up, adapted from Marzin and informed by our observations.[1,2] The following schedule of clinic visits is recommended: monthly evaluations until 6 months of age, every 3 months until 2 years of age, every 6 months until 3 years of age, and then annually. At each visit, perform a clinical evaluation, including growth assessment, motor development assessment, cardiorespiratory physical examination, and liver palpation. Inquire about sleep disturbances, ear infections, language, and hearing.

It is important to provide genetic counseling to the patient and their family members, explaining the consequences of the disorder, the likelihood of developing and passing it on (inheritance pattern and risk of recurrence), and ways to prevent it, to facilitate medical, personal, and reproductive decision-making.[1]

CONCLUSION

We describe a series of children with a very

rare skeletal disorder associated with variants in the *FBN1* gene, characterized by predominantly acral involvement, severe short stature, and short limbs. We demonstrate clinical variability, as well as variability in natural history and prognosis, with previously described organ involvement and high morbidity and mortality. We reinforce the recommendations suggested in the literature and the need for a multidisciplinary, early, and sustained approach throughout life, given the possibility of progressive multiorgan involvement. We emphasize the importance of genetic counseling for the patient and their family members. ■

The supplementary material provided with this article is presented as submitted by the authors. It is available at: https://www.sap.org.ar/docs/publicaciones/archivosarg/2026/10995_RC_Melgarejo_Anexo.pdf

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