Open Access Library Journal
2026, Volume 13, e15840
ISSN Online: 2333-9721
ISSN Print: 2333-9705

Three Affected Siblings in a Consanguineous Family with ECEL1-Related Distal Arthrogryposis Type 5D: Intrafamilial Phenotypic Variability—A Case Report

Luay Abdalwahab, Somar Alhourany, Nuha Al Zaabi, Ahmed Adnan, Hussein Eleimy, Olfat Al Zaabi, Reem Mahmoud, Mohamed Ali Kasem, Mohammed Allam, Ahmed Shehada, Marwa Fatima, Ribal Kasem, Mena Ayad, Sumayah Alnuami, Yasser El Gohary*

Department of Pediatrics and Neonatology, Fujairah Hospital, Emirates Health Services (EHS), Fujairah, United Arab Emirates
Email: *dr_yaser44@yahoo.com

How to cite this paper: Abdalwahab, L., Alhourany, S., Al Zaabi, N., Adnan, A., Eleimy, H., Al Zaabi, O., Mahmoud, R., Kasem, M.A., Allam, M., Shehada, A., Fatima, M., Kasem, R., Ayad, M., Alnuami, S. and El Gohary, Y. (2026) Three Affected Siblings in a Consanguineous Family with ECEL1-Related Distal Arthrogryposis Type 5D: Intrafamilial Phenotypic Variability—A Case Report. *Open Access Library Journal*, **13**: e15840.
https://doi.org/10.4236/oalib.1115840

Received: August 2, 2026
Accepted: September 12, 2026
Published: September 15, 2026

Abstract

Distal arthrogryposis type 5D (DA5D) is a rare autosomal recessive congenital contracture disorder caused by biallelic variants in ECEL1. We describe a consanguineous family with three affected brothers showing a highly concordant DA5D phenotype with variable clinical severity. The index patient was a 3-month-old male infant with bilateral genu recurvatum, adducted thumbs, bilateral hip flexion contractures, congenital ptosis, micrognathia, high-arched palate, cryptorchidism, and mild facial dysmorphism. Molecular genetic testing in all three affected siblings identified the same homozygous ECEL1 variant, NM_004826.4:c.104del, p.(Pro35ArgfsTer168), classified by the diagnostic laboratory as likely pathogenic. In the available laboratory report, the deletion was shown to disrupt the translational reading frame and was reported at a gnomAD allele frequency of 0.012%, with no homozygous individuals reported at the time of testing. Across the three siblings, the most consistent manifestations were congenital knee extension deformity/genu recurvatum, thumb adduction, hip involvement, ptosis, and craniofacial abnormalities. The older siblings had greater orthopedic morbidity, including hip dislocation requiring surgery, and one had more extensive upper-limb contractures, pterygia, and developmental-language delay. The shared homozygous ECEL1 variant, together with the recurrent characteristic phenotype, supports familial segregation of ECEL1-related DA5D among the three affected brothers and illustrates intrafamilial phenotypic variability. Early recognition, multidisciplinary orthopedic and ophthalmologic care, rehabilitation, and genetic counseling are important.

Subject Areas

Pediatrics

Keywords

Distal Arthrogryposis Type 5D, ECEL1, Congenital Contractures, Genu Recurvatum, Ptosis, Consanguinity, Intrafamilial Variability, Genetic Counseling

1. Introduction

Distal arthrogryposis (DA) comprises a heterogeneous group of inherited disorders characterized by congenital contractures that predominantly affect the distal joints. Distal arthrogryposis type 5D (DA5D; OMIM #615065) is an autosomal recessive form caused by biallelic variants in the endothelin-converting enzyme-like 1 (ECEL1) gene [1] [2]. ECEL1 is highly expressed in motor neurons and is involved in terminal motor axon arborization and neuromuscular junction development during fetal life [2].

The recognizable clinical pattern includes congenital contractures of the hands and lower limbs, adducted thumbs, knee extension contractures, hip involvement, ptosis and/or ophthalmoplegia, and craniofacial findings such as micrognathia and a high-arched palate [1]-[4]. Additional manifestations, including hip dislocation, scoliosis, respiratory involvement, cryptorchidism, and variable musculoskeletal abnormalities, have been reported [5]-[7]. Recent cohort data have emphasized fixed knee extension contractures as a useful early clinical clue to ECEL1-related DA5D [8].

We report a family with three affected brothers born to first-cousin parents. Rather than attributing novelty to features already established in DA5D, this report emphasizes the recurrence of the characteristic phenotype across siblings and the clinically important intrafamilial variation in orthopedic severity, distribution of contractures, ocular findings, and developmental outcome.

2. Case Presentation

2.1. Index Patient

A 3-month-old male infant was referred for evaluation of multiple congenital contractures and dysmorphic features. He was born at 38 weeks and 2 days of gestation by elective cesarean section because of previous cesarean deliveries. Birth weight was 3.21 kg. Apgar scores were 4, 8, and 9 at 1, 5, and 10 minutes, respectively. After delivery, he required brief positive-pressure ventilation and was admitted to the neonatal intensive care unit for respiratory distress characterized by tachypnea, nasal flaring, and intercostal retractions. He received non-invasive respiratory support and improved clinically.

The parents were first cousins. Two older brothers had a similar congenital con-

tracture phenotype, while two sisters were unaffected. Molecular testing of the three affected brothers demonstrated the same homozygous ECEL1 c.104del, p.(Pro35ArgfsTer168) variant, supporting segregation of the disorder among the affected siblings.

Examination showed marked bilateral genu recurvatum; bilateral hip flexion contractures, with the hips maintained at approximately 90 degrees but with partial spontaneous movement; and bilateral adducted thumbs that could be passively abducted. Additional findings were bilateral congenital ptosis, micrognathia, high-arched palate, bilateral undescended testes, and mild facial dysmorphism. Spontaneous movements and muscle bulk were preserved, and no clinical weakness was observed at the reported 3-month assessment. Feeding was adequate without choking or swallowing difficulty, and weight tracked around the 9th percentile.

Newborn metabolic screening was normal. Echocardiography showed a small 2-mm patent foramen ovale without other structural cardiac abnormalities. Molecular genetic analysis was performed by whole-exome sequencing (WES), with enrichment and sequencing of the coding exons of more than 20,000 genes. WES identified a homozygous frameshift variant in ECEL1 (NM_004826.4), c.104del, p.(Pro35ArgfsTer168), chr2:233351259. The deletion disrupts the translational reading frame. The laboratory reported the variant at a gnomAD allele frequency of 0.012%, with one heterozygous individual and no homozygous individuals reported at the time of testing, and stated that it had not previously been described in the literature according to HGMD 2020.3. Considering the molecular finding together with the strongly supportive phenotype, the diagnostic laboratory classified the variant as likely pathogenic and considered a genetic diagnosis of ECEL1-related distal arthrogryposis type 5D (OMIM 615065) very likely. Parental segregation analysis was recommended to confirm homozygosity, with targeted molecular testing offered to family members. The formal criteria framework used by the laboratory to classify this primary ECEL1 variant was not explicitly stated in the available report.

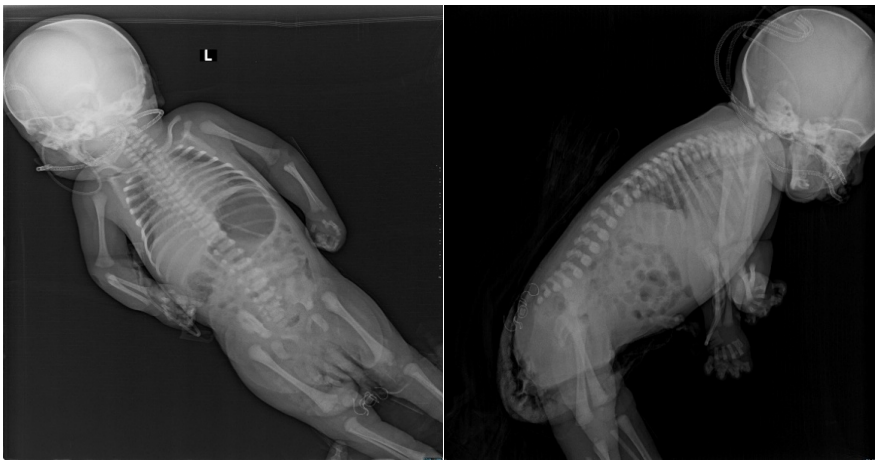

Figure 1. Skeletal survey images of the index patient. The right paracardiac opacity seen on the chest radiograph/scout image corresponds to the dome of the liver.

The patient was referred to orthopedic surgery, ophthalmology, physiotherapy, and clinical genetics. At the time represented by the available records, no long-term post-referral outcome was documented; therefore, the manuscript does not infer outcomes beyond the reported assessment (See Figure 1 and Figure 2).

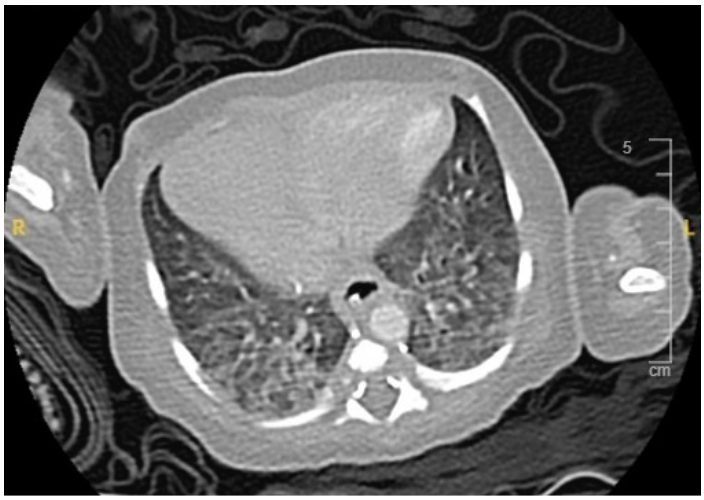

Figure 2. Chest CT of the index patient showing scattered atelectatic bands with granular opacity in segments of the right upper and lower lobes.

2.2. Older Affected Sibling 1

The first older affected brother had bilateral hyperextension of the knees (genu recurvatum) from birth, which was partially corrected with casting. He also had adducted thumbs that could be passively abducted, bilateral hip flexion contractures, micrognathia, dysmorphic facial features, and partial right-sided ptosis. Later examination additionally documented rocker-bottom feet and restricted shoulder rotation. He was followed by orthopedic services and underwent surgical treatment for bilateral hip dislocation and bilateral femoral shortening.

His genetic testing demonstrated the same homozygous ECEL1 NM_004826.4:-c.104del, p.(Pro35ArgfsTer168) variant identified in the index patient, supporting ECEL1-related distal arthrogryposis type 5D. Cognitive ability was reported as normal. Respiratory history was incompletely documented; a later ENT review recorded no shortness of breath or cough and described him as clinically well. Ongoing orthopedic and ophthalmologic follow-up and educational assistance for physical tasks were recommended (See Table 1).

2.3. Older Affected Sibling 2

The second-oldest affected brother had bilateral knee extension deformity/genu recurvatum, an adducted thumb, hip flexion abnormality, micrognathia, ptosis, and dysmorphic features. His musculoskeletal involvement was more extensive, with contractures of the shoulders, elbows, wrists, and knees, and pterygia of the neck and elbows. He also underwent surgery for bilateral hip dislocation and bilateral femoral shortening. Examination documented clear lungs with non-la-

bored respiration, and no chronic respiratory complication was recorded in the available report.

Earlier documentation described normal cognitive function; however, later developmental assessment recorded delayed milestones and language delay. At a chronological age of 3 years 8 months, his language age was estimated at approximately 2 years 6 months, with phonological errors affecting speech intelligibility. He was described as cooperative and sociable with good attention, and speech/language therapy and peer integration were recommended. Because the available records contain differing descriptions of cognition, we report the objective developmental-language findings without attributing a specific intellectual phenotype to ECEL1.

Table 1. Clinical comparison of the three affected siblings.

Feature	Index Patient	Older Sibling 1	Older Sibling 2	Interpretation in DA5D
Knee extension deformity/genu recurvatum	Bilateral, marked	Bilateral; partially corrected with casting	Bilateral extension contractures/genu recurvatum	Highly characteristic; one of the most consistent features in this family
Thumb involvement	Bilateral adducted thumbs, passively abductable	Adducted thumb (s), passively abductable	Adducted thumb	Common and characteristic
Hip involvement	Bilateral flexion contractures	Bilateral flexion contractures; later bilateral hip dislocation surgery	Hip flexion abnormality; later bilateral hip dislocation surgery	Common; severity increased in older siblings
Ptosis/ocular finding	Bilateral congenital ptosis	Partial right unilateral ptosis	Ptosis documented; examination also described bilateral ptosis	Common ocular manifestation; variable laterality/severity
Micrognathia/facial dysmorphism	Micrognathia, high-arched palate, mild dysmorphism	Micrognathia, flat nasal bridge, low-set ears, full forehead	Micrognathia, round face, short neck	Recognized craniofacial spectrum
Other contractures/pterygia	No additional sites documented beyond hips/knees/thumbs	Restricted shoulder rotation; rocker-bottom feet	Shoulder, elbow, wrist and knee contractures; neck and elbow pterygia	Shows intrafamilial variability in distribution/severity
Respiratory course	Transient neonatal respiratory distress; improved with non-invasive support	Later review: no shortness of breath/cough; full early history unavailable	Clear lungs, non-labored respiration; no chronic respiratory complication documented	No persistent respiratory phenotype established in available records
Development/cognition	No clinical developmental concern reported at 3 months	Cognitive function reported as normal	Language/developmental delay documented on later assessment	Mostly preserved cognition is typical, but developmental outcome can vary
Molecular evidence	Homozygous ECEL1 NM_004826.4:c.104del, p.(Pro35ArgfsTer168); laboratory classification: likely pathogenic	Same homozygous ECEL1 NM_004826.4:c.104del, p.(Pro35ArgfsTer168) variant confirmed	Same homozygous ECEL1 NM_004826.4:c.104del, p.(Pro35ArgfsTer168) variant confirmed	Same homozygous variant in all three affected brothers supports familial segregation and autosomal recessive inheritance

Molecular testing demonstrated the same homozygous ECEL1 NM_004826.4:-c.104del, p.(Pro35ArgfsTer168) variant identified in the index patient and the other

affected brother. The concordant molecular finding, together with his characteristic congenital contracture phenotype, supports the diagnosis of ECEL1-related distal arthrogryposis type 5D (See **Table 1**).

3. Discussion

ECEL1-related DA5D is a rare autosomal recessive congenital contracture syndrome with a recognizable but variably expressed phenotype [1] [2]. Across published series, the most frequently recurring manifestations include adducted thumbs and other hand contractures, fixed knee extension contractures, hip contractures or dislocation, ptosis or ophthalmoplegia, and craniofacial abnormalities such as micrognathia [1]-[4]. The three brothers in this family reproduce this core pattern remarkably consistently: all had knee extension deformity/genu recurvatum, thumb adduction, hip involvement, ptosis, and craniofacial abnormalities. This concordance is the strongest clinical justification for interpreting the family phenotype as DA5D.

The present family should not be interpreted as establishing genu recurvatum, ptosis, hip disease, or micrognathia as novel manifestations, because each is already recognized in ECEL1-related disease. Instead, its contribution is the demonstration of marked intrafamilial variability superimposed on a shared core phenotype. The index infant had severe bilateral genu recurvatum and hip flexion contractures but preserved spontaneous movement and no clinical weakness at 3 months. The older siblings showed greater orthopedic burden, including bilateral hip dislocation requiring surgery and femoral shortening; one also had contractures of the shoulders, elbows, and wrists, and pterygia of the neck and elbows. Hip dislocation, pterygia, scoliosis, and broader musculoskeletal involvement have been reported in the expanded DA5D spectrum [5]-[7].

Fixed knee extension contractures are particularly relevant. An Indian cohort identified this pattern as a recognizable early musculoskeletal clue to ECEL1-related arthrogryposis [8]. Bilateral genu recurvatum or knee extension contractures were present in all three affected brothers in the present family, making this the most consistent and clinically useful shared orthopedic feature. In a neonate or infant from a consanguineous family, the combination of knee extension deformity with adducted thumbs, hip contractures, ptosis, and micrognathia should therefore prompt consideration of ECEL1-related DA5D.

The mechanism is consistent with impaired development of motor innervation rather than a progressive primary myopathy. ECEL1 encodes a neuronal membrane-associated metalloprotease involved in terminal motor axon branching; experimental data support impaired axonal arborization and abnormal neuromuscular junction development as a basis for fetal hypokinesia and congenital contractures [9]. This also explains why the disease is generally non-progressive and why cognition is often preserved despite substantial orthopedic disability. Long-term studies nevertheless demonstrate persistent orthopedic and ophthalmologic morbidity requiring multidisciplinary care [10] [11].

Developmental findings in the second older sibling warrant cautious interpretation. However, an earlier record described normal cognitive function, and a later assessment documented developmental-language delay. Because the available data do not establish causality or a consistent intellectual phenotype, the finding is best presented as an associated outcome in this individual rather than as a defining or novel feature of ECEL1-related DA5D. This cautious approach is consistent with the broader literature, in which phenotypic severity can vary among individuals carrying ECEL1 variants, including within families [5] [10] [12].

Molecular testing in all three affected brothers demonstrated the same homozygous ECEL1 NM_004826.4:c.104del, p.(Pro35ArgfsTer168) frameshift variant. In the available diagnostic laboratory report, this variant was classified as likely pathogenic, was reported at a gnomAD allele frequency of 0.012%, with one heterozygous carrier and no homozygotes reported at the time of testing, and was predicted to disrupt the translational reading frame. The identification of the same homozygous variant in all three clinically affected brothers provides strong familial segregation evidence and, together with the first-cousin parental relationship and absence of the phenotype in the two sisters, is consistent with autosomal recessive inheritance. Parental carrier testing was recommended by the laboratory; parental molecular results were not available in the records reviewed.

Early molecular diagnosis is clinically valuable because it can prevent unnecessary investigations, guide anticipatory orthopedic and ophthalmologic management, support rehabilitation planning, and permit accurate recurrence-risk counseling. For an autosomal recessive condition, the recurrence risk is 25% for each pregnancy when both parents are confirmed carriers. Prenatal or preimplantation genetic testing can be considered when the familial pathogenic variant is molecularly established.

4. Limitations

This report is limited by its retrospective reliance on available clinical records. Molecular laboratory results confirmed the same homozygous ECEL1 NM_004826.4:-c.104del, p.(Pro35ArgfsTer168) variant in all three affected siblings, supporting familial segregation among the affected brothers. A detailed WES report was available and documented the testing method, ECEL1 transcript, zygosity, population frequency, and laboratory classification of the variant. However, the formal criteria framework applied by the laboratory to the classification of the primary ECEL1 variant was not explicitly stated, and parental segregation results were not available. Follow-up data for the index infant after multidisciplinary referrals were also not available. These limitations are stated explicitly to avoid overinterpretation of parental carrier status or long-term outcome.

5. Conclusion

This consanguineous family with three genetically confirmed affected brothers demonstrates the highly recognizable clinical pattern of ECEL1-related distal ar-

throgryposis type 5D. All three siblings carried the same homozygous ECEL1 NM_004826.4:c.104del, p.(Pro35ArgfsTer168) variant, classified by the diagnostic laboratory as likely pathogenic, providing strong molecular support for familial segregation. The most consistent shared findings were bilateral knee extension deformity/genu recurvatum, adducted thumbs, hip involvement, ptosis, micrognathia, and facial dysmorphism. These manifestations are established rather than novel features of DA5D. The principal contribution of the family is the demonstration of intrafamilial variability in severity despite an identical homozygous ECEL1 variant: the older siblings had more substantial orthopedic morbidity, and one had broader upper-limb contractures, pterygia, and developmental-language delay. Marked knee extension deformity in combination with adducted thumbs, hip contractures, and ptosis should raise early suspicion for ECEL1-related disease, especially in consanguineous families. Molecular confirmation, multidisciplinary management, and genetic counseling remain central to care.

Author Contributions

Conceptualization: L.A., S.A., and Y.E.G.; Methodology: L.A., S.A., and Y.E.G.; Investigation: L.A., S.A., N.A.Z., A.A., H.E., O.A.Z., R.M., M.A.K., M.A., A.S., M.F., R.K., M.A., and S.A.; Resources: L.A., S.A., and Y.E.G.; Data curation: L.A. and S.A.; Writing—original draft preparation: L.A., S.A., and Y.E.G.; Writing—review and editing: All authors; Visualization: L.A. and S.A.; Supervision: Y.E.G.; Project administration: Y.E.G. All authors have read and agreed to the published version of the manuscript.

Consent for Publication

Written informed consent was obtained from the parents for publication of the case report and accompanying clinical information and images.

Conflicts of Interest

The authors declare no conflict of interest.

References

[1] McMillin, M.J., Below, J.E., Shively, K.M., Beck, A.E., Gildersleeve, H.I., Pinner, J., *et al.* (2013) Mutations in ECEL1 Cause Distal Arthrogryposis Type 5D. *The American Journal of Human Genetics*, **92**, 150-156. https://doi.org/10.1016/j.ajhg.2012.11.014

[2] Dieterich, K., Quijano-Roy, S., Monnier, N., Zhou, J., Fauré, J., Smirnow, D.A., *et al.* (2013) The Neuronal Endopeptidase ECEL1 Is Associated with a Distinct Form of Recessive Distal Arthrogryposis. *Human Molecular Genetics*, **22**, 1483-1492. https://doi.org/10.1093/hmg/dds514

[3] Patil, S.J., Rai, G.K., Bhat, V., Ramesh, V.A., Nagarajaram, H.A., Matalia, J., *et al.* (2014) Distal Arthrogryposis Type 5D with a Novel ECEL1 Gene Mutation. *American Journal of Medical Genetics Part A*, **164**, 2857-2862. https://doi.org/10.1002/ajmg.a.36702

[4] Barnett, C.P., Todd, E.J., Ong, R., Davis, M.R., Atkinson, V., Allcock, R., *et al.* (2014) Distal Arthrogryposis Type 5D with Novel Clinical Features and Compound Heter-

ozygous Mutations in ECEL1. *American Journal of Medical Genetics Part A*, **164**, 1846-1849. https://doi.org/10.1002/ajmg.a.36342

[5] Huddar, A., Polavarapu, K., Preethish-Kumar, V., Bardhan, M., Unnikrishnan, G., Nashi, S., *et al.* (2021) Expanding the Phenotypic Spectrum of ECEL1-Associated Distal Arthrogryposis. *Children*, **8**, Article No. 909. https://doi.org/10.3390/children8100909

[6] Alesi, V., Sessini, F., Genovese, S., Calvieri, G., Sallicandro, E., Ciocca, L., *et al.* (2021) A New Intronic Variant in ECEL1 in Two Patients with Distal Arthrogryposis Type 5D. *International Journal of Molecular Sciences*, **22**, Article No. 2106. https://doi.org/10.3390/ijms22042106

[7] Jing, S., Peng, M., He, Y., Hua, Y., Li, J. and Li, Y. (2024) A Novel Compound Heterozygous Variant of ECEL1 Induced Joint Dysfunction and Cartilage Degradation: A Case Report and Literature Review. *Frontiers in Neurology*, **15**, Article ID: 1343025. https://doi.org/10.3389/fneur.2024.1343025

[8] Endrakanti, M., Sharma, J., Ethayathulla, A.S., Kaur, P., Khan, S.A., Kabra, M., *et al.* (2024) ECEL1 Related Distal Arthrogryposis 5D in an Indian Cohort—Report of Recognizable Musculoskeletal Phenotype and a Possible Founder Variant. *American Journal of Medical Genetics Part A*, **194**, e63592. https://doi.org/10.1002/ajmg.a.63592

[9] Nagata, K., Kiryu-Seo, S., Tamada, H., Okuyama-Uchimura, F., Kiyama, H. and Saido, T.C. (2016) ECEL1 Mutation Implicates Impaired Axonal Arborization of Motor Nerves in the Pathogenesis of Distal Arthrogryposis. *Acta Neuropathologica*, **132**, 111-126. https://doi.org/10.1007/s00401-016-1554-0

[10] Ullmann, U., D'Argenzio, L., Mathur, S., Whyte, T., Quinlivan, R., Longman, C., *et al.* (2018) ECEL1 Gene Related Contractural Syndrome: Long-Term Follow-Up and Update on Clinical and Pathological Aspects. *Neuromuscular Disorders*, **28**, 741-749. https://doi.org/10.1016/j.nmd.2018.05.012

[11] Cohen, D., Sloma, R., Pizem, H., Fedida, A., Kalfon, L., Ovadia, R., *et al.* (2023) Long Term Ophthalmic Complications of Distal Arthrogryposis Type 5D. *Ophthalmic Genetics*, **44**, 28-34. https://doi.org/10.1080/13816810.2022.2141791

[12] Gowda, M., Mohan, S., Ramesh, D. and Chinta, N. (2021) Distal Arthrogryposis Type 5D in a South Indian Family Caused by Novel Deletion in ECEL1 Gene. *Clinical Dysmorphology*, **30**, 100-103. https://doi.org/10.1097/mcd.0000000000000364

Abbreviations

DA: Distal Arthrogryposis; DA5D: Distal Arthrogryposis Type 5D; ECEL1: Endothelin-Converting Enzyme-Like 1; OMIM: Online Mendelian Inheritance in Man; NICU: Neonatal Intensive Care Unit; PPV: Positive-Pressure Ventilation; PFO: Patent Foramen Ovale.