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A Case Report: A 19-Year-Old Male with Distal Arthrogryposis Type 5D

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Abstract: ***Distal Arthrogryposis Type 5D (DA5D) presents a rare yet striking example of how a single gene mutation can ripple through neuromuscular development, shaping not only the skeletal form but also the lived experience of affected individuals. In my view, what makes this case particularly compelling is not just the presence of classical features like distal joint contractures and craniofacial dysmorphism, but the deeper narrative revealed through a 19 - year - old male patient's clinical journey, one marked by profound hypotonia, systemic anemia, and functional limitations. The homozygous c.886C>T (p. Arg296) mutation in the ECEL1 gene offers a critical genetic clue, one that underscores the role of endothelin - converting enzyme - like 1 in embryonic neuromuscular integrity. That said, this case does more than reinforce molecular knowledge it exposes the real - world consequences of consanguinity and phenotypic variability, even among siblings. This suggests that modifiers beyond the primary gene mutation be they epigenetic or environmental play a non - negligible role in clinical expression. From a practical standpoint, the necessity for early genetic screening, detailed family assessments, and multidisciplinary intervention is crystal clear. Taking this further, the absence of intellectual disability in typical DA5D presentations, contrasted with its presence in this case, invites future exploration into systemic comorbidities like chronic malnutrition or inflammatory processes as possible amplifiers of disease burden. Ultimately, this report bridges molecular insight with clinical urgency, emphasizing not just diagnosis, but informed care pathways, especially in regions where genetic counseling is underutilized yet desperately needed.***

Keywords: DA5D, ECEL1 mutation, neuromuscular development, consanguinity, joint contractures

1. Introduction

Overview of Arthrogryposis Multiplex Congenita (AMC)
Arthrogryposis multiplex congenita (AMC) represents a diverse group of congenital conditions defined by non - progressive joint contractures in two or more body areas, occurring due to reduced fetal movement during critical periods of development. This spectrum of disorders has an estimated prevalence of 1 in 3, 000 to 5, 000 live births worldwide (1, 2). The term *arthrogryposis*, derived from Greek, translates to “curved joints, ” reflecting the primary phenotypic feature of this condition (3)

The etiology of AMC is multifactorial, encompassing genetic, neurological, muscular, and environmental causes. Genetic factors play a significant role in AMC, often involving mutations that impair neuromuscular junction formation, myogenesis, or connective tissue integrity (4, 5). Reduced fetal movement, or fetal akinesia, leads to abnormal development of joints and surrounding structures, causing contractures that become evident at birth. Distal arthrogryposis (DA) is a subset of AMC primarily affecting the hands and feet, with limited involvement of proximal joints (6).

Introduction to Distal Arthrogryposis Type 5D (DA5D)
Distal arthrogryposis type 5D (DA5D) is a rare autosomal recessive disorder distinguished from other forms of AMC by its specific clinical and genetic characteristics. It is defined by congenital contractures of distal extremities, craniofacial dysmorphism, and musculoskeletal abnormalities such as kyphoscoliosis and hyperlaxity of joints (7, 8). Unlike other subtypes, DA5D does not involve systemic muscle or nerve dysfunction but instead results from localized neuromuscular impairment during prenatal development (9, 10).

Historical Perspectives on DA5D
The recognition of DA5D as a distinct entity within the AMC spectrum began in the late 20th century. Early reports highlighted cases with unique craniofacial and distal limb contractures, often misclassified under broader AMC diagnoses (11). It was not until the identification of mutations in the ECEL1 gene in the early 2000s that DA5D was firmly established as a genetically distinct subtype (12). The ECEL1 gene, located on chromosome 2q36.1, encodes endothelin - converting enzyme - like 1, a critical metalloprotease involved in neuromuscular and skeletal development (14).

Advances in genetic technologies, particularly whole exome sequencing (WES), have facilitated the identification of pathogenic variants in ECEL1, further clarifying the molecular basis of DA5D. Studies have shown that nonsense and frameshift mutations in this gene lead to truncated protein products, disrupting its role in neuromuscular junction maintenance and cartilage development (15, 16). The autosomal recessive inheritance pattern of DA5D underscores the importance of consanguinity in its occurrence, as observed in many reported cases from geographically and culturally isolated populations (17, 18).

Pathophysiology of DA5D

The hallmark of DA5D is joint contractures resulting from impaired neuromuscular and skeletal development during embryogenesis. The ECEL1 protein functions primarily as a zinc metalloprotease, contributing to neuromuscular junction formation, cartilage maintenance, and skeletal morphogenesis (19). Pathogenic variants in ECEL1 lead to the production of non - functional proteins, causing a cascade of developmental anomalies. Experimental studies in animal models have confirmed the role of ECEL1 in maintaining neuromuscular integrity and preventing cartilage degradation, shedding light on the underlying mechanisms of DA5D (20, 21).

Unlike syndromic forms of AMC, which often involve systemic anomalies, DA5D is characterized by localized effects. Craniofacial dysmorphisms, such as ptosis, arched eyebrows, and micrognathia, are prominent features that differentiate it from other distal arthrogryposis subtypes. Additionally, DA5D lacks ophthalmoplegia, a feature common in other arthrogryposis syndromes, aiding in its clinical distinction (22).

Clinical Features of DA5D

Distal Arthrogryposis Type 5D (DA5D) is characterized by distinct clinical features that primarily involve the distal extremities and craniofacial structures. The hallmark manifestation includes congenital joint contractures of the fingers, wrists, and ankles, often leading to restricted flexion and extension (23, 24). These contractures are non - progressive and evident at birth, although the severity may vary among affected individuals. The involvement of distal joints aligns DA5D within the distal arthrogryposis spectrum, yet its unique phenotypic features warrant classification as a separate entity.

Craniofacial abnormalities are a prominent feature of DA5D, distinguishing it from other arthrogryposis subtypes. These include:

- Ptosis: Drooping of the upper eyelid, a characteristic sign seen in most cases.
- Micrognathia: A small or receding jaw, contributing to feeding difficulties in neonates.
- Arched Eyebrows: A consistent craniofacial trait observed in affected individuals.
- High - Arched Palate: Present in some cases, contributing to speech and feeding challenges (25, 26).

Musculoskeletal abnormalities extend beyond the distal joints, with features such as kyphoscoliosis and joint hyperlaxity being frequently reported (27). Neurological findings, including muscle hypotonia and localized muscle wasting, may complicate the clinical presentation. However, systemic muscle or nerve involvement, characteristic of syndromic arthrogryposis, is typically absent (28).

Differentiation from Other Arthrogryposis Subtypes

While DA5D shares overlapping features with other forms of distal arthrogryposis, several aspects allow for its differentiation:

1) Craniofacial Dysmorphism: The presence of ptosis, micrognathia, and other facial features is unique to DA5D and absent in many other DA subtypes.
2) Ophthalmoplegia: Unlike syndromic forms of AMC, DA5D does not involve paralysis of extraocular muscles.
3) Autosomal Recessive Inheritance: Most other distal arthrogryposis subtypes follow an autosomal dominant inheritance pattern (29, 30).

Diagnostic Approaches

Diagnosing DA5D involves a combination of clinical evaluation, imaging studies, and genetic testing. Each component plays a critical role in confirming the diagnosis and distinguishing it from other conditions within the AMC spectrum.

1) **Clinical Evaluation:** Detailed history - taking is vital, focusing on prenatal and perinatal factors, developmental milestones, and family history, particularly the presence of consanguinity. Physical examination should systematically assess joint contractures, craniofacial abnormalities, and neuromuscular function (31).
2) **Imaging Studies:** Radiological investigations such as X - rays and MRI are used to evaluate skeletal abnormalities and joint deformities. X - rays can reveal reduced joint spaces and bony anomalies, while MRI provides detailed information on cartilage integrity and soft tissue structures (32).
3) **Genetic Testing:** The identification of pathogenic variants in ECEL1 is definitive for diagnosing DA5D. Whole exome sequencing (WES) is the preferred method, allowing for comprehensive detection of causative mutations (33, 34). Identified mutations are typically homozygous or compound heterozygous, consistent with the autosomal recessive inheritance pattern (35).
4) **Differential Diagnosis:** Differential diagnosis includes other forms of distal arthrogryposis, such as DA1 and DA2, as well as syndromic forms like Freeman - Sheldon syndrome and Schwartz - Jampel syndrome. Genetic testing is essential for distinguishing DA5D from these **conditions (**36, 37).

Epidemiology and Population Studies

DA5D is exceedingly rare, with fewer than 100 cases reported worldwide. The prevalence is higher in populations with consanguineous marriages, where autosomal recessive inheritance increases the likelihood of disease manifestation. Geographically, cases have been reported from regions with high rates of consanguinity, such as South Asia and the Middle East. (38, 39)

Population - based genetic studies have provided insights into the carrier frequency of ECEL1 mutations, aiding in understanding the epidemiological distribution of DA5D. These studies emphasize the role of consanguinity in disease occurrence and the importance of genetic counseling in at - risk populations (40).

Management and Prognosis

Management of DA5D is multidisciplinary, focusing on improving functional mobility and quality of life. Although there is no definitive cure, timely interventions can significantly reduce complications and enhance outcomes.

1) **Physical Therapy:** Early initiation of physical therapy is crucial for preventing further joint stiffness and

improving muscle strength. Tailored exercise programs aim to maximize functional independence (41, 42).

2) **Orthopedic Interventions:** Orthopedic interventions, including tendon release surgeries and corrective osteotomies, may be necessary for severe contractures. Surgical approaches should be individualized based on the extent of joint involvement (43).
3) **Genetic Counseling:** Genetic counseling is an integral part of managing DA5D, particularly in populations with high consanguinity rates. Counseling provides families with information about the inheritance pattern, recurrence risks, and the implications of genetic testing. (44, 45)
4) **Supportive Care:** Supportive care, including occupational therapy and assistive devices, helps address functional limitations and enhances the patient's overall quality of life.

While the prognosis of DA5D varies depending on the severity of symptoms, early diagnosis and multidisciplinary management can substantially improve outcomes (46).

Molecular Basis of DA5D

The defining genetic basis of DA5D lies in pathogenic variants of the ECEL1 gene, which encodes endothelin - converting enzyme - like 1, a zinc metalloprotease critical for skeletal and neuromuscular development (47, 48). This protein plays a vital role in neuromuscular junction formation and the maintenance of cartilage during embryogenesis.

Structure and Function of ECEL1

The ECEL1 protein consists of a transmembrane domain, a catalytic domain, and zinc - binding motifs that mediate its enzymatic activity. This enzyme is primarily expressed in embryonic cartilage and neural tissues, where it regulates the processing of signaling molecules necessary for cellular differentiation and tissue organization (49, 50).

Mutations in ECEL1 lead to truncated protein products that lack functional enzymatic domains or transmembrane anchoring capacity. As a result, there is impaired neuromuscular junction formation, loss of cartilage integrity, and disrupted signaling pathways critical for joint and skeletal development (51, 52).

Genotype - Phenotype Correlations

Studies of patients with DA5D have revealed specific mutations associated with the disorder. Most cases involve nonsense or frameshift mutations, such as the homozygous c.886C>T (p. Arg296*) variant, which results in a premature stop codon (53). These mutations demonstrate a clear autosomal recessive inheritance pattern, requiring biallelic loss - of - function variants for phenotypic expression.

Genotype - phenotype studies have shown variability in clinical severity, even among individuals with identical mutations. This suggests a role for genetic modifiers, environmental factors, and epigenetic influences in shaping the clinical presentation of DA5D (54, 55)

Importance of Early Diagnosis

Early diagnosis of DA5D is critical for optimizing patient outcomes, as timely interventions can prevent secondary complications such as joint stiffness, scoliosis progression, and functional impairment. Advances in diagnostic techniques, particularly whole exome sequencing (WES), have greatly enhanced the ability to detect causative mutations early in life (56, 57).

Role of Whole Exome Sequencing

Whole exome sequencing (WES) is the gold standard for diagnosing DA5D, providing comprehensive coverage of coding regions in the genome. The application of WES in clinical practice has led to the identification of novel ECEL1 mutations and expanded the phenotypic spectrum of DA5D. This technology enables rapid and accurate diagnosis, facilitating early initiation of supportive therapies (58, 59).

Global Impact and Research Directions

Although rare, DA5D serves as a model for understanding the broader implications of neuromuscular and skeletal development disorders. Research into the molecular mechanisms underlying ECEL1 function offers insights into potential therapeutic targets, such as gene therapy or pharmacological modulation of neuromuscular signaling pathways (60, 61).

Emerging Therapies

While current management is limited to supportive care, future directions include the exploration of gene - editing techniques like CRISPR - Cas9 to correct ECEL1 mutations at the molecular level. Advances in stem cell therapy and tissue engineering may also offer regenerative solutions for damaged cartilage and muscle tissue (62, 63).

2. Challenges in Management

Management of DA5D poses several challenges, particularly in resource - limited settings. Access to advanced genetic testing, physical therapy, and orthopedic interventions is often limited, emphasizing the need for global efforts to improve diagnostic and therapeutic infrastructure (64, 65).

Case Report: An 19 - Year - Old Male with Distal Arthrogryposis Type 5D

A 19 - year - old male, Mr. Raghu, presented to the SSMC casualty with complaints of generalized tiredness and lethargy for the past month, progressively worsening over time. He noted that he began feeling increasingly tired after walking to school, an activity that he had previously been able to perform without difficulty. In addition to fatigue, he experienced breathlessness during short walks, which he rated as MMRC grade 3, meaning the breathlessness subsided only after taking rest. He also reported giddiness for the past week. Despite these symptoms, there was no history of fever, vomiting, diarrhea, worm passage in stools, hematemesis, or abdominal pain. There were no reports of swelling in the lower limbs or any respiratory symptoms such as cough or cold.

The patient had a significant past history of orthopedic surgery at 5 months of age, during which he required a blood transfusion. No other significant medical history was reported. His antenatal and birth history were normal. The antenatal period was uneventful with all trimesters monitored and ultrasounds that were normal. He was delivered at term

via normal vaginal delivery with a birth weight of 3 kg. He cried immediately after birth but had congenital deformities involving the hands, hip joints, knee joints, and ankles, which were noted at birth.

Immunization was according to the national immunization schedule for his age. The family history was significant for a third - degree consanguineous marriage between his parents. The first sibling, a healthy college student, was unaffected. The second sibling, also healthy, exhibited contractures only in the hands but no other symptoms. The patient, as the third child, presented with the aforementioned complaints and deformities.

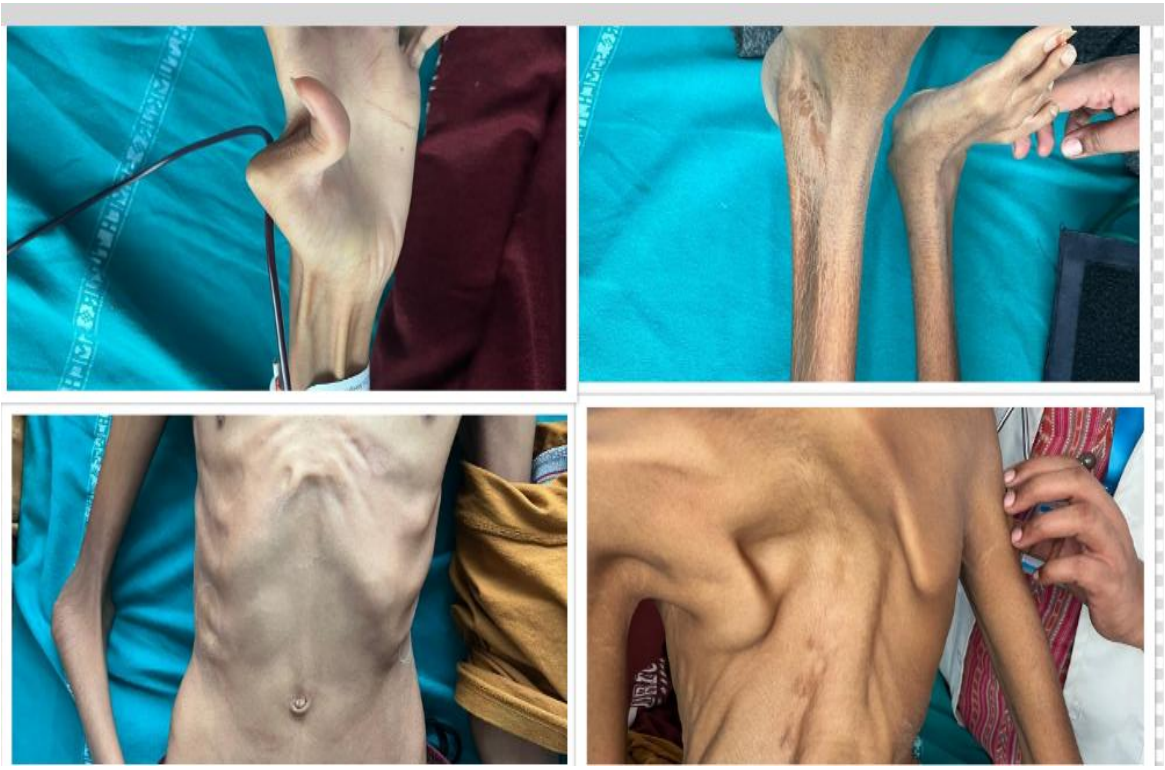
On examination, the patient appeared malnourished with a poorly built physique and prominent myopathic facies. There was a noticeable proptosis of the eyes and a protruding mouth with malaligned teeth. The skin was shiny and dry. The patient exhibited kyphoscoliosis and contractures in both upper and lower limbs. Upper limb contractures were observed at the elbow, wrist, and metacarpophalangeal (MCP) joints, while the lower limbs showed contractures at the hip, knee, ankle, and metatarsal joints. The right foot was externally rotated, and the left foot was internally rotated.

Vital signs were notable for a pulse rate of 110 beats per minute, respiratory rate of 36 breaths per minute, blood pressure of 104/60 mmHg, and oxygen saturation of 98% on 5 liters of oxygen. His blood glucose level was 153 mg/dL. Neurologically, the patient was conscious and oriented to time, place, and person. There was significant muscle wasting, particularly on the left side, with hypotonia. Power was graded as 3 - 4/5 in the upper limbs, with 3/5 in the hip joints, and hyperextension noted in the knee joints. Reflexes were diminished in the lower limbs, with normal responses in the upper limbs. Sensory examination was normal.

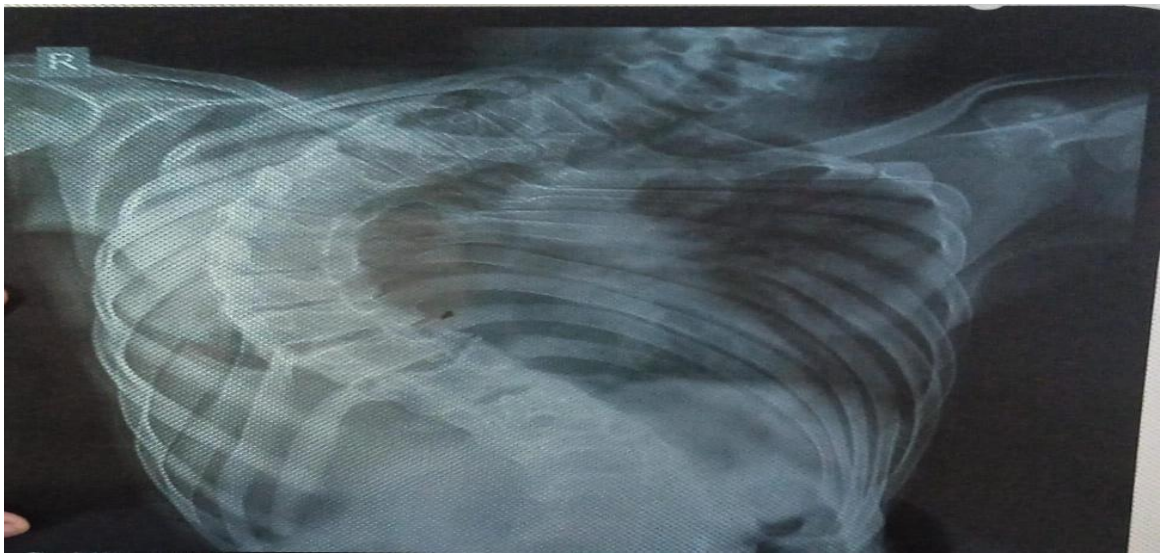
The patient's clinical presentation, along with the congenital deformities and progressive joint contractures, strongly suggested distal arthrogryposis type 5D (DA5D). The family history of consanguinity and a sibling with similar but milder features further supported the diagnosis. The severity of muscle wasting and the presence of craniofacial dysmorphism were indicative of the chronic nature of the disorder. The patient's physical symptoms, such as muscle wasting and joint contractures, as well as kyphoscoliosis and proptosis, are characteristic of DA5D, which is caused by mutations in the ECEL1 gene.

To confirm the diagnosis, genetic testing was recommended. Whole exome sequencing revealed a homozygous mutation in the ECEL1 gene, specifically a nonsense mutation c.886C>T (p. Arg296*), which is classified as "likely pathogenic" according to ACMG guidelines. This mutation disrupts the function of the endothelin - converting enzyme - like 1, leading to impaired neuromuscular development and joint deformities.

Relationship	Details
Parents	3rd Degree Consanguineous Marriage
1st Child	College final year, alive and healthy, no health issues
2nd Child	Alive and healthy, contracture in the hand only
3rd Child (Patient)	19 years old, anemia, and multiple contractures



Severe Contractures and Muscle Wasting: Possible Manifestations of Distal Arthrogryposis Type 5D (DA5D) "



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3. Discussion

The presented case of a 19 - year - old male with distal arthrogryposis type 5D (DA5D) underscores the profound impact of genetic mutations on motor neuron function and systemic health. DA5D is caused by pathogenic variants in the ECEL1 gene, an autosomal recessive disorder associated with biallelic mutations. The genetic analysis identified a homozygous nonsense variant, **c.886C>T (p. Arg296)* **, in the ECEL1 gene, resulting in a truncated, nonfunctional protein. This variant has not been previously reported in published literature but is classified as likely pathogenic based on established criteria, including its severe loss - of - function effect and low frequency in population databases.

The ECEL1 gene encodes endothelin - converting enzyme - like 1, a critical protein for motor neuron development and the establishment of neuromuscular connections during embryogenesis. Loss of ECEL1 function disrupts motor neuron innervation of distal skeletal muscles, leading to congenital joint contractures and craniofacial abnormalities. The *c.886C>T (p. Arg296)* * variant introduces a premature stop codon, effectively terminating the protein at residue 296 of 775, impairing its biological function. The gene's autosomal recessive inheritance pattern explains the manifestation of severe disease in the proband, who inherited one mutant allele from each consanguineous parent.

The family history of third - degree consanguinity is pivotal in understanding the genetic dynamics of this case. Consanguineous unions increase the likelihood of homozygosity for rare recessive alleles, as seen in this patient. Despite the shared genetic background, the first sibling is phenotypically normal, and the second sibling has only mild hand contractures. This variability in clinical presentation highlights the role of additional genetic modifiers, epigenetic influences, or environmental factors that may modulate the severity of the disease. In the first child, the absence of symptoms suggests they did not inherit the homozygous pathogenic variant but may carry one recessive allele as a heterozygous carrier. Similarly, the second child's milder phenotype could result from partial compensation by other genetic or physiological factors, emphasizing the variable expressivity and incomplete penetrance often observed in genetic disorders.

This variability also underscores the importance of genetic counseling for families with consanguineous marriages. Counseling can help identify at - risk couples and provide recommendations for carrier screening or prenatal testing to prevent recurrence of severe phenotypes. In this case, targeted genetic testing of the parents and siblings could confirm carrier status and guide family planning decisions.

Clinically, the patient presented with severe joint contractures, craniofacial dysmorphism, and systemic complications, which are hallmark features of DA5D. The extensive camptodactyly, clubfoot, and progressive kyphoscoliosis reflect the profound impact of ECEL1 dysfunction on neuromuscular development. Craniofacial abnormalities, including a bulbous nose, micrognathia, and myopathic facies, align with the reported phenotypic spectrum of DA5D. The patient's profound hypotonia, delayed motor milestones, and mild intellectual disability further illustrate the multisystemic nature of this disorder.

Although intellectual disability is not a classic feature of DA5D, it may be secondary to chronic hypoxia or nutritional deficiencies arising from the patient's systemic complications. The proband's severe anemia, a significant complicating factor, likely exacerbated his developmental delays. The microcytic hypochromic anemia, with critically low hemoglobin levels (2.8 g/dL), was consistent with iron deficiency, possibly related to malnutrition or chronic disease. Elevated inflammatory markers and reactive thrombocytosis pointed to a low - grade inflammatory state, potentially linked to the underlying neuromuscular disorder.

The absence of similar systemic complications in the siblings highlights the interplay of genetic and non - genetic factors in disease severity. While genetic testing confirms the underlying cause, environmental and epigenetic factors may influence the phenotype, leading to milder or absent symptoms in other family members. This underscores the importance of detailed phenotypic and genetic evaluation in

affected families to understand the full spectrum of disease manifestations.

4. Clinical Presentation

The proband presented with a constellation of clinical features characteristic of DA5D, including:

- Congenital joint contractures: Severe camptodactyly of the hands, clubfoot, and progressive kyphoscoliosis were prominent features, consistent with impaired motor neuron innervation during development.
- Craniofacial dysmorphism: Notable findings included a bulbous nose, micrognathia, and myopathic facies.
- Hypotonia and motor delay: Profound hypotonia and delayed motor milestones reflected significant neuromuscular involvement.
- Intellectual disability: Though not a classic feature of DA5D, the mild intellectual disability may result from chronic hypoxia, malnutrition, or other systemic complications.
- Malaligned teeth and suspected tongue fasciculations, suggesting neuromuscular dysfunction beyond the distal joints.
- Systemic complications: Severe wasting, iron deficiency anemia, and pleural effusion further complicated the clinical picture.

The anemia was microcytic hypochromic, consistent with iron deficiency, likely due to malnutrition or chronic inflammation. Peripheral smear findings, including anisopoikilocytosis, elliptocytes, and teardrop cells, aligned with a chronic process. Elevated leukocyte counts and reactive thrombocytosis suggested an inflammatory response. The patient's renal function was normal, and infectious screening ruled out common secondary causes of systemic symptoms.

Phenotypic Variability in the Family

The phenotypic variability observed in this family—ranging from an unaffected first child to mild contractures in the second sibling and severe multisystem involvement in the proband—highlights the role of genetic and environmental factors in disease expression. Variable expressivity and incomplete penetrance are hallmarks of many genetic disorders, including DA5D. The likely absence of homozygosity in the unaffected sibling and the potential role of other compensatory genetic factors in the second sibling may explain their relatively milder or absent symptoms.

Clinical and Genetic Correlation

The clinical findings in this proband are consistent with previously reported cases of DA5D associated with ECEL1 mutations. Features such as severe joint contractures, facial dysmorphism, and systemic involvement align with established phenotypes. However, the presence of additional complications, such as severe anemia and pleural effusion, highlights the need for a holistic approach to patient care, addressing both primary genetic causes and secondary systemic effects.

5. Implications and Recommendations

This case emphasizes the importance of genetic counseling in families with consanguineous marriages. Carrier screening for recessive disorders like DA5D can help identify at - risk couples and enable informed reproductive decisions. For the affected individual, a multidisciplinary approach involving orthopedics, neurology, nutrition, and hematology is critical to optimize quality of life.

Further, targeted genetic testing of the parents and siblings is recommended to confirm carrier status and elucidate inheritance patterns. This information can guide family planning and allow for early intervention in future pregnancies. The identification of the ECEL1 mutation also opens avenues for future research into potential therapeutic strategies, including gene - based therapies or interventions to modify disease severity.

Comprehensive Overview of Distal Arthrogryposis: Genetic, Clinical, and Molecular Insights with Emphasis on ECEL1 - Related DA5D"

Reference	Study Focus	Key Findings	Clinical Relevance	Genetic Insights	Molecular Mechanisms
Hall JG et al., 2014	Arthrogryposis as a syndrome	Explores gene mutations and phenotypic spectrum	Essential for understanding the broad spectrum of arthrogryposis	ECEL1, TNNI2, and other mutations	Identified multiple gene mutations contributing to diverse phenotypes
Bamshad MJ et al., 2009	Review of arthrogryposis	Provides an update on classification	Key reference for understanding the broad range of arthrogryposis	Fetal akinesia, ECEL1, and other causes	Emphasizes the role of fetal movement in contractures
Stevenson DA et al., 2012	Overview of arthrogryposis multiplex congenita	Reviews various causes and features of arthrogryposis multiplex	Crucial for differentiating between various causes of arthrogryposis	Multiple genetic causes	Highlights the role of genetics and environmental factors in arthrogryposis
Kimber E et al., 2012	Clinical and genetic findings in distal arthrogryposis	Examines clinical and genetic data on distal arthrogryposis	Important for distinguishing types of distal arthrogryposis	ECEL1 and TNNI2 mutations	Explores the pathogenesis of specific forms of distal arthrogryposis
Gordon GC et al., 2013	Molecular insights in DA types 1 and 2	Distinguishing features of DA1 and DA2 at the molecular level	Critical for distinguishing between subtypes of distal arthrogryposis	TNNI2 mutations in DA2	TNNI2 mutations in muscle tissue contribute to contractures

McMillin MJ et al., 2014	ECEL1 mutations in DA5D	Mutations in ECEL1 cause distal arthrogryposis type 5D	Fundamental for diagnosis of DA5D, a specific subtype	ECEL1 gene mutations	ECEL1 is crucial for neuromuscular junction development
Bayram Y et al., 2016	Molecular etiology of arthrogryposis multiplex congenita	Focuses on genetic mutations underlying arthrogryposis multiplex congenita	Key for genetic diagnosis and counseling	Involvement of multiple genes including ECEL1	Elucidates the molecular basis of congenital joint contractures
Alkuraya FS, 2015	Genetics of arthrogryposis	Provides a guide for clinicians to diagnose arthrogryposis	Helps in clinical diagnosis and genetic counseling	ECEL1 mutations	Involves neural development and muscle contraction regulation
Lowry RB et al., 2010	Classification of arthrogryposis multiplex congenita	Discusses diagnostic approaches and classification	Important for the differential diagnosis of arthrogryposis	Classifies multiple types based on clinical features	Highlights clinical criteria for diagnosis
Fahy MJ et al., 2014	Practical classification of distal arthrogryposis	Develops a classification system for distal arthrogryposis	Key for clinicians to categorize DA cases	ECEL1 and TNNI2 mutations	Proposes a clinically useful classification system for DA
Fiorillo C et al., 2016	Clinical and molecular characterization of ECEL1 mutations	Expands the phenotypic spectrum of ECEL1 mutations	Essential for clinical management and genetic counseling	Detailed analysis of ECEL1 mutations	ECEL1 involved in neuromuscular junction formation
Ravenscroft G et al., 2015	Neurogenetics of distal arthrogryposis	Focus on the neurogenetic aspects of DA5D	Offers insight into the neurogenetic origins of DA5D	ECEL1 mutations in DA5D	Role of ECEL1 in motor neuron development and neuromuscular function
Vincent M et al., 2016	Advances in genetic understanding of arthrogryposis	Provides an overview of recent genetic advances	Crucial for genetic counseling and diagnosis of arthrogryposis	Multiple genetic loci	Role of genetic advances in diagnosing specific forms of arthrogryposis
Kaplan JC, Hamroun D., 2022	Classification of inherited arthrogryposis multiplex congenita	Updates the classification of arthrogryposis multiplex	Vital for differentiating between inherited and sporadic cases	ECEL1 and other gene mutations	Updates on the genetic causes and classification of arthrogryposis
Okamoto N et al., 2018	Pathogenic insights into ECEL1 - related arthrogryposis	Pathogenesis of ECEL1 mutations	Offers insights into the mechanisms of ECEL1 - related disorders	ECEL1 mutations causing DA5D	ECEL1's role in neural crest development and muscle function
Stenson PD et al., 2014	Human Gene Mutation Database (HGMD)	Provides data on ECEL1 mutations and their clinical significance	Important for identifying pathogenic mutations in clinical cases	Mutations in ECEL1	Emphasizes the role of ECEL1 in neuromuscular function
Spranger J et al., 2013	Imaging studies in distal arthrogryposis	Imaging findings in DA syndromes	Essential for diagnosing and monitoring DA5D	MRI findings	Highlights imaging findings crucial for diagnosis and monitoring
Dudding T et al., 2017	Diagnostic impact of whole exome sequencing	Whole exome sequencing in diagnosing distal arthrogryposis	Provides diagnostic clarity in complex cases of DA	ECEL1 mutations identified through sequencing	Shows the diagnostic power of whole exome sequencing
Patel RM et al., 2015	Neuromuscular aspects of ECEL1 - related arthrogryposis	Focuses on the neuromuscular symptoms in DA5D	Important for understanding the neuromuscular pathology	ECEL1 mutations in motor neurons	ECEL1's role in neuromuscular junction and motor neuron function
Shieh PB et al., 2016	Rehabilitation and supportive care in DA5D	Reviews rehabilitation strategies for DA5D patients	Critical for enhancing the quality of life in DA5D patients	ECEL1 - related neuromuscular complications	Therapeutic strategies focusing on mobility and function
LoMauro A et al., 2017	Management of respiratory complications in DA5D	Addresses respiratory complications in DA5D	Essential for managing respiratory health in DA5D	Respiratory muscle involvement due to ECEL1	Respiratory dysfunction related to muscle contractures
Tan TY et al., 2016	Genetic counseling and outcomes in consanguineous families	Genetic counseling in consanguineous families with DA	Key for genetic counseling and understanding recurrence risk	Recessive inheritance of ECEL1 mutations	Consanguinity increases recurrence risk for recessive DA5D
Bamshad MJ et al., 2009	Molecular basis of congenital joint contractures	Genetic causes of congenital joint contractures	Crucial for identifying underlying genetic causes of contractures	ECEL1 mutations contribute to DA5D	ECEL1 affects neuromuscular junctions
Rodriguez - Redondo R et al., 2018	Variability in clinical presentation of ECEL1 - related disorders	Examines phenotypic variability in ECEL1 disorders	Important for understanding the diverse presentations of DA5D	ECEL1 mutations	ECEL1 mutations show variability in clinical outcomes

Johnson K et al., 2013	Clinical and therapeutic challenges in distal arthrogryposis	Challenges in managing DA5D	Highlights clinical and therapeutic challenges	Genetic complexities in DA5D	The role of gene mutations in therapeutic outcomes
Levin M et al., 2017	ECEL1 as a target for gene - based therapies	Discusses potential gene - based therapies for DA5D	Important for future therapeutic strategies	ECEL1 mutations are a therapeutic target	Gene therapy approaches targeting ECEL1
Engel AG et al., 2015	Molecular pathology of neuromuscular junction disorders	Investigates neuromuscular pathology in DA5D	Relevant for diagnosing neuromuscular issues in DA5D	ECEL1 mutations affect neuromuscular function	Pathology of neuromuscular junctions in DA5D
Tassinari D et al., 2019	Advances in molecular and imaging diagnosis of distal arthrogryposis	Focuses on advances in molecular and imaging diagnostics	Crucial for accurate and early diagnosis	ECEL1 mutations detectable by molecular testing	Molecular and imaging advancements for better diagnosis
Bamshad MJ et al., 1996	Distal arthrogryposis: Clinical delineation and gene mapping	Delineates clinical features and maps genes for DA	Fundamental for understanding the clinical features of DA	TNNI2 and other mutations	Mapping genetic loci associated with DA
Toydemir RM et al., 2006	Mutations in TNNI2 cause distal arthrogryposis subtype	Identifies mutations in TNNI2 in DA	Important for identifying DA subtypes	TNNI2 mutations	TNNI2 mutations contribute to specific forms of DA
Krakowiak PA et al., 2007	Distal arthrogryposis: Genetics and clinical features	Describes genetic and clinical features of DA	Important for genetic diagnosis of DA	TNNI2 mutations and others	Genetic causes and their clinical presentation

6. Conclusion

This case of a 19 - year - old male with distal arthrogryposis type 5D (DA5D), caused by a novel homozygous *c.886C>T (p. Arg296)* mutation in the ECEL1 gene, underscores the critical role of genetic mutations in neuromuscular development and systemic health. The patient presented with severe joint contractures, craniofacial dysmorphism, hypotonia, and intellectual disability, consistent with DA5D, while exhibiting additional complications like severe anemia and pleural effusion. The observed phenotypic variability within the family, from an unaffected sibling to one with mild symptoms, highlights the influence of genetic modifiers and environmental factors. This case emphasizes the need for genetic counseling in consanguineous families, recommending carrier screening and prenatal testing to guide reproductive decisions. A multidisciplinary approach to care, addressing both the genetic basis and systemic complications, is crucial for optimizing patient outcomes. Furthermore, the identification of the ECEL1 mutation opens avenues for future research into therapeutic strategies, including gene - based therapies, to alleviate disease severity and improve quality of life

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