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# Undifferentiated Connective Tissue Dysplasia in the Pediatric Population

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**Abstract:** Undifferentiated Connective Tissue Disease (UCTD) in children poses a difficult nosological challenge due to a critical dual definition in global medicine: the Western immunological paradigm (an early, unclassified autoimmune condition) and the Eurasian structural paradigm (Undifferentiated Connective Tissue Dysplasia, UCTD/CTD). This study focuses on the relatively widespread, multifactorial structural abnormalities of the extracellular matrix (ECM) in children [1]. We investigate the etiopathology of collagen and elastin fibrillogenesis abnormalities, which result in systemic tissue laxity and widespread phenotypic variability [2,3]. Multi-systemic involvement dominates the clinical picture, with high prevalence of musculoskeletal disorders such as Joint Hypermobility Syndrome and severe visceral manifestations such Minor Congenital Heart Defects and congenital urinary system anomalies [3]. Classification relies on organized scoring systems. This review emphasizes the critical need for a single, worldwide consensus to direct risk assessment, diagnosis, and treatment plans for kids with structural UCTD.

**Key words:** Undifferentiated Connective Tissue Dysplasia, Extracellular Matrix, Joint Hypermobility Syndrome, Minor Congenital Heart Defects.

**Introduction.** The wide range of disorders known as connective tissue diseases includes both hereditary structural faults and acquired autoimmune problems. In all organ systems, connective tissues which are mainly made up of extracellular macromolecules and minerals including collagen, elastin and different glycoproteins offer essential structural, mechanical, and metabolic support. Since these structural elements are ubiquitous and compose blood vessels, tendons, ligaments, skin, cartilage, and bone, flaws in them inevitably lead to highly polymorphic, multi-systemic clinical manifestations [1,3].

Pediatric patients who have systemic symptoms of a connective tissue illness that do not exactly fit into pre-established, categorized nosologies present a diagnostic problem. A popular term used to describe this unclassifiable state is "undifferentiated connective tissue disease" (UCTD). Importantly, there is a notable dichotomy surrounding the term UCTD in international medical literature, signifying two different pathophysiological paradigms: the structural/heritable Undifferentiated Connective Tissue Dysplasia (UCTD/CTD), which is commonly studied and classified in Eurasian pediatric medicine, and the primarily immunological UCTD that is recognized in Western rheumatology. For children to have an accurate diagnosis and prognosis, it is essential to comprehend this dual meaning [1].

According to systemic autoimmune rheumatology, UCTD is a clinical entity that exhibits clinical and serological signs and symptoms that are suggestive of a systemic autoimmune disease, but not enough to meet the comprehensive classification criteria for specific connective tissue diseases like

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Sjögren's syndrome, RA, or Systemic Lupus Erythematosus (SLE). It essentially serves as an exclusionary diagnostic.

The majority of patients with autoimmune UCTD have a moderate clinical course, which is distinguished by the lack of significant organ damage, especially to the neurological and renal systems. Arthritis, arthralgias (pain in the joints), and Raynaud's phenomenon are common initial symptoms. In terms of immunology, about 80% of these patients have a single autoantibody specificity, most commonly anti-Ro and anti-RNP antibodies. While the epidemiology is usually adult-centric (more than 90% of patients are female and between the ages of 30 and 45), pediatric rheumatologists must be aware of this classification in order to monitor young patients who might be in the early, undifferentiated stage of a systemic inflammatory disease that develops later in life [5,6].

"Undifferentiated Connective Tissue Dysplasia" (UCTD) or simply "CTD" is used in the Eurasian and specialized pediatric literature, especially from Russian scientific recommendations, to refer to a common group of heritable and multifactorial disorders that have their roots in widespread structural defects of the mesenchymal matrix. According to this paradigm, the disorder is a common congenital mesenchymal abnormality characterized by visceral manifestations and phenotypic polymorphisms that are either too numerous or non-specific to fit into established monogenic syndromes, such as Marfan syndrome (MFS) or Ehlers-Danlos syndromes (EDS) [1,3].

One system focuses on immunological activity, while the other system tackles structural vulnerability. This crucial difference in nosology is the source of the confusion surrounding the term UCTD. A thorough examination of the structural, congenital defect focus is required because the query specifically mentions "dysplasia" and calls for the application of Eurasian diagnostic instruments (such as the Kadurina classification). International criteria for autoimmune illnesses sometimes overlook the high incidence and particular somatic and visceral indicators that characterize this non-syndromic, structural connective tissue pathology in the juvenile population, which is why this framework is necessary.

**Objective of the study.** This thorough narrative review's main objective is to methodically examine the complex disorder known as undifferentiated connective tissue dysplasia (UCTD/CTD) in children, with an emphasis on the structural, non-syndromic type that is commonly seen in Eurasian pediatric practice.

**Materials and Methods.** A comprehensive narrative analysis of peer-reviewed literature and established national and international recommendations for undifferentiated systemic autoimmune diseases and undifferentiated connective tissue dysplasia (UCTD) in children provided the basis for this paper.

The methodology involved a focused analysis of primary research addressing:

1. The genetic and molecular basis of inherited connective tissue defects, particularly concerning extracellular matrix components.
2. Clinical cohort studies documenting the prevalence of phenotypic markers (e.g., Joint Hypermobility Syndrome, skeletal asymmetry) and visceral involvement (e.g., Minor Congenital Heart Defects, congenital urinary malformations) in children and adolescents.
3. Published classification and diagnostic recommendations. Critical review focused on Eurasian publications detailing the diagnosis, treatment, and rehabilitation algorithms for Connective Tissue Dysplasia in children, including the Russian national recommendations and the Kadurina and Abbakumova scale for severity assessment. The synthesis adopted a dual-paradigm comparative analysis to clarify the nosological divergence between the autoimmune and structural definitions of UCTD.

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**Results.**

***1. Etiology and Molecular Pathogenesis: Structural Failure of the Extracellular Matrix.***

According to whether the fundamental problem is structural/genetic or regulatory/autoimmune, the etiopathogenesis of connective tissue illnesses is divided into two categories.

***1.1. Genetic Susceptibility in Autoimmune UCTD.***

It is known that the genesis of autoimmune CTDs, such as UCTD, is complex, involving both genetic predisposition and interaction with particular environmental factors. The pathophysiology of these disorders is confirmed to be influenced by genetics, with specific connections found in the Human Leukocyte Antigen (HLA) region. Numerous genes may contribute to general autoimmune vulnerability, according to studies, which could account for the common overlap in clinical and serological profiles seen in different CTDs [6,7].

Environmental variables have the potential to initiate or intensify disease activity in genetically sensitive individuals by acting as crucial triggers. Exposure to air pollution, hazardous chemicals, and ultraviolet (UV) light are examples of such causes. Smoking, for example, has been shown to have detrimental effects on the expression of type I and III collagen and to change the turnover of extracellular matrix (ECM), which further exacerbates disease progression in people who are already genetically predisposed. Autoantibodies or antigen-specific T-cells that target autoantigens in different organs are produced as a result of the pathogenic process, which involves an overreaction of the immune system [6,8].

***1.2. Core Pathogenesis of Dysplasia: Extracellular Matrix (ECM) Defects.***

Conversely, Undifferentiated Connective Tissue Dysplasia is essentially a structural condition that stems from ECM flaws. In genetic connective tissue disorders, the genes that encode the structural components of connective tissue, mainly collagen and elastin, are affected by pathogenic variations. The ensuing disease shows up as observably aberrant tissues [8].

A disorganized matrix with a decreased capacity to tolerate mechanical stress is the outcome of the disarray of vital fibers, which compromises normal collagen biosynthesis and fibrillogenesis and is the molecular basis of dysplasia. The essential building blocks that are impacted include multidomain glycoproteins such as collagens and fibrillins. At the molecular level, these defects are caused by two global mechanisms: quantitative defects, in which the production of ECM proteins is decreased overall due to mutations like nonsense or frameshift, resulting in a reduced matrix integrity; and qualitative defects, in which structural mutations introduce dominant negative effects that affect the formation, structure, secretion, or stability of proteins [4,9].

Systemic tissue weakening is caused by the extensive breakdown of the ECM architecture, which affects the musculoskeletal, cutaneous, vascular, ophthalmic, and renal systems. For many of the severe clinical manifestations seen in pediatric dysplasia, this structural abnormality offers a clear molecular explanation. Organ laxity and possible ptosis (e.g., gastrointestinal prolapse, nephroptosis) are inevitable consequences of a systemic deficiency in collagen or elastin because connective tissue components support and bind organs. Because of its high degree of collagenation, the gastrointestinal system is the second most frequently involved system after the cardiovascular system. As such, it offers a strong example of this structural-functional pathology, where abnormalities like diaphragmatic hernia or ptosis of abdominal organs are direct and predictable results of systemic ECM failure. The ECM plays a crucial role in postnatal tissue homeostasis, as evidenced by the correlation between dysregulated development and differentiation processes and tissue weakening brought on by ECM abnormalities [3,9].

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### *2. Classification Systems and Severity Grading.*

Depending on the focus, such as the morphological severity in pediatric dysplasia or the prognostic risk in autoimmune UCTD, the classification of undifferentiated connective tissue disorder varies greatly.

### *2.1. Classification of Autoimmune UCTD (Prognostic Focus).*

The primary stratification of autoimmune UCTD is based on its evolutionary potential, which directs long-term surveillance and clinical treatment [10].

*Evolving UCTD (eUCTD).* As UCTD progresses, patients eventually fulfill the diagnostic requirements for a specific connective tissue disease, usually RA or SLE. Approximately 28% of patients, according to data from longitudinal cohorts, go through this changing trajectory, usually acquiring the specified syndrome five to six years after being first diagnosed with UCTD [6,10].

*Stable UCTD (sUCTD).* The majority of individuals (about 75%) never acquire a definite CTD and either achieve remission (roughly 18%) or have a stable undifferentiated clinical state. With survival rates above 90% over a ten-year span, this steady profile is frequently linked to exceptional long-term results. Within the first five years after the commencement of the disease, the risk of advancement is highest and gradually declines [5,10].

### *2.2. Classification of Connective Tissue Dysplasia (CTD) in Children (Structural Focus).*

A distinct set of standards is required for evaluating multifactorial, undifferentiated dysplasia because the international classification criteria for major monogenic illnesses (such as the updated Ghent criteria for Marfan syndrome) only apply to well-defined syndromes [8,11].

*Russian National Recommendations.* Certain national guidelines (such as those published by Martynov, Nechaeva, et al.) are used in Eurasian pediatric practice for the diagnosis, treatment, and rehabilitation of CTD. These guidelines place a strong emphasis on the methodical identification and measurement of phenotypic and visceral indicators [4,12].

*The Kadurina and Abbakumova Scale.* This scale is a crucial evaluation instrument for determining the prevalence of mesenchymal abnormalities in pediatric cohorts in Russia. With the use of this approach, qualitative clinical observations are converted into objective, quantitative metrics for risk assessment and disease burden. Markers like skeletal asymmetry or joint hypermobility are given a clinical significance grade, usually between 1 and 4, which is then added up to define the dysplastic syndrome's total severity [4,13].

The severity grading facilitates clinical decision-making:

- *Mild Grade:* Total score ranging from 9 to 14 points.
- *Severe Grade:* Total score higher than 15 points.

Examples of scored markers are X- and O-shaped legs (Grade 3), joint hypermobility (Grade 3), and spinal discomfort (Grade 4). In clinical contexts where thorough molecular genetic testing might not be easily accessible, this structured scoring system is essential for patient classification. A high likelihood of complex visceral consequences (such as significant congenital heart abnormalities) is instantly indicated by a severe score, which calls for prompt, focused screening and preventative treatment measures [4,13].

The distinction between the two UCTD paradigms can be summarized in the following table:

**Table 1: Comparative Nosology and Pathophysiology of Undifferentiated Connective Tissue Conditions.**

| Condition | Primary Etiology | Target Population | Key Pathophysiology | Diagnostic Focus |
|---|---|---|---|---|
| Autoimmune UCTD (Western) | Autoimmune/Multifactorial | Adults (30-45 yrs), 90% female | Systemic immune dysregulation, autoantibody production (anti-Ro, anti-RNP) | Serological markers (ANA) + Symptoms; Diagnosis of Exclusion |
| Undifferentiated CTD/CTD (Dysplasia, Eurasian) | Heritable/Multifactorial | Children and Adolescents | Primary genetic defect/abnormality in ECM structure (collagen and elastin fibrillogenesis) | Phenotypic somatic markers, visceral defect screening, severity grading (Kadurina/Nechaeva) |

### *3. Clinical Signs and Systemic Manifestations in Children.*

Because the afflicted connective tissue is so widely distributed, undifferentiated connective tissue dysplasia manifests as a wide range of clinical symptoms. Clinical indicators can be broadly divided into two categories: visceral (internal organ) and somatic (external/musculoskeletal) [3].

### *3.1. Musculoskeletal System (The Somatic Phenotype).*

The most obvious and early symptoms of dysplasia are frequently seen in the musculoskeletal system. When measured with instruments like the Beighton scoring assessment, Joint Hypermobility Syndrome (JHS) is a very common symptom. JHS was verified in 62% of patients in cohorts of kids and teenagers who showed signs of UCTD [14].

Skeletal and muscular defects are common, including:

- *Skeletal Anomalies:* Signs such as X- and O-shaped legs (genu varum/valgum) and asymmetry of the pelvic bones are frequently reported (50% prevalence in affected cohorts) [4].
- *Pain and Instability:* Pain in the spine has been noted in 100% of assessed cohort participants. Chronic musculoskeletal complaints, including arthralgia (present in up to 86% of UCTD patients) and prolonged morning stiffness, contribute significantly to impaired quality of life [4].
- *Muscular Defects:* Proximal muscle weakness, tenderness, and muscle atrophy are characteristic findings in various connective tissue dysplasia variants [6].

### *3.2. Cardiovascular System (Primary Visceral Markers).*

Congenital mesenchymal abnormalities mostly impact the cardiovascular system. Significant structural compromise results from defective collagen and elastin in the heart and circulatory structures [3,13].

According to clinical investigations, a significant percentage of children and adolescents with UCTD symptoms also have minor congenital heart defects (MCHDs), with a reported frequency of 38%. Mitral valve prolapse is one of the valvular abnormalities that are frequently included in these problems. Cardiomegaly, heart murmurs, pericardial rub, and irregular heartbeat are other indicators of cardiac involvement. Additionally, venous insufficiency and vascular remodeling are examples of extracardiac symptoms that result from structural protein abnormalities in the arterial walls. Another often mentioned autoimmune overlap symptom is Raynaud's phenomenon [6,13,14].

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### *3.3. Renal and Urinary System (Congenital Markers).*

The assessment of the urinary system is essential for diagnosing dysplasia in infants and young children. UCTD is quite common in young children (ages 2 weeks to 3 years) who present with congenital urinary system abnormalities, according to studies. Congenital malformations of this kind are acquired from birth and are thought to be a clear-cut visceral indicator of undifferentiated connective tissue dysplasia. This structural pathology greatly affects how the disease progresses and is managed, especially when linked to aberrant kidney tissue development or function. Nephroptosis (kidney prolapse) and other renal indications of laxity are also known extracardiac symptoms [13,15].

### *3.4. Pulmonary and Gastrointestinal Systems.*

The gastrointestinal (GI) and pulmonary systems are also affected by the compromised structural integrity.

- *Pulmonary Manifestations:* Pleuritis, pleural effusion, wheezing, rales, and, less commonly, interstitial pneumonia are among them. The absence of rigidity in the airway structure, or tracheobronchial dyskinesia, is a recognized extracardiac symptom of UCTD [6,13].
- *Gastrointestinal Manifestations:* The GI tract's high collagen concentration directly correlates with its status as the second most frequently involved location, behind the cardiovascular system. A diaphragmatic hernia, ptosis (prolapse) of the abdominal organs, and cardiac insufficiency are examples of structural abnormalities that can result from dysplastic alterations and lead to a number of functional digestive diseases [3].

### *3.5. Dermatological, Ocular, and Immunological Findings.*

As with well-defined Heritable Connective Tissue Disorders (HCTDs), including Ehlers-Danlos syndromes, hyperextensibility, tissue fragility, and poor healing are frequently reported, reflecting the underlying abnormalities in collagen fibrillogenesis. Non-specific symptoms like sun-sensitive rash and hair loss can also be a part of autoimmune presentations [9,16].

Iritis, uveitis, scleral/episcleral disease, and dry eyes (keratoconjunctivitis sicca, KCS) are examples of ocular involvement. Constitutional symptoms like as fever, exhaustion, and general malaise are common early manifestations in immunology. Common minor criteria in autoimmune UCTD include laboratory symptoms including anemia and leukopenia [5,6,17].

Congenital structural abnormalities may also produce a milieu that is vulnerable to subsequent inflammatory processes, according to clinical observation. Infants who present with neonatal indicators of UCTD later have higher rates of morbidity related to autoimmune or allergic disorders (food allergies, asthma, juvenile idiopathic arthritis, JIA) and infectious diseases (acute respiratory infections, acute intestinal infections, and infectious mononucleosis). This finding implies that the faulty extracellular matrix, which has an ontogenetic attraction for immune system cells, may expose cryptic antigens or impair localized immune control, which could lead to the emergence of secondary inflammatory cascades such as JIA [18,19].

**Table 2: Major Phenotypic and Visceral Markers of Undifferentiated Connective Tissue Dysplasia in Children.**

| System/Marker Type | Example Phenotypic Sign | Reported Prevalence (CTD/Migraine Cohorts) | Clinical Significance Grade (Kadurina Scale) | Associated Visceral Pathology |
|---|---|---|---|---|
| Musculoskeletal (Somatic) | Joint Hypermobility (JHS) | Confirmed in 62% of UCTD Cohorts | Grade 3 (Moderate) | Arthralgia, chronic pain, early osteoarthritis |

| | | | | |
|---|---|---|---|---|
| Skeletal/Anthropometric | Arm swing/height ratio | 31.3±6.7% | Diagnostic Value (≥ 15%) | Marfanoid habitus, Aortic involvement risk |
| Cardiovascular (Visceral) | Minor Congenital Heart Defects (MCHDs) | Found in 38% of UCTD Cohorts | Highly Variable (Often Grade 3/4) | Valvular insufficiency (e.g., MVP), arrhythmias |
| Renal/Urological (Visceral) | Congenital Urinary System Malformations | Considerable Prevalence in young children | High (Grade 4 Visceral Marker) | Abnormal kidney function, nephroptosis |
| Gastrointestinal (Visceral) | Organ Ptosis/Hernia (e.g., Cardia insufficiency) | High frequency (Second most involved system) | Highly Variable (Often Grade 3/4) | Functional digestive disorders, malabsorption |
| Respiratory (Visceral) | Tracheobronchial Dysplasia | Present (Extracardiac manifestation) | Highly Variable | Recurrent infections, interstitial pneumonia risk |

### *4. Diagnostic Criteria and Clinical Assessment.*

#### *4.1. General Principles: Diagnosis of Exclusion and Longitudinal Monitoring.*

A thorough exercise in exclusion is the first step in the diagnostic process for both structural dysplasia and autoimmune UCTD, making sure that the patient's presentation does not fit the predetermined criteria for any specific CTD. Given that the risk of developing a specific disease state is concentrated in the first five years after initiation, longitudinal surveillance is essential for autoimmune UCTD [6].

#### *4.2. Autoimmune UCTD Criteria (Western, Preliminary).*

Clinicians usually use preliminary recommended criteria for autoimmune UCTD since globally accepted, consistent classification criteria are currently being developed.

According to UCTD's preliminary classification standards, there are two main requirements:

1. Unclassifiable features must be present for at least three years and include signs and symptoms suggestive of a connective tissue disease but not meeting the categorization criteria for any known connective tissue disease.
2. Antinuclear antibodies (ANAs) were detected twice with varied results.

Most UCTD patients have a positive ANA test, according to serological analysis. It is common to find particular autoantibodies, usually anti-Ro/SSA and anti-RNP, which often show only one specificity. There may also be nonspecific indicators of inflammation, like increased C-Reactive Protein (CRP) or Erythrocyte Sedimentation Rate (ESR) [5,6].

**Table 3: Preliminary Diagnostic Criteria for Undifferentiated Connective Tissue Disease (UCTD, Autoimmune).**

| Criterion Category | Specific Finding | Requirement | Clinical Implication |
|---|---|---|---|
| Clinical Signs | Symptoms suggestive of a systemic CTD (e.g., Arthralgias, Raynaud's phenomenon) | Must *not* fulfill classification criteria for defined CTDs | Diagnosis is longitudinal; rule out full-blown SLE, SSc, etc. |

| | | | |
|---|---|---|---|
| Duration | Persistence of unclassifiable signs/symptoms | Must persist for at least three years | Necessary to differentiate transient symptoms from stable UCTD |
| Serology | Antinuclear Antibodies (ANAs) | Identified on two different occasions | Confirms immunological activity, though often low levels |
| Additional Serology | Specific Autoantibodies (e.g., Anti-Ro, Anti-RNP) | Usually present with only a single specificity (80%) | Guides monitoring toward potential progression (e.g., Anti-RNP towards MCTD) |

### *4.3. The Dysplastic Scoring Approach.*

In cases when molecular confirmation is not available, the diagnosis of undifferentiated connective tissue dysplasia mostly depends on a thorough clinical and anthropometric evaluation intended to characterize mesenchymal abnormalities.

The Kadurina/Abbakumova Scale and other structured scoring systems are used to evaluate phenotypic burden in the Eurasian approach. Objectively identifying dysplastic phenotypes like Marfanoid habitus is made easier by this methodical quantification, which uses particular anthropometric indices like an arm swing/height ratio >15% or a Pigne Index ≥30%. A concrete, evidence-based indicator of systemic connective tissue compromise is given to the clinician by giving somatic indications numerical grading [4].

### *4.4. Laboratory and Instrumental Diagnosis.*

The Kadurina/Abbakumova Scale and other structured scoring systems are used to evaluate phenotypic burden in the Eurasian approach. Objectively identifying dysplastic phenotypes like Marfanoid habitus is made easier by this methodical quantification, which uses particular anthropometric indices like an arm swing/height ratio >15% or a Pigne Index ≥30%. A concrete, evidence-based indicator of systemic connective tissue compromise is given to the clinician by giving somatic indications numerical grading [4].

- *Cardiovascular Assessment:* Echocardiography is crucial for MCHD screening, valvular defect detection (including mitral valve prolapse), and early detection of aortic root dilatation [6,14].
- *Pulmonary Function:* When signs of respiratory illness point to possible interstitial lung disease, pulmonary function tests, such as spirometry and carbon monoxide-diffusing capacity, are recommended [6].
- *Renal/Urinary Imaging:* Because congenital abnormalities of the urinary system are known to be powerful visceral indicators in neonates, ultrasound imaging is required if such deformities are suspected [15].
- *Molecular Genetic Testing:* Nowadays, genetic testing is frequently saved for individuals whose phenotypic strongly points to a specific monogenic HCTD (such as classical EDS or MFS). Although gene panels can validate suspected diagnoses, most undifferentiated cases cannot be definitively confirmed by molecular means because the molecular basis for the most prevalent types of undifferentiated connective tissue dysplasia, such as Hypermobility Spectrum Disorder (HSD)/hypermobile EDS (hEDS), is still unknown [8,16].

Because most cases of undifferentiated dysplasia lack molecular confirmation and have complex presentations, a practical, integrated diagnostic approach is required. This includes using comprehensive clinical scoring (Kadurina) to define phenotypic burden and saving advanced visceral screening and molecular testing for children who have been identified as high risk. This method guarantees the effective identification of serious, progressive diseases such as MCHDs while following the recommendations made in pediatric protocols [1,8,16].

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**Conclusion.** Children's undifferentiated connective tissue disease is a major difficulty because of its extreme heterogeneity and the crucial differences in international nomenclature. Undifferentiated Connective Tissue Dysplasia (UCTD) is a structural, multifactorial condition characterized by widespread ECM failure. Clinicians must recognize the basic difference between autoimmune UCTD, an immunological state that requires longitudinal monitoring for progression to defined CTDs like SLE.

The clinical finding that congenital structural anomalies seem to put children at risk for developing secondary infectious and autoimmune disorders (such as asthma and JIA) underscores the importance of further research in the structure-inflammatory feedback loop. To understand how impaired ECM integrity affects local tissue homeostasis, exposes cryptic antigens, or dysregulates immune cell activity, acquired inflammatory illnesses in children with underlying dysplasia must be the main focus of research.

Finally, a common definition and a uniform, international categorization system for multifactorial/undifferentiated connective tissue dysplasia in the pediatric population are desperately needed. To determine the precise genetic variations causing prevalent hypermobile and dysplastic phenotypes, more molecular research is necessary. This will open the door to conclusive molecular diagnoses and focused therapeutic approaches that go beyond treating symptoms and instead target the fundamental flaws in the extracellular matrix.

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