

REVIEW



Changes in skeletal dysplasia nosology

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Abstract

Skeletal dysplasia (SD), also called osteochondrodysplasia (OCD), is a large group of skeletal disorders (over 400 distinct entities) caused by abnormalities in bone development and growth. SDs varies according to different natural histories, prognoses, hereditary patterns to etiopathogenetic mechanisms. At birth, the incidence is low, reported at the level of each entity, but taken collectively; the incidence is estimated at 1:5000 births. Nosology is a branch of medical science. It deals with the systematic classification of diseases and disorders. Thus, combining information about the catalogue of clinically distinct disorders, pending molecular explanations, and genotype–phenotype correlations, the classification of SDs will be more accurate. This is extremely useful for diagnosing patients with genetic skeletal diseases, especially given the expected flow of information with new sequencing technologies. Over the years, various terms and classifications of SD have been used and have attempted to order and classify this group of genetic diseases according to clinical, radiological, and molecular criteria. In 2019, the *Nosology Committee* of the *International Skeletal Dysplasia Society* (ISDS) updated the classification of SD. This new classification divides SD into 42 large groups that include 461 entities. Advances in next-generation sequencing techniques have revolutionized the entire field of genetics, with 437 different genes are currently identified in 426 (92.4%) of SDs. Nosology is a real help for the clinician in establishing a diagnosis as accurately as possible, for the recognition of new diseases while serving as a guide for the interpretation of new genetic variants.

Keywords: skeletal dysplasia, osteochondrodysplasia, nosology, genetic disorder.

Introduction

Skeletal dysplasia (SD) is a challenge for any geneticist due to its clinical diversity and genetic heterogeneity. Genetic disorders that affect bone tissue result from the processes of bone development and growth. In terms of nosology, combining the information about the catalogue of clinically distinct disorders, pending molecular explanation, and the description of the phenotypic spectrum produced by changes in distinct genes, the classification of SDs will be more accurate. This is extremely useful for diagnosing patients with genetic skeletal diseases, especially given the expected flow of information with new sequencing technologies.

Aim

The authors do not intend to describe each SD. They reviewed the main groups of SD to offer their colleagues geneticists, pediatricians, radiologists, orthopedists (and other specialties) an updated list of recognized genetic skeletal disorders. This new knowledge is useful not only in diagnosing and treating individual cases but also in describing a new condition as well as in establishing bridges between clinicians and researchers.

Method

The study is a systematic literature review. It aims to identify, evaluate, and synthesize best research evidence and clinical expertise to make a summary of current data that help to achieve best patients' outcomes in medical practice. An electronic literature search was conducted using different biomedical databases (such as *PubMed/MEDLINE* database) and the key search terms such as 'skeletal dysplasia', 'prevalence', 'diagnosis', 'genetic heterogeneity', and 'patterns of inheritance', until July 2021. Articles of interest (including medical studies, case reports, and academic research) were reviewed to determine which were relevant and subjected to analysis.

Throughout the time, there were many attempts to classify SD. Clinical, radiological, or molecular criteria have been used in trying to subdivide this heterogeneous group of genetic disorders [1]. In 1969, an international team of experts with various specialties (radiologists, orthopedists, pediatricians, geneticists) agreed at a scientific meeting in Paris to set up an International Nomenclature of "constitutional" bone diseases. The main aim of the meeting was to achieve some agreement on the nomenclature

of known genetic disorders of the skeleton that have been reported since the early 1960s [2–5]. There was growing evidence that genetic skeletal disorders became more heterogeneous and complex than previously known. The clinical and radiological diversity among people with “constitutional” bone disease was becoming much clearer. It has become evident that if a patient has short limbs, it does not mean that he must have uneven achondroplasia or if the patient has a shortened chest to have type IV myelin protein zero (MPZ) [6–8].

Due to the new diseases identified in increasing numbers, numerous revisions of the initial nomenclature were necessary (1977, 1983, and 1987). After establishing the *International Skeletal Dysplasia Society* (ISDS) in 1999, the revision of nosology fell to a group of clinicians, radiologists, geneticists. The first was performed in 2002, followed by other revisions, at regular intervals [9–11].

In 2019, the *Nosology Group* of ISDS updated the classification of SD. Thus, the SD was divided into 42 large groups that included 461 entities. Due to the increasingly accelerated development of next-generation sequencing techniques, 437 distinct genes caused 426 (92.4%) of SDs. It has been proven that pathogenic variants of a single gene can cause different phenotypes (groups 1, 2, 5, 6, 8) but can also occur the phenomenon of gene heterogeneity in which a phenotype is caused by different variants of distinct genes (groups 9, 25). Another observation was that moderate forms of the disease, such as idiopathic short stature, premature joint degenerative diseases, are caused by pathogenic variants in fibroblast growth factor receptor 3 (*FGFR3*), collagen type II alpha 1 chain (*COL2A1*), cartilage oligomeric matrix protein (*COMP*), natriuretic peptide receptor 2 (*NPR2*), and aggrecan (*ACAN*) [12, 13]. A permanent revision of the nosology of SD is necessary because it is of maximum help for the clinician who takes care of a patient with such pathology. It can facilitate the recognition of new diseases, and at the same time, it can also be a guideline for interpreting new genetic variants.

In the latest nosology update, the first 32 groups refer to bone dysplasia, and the last 10 to bone dysostoses. It must be recognized the difference between dysostoses and

dysplasia. Dysostoses involve affecting a single bone or group of bones. By dysplasia is meant the abnormal organization of the cells of tissue following a defect of embryogenesis and leading to the appearance of malformation syndromes. The mechanisms that lead to bone dysplasia cause defects in the structure of structural proteins, alteration of a metabolic process, or the appearance of disturbances in the regulation of the growth plate. In present, the boundaries between the two categories, metabolic are difficult to prove, and a correct diagnosis must work multidisciplinary [14]. The incidence at the birth of SD is low at the individual level, but the collective incidence is estimated at 1:5000 births. They have an evident contribution to infant morbidity and even to perinatal mortality [15–17].

According to the *ISDS Nosology Group*, the criteria for classifying SD into the 42 groups must be targeted with the following information:

1. This skeletal involvement may be significant in the annotation of SD, metabolic bone diseases, dysostoses, and bones malformations, limb deficiencies.
2. The disease has previously been published and/or listed in *Mendelian Inheritance in Man* (MIM), *PubMed*.
3. Genetic disease to be proven by family history (pedigree) or between the similarities of the clinical aspects in different families (unrelated).
4. Nosological is confirmed by deoxyribonucleic acid (DNA) analysis and the presence of different diagnostic and observational features in several patients or families.

In the revised nomenclature, the pattern of inheritance, causal genes, MIM catalogue number were considered. Compared to the old update from 2011, the gene locus and the encoded protein were not noted, they can only be identified by knowing the causative gene.

Table 1 summarizes the 42 groups of SD. The first 30 groups refer to dysplasia, the group from 32–42 refers to bone dysostoses. The grouping in these 42 categories was done on various criteria: some were grouped based on the gene involved, others according to common radiological changes, and others due to the similarity of the clinical picture and finally according to the skeletal part involved.

Table 1 – Classification of skeletal dysplasia groups

No.	Name of the group	Observations
1.	Group of <i>FGFR3</i> chondrodysplasias	Classified based on molecular criteria
2.	Group of type 2 collagen and similar conditions	
3.	Group of type 11 collagen	
4.	Group of sulfactation disorders	
5.	Perlecan group	
6.	Aggrecan group. It is one of the most important molecules in the structure of cartilage, especially growth cartilage	
7.	Filamin group and associated disorders include relatively common illnesses with a variable expression from light forms to lethal forms	
8.	<i>TRPV4</i> group	
9.	Ciliopathies with major skeletal involvement	Newly introduces into the classification. We have here autosomal recessive diseases determined. The mutation appears in genes which codify primary cilia. They include thoracic hypoplasia with respiratory failure, disharmonic dwarfism with normal thorax but short limbs and very short fingers sometimes associated with polydactyly

No.	Name of the group	Observations	
10.	Multiple epiphyseal dysplasia and the pseudo-achondroplasia group	Classification is based on the location of the radiological modifications of the specific bone structures (vertebrae, epiphysis, metaphysis, diaphysis, or combinations of them) or based on the involved segment (rhizo, mezo or acro)	
11.	Metaphyseal dysplasia		
12.	Spondylometaphyseal dysplasias (SMDs)		
13.	Spondylo-epi-metaphyseal dysplasias (SE(M)Ds)		
14.	Severe spondylodysplastic dysplasias		
15.	Acromelic dysplasias		
16.	Acromesomelic dysplasias		
17.	Mesomelic dysplasias and rhizo-mesomelic dysplasias		
18.	Dysplasia of curved bones		
19.	Primordial dwarfism and the thin bones group. Dysplasias of thin bones		They are defined based on macroscopic signs in conjunction with the phenotype (curved and/or thin bones, joint dislocations)
20.	Dysplasias with multiple joint dislocations	From 21–25 various mineralization defects	
21.	Dotted chondroplasia group		
22.	Neonatal osteosclerotic dysplasias	The group includes the variants of osteoporosis (OP); the identification of new genes in different variants of OP has led to the expansion of this group, so, the presence of diverse molecular mechanisms, clinical and biochemical features in different entities of osteoporosis, justifies the fragmentation into numerous subtypes	
23.	Group with expanded bone density (no abnormalities in bone shape)		
24.	Other otosclerotic changes The group with increased bone density with metaphyseal or epiphyseal involvement		From 21–25 different mineralization defects (increase or decrease in bone density, impaired mineralization, osteolytic)
25.	<i>Osteogenesis imperfecta</i> (OI) and the group with fragile bones		OI and the group with low bone density – they receive special attention
26.	The group with abnormal mineralization		Molecular mechanisms lead to the appearance of hypophosphatemia rickets
27.	Storage diseases with skeletal involvement		It includes the large group of lysosomal diseases with skeletal involvement
28.	Osteolytic		Mineralization defect
29.	Disorganized development of skeletal components		It includes diseases formerly “anarchic” development of bones parts: bone spur, enchondromatoses, and abnormal position of calcifications. This group is very heterogeneous (it is important a new re-examination in the next years using newer molecular data
30.	Overgrowth syndromes with skeletal involvement		Dysostoses
31.	Inflammatory/rheumatoid-like osteoarthropathies		
32.	Cleidocranial dysplasia and cranial ossification defects		
33.	Craniosynostosis syndromes		
34.	Dysostoses with predominantly craniofacial involvement		
35.	Dysostoses with predominantly vertebral involvement with or without costal involvement		
36.	Patellar dysostoses		
37.	Brachydactyly (without extraskelatal manifestations)		
38.	Brachydactyly (with extraskelatal manifestations)		
39.	Limb hypoplasia – the group of limb reduction defects		
40.	Ectrodactyly with/without other manifestations		
41.	Polydactyly–syndactyly–triphalangism group		
42.	Defects in joint formation and synostosis		

FGFR3: Fibroblast growth factor receptor 3; *TRPV4*: Transient receptor potential cation channel subfamily V member 4. Adapted after Warman *et al.* Nosology and classification of genetic skeletal disorders: 2010 revision. *Am J Med Genet A*, 2011, 155A(5):943–968 (<https://doi.org/10.1002/ajmg.a.33909>) [13] and Mortier *et al.* Nosology and classification of genetic skeletal disorders: 2019 revision. *Am J Med Genet A*, 2019, 179(12):2393–2419 (<https://doi.org/10.1002/ajmg.a.61366>) [12].

☞ Notions of embryology. Signaling pathways

Skeletal formation involves two main steps: intramembranous ossification and endochondral ossification. In intramembranous ossification, osteoblasts differentiate from mesenchyme and form flat bones such as clavicles, cranial bones. At the end of this period, osteoblasts die by

cellular apoptosis. In endochondral ossification, mesenchymal cells condense and subsequently transform into chondrocytes. Chondrocytes in turn proliferate and will form the growth plateau secreting cartilage specific to the extracellular matrix (ECM). Subsequently, the division of chondrocytes in the center of the growth cartilage stops, they will increase in volume giving rise to hypertrophic chondrocytes that will be able to mineralize their ECM and will evolve in two

directions: either die by apoptosis or differentiate into osteoblasts. With the invasion of the cartilage by blood vessels, stem cells from different lines give rise to bone deposition osteoblasts and bone resorption osteoclasts forming the primary ossification center. It should be noted that chondrocytes will interact directly with the ECM consisting of a multitude of different molecules that define the well-being structure and the specific composition of the articular cartilage as well. These things allow the cartilage to fulfil its role as a lubricant and bearing surface of the joints [18]. Within the cartilaginous epiphyses, the second ossification center will be formed immediately after birth; the definitive growth plateau can be identified by well-defined cell delimitation areas, representing the steps of chondrocyte maturation (rest, proliferative, prehypertrophic, hypertrophic) and remain until the end of the growth period, although bone remodeling continues throughout life [19, 20]. The old bone is continuously replaced with new bone; this process takes place every 10 years and consists of total bone resorption under the action of osteoclasts and new bone formation under the action of osteoblasts, both processes being coordinated by osteocytes. These are the main parts in this remodeling process by regulating the action but also the recruitment in osteoclasts and osteoblasts. Disequilibrium among these cells determines a change in the structure with either bone loss or gain [21, 22].

Both ossification mechanisms are regulated by several signaling pathways grouped according to their response to certain signal families: hedgehog (HH), parathyroid hormone-related protein (PTHrP), wntless and int-1 (Wnt), Notch, transforming growth factor-beta (TGF- β), bone morphogenetic protein (BMP) and the fibroblast growth factor (FGF) [23, 24].

Any disturbance in the mechanism of formation, mineralization or signaling pathways leads to the appearance of SD with a wide range of clinical manifestations, such as disharmonious dwarfism, frequent fractures due to bone fragility, ectopic ossifications. It is important to understand all the mechanisms of embryology and bone homeostasis to have a correct diagnosis and treatment.

☞ Clinical aspects

The onset of SD is variable from newborn to adult; the earlier it is, the worse the prognosis. The spectrum of manifestation varies from perinatal to mild forms, including patients of normal stature and normal life expectancy but with early onset of osteoarthritis [25–27]. Multiple medical needs are necessary at individuals with SD diagnosis [28]. The main clinical manifestation in SD is a small, disproportionate stature; it is common but not mandatory. In some SDs, such as those with bone mineralization defects [*osteogenesis imperfecta* (OI), hypophosphates], the proportions are sometimes almost normal. Anthropometric measurements are essential and refer to the trunk–limb disproportion; abnormal shortage of the limbs is seen when the upper limbs (Us) do not extend beyond the middle of the pelvis in the infant or the upper thigh in the older child. Disproportionate shortening of the torso is suspected when the neck is short, the thorax small and the abdomen enlarged.

In addition to the limb–trunk disproportion, there may be disproportions of different limb segments: shortening of the proximal segment, called rhizomelic; shortening of the middle segment, called mesomelic; shortening of the distal segment, called acromelic.

Anthropometric measurements include height, sitting height, pubis–floor distance, large opening of the arms. UL: total length UL, rhizomelic segment length UL, mesomelic segment length UL, hand length. Lower limbs (LL): total length LL, rhizomelic segment length LL, mesomelic segment length LL, leg length.

All data obtained is correlated with the corresponding charts growths [29].

Other skeletal abnormalities (usually symmetrical) that may occur are deformities and/or periarticular protuberances, abnormal joint mobility, angular deformations; compressions on the spinal cord, narrow chest due to shortening or other costal abnormalities with consecutive breathing difficulties, cleft palate. SD may also be associated with non-skeletal abnormalities detailed in Table 2.

Table 2 – Examples of non-skeletal abnormalities associated with skeletal dysplasias

Anomaly	Skeletal dysplasias
Cleft palate	Diastrophic dysplasia
Nail dysplasia	Campomelic dysplasia
Hydrocephalus	Achondroplasia
Dental anomalies	Ellis–van Creveld syndrome
Blue sclera	<i>Osteogenesis imperfecta</i>
Cataract, retinal detachment	Stickler syndrome
Ichthyosis	Dotted chondrodysplasia
Genital hypoplasia	Robinow syndrome
Myopia	Kniest syndrome
Thin upper lip	Chondroectodermal dysplasia
Multiple joint dislocations	Larsen syndrome, Ehlers–Danlos syndrome
Heart abnormalities	Majewski syndrome, Saldino–Noonan syndrome

Family and reproductive history play a key role in establishing the etiology and diagnosis of SD. The pedigree may be relevant to a particular mode of Mendelian inheritance. Most cases have a negative family history, most often new mutations, especially in autosomal dominant forms, such as lethal neonatal SD (thanatophoric dysplasia, OI), or most cases of achondroplasia. Pay attention to medium or discrete forms of anomalies in family members: small stature, disproportions, deformations, etc. Examining relatives, photographs, X-rays, or medical documents can sometimes be very helpful. Reproductive history can reveal stillbirths, abortions, or other issues. Pregnancy history may reveal polyhydramnios, or reduction in fetal movements, common in lethal neonatal variants [30].

☞ Radiological examination

“Genetic study of the skeleton” is essential for diagnosis, sometimes being the only diagnostic criteria. It involves bone radiographs of the entire skeleton: antero-posterior (AP) and latero-lateral skull, AP and latero-lateral backbone,

pelvis and AP limbs, hand and foot [31]. It is necessary to see which bones and which bone parts are involved. Radiographs must be repeated in evolution, and those performed before puberty bring more information because the epiphyseal closure at puberty hides many of the signs of radiological diagnosis. Table 3 highlights the main radiological changes in SD [32–34].

Table 3 – Specific radiological changes in some skeletal dysplasias

Radiological changes	Example of diseases
Dot calcification of the calcaneus	Dotted chondrodysplasia
Flat acetabulum and narrow sacroiliac ridge	Achondroplasia
Dumbbell shape of long bones	Kniest syndrome, metatropic dysplasia
Curved limbs	<i>Osteogenesis imperfecta</i> (OI), campomelic dysplasia, hypophosphatasia, thanatophoric dysplasia
Ribbed and long bone heads in the shape of a cup	Achondroplasia, metaphyseal dysplasia, chondroectodermal dysplasia
Fractures	OI, osteopetrosis, pycnodysostosis
Ossification delay	Spondyloepiphyseal dysplasia, Kniest syndrome
Shortening of the ribs	Short ribs–polydactyly syndrome, asphyxiating thoracic dysplasia, chondroectodermal dysplasia
Reduced or absent ossification of the vertebral bodies	Achondrogenesis, Kniest syndrome, spondyloepiphyseal dysplasia
Severe platyspondyly	Metatropic dysplasia, Morquio syndrome, lethal perinatal OI, thanatophoric dysplasia
Coronal vertebral fissures	Kniest syndrome, Saldino–Noonan syndrome, dotted chondrodysplasia

☞ Molecular classification of SD

From a molecular point of view, according to Savarirayan & Rimoin, SD are classified into five major categories [35]: (1) Defects in the structure of the structural proteins of the cartilage. These include type I, II, IX, X, XI collagen and ECM proteins [36]. The phenotypes that occur are diverse, depending on the mutations in those genes. (2) Defects in the metabolic pathways of cartilage involve enzymatic abnormalities, ion channels and transporters abnormalities, *e.g.*, the alteration of sulphate transport inside chondrocytes (essential for the ECM), which leads to abnormal chondrogenesis depending on the degree of compromised transporter [37]. (3) Defects in the local regulation of growth cartilage include genetic diseases caused by abnormalities of hormones, growth factors, their receptors through paracrine, autocrine, and endocrine regulatory signals, *e.g.*, mutations in *FGFR1*, *FGFR2*, and *FGFR3* can lead to either isolated cranio-stenosis or achondroplasia [38]. (4) Defects of transcription factors cause a wide range of SD from extremely severe to mild forms of the disease [39], *e.g.*, mutations in the short stature homeobox (*SHOX*) gene family [40]. (5) Defects in tumor suppressor genes lead to hereditary multiple exostoses with abnormal growth of growth cartilage at risk of malignancy [41].

☞ Anatomical pathology

Morphopathologically, SD can be classified into three types: (1) SD with minimal abnormalities or absence of qualitative endochondral ossification abnormalities, *e.g.*, in achondroplasia, endochondral ossification is normal but with abnormal length of the proliferative columns especially in the central part of the growing plateaus; electron microscopy shows an increased number of dead cell chondrocytes and an increase in cytoplasmic glycogen. (2) SD with abnormalities of cell morphology, *e.g.*, in achondrogenesis, the chondrocytes are large and contain Periodic Acid–Schiff (PAS)-positive inclusions; endochondral ossification is deeply affected, with the lack of proliferative cell columns and lack of cellular hypertrophy; in thanatophoric dysplasia and in short ribs–polydactyly syndrome, chondrocytes are immature, with reduced and disorganized formation of columns; hypertrophic chondrocytes are irregularly organized in the chondro–bone transformation zone. (3) SD with matrix morphology anomalies, *e.g.*, in Kniest syndrome, the endochondral cartilage has the dehiscent matrix and gives it the appearance of Swiss cheese [42].

☞ Treatment

Long-term therapies to normalize bone growth in any of the clinical forms of SD are not yet known. Preventive treatment as well as surgical treatment of bone deformities, treatment of complications, genetic counseling and last but not least, helping parents to cope with the given situation are the main objectives that should be followed by any clinician. The measures must be adapted to each case because each anomaly has its own set of problems. It is good to know a few problems that occur and are common to all forms of SD: sports and other activities that can cause injuries or joint injuries should be avoided; diet should prevent or reduce obesity; tooth care should be started early. Patient associations play an important role in the life of a patient with SD so it is recommended that he join these associations, participate in various support groups.

Two issues remain controversial: the usefulness of surgical procedures for lengthening bones with good results in achondroplasia (in adolescence); the use of growth hormone is still ambiguous, except for its beneficial effects in the treatment of patients with hypochondroplasia [43, 44]. Currently, several treatments are available for SD, but more and more new drugs, in various clinical trials, are waiting to be validated so that they can be used to target the mechanism of action of the disease [45]. An example is the administration of *Burosumabum* to patients with familial hypophosphatemic rickets, this monoclonal antibody acting directly on fibroblast growth factor 23 (FGF23) inhibiting its activity by limiting urinary phosphorus loss [46–50].

☞ Special considerations

People with SD should be evaluated by a coordinated multidisciplinary care team offering them an individualized

care depending on the type of SD, as well as associated abnormalities.

Genetic counselling

Genetic counselling is essential when a mutation is identified that leads to the appearance of a certain form of SD in a member of a family and it is recommended to perform predictive tests on his relatives. If that mutation is present, family members will be evaluated later clinically. Prenatal diagnosis can be offered if a known mutation has been identified. In families in which a mutation is not identified, the mutation is not known, or the patient has not benefited from molecular diagnosis, clinical evaluation is extremely important (clinical screening).

Adaptive needs requirements

Environmental modifications of the home and school may be necessary.

Rehabilitative services

For people with long-term physical impairments, rehabilitation services help to recover or improve their functional abilities for daily lives. Special healthcare services provide, as main purpose, physical and occupational therapy, speech therapy, psychiatric rehabilitation services and help patients to gain their relief, mobility, and independence.

Psychosocial counselling

Persons with SD may face psychosocial reactions, such as depression, anxiety, high levels of stress, inability to provide self-care, low self-esteem, social isolation, or other symptoms associated with the disorder. All these problems have a negative impact on the quality of life [51]. Psychosocial services provide emotional support, education, and guidance to people with SD and their families, reducing the stress associated with the disorder and regaining emotional well-being and a better quality of life. Ireland *et al.* proposed a “Screening Tool for Everyday Mobility and Symptoms (STEMS)”. According to it, the pain associated with physical fatigue is the major problem. This study helps both clinicians and patients by showing the importance of physical mobility, adapting exercise to the disease itself; at the same time, it correlates the physical effort with the appearance of pain, identifies new symptoms that appeared with the advancing age, thus allowing a better monitoring of the patients with SD [52–55].

☒ Conclusions

The systematic classification of SD avoids confusion in clinical practice and helps clinicians to include the patient with a certain form of SD in the appropriate group of differential diagnosis, thus making it possible. Moreover, nosology provides a uniform standard for referring to a specific SD in public health, both for clinicians and medical administration (health insurance claims, patient records). Such updates are needed as the rapid pace of progress in genetic research.

Conflict of interests

The authors declare that they have no conflict of interests.

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