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Skeletal Dysplasia: Introduction, Definition & Classification

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Abstract

Skeletal dysplasias comprise a wide-ranging and intricate category of inherited conditions that interfere with the normal formation, growth, and structural upkeep of bones and cartilage. Historically, their rarity and phenotypic heterogeneity have posed significant diagnostic and classification challenges. This article provides a comprehensive overview of the evolution of skeletal dysplasia nosology, tracing its development from Mendelian principles of inheritance to modern molecular taxonomies.

Early nosological frameworks were primarily clinico-radiological; however, the current paradigm emphasizes molecular and functional classification, reflecting the broader trend toward precision medicine. The International Skeletal Dysplasia Society (ISDS) has played a pivotal role in this shift, with its 2023 Nosology incorporating over 750 distinct disorders grouped by genetic and molecular criteria. The adoption of a dyadic taxonomy—linking gene variants with specific phenotypic descriptors—has enhanced clarity and consistency, besides facilitating better interdisciplinary communication among clinicians, radiologists, and geneticists.

While the nosological framework has considerable utility, it must strike a careful equilibrium between conventional terminology and advancing scientific knowledge. Frequently, it retains historical classifications to ensure continuity in clinical practice and maintain practitioner familiarity. The article also discusses the Bone Dysplasia Ontology as a community-driven alternative to static classifications, promoting dynamic and collaborative knowledge curation.

The purpose of nosology in skeletal dysplasia is not only academic but profoundly clinical: to assist in diagnosis, guide genetic testing, and facilitate research into novel disorders and therapies. While a perfect classification system remains elusive, the trajectory of nosological development mirrors the rapid advancements in genomic medicine and reflects a growing commitment to systematic, inclusive, and adaptive frameworks in the study of skeletal disorders

Keywords: Skeletal Dysplasia, Osteochondrodystrophy, Nosology, Bone Dysplasia Ontology

Introduction

Skeletal Dysplasias, although rare, have been extremely heterogeneous in terms of etiology and clinical presentation. This rarity invoked an inquisitiveness strong enough to propel persistent efforts towards understanding these disorders. In order to know how our concept of knowing skeletal dysplasias evolved, a little rumination of history is imperative.

Familial associations of some disease have always been known to mankind from the very infancy of medical science. That attributes as well as diseases could be passed on from one generation to the progeny was perceived through observation [1]. However, till the 19th century, it was thought that these disease or attributes were inherited by sheer blending of the traits from both parents [2]. Gregor Mendel in

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Table 1 :Groups in ISDS 2023 Nosology for Skeletal Dysplasia

Group No.	Group Name	Brief Description
1	FGFR3 Chondrodysplasias	Short-limbed dwarfism due to FGFR3 mutations; includes achondroplasia, thanatophoric dysplasia.
2	Type 2 Collagen Disorders	Disorders like spondyloepiphyseal dysplasia involving COL2A1 gene; spine and joint abnormalities.
3	Type 11 Collagen Disorders	Similar to group 2; affect spine and joints; includes Stickler and Marshall syndromes.
4	Sulfation Disorders	Impaired proteoglycan modification; joint dislocations, skeletal dysplasia, short stature.
5	Dysplasias with Multiple Joint Dislocations	Includes Desbuquois dysplasia; joint laxity and soft tissue abnormalities.
6	Filamin and Related Disorders	FLNA gene-related; skeletal, brain, and vascular malformations.
7	Proteoglycan Core Protein Disorders	Aggrecanopathies and related chondrodysplasias; short stature and joint abnormalities.
8	TRPV4 Disorders	Range from brachyolmia to lethal dysplasia due to ion channel gene mutations.
9	Pseudoachondroplasia & MED	Cartilage disorders from COMP and related gene defects; joint pain, short stature.
10	Type 10 Collagen Disorders	Metaphyseal dysplasia from COL10A1 mutations; affects growth plates.
11	Metaphyseal Dysplasias	Heterogeneous disorders affecting metaphyses; short stature and bowing.
12	Spondylometaphyseal Dysplasias	Affect spine and metaphyses; often with neurological or immune components.
13	Spondyloepiphyseal Dysplasias	Involves spine and epiphyses; associated with early arthritis, hearing, and eye issues.
14	Other Spondyloepiphyseal Dysplasias	Residual group of SED-like conditions not fitting other categories.
15	SEMD (Spondyloepimetaphyseal Dysplasias)	Involves spine, epiphyses, and metaphyses; severe growth and joint issues.
16	Acromesomelic Dysplasias	Severe shortening of middle and distal limb segments.
17	Acromelic Dysplasias	Shortening focused on hands/feet; often with contractures.
18	Isolated Brachydactylies	Short digits without systemic features; dominantly inherited.
19	Syndromic Brachydactylies	Short digits with systemic signs like ID or endocrine disorders.
20	Mesomelic Dysplasias	Marked shortening of forearm and legs.
21	Chondrodysplasias with Cystic/Spongy Bones	Includes spondyloenchondrodysplasia; retained cartilage zones.
22	Campomelic Dysplasias	Bent long bones; may involve sex reversal and be lethal.
23	Diaphyseal Dysplasias	Affect long bone shafts; lead to thick or thin cortex.
24	Craniotubular Dysplasias	Skull and long bone defects, usually with sclerosis.
25	Osteopetrosis & Osteoclast Disorders	Dense, brittle bones from defective bone resorption.
26	Non-Osteopetrotic Bone Density Disorders	High/low bone mass with differing underlying causes.
27	Bone Mineralization Disorders	Include hypophosphatasia; impaired bone calcification.
28	Bone Fragility Disorders	Osteogenesis imperfecta and related collagen disorders.
29	PTH Signaling Disorders	Affect calcium/phosphate metabolism; newly defined group.
30	Overgrowth Syndromes	Tall stature syndromes like Marfan; can include segmental overgrowth.
31	Primordial Short Stature Syndromes	Severe growth delay from fetal life; includes Seckel syndrome.
32	Syndromes with Craniosynostosis	Premature skull suture fusion; may involve limbs.
33	Craniofacial Dysostoses	Affect skull and facial bones; e.g., cleidocranial dysplasia.
34	Limb Dysostoses	Includes radial ray defects and split hand/foot malformations.
35	Vertebral Segmentation Syndromes	Abnormal vertebral development; e.g., spondylocostal dysostosis.
36	Mixed Dysostoses	Involve multiple skeletal regions not classifiable elsewhere.
37	Chromosomal Disorders with Skeletal Features	Includes trisomy 21 and other chromosomal imbalances.
38	Teratogenic/Acquired Skeletal Disorders	Non-genetic but congenital skeletal anomalies.
39	Skeletal Ciliopathies	Disorders from cilia dysfunction; e.g., Jeune syndrome.
40	Skeletal Disorders with Multisystem Involvement	Storage disorders and syndromes affecting skeleton plus other organs.
41	Unclassified Disorders	Phenotypes that don't clearly fit defined groups yet.

1865 challenged this existing theory and proposed his theory of inheritance. He proposed that each trait was determined by pairs of "antagonistic elements", of which one may "dominate" over the other and that, they "segregate" in a "particulate" nature in the progeny rather than blending. These "particulate" units of inheritance are now better known as genes [3]. With better abilities in finding out chromosomal aberrations and genetic problems, most of Mendel's theories were proved right. With discovery of more and more genetically associated disorders affecting the skeletal system, experts soon realised the importance of defining and grouping the entities in a systematic manner [4]. However, till 1990s, only a few dozen skeletal dysplasias were known to humans. It was thought that alteration of one gene could give rise to only one disorder with only one phenotype: the so-called aphorism of "one gene one disease". Now we know that this is not correct in many diseases. It has been seen that variant in single gene, for example the fibrilin 1 gene (FBN1 [MIM: 134797]) are associated with several phenotypically distinct entities involving multiple organ systems. The converse is true for diseases like Bardet Biedl syndrome (MIM: 209900), which appears like a single phenotype, is actually caused by variants in more than two dozen genes [5]. Hence our understanding of genetic disorders has come a long way from the age-old adage of one to one association of gene with a single disease. This has led to the realization that phenotypic heterogeneity arising from a single genetic aberration is much more prevalent than previously suspected. Also, the possibility of targeted gene therapy in near future for genetic disorders requires that a molecular taxonomy be followed rather than depending overtly on the phenotype only.

Definition

Skeletal dysplasias, also known as osteochondrodysplasias, are a heterogeneous group of genetic disorders characterized by abnormal growth, development, and maintenance of bone and cartilage, leading to structural and functional impairments of the skeletal system [6]. These disorders exhibit significant phenotypic variability, ranging from mild short stature to severe, often lethal, skeletal deformities. The most widely accepted definition emphasizes their genetic etiology, with pathogenic variants in genes regulating skeletal morphogenesis, extracellular matrix composition, and growth plate function [7].

However, many disorders, despite advancements in molecular diagnostics, lie in the grey zone of the definition of skeletal dysplasias due to overlapping phenotypes and genetic heterogeneity. Conditions such as osteogenesis imperfecta and fibrous dysplasia, though primarily affecting bone, are sometimes excluded from classical skeletal dysplasia classifications due to differences in pathogenesis. Conversely,

disorders like mucopolysaccharidoses, which present with secondary skeletal involvement, are almost always included, creating diagnostic confusion [8].

Classification/Nosology

One of the earliest systematic attempts in categorizing skeletal dysplasia was performed by the International Skeletal Dysplasia Society in the year 1972, when "Nosology of Genetic Skeletal Disorders" was conceptualized. Since then, the ISDS Nosology gets updated every four years. This is because evermore genes have been identified and their intricacies have been discovered. It is based on grouping all known genetic disorders by clinico-radiological and/or molecular disease mechanisms. While the ISDS Nosology is widely accepted as the "official" nomenclature for skeletal dysplasias within the biomedical community, it is not without its shortcomings [9]. Firstly, it groups disorders in a rather inflexible way: each disorder is listed according to the clinico-radiological or molecular characteristics which may not have one-to-one relationship. Since the updates take place once every four years, so there can be a considerable lag period in the flow of information from their discovery to their publication in the nosology. To address these shortcomings Groza et al came up with the concept of "Bone Dysplasia Ontology" which relied on a shared conceptualisation of the domain, and proposed to provide a platform for community-driven knowledge curation to enable sustainable evolution of ontology with the direct use of the ontology for semantic annotation of clinical summaries and collaborative decision-making. This concept was one of the important steps for the present-day nosology for skeletal dysplasias.

Now comes the concept of Dyadic Taxonomy in addressing the complex problem. A dyad in its literal form is a set of two elements. Here the first element is the single "gene" whose pathogenic variance is responsible for causing a disorder. These are essentially the single gene or Mendelian disorders. The second element is the "descriptor" or a label that defines the entity. This is essentially a "unitary, distinct, Mendelian disease entity." It is a single entity that is discrete and meaningfully different from other diagnostic entities: something which defines the entity distinctly. It is accepted that all such descriptors are heuristics, that is, practical approaches, though not always optimal, provide clinicians and geneticists with workable strategies to identify, characterize, and manage affected individuals. These methods often follow naming conventions such as '(gene)-(phenotype)', '(gene)-related (phenotype)', or '(gene)-associated (phenotype)', which were originally established in key genetics resources like Online Mendelian Inheritance in Man (OMIM) and GeneReviews. Building on this framework, Biesecker et al. advocated for the standardization of a classification system inspired by entries in the NCBI Bookshelf Gene Reviews, as initially developed by Pagon and colleagues [10].

Historically, disease nosology has been structured into disorder groups—first defined by radiographic features, later by biochemical and metabolic pathways, and increasingly by molecular and functional criteria. The ISDS2023 revision retains this grouped organization, as it facilitates the efficient identification of disorders relevant to specific clinical cases or research findings [12]. On the flip side, the categorization of disorders is a mere arbitrary over-simplification of the true complexity of Nature. It is difficult to capture this in reality, as many disorders might warrant classification in more than one group. Thus, authors have elected to drop the term "classification" from the title; this is just a "Nosology". The dyadic representation as discussed above has been adopted by the ISDS 2023 Nosology which has allowed for more direct access to information along with the linkage to the causative gene abnormality, with lesser possibilities for ambiguity. The table 1 provides a short description of the groups enlisted in the ISDS 2023 Nosology.

However, the ISDS 2023 Nosology is still not completely impervious to traditional numbering pattern classification as seen for example, in Osteogenesis Imperfecta [12]. Hence some compromises have been made to honour the traditional evolution of nosology and to preserve the traditional and prevalent picture of some of the dysplasia entities. The ISDS 2023 Nosology also maintains a strong bridge to MIM (Mendelian Inheritance in Man) database. Again, it is true that MIM sometimes uses eponymous references much more than what a streamlined nosology would comfortably accept. For example, Shprintzen-Goldberg and Goldberg-Shprintzen syndromes represent distinct disorders [13]. Nevertheless, this ISDS 2023 Nosology remains the most comprehensive, well-structured and inclusive nosology. The dyadic system adopted therein allows the Nosology to group, lump and/or dump disorders based on their molecular basis while keeping a mention of their respective MIM numbers.

Discussion

The aim of Skeletal Dysplasia Nosology is to guide the clinician to narrow down this list of differential diagnosis. To an untrained pair of eyes, many skeletal disorders would look and sound similar. All the efforts in the study of skeletal dysplasias are directed towards lessening the burden on the clinician by providing a catalogue to find the exact match for the disorder in question. This allows the clinician to get a lucid idea of the disease in terms to which group it belongs to, what genes are responsible, what the inheritance pattern may be, how to get additional information and possibly how to treat the patient better. What is more, this provides a commonly understood platform across multiple disciplines: viz. Clinicians

(Pediatricians, Orthopaedic Surgeons), Radiologists, Geneticists and Researchers. Such shared perception facilitates delineation of novel disorders, adding more information to the existing database, leading to less random upgradation of the information library. Nosology may also play a key role in molecular genetic testing. Even prior to the test, the nosology may suggest a specific set of genes to evaluate based on the existing grouping and genetic aberration commonly associated. In the post-test scenario, it may expedite the action by providing a ready reference.

Finally, the spectrum of skeletal dysplsias along with the genes involved reflects how complex and orchestrated the development of the skeletal system is. With more than 750 entries in the nosology (Annexure 1), this wealth of information is a breath-taking display of human genetics. This becomes all the more intricate when one-gene one-disorder oversimplification is proven superfluous. Perhaps clinical, radiological, molecular aspects of the disorders, which lead to difficulties in classification of the skeletal dysplasia and are thought to be rather hurdles, are in reality the strengths of such a hybrid nosology, as they allow a more holistic understanding of the disease and accept participation and contribution from diverse disciplines.

Conclusion

The pursuit for a perfect nosology is only a Utopia, at least for now and few more years to come. It is always dynamic and evolving, just like our understanding of skeletal dysplasia itself. However it is heartening to witness a new piece of information in the field of skeletal dysplasia becoming obsolete the moment it is published: for it only tracks the pace of our progress in the field. It remains to be seen how exponentially increasing information from all fields is knitted into a streamlined understanding. The future is exciting.

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