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The new Nosology and classification of genetic skeletal disorders

In the last four-month period of 2019, the American Journal of Medical Genetics published the new Nosology and classification of genetic skeletal dysplasias, which had been greatly anticipated by primary care physicians. The publication groups these disorders by phenotype and molecular basis. Therefore, their nature still constitutes a “hybrid” system because the same criterion is not always strictly applied. Some conditions are grouped based on the causative gene, others share common radiological features, a similar clinical course (lethality) or the involvement of similar skeletal parts.

A group of experts in Radiology, Orthopedic Surgery, Pediatrics, and Genetics met in Paris 50 years ago and proposed to develop the International Nomenclature of Constitutional Disorders of Bone in order to reach an agreement about the different skeletal disorders. The experts presented a large body of evidence regarding heterogeneity, which was highly valued by the medical community, who started to perceive the diversity in terms of clinical and radiological findings, and it became clear that not all subjects with short limbs suffer achondroplasia (OMIM 100800) and also that not all subjects with a short trunk have Morquio syndrome or mucopolysaccharidosis type 4 (OMIM 25300 and 253010). Several meetings were held until, 30 years later, in 1999, the International Skeletal Dysplasia Society (ISDS) was established, whose nomenclature reviews (nosology) were delegated to the Committee experts designated from within the Society, which offers a combination of clinical, radiological, and genetic experience. The experts, progressively submitted their reviews. The most

recent review is the 10th edition of the Nosology and classification of genetic skeletal disorders.¹

It encompasses 461 disorders divided into 42 different groups.¹ The prior classification (2015) included 436 disorders and the same number of groups,² but two of them (18 and 19) have changed their name. There are 437 genes currently mentioned in 425 disorders, accounting for 92%,¹ compared to 58 % in 2006.³

It is worth noting the following:

- Different pathogenic variants in a gene may cause different phenotypes, for example: (group 1), called *FGFR3* chondrodysplasia, a set of disorders caused by mutations in the *FGFR3* gene and whose different mutations (allelic genetic heterogeneity) may lead to thanatophoric dysplasia type 1 and 2 (OMIM 187600 and 187601, respectively), hypochondroplasia (OMIM 146000), severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) (OMIM 616482), and camptodactyly, tall stature and hearing loss syndrome (CATSHL) (OMIM 610474). Except for the latter, all these disorders have an autosomal dominant inheritance pattern; the CATSHL syndrome may show an autosomal dominant or recessive inheritance pattern. In addition to the disorders mentioned above, there are 33 different craniosynostosis syndromes linked to *FGFR3* mutations, such as LADD syndrome (OMIM 149730) and 41 diverse phenotypes.

Group 33, called craniosynostosis syndromes, includes Crouzon-like craniosynostosis with acanthosis nigricans (OMIM 612247), Muenke

type craniosynostosis (OMIM 602849), and the phenotype similar to Saethre-Chotzen syndrome, which are also caused by *FGFR3* mutations.

- A phenotype may be the result of several genes (locus genetic heterogeneity), for example: (group 25), called osteogenesis imperfecta or decreased bone density group. Osteogenesis imperfecta type 1, non-deforming form with persistently blue sclerae (OMIM 166200), may be caused by *COL1A1* or *COL1A2* mutations, both genes with an autosomal dominant inheritance pattern. These two genes, in addition to *CRTAP*, *LEPRE1*, and *PPIB*, may be responsible for osteogenesis imperfecta type 2, a perinatal lethal form (OMIM 166210, 610854, 610915, 259440). When it comes to the *COL1A1* or *COL1A2* genes, the autosomal dominant inheritance pattern prevails. The rest of the described genes have an autosomal recessive inheritance pattern, and thus with the rest of the disorders included in this group.

The Nosology also includes phenotypes that show locus genetic heterogeneity but that are clinically and/or radiologically indistinguishable from each other. For example, multiple epiphyseal dysplasia with an autosomal dominant inheritance pattern (group 10), microcephalic osteodysplastic primordial dwarfism (group 19), rhizomelic chondrodysplasia punctata (group 21), and osteopetrosis, severe infantile form (group 23).¹

The spondylo-epi-(meta)-physeal dysplasias (SEMD) group (group 13) now includes new disorders that had been previously ill-defined and classified as unknown types of SEMD. On the other side, the current Nosology includes the first example of a pathogenic variant in mitochondrial RNA called spondyloepiphyseal dysplasia MIR140 type (group 15).¹

Some pathogenic variants in the *FGFR3*, *COL2A1*, *COMP*, *NPR2*, and *ACAN* genes that may cause mild phenotypes, such as isolated short stature or early degenerative joint disease, did not meet the inclusion criteria due to a lack of significant skeletal involvement and were therefore not introduced in the classification.¹

The *Archivos Argentinos de Pediatría* has published articles on skeletal dysplasias written by our task force, such as metatropic dysplasia

(OMIM 156530),⁴ which is included in group 8, TRPV4, whose name is derived from its causative gene and includes both the non-lethal and lethal hyperplastic forms. Also, multiple cartilaginous exostoses (osteochondromas) (OMIM 133700),⁵ which is included in group 29, called disorganized development of skeletal components, and is caused by *EXT1* and *EXT2* mutations. Finally, cleidocranial dysplasia (OMIM 119600),⁶ in group 32, called cleidocranial dysplasia and related disorders, and is caused by mutations in gene *RUNX2*. All these disorders show an autosomal dominant inheritance pattern.

Not only genes coding specific bone tissue proteins are critical for bone and cartilage formation and maintenance, but also other proteins that play a more ubiquitous role, as a gene transcription, cell division or intracellular transport regulator, account for another well-established cause of skeletal disorders. The advances made in sequencing techniques (whole genome or exome sequencing) have settled doubts and defined disorders within these groups, in addition to clarifying their etiopathogenesis. Therefore, this new Nosology may help primary care physicians with the difficult diagnosis posed by many disorders and, thus, provide a timely family genetic counseling. In addition, it will facilitate the recognition of new disorders and promote future research.

Dedication

This article is dedicated to Ana Bracho, Pediatrician, Geneticist, and Professor at Universidad del Zulia, who teaches courses on skeletal dysplasias, in addition to other subjects.

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