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Exploring human genetic skeletal disorders provides important insights into skeletogenesis and elucidates basic developmental signaling pathways

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To date, over 5900 human Mendelian disorders have been established as disease entities (https://www.omim.org/). The list of monogenic disorders has been extensively growing over the last decade since massively parallel sequencing (MPS) was introduced into clinical practice [1]. MPS-based analyses applied in clinical diagnostics include phenotype-oriented gene panels, exome sequencing (ES), and genome sequencing (GS). ES examines protein-coding regions (1–2% of the genomic DNA) and may detect 20,000 variants per person. GS addresses all 3 billion base pairs and can reveal 4–5 million variants in each single individual [1]. In current clinical practice, genetic assessment for monogenic disorders often begins with a gene panel. Such panels target genes selected according to their known associations with specific diseases, abnormalities, or malformations. In general, they enable diagnosis in 30–50% of the affected individuals. Correlation of the clinical findings with the detected variants is of prime importance to achieve a diagnosis. For individuals whose genetic conditions are not solved by gene panels, the next step is ES or GS, which is usually conducted in a family setting, where the patient's data is compared to those of parents and/or siblings. The power of ES and GS is the possibility to pinpoint a probable pathogenic variant or variants in a gene previously not associated with the specific phenotype or not yet associated with human disease. To ascertain the pathogenicity of those variants, clinical-molecular reproducibility (e.g. more patients with the same disorder and pathogenic variants in the same gene) and/or functional-biochemical studies are needed. Those require a multidisciplinary team approach and collaborative networks between different medical specialists, clinical and basic scientists.

The latest Nosology and classification of genetic skeletal disorders comprises 42 groups including 461 different disorders, in which 425 clinical phenotypes (92%) are already known to be related to mutations in 437 different genes [2]. The successful classification and genetic characterization of those disorders are mostly due to two reasons: 1) genetic conditions in the human skeleton can be precisely categorized into groups according to the radiographic features and 2) mutations in genes directing skeletogenesis give rise to similar phenotypic consequences between humans and experimental animals. In clinical practice, however, there remains a number of individuals with unclassifiable skeletal phenotypes which are due to yet unsolved molecular causes.

In an article in *EBioMedicine*, Barad et al [3] describe the identification of pathogenic variants in *LAMA5* in 3 siblings with a novel congenital skeletal disorder. The lethal syndrome is characterized by bent bones with decreased skeletal mineralization, delayed vertebral ossification (platyspondyly with coronal clefts), and joint dislocations with limb contractures. The affected siblings also had congenital cardiac defects and dysmorphic features. To prove the pathogenicity of the *LAMA5* variants, the team of experienced researchers performed cell studies on primary cells and tissues from the patients and those of age-matched controls as well as on genetically modified cell lines. The investigations showed that the pathogenic *LAMA5* variants led to decreased expression of the protein and altered the ß1-integrin signaling pathway involving the non-canonical downstream kinases PYK2 and FYN in chondrocytes.

The skeletal hallmark of the novel syndrome was the bending of long bones. A group of human bent bone dysplasias includes several clinical entities, such as camptomelic dysplasia, Stüwe–Wiedeman syndrome, FGFR2-related bent bone dysplasia, and kyphomelic dysplasia. Bent bones are also a feature of other skeletal diseases, such as those with osseous fragility or bone metabolic disorders. The work of Barad et al sheds light on novel causes and molecular defects leading to a better understanding of the latter bent bone group. The article shows that the non-canonical LAMA5-ß1-integrin signaling cascade plays a pivotal role in human skeletogenesis. Furthermore, this study

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indicates that a complex interaction between the chondrocytes and perichondrocytic basement membrane equivalent (a specific part of extracellular matrix) influences intracellular signaling that in turn affects other signaling pathways, such as the WNT cascade. The article of Barat et al is an example of a successful elucidation of mechanisms involved in congenital bone disorders through a tight collaboration between skillful clinicians and proficient basic researchers.

Molecular maps regulating the development of different organ systems are keys to understanding how malformations and congenital conditions occur. However, drawing the molecular maps for human development is still a challenge to both the medical community and basic scientists. Novel technical advancements such as long-range DNA sequencing, chromosome conformation capture, transcriptomics, and methylomics will enable further research, deepening our knowledge in this area and contributing to improved molecular diagnostics. Nevertheless, interpretation of possibly pathogenic variants located in non-coding DNA, regulatory regions, small RNAs as well as epigenetic modifications will be demanding. These challenges can only be undertaken in multidisciplinary collaborative projects performed by teams of experienced clinicians and fundamental researchers.

Disclosure

The authors have nothing to disclose.

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