Rare genetic diseases are rare because the genes mutated in and responsible for these disorders are poorly tolerated developmentally and physiologically. Selection against these changes thus makes these mutations rare in the population but also identifies the corresponding genes as critical to cell function and organism well-being and growth. This special issue of JBMR Plus presents examples of our growing knowledge and new perspectives of musculoskeletal biology and of cell and tissue processes impacting skeletal health that are being gained through the study of rare diseases. Several rare bone diseases are discussed in this issue, each caused by genetic mutations that impact bone and cartilage in multiple ways, including altering signals that direct the induction of endochondral ossification (fibrodysplasia ossificans progressiva [FOP]), increased proliferation of immature osteoblasts (melorheostosis), fibrous dysplasia of bone (McCune-Albright Syndrome [MAS]), bone fragility and impaired mineralization (osteogenesis imperfecta [OI], hypophosphatasia [HPP]), FGF23-mediated hypophosphatemia, and tooth and enamel development (in a mouse model of decreased FGF signaling).

Increased understanding of the underlying causes of these conditions is leading to advances in treatments. Additionally, several of the articles emphasize the importance of multidisciplinary care in treating these conditions. Because the effects of gene mutations that cause rare conditions are often not limited to a single clinical consequence, more attention is being given to gaining a more complete understanding of both the full pathological effects of the disease and systemwide effects beyond the primary clinical concern. This approach is not only providing new directions to improve overall health and well-being of those affected but also revealing previously unrecognized direct and indirect consequences of the underlying mutations.

The case report by Corsi and colleagues describes an example of the rarest of the rare—a case of neonatal lethal multiorgan MAS caused by somatic gain-of-function mutation of the GNAS gene. The clinical consequences of somatic mutations are limited to a single clinical consequence, more attention is being given to gaining a more complete understanding of both the full pathological effects of the disease and systemwide effects beyond the primary clinical concern. This approach is not only providing new directions to improve overall health and well-being of those affected but also revealing previously unrecognized direct and indirect consequences of the underlying mutations.

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quality. Marangoni and colleagues have developed an informative transgenic mouse model in which the FGF pathway inhibitor Sprouty4 is overexpressed to investigate the impact of FGF signaling on odontogenesis.

Patient support and advocacy organizations are critically important partners for research and clinical advances for rare disorders. Information is included for the Rare Bone Disease Alliance (RBDA) and its member organizations, which have been instrumental in providing education about and advocacy for rare bone conditions.

In sum, this special issue of JBMR Plus highlights the significant progress being made in the field of rare musculoskeletal diseases and underlines the importance of these efforts to clarify the pathogenesis of these diseases in greater and greater detail and in so doing, identify ever more effective and safe treatments and patient care modalities.

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Rare Bone Disease Alliance

The Rare Bone Disease Alliance is a program of the Osteogenesis Imperfecta Foundation, www.oif.org. The Alliance director is Charlene Waldman, waldmancharlene234@gmail.com.

The Rare Bone Disease Alliance (rbdalliance.org), originally created in 2006 as a patient advocacy network, is a coalition focused on educating medical professionals, expanding research, and assisting patients and families affected by rare bone diseases.

The Alliance encourages professional, medical, and scientific societies to expand their educational programs on rare bone disease and organizes its own meetings and workshops. In September 2018, the Alliance organized the conference Mechanistic and Therapeutic Advances in Rare Skeletal Diseases. Meeting summary and abstracts in the journal JBMR Plus are available at https://onlinelibrary.wiley.com/doi/10.1002/jbm4.10136.

Alliance participants include rare bone disease physicians and scientific thought leaders, the Rare Bone Disease Patient (RBDPN) organizations, and pharmaceutical companies working in the rare bone field.

RBDPN organizations: Fibrous Dysplasia Foundation, International Fibro dysplasia Ossificans Association (IFOPA), Lymphangiomatosis & Gorham’s Disease Alliance, Lymphatic Malformation Institute, The MHE Research Foundation, Osteogenesis Imperfecta Foundation, The Osteopetrosis Society, Soft Bones: The U.S. Hypophosphatasia Foundation, and XLH Network.