Next-Generation Sequencing and Molecular Diagnosis in Musculoskeletal Disorders

Muscles and bones are two different and diverse tissues. However, they share surprising similarities being originated from a common mesoderm. During early development and musculoskeletal system regeneration, both muscles and bones come together and function as a unit. Studies of mesoderm-mesenchymal interactions and developmental pathways have revealed some common links between muscles and bones. For instance, connexins and pannexins are crucial for the development and maintenance of both muscles and bones.[1,2] In skeletal muscles, connexins, and pannexins play important roles during development and regeneration through synchronized regulation of metabolic functions through cell-to-cell communication. In bone, the presence of connexin and more recently of pannexin channels in osteoblasts, osteoclasts, and osteocytes has been described and shown to be essential for normal skeletal development and bone adaptation.[2,3] This highlights the important role of common players in the development, maintenance, and regeneration of musculoskeletal tissue.

In this issue of the journal, Alkhiary *et al*.[4] have reported a heterozygous variant in a Saudi family segregating a musculoskeletal disorder specifically osteogenesis imperfect (OI) Type 4. They used state-of-the-art technique of whole exome sequencing for the molecular diagnosis of this clinically overlapping phenotype to clearly specify the subclinical of this rare disease/condition. Authors show that the missense variant is indeed damaging which disrupt the normal collagen protein structure. Although the variant identified is recurrent; however, it is the first report in Saudi Arabian population. Rapid development and advancement of next-generation genomic technologies have contributed to the understanding of diseases. Genome-wide SNP genotyping, transcriptome analysis, whole exome, and whole genome sequencing have assisted in the identification of the genetic factors of monogenic and complex disorders including musculoskeletal disorders. Next-generation sequencing (NGS) technology has made possible to associate the phenotype, the very core of clinical medicine, to changes in the genetic material. NGS is capable of sequencing complete human genome, however, limitations of our current understanding of the function of noncoding part of the genome made its deployment difficult in a diagnostic setup. Therefore, exome sequencing, sequencing of the coding part of genome, has quickly penetrated clinical medicine and established its utility in a wide range of applications that cover the entire spectrum of diseases from the extremely rare to the very common.

Musculoskeletal disorders are conditions that affect muscles, bones, and joints. Musculoskeletal disorders are multifactorial, and apart from genetic factors, environmental causes also contribute to disease pathogenesis. Therefore, detection of susceptibility genes and underlying genetic variants may provide clues to their etiology and pathogenesis. Extensive genetic studies are demanded to gain better insight into advanced diagnosis and treatment for these disorders. OI, osteoarthritis (OA) of hip and knee joints, degenerative disc disease, clubfoot and developmental dysplasia of the hip are common musculoskeletal disorders. The genes responsible for Mendelian inherited musculoskeletal conditions are known which, when mutated, lead to a variety of skeletal dysplasias including OI. Several genetic studies including genome-wide association studies and whole exome sequencing have revealed several interesting predisposing candidate genes, linkage intervals, pathogenic variants, and microRNAs for these disorders.[5-16] For other more common musculoskeletal conditions (such as scoliosis and OA) with complex inheritance pattern, the etiology and pathogenesis have not been revealed. Only a few genes have so far been associated with the above-mentioned disorders at genome-wide significance levels. Hence, we have to discover additional susceptibility alleles for these disorders.

Most of the genes implicated in monogenic and complex forms of musculoskeletal disorders play roles in common signaling pathways crucial for mesenchymal cell differentiation, bone mineral density, muscle differentiation, proliferation, differentiation and apoptosis in chondrocytes, skeletal muscle development, and bone remodeling and metabolism. Some of the newly identified genes need functional studies to reveal their role in musculoskeletal biology and bone morphogenesis. The insight provided by genetic studies is aiding in the identification of biomarkers predictive of disease, redefining disease, response to treatment, and a possibility to discovery novel drug targets for musculoskeletal disorders.

Although the current advancement in molecular diagnostic tools has revolutionized our knowledge of underlying genetic causes of musculoskeletal disorders, however, we are still far behind to offer treatment in most of the cases. Clinicians who are up to date with recent genetic progress can deliver better services to the community by offering better counseling, diagnostic tests, and treatment options for the patients. It is the need of the hour that clinicians or orthopedic surgeons should pay attention to understand genomics role in their clinics. The number of available genetic tests for musculoskeletal conditions are increasing as more disease-specific genes are identified. Access to up-to-date genetic resources such as the Online Mendelian Inheritance in Man (OMIM; https://www.omim.org/) and

GeneTests (an online list of disorders for which genetic testing is available; https://www.genetests.org/) is critical.

The orthopedic surgeon can assist in identifying patients with inherited musculoskeletal disorders and refer them, if appropriate, to a clinical geneticist. It is critical that genetic counseling is available to help future generations make informed decisions regarding musculoskeletal disorders. To conclude, by incorporating genetic knowledge and understanding in diagnostic and therapeutic algorithms, clinicians can help increase overall diagnostic efficacy and offer improved medical care.

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DOI: 10.4103/jmsr.jmsr_30_17

How to cite this article: Basit S. Next-Generation sequencing and molecular diagnosis in musculoskeletal disorders. J Musculoskelet Surg Res 2017;1:23-4.