Editorial
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Application of Optical Genome Mapping to the Genetic Diagnosis of Facioscapulohumeral Muscular Dystrophy 1

Structural variants (SVs) are important in constitutional disorders and cancers. Various methods can be used to detect SVs in the human genome [1]. Conventional G-banding karyotyping enables the detection of abnormalities across entire chromosomes simultaneously; however, it has the disadvantage of low resolution. Array comparative genomic hybridization or a single-nucleotide polymorphism array can be used to detect copy number variations but cannot detect balanced changes. Fluorescence *in situ* hybridization can detect structural abnormalities using specific probes but is time- and effort-intensive and cannot detect novel changes. Next-generation sequencing also detects SVs but is limited by the short read length, making accurate SV analysis challenging. Single-molecule strategies, such as long-read sequencing and optical genome mapping (OGM), can be used to overcome these limitations [2].

OGM involves the imaging of DNA molecules to construct a genome map. Ultra-high-molecular-weight DNA is fluorescently labeled, linearized in nanochannels, and scanned using a camera. A genome map is constructed based on the labeling pattern of each strand, and pattern differences detected by comparison with reference data can reveal SVs and large-scale tandem repeat arrays. Studies have applied OGM to diagnose hematologic malignancies [3-6], solid tumors [7, 8], and constitutional genetic disorders [9-12].

Facioscapulohumeral muscular dystrophy (FSHD), an autosomal dominant genetic disorder that mainly affects skeletal muscles, is the third most common form of muscular dystrophy [13]. The clinical manifestation of FSHD is highly heterogeneous and depends on the age of onset, severity, and progression [14]. FSHD is classified into types 1 and 2 according to the genetic cause [15]. FSHD1 accounts for 95% of FSHD cases and is caused by a heterogeneous pathogenic contraction of the D4Z4 repeat. FSHD2 accounts for 5% of FSHD cases and is caused by variants in *SMCHD1* and *DNMT3B* or unknown causes of hypomethylation of the D4Z4 repeat array at chromosome 4q35. The D4Z4 repeat count in healthy individuals ranges from 8 to 100 units, whereas in patients with FSHD1, it is only 1 to 10 units. FSHD1 is conventionally diagnosed using Southern blot analysis because of the large size of the repeat array (3.3 kb). However, the implementation of Southern blotting in routine testing presents challenges owing to its time-consuming and labor-intensive nature.

In this issue of Annals of Laboratory Medicine, Shim, *et al*. [16] report the results of applying OGM for the genetic diagnosis of FSHD1. They studied 25 patients with clinically confirmed or suspected/probable FSHD and their families. In 10 patients with clinically confirmed FSHD1, repeat number and haplotype analysis results from OGM were concordant with Southern blot analysis results. Among nine patients with clinically suspected or probable FSHD, six carried pathogenic alleles as identified using OGM. According to the authors' comparison, OGM has a simpler and faster workflow than Southern blot analysis (4 days vs. 7

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days). They reported that OGM is a feasible tool for diagnosing FSHD1. The application of OGM is expected to aid the genetic diagnosis of FSHD1.

AUTHOR CONTRIBUTIONS

Lee ST wrote the manuscript and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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