Diagnosis of inherited myopathies: next generation sequencing in action

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The advent of next generation sequencing (NGS) and its application to clinical practice will have a huge impact on our approach to the diagnosis and study of inherited myopathies. Exome sequencing will be much quicker and cheaper than our past practice of sequencing candidate genes one by one; however the reality is that genome-wide sequencing of individual families will yield a tsunami of genetic variants in multiple different genes that need to be tested and validated as the possible disease-causing mutations. This will be particularly true for large and repetitive genes such as nebulin, titin and RYR1. In addition, most inherited myopathies can be caused by mutations in more than one gene and many of the causative genes are associated with more than one histological diagnosis.

To date, we have used next generation sequencing in diagnosis and gene discovery in 33 families and have reached a diagnosis in ˜70% and have identified 4 novel disease genes. Identification of specific diagnostic clinical clues, muscle biopsy findings, and an understanding of the underlying disease mechanism play an increasingly important role in prioritizing gene testing, validating gene discovery and in reaching a final genetic diagnosis.