Expanding Genotype and Phenotype of Inherited Neuromuscular Diseases Using Next Generation Sequencing

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Inherited neuromuscular diseases (INMDs) are genetically and clinically heterogeneous diseases, mainly involving spinal motor neurons, neuromuscular junctions, nerves, and muscles. The majority of INMDs are hereditary, degenerative, rare, and delayed diagnosis. A timely molecular diagnosis of INMDs is crucial for providing precise drug treatment, genetic counseling including prenatal diagnosis, therapeutic strategies including standard of care, the available clinical trials, long-term care plans, and to avoid preventable complication such as malignant hyperthermia, to expand phenotype-genotype correlations, and to predict long-term prognosis.

With the ever-increasing numbers of causative genes, and phenotypic and genetic heterogeneity, a comprehensive molecular approach with the feasibility to add newly discovered genes for analysis in a cost- and time-effective manner is needed. The recent development of next-generation sequencing (NGS) including customized target capture panels, whole exome sequencing, and whole genome sequencing has accelerated the discovery of novel INMD phenotypes and genotypes. Compared with the traditional one gene at-a-time Sanger sequencing, NGS is a radically different approach to genetic sequencing. NGS allows for a large number of genes to be captured and sequenced in parallel, making a huge amount of data in a relatively short period of time at much lower cost “per gene.”

In this presentation, we will share our experiences of using target capture/deep sequencing approach to improve the molecular diagnosis of INMDs, and demonstrate the power of NGS in confirming and expanding phenotypes/genotypes of the extremely heterogeneous INMDs. We would stress the importance of deep phenotyping including physical and neurological examinations, electrophysiological, muscle radiological and histopathological findings, ancillary investigations of multiple systems, and familial aggregation will aid in interpreting NGS data.