SCIENTIFIC ABSTRACT

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TITLE OF PROJECT *(Titles exceeding 81 characters, including spaces and punctuation, will be truncated.)*

Improving the diagnosis of neuromuscular diseases

This Scientific Abstract will become public information; therefore, do not include proprietary/confidential information.

An accurate genetic diagnosis is paramount in empowering patients to plan their futures, through family planning, living assistance and therapeutic options. The current cost effective practice involves the use of exome sequencing to identify causal mutations in rare disease patients. However, exome analysis is able to identify causal mutations in only 30-50% of sequenced families, indicating much work remains to be done to discover and interpret the genetic variation that underlies severe disease.

We currently have the largest exome sequenced neuromuscular disease (NMD) cohort with over 1,030 individuals from 678 families. The current diagnosis rate for our cohort is ~40% and is comparable to other published NMD cohorts. The project aims to increase the diagnosis rate of NMD through the use of whole genome sequencing (WGS) and RNA sequencing (RNA-Seq), while reducing false reporting through providing a framework to improve assessment and interpretation of potentially pathogenic variants in NMD genes.

WGS allows for the unbiased sequencing of both protein-coding and non-coding regions of the genome. Current exome capture technologies provide incomplete coverage of known protein-coding genes, and in any case an estimated 20% of Mendelian mutations lie outside of protein-coding regions and will not be detected by exome sequencing. We have sequenced 95 genomes from over 40 families where exome sequencing has failed and in two cases have identified inversions in DMD that standard clinical sequencing failed to detect.

RNA-Seq is a complementary approach to WGS, providing a powerful approach to observe the consequences variants may have on transcript expression and splicing. The availability of muscle tissue from undiagnosed NMD patients provides a unique opportunity to investigate the effects mutations may have on transcription. We have sequenced RNA from 46 muscle biopsies and have identified splice disrupting mutation in over 25% of samples.

Inconjunction with these technological advances to improve diagnosis, we also aim to develop advances in interpretation of variants observed in NMD cohorts. We have established the Exome Aggregation Consortium (ExAC) as a powerful resource, allowing patient variants to be interpreted in the context of over 60,000 healthy individuals. Using the ExAC data set, we aim to assess pathogenic variants in patient exome or genome data and compare against our collected NMD cohorts to identify novel disease genes.

The comprehensive identification of NMD genes will provide deeper understanding of common pathways and mechanisms underlying NMD. Treatment known to be effective for particular gene mutations may also be effective for other mutations in common pathways, thus benefiting a larger number of patients. Identifying novel NMD genes and improving the accuracy of patient diagnosis ultimately translates to improvement in patient quality of care; important in anticipation for effective treatments.