Progress Report

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Title of Project:
Diagnosing hereditary myopathies and dystrophies with WGS and RNA sequencing: translating research innovations into diagnostic practice

Summary:

Hypothesis vs Findings

Establishing a genetic diagnosis for neuromuscular disease patients is essential to improve patient care as this allows screening for potential complications that may be associated with the underlying disorder, determining prognosis and the risk to other family members. A multi-omics approach using whole genome sequencing (WGS) and RNA sequencing (RNAseq) using a targeted capture panel on blood and RNA seq of muscle would increase our diagnostic yield for undiagnosed families.

A multi-omics approach was implemented whereby patients with undiagnosed limb girdle muscular dystrophies received whole-genome sequencing, capture RNA Seq and methylation profiling on nucleic acids extracted from peripheral blood. This approach was validated on 9 patients with known disease and then applied to 17 retrospective patients with a suspected but yet undiagnosed LGMD. A total of 4/17 (23.5%) new diagnoses were made, using whole-genome sequencing and capture RNA sequencing on blood. Blood was found to be a good substitute for muscle for RNA studies for muscle genes that were expressed in blood. Methylation studies are still ongoing.

Unanswered Questions

We are still far away from achieving a 100% diagnosis for neuromuscular patients presenting to the NMD clinics. RNA-Seq has been more recently applied in Mendelian disorders in an attempt to further identify variants that may affect RNA splicing and or expression. Interpreting transcriptomic data (RNA data) on its own proved challenging due to the complexity of interpreting novel findings.

What these research outcomes mean

Whole-genome was most useful especially if trio WGS was performed. If still unresolved, then RNA capture sequencing on blood was performed. Methylation studies are still ongoing.