CHRD 2024: Abstract Submission Form

Presenter Name
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Presenter Status
Non-Trainee

Role in the project
Design
Write Abstract

Research Category
Basic Science

Title
Preliminary evidence supporting loss-of-function as a disease mechanism in myofibrillar myopathy-4

Background
Heterozygous variants in the LDB3 gene are associated with cardiomyopathy and myofibrillar myopathy-4. Currently, the vast majority of LDB3 variants classified as disease-causing (i.e., pathogenic) are missense. Here, we present preliminary evidence supporting loss-of-function as a disease mechanism in myofibrillar myopathy-4.

Objective
To generate evidence that loss-of-function variants in the LDB3 gene cause myofibrillar myopathy-4.

Methods
The patient was referred to the Canadian Prairie Metabolic Network project for whole exome and mitochondrial DNA sequencing and subsequently enrolled in the Mainstreaming Genomics in Manitoba study for proteomics investigations. This female patient presented at age 28 with gait instability and incoordination. At age 45, she reported upper extremity weakness, which progressed to involve the hip flexors. Family history was non-contributory. MRI brain showed extensive leukodystrophy. EMG showed modest myopathic features in the proximal upper and lower extremities. Biochemical testing was unremarkable. Whole exome sequencing revealed a heterozygous variant in the LDB3 gene (c.811C>T, p.(Gln271Ter)); mitochondrial DNA sequencing was negative. Re-analysis of her non-diagnostic muscle biopsy from age 56 revealed rare ubiquitin/TDP43 immunoreactive inclusions consistent with early-stage myofibrillar myopathy. Quantitative proteomics of the patient biopsy and a matched control was performed.

Results
Quantitative proteomics of the patient biopsy and a matched control indicated ~50% reduced full-length LDB3 protein and supports a myopathy-like phenotype. Out of >5500 quantified proteins, 253 showed a >3-fold difference between patient and control, ca. ¼ of these being associated with mitochondria. Mapping the differential proteins against the human phenotype Monarch Initiative indicates an abnormality of metabolism/homeostasis (ca. 1/4), and myopathies (ca. 1/10) including Desmoplakin (>50-fold up) and TPM1 (3-fold down). Moreover, cellular pathways such as TCA cycle and oxidative phosphorylation (up), Val/Leu/Ile degradation (up) are clearly elevated, indicating potential muscle wasting.

Conclusion
We present preliminary evidence that loss-of-function variants in LDB3 can cause myofibrillar myopathy-4. More healthy controls will be required to confirm these observations.Our approach illustrates the importance of collaborations between clinicians and basic scientists to establish diagnoses and elucidate disease mechanisms.

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