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Abstract Title
Exome and genome sequencing are not enough: The role of multi-omics in understanding rare genetic diseases

Background
While exome and genome sequencing (ES/GS) are increasingly offered to patients with suspected rare genetic diseases (RD), fewer than half receive a diagnosis from these tests. For those who receive a diagnosis, there may be little known about the condition and limited treatment options. Other omics modalities may help resolve molecular diagnoses and improve our understanding of disease pathogenesis.

Objective
Enhance genomic variant interpretation and elucidate etiologies of RD.

Methods
The multi-omics pipeline of the Mainstreaming Genomics in Manitoba research study brings together six research scientists. Patients with non-diagnostic genetic testing (i.e., variant of uncertain significance/VUS or uninformative results) or known genetic conditions with poorly understood pathogenesis are referred. We present illustrative cases that highlight the utility of omics modalities.

Results
Case 1 is a 32-yr female with a clinical diagnosis of hypophosphatemic rickets made by skeletal survey. While ES did not identify any causative variants, RNA sequencing detected an aberrant PHEX transcript. Case 2 is a 64-yr female with gait instability and incoordination at 28-yrs and later, weakness in the upper extremities and hip flexors. ES identified a heterozygous truncating VUS in LDB3; however, loss-of-function is not a recognized mechanism of this disease. Quantitative proteomics of patient and matched control biopsies showed ~50% reduced full-length LDB3, preliminary evidence of loss-of-function as a disease mechanism. Case 3 is a 22-yr female with epilepsy and two GOSR2 VUS in trans. Ubiquitous overexpression of the variant cDNAs in Drosophila models led to viable, normal flies, suggesting both cause loss-of-function. Cases 4 to 6 are patients with known hypophosphatasia. Patient-specific induced pluripotent stem cell models were differentiated into osteoblasts. Cellular assessment revealed energy deficits, metabolic reprogramming, and mitochondrial dysfunction, potential therapeutic targets.

Conclusion
The cases described here demonstrate the utility of various omics modalities to resolve diagnoses and better understand RD.

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