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Abstract Title

Leveraging Nanopore Long-Read Sequencing to Resolve Undiagnosed Rare Disease Patients

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Background

Rare diseases affect approximately 1 in 12 Canadians, with nearly 80% having a genetic basis, yet many patients remain undiagnosed despite extensive conventional testing. Long-read whole genome sequencing (LR-WGS) using Oxford Nanopore Technologies (ONT) enables detection of complex genomic variation that may be reained undetected by conventional methods.

Objective

To assess genetic diversity and identify clinically relevant genomic variation in more than 3,000 individuals from Manitoba and Saskatchewan through PrairieGen, a Genome Canada Canadian Precision Health Initiative, building on previous precision medicine initiatives including CPMN and MGM.

Methods

We present the implementation of an ONT LR-WGS pipeline for 35 patients within the MGM rare disease program. This project serves as a pilot framework for applying LR-WGS through PrairieGen to approximately 400 predominantly rare disease patients with prior negative genetic testing. Sequencing was performed on the PromethION 24 platform, followed by analysis using an in-house bioinformatics workflow incorporating the Epi2ME human variation workflow, a custom tertiary analysis and multidisciplinary interpretation by a Genomic Case Review Board.

Results

Initial benchmarking demonstrated high SNP (99.92%) and indel (99.55%) precision, high-confidence SV detection (89.7%), and 100% concordance with variants previously identified in 12 patients. LR-WGS identified candidate disease-associated findings missed by prior testing strategies, including intronic variants with predicted splicing impact and a novel cryptic exon event identified through integrated LR-WGS and RNA sequencing.

Conclusion

Our findings confirm the clinical utility of ONT LR-WGS as a unified assay capable of improving diagnostic yield in rare disease patients, while also supporting the broader integration of LR-WGS across centers offering diagnostic genomic sequencing.