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Evaluation of Long-Read Whole Genome Sequencing Technologies and Tools for SV Detection

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Abstract:
Background/Objectives: Compared to short-read sequencing (SRS), long-read sequencing (LRS) technologies provide advantages for detection of structural variants (SVs) in whole genome sequencing (WGS). Many SV callers exist but their performance differs significantly. We have optimised the preparation steps for PacBio and ONT libraries to minimise short fragment bias and tested several tools for their ability to detect a known set of challenging SVs due to multiple events or breakpoints in non-unique sequence regions.
Methods: Four DNA samples with challenging SVs previously detected by SRS (PCR-free WGS, PE150, 60x) were sequenced on a PacBio Revio as well as on an ONT PromethION platforms (30x) after library preparation optimisation. Sequencing data was analysed with the respective standard pipelines. CPU and GPU accelerated pipeline versions by Sentieon Genomics and Nvidia Parabricks were tested as alternatives. Several SV callers where applied and results manually reviewed using Integrative Genomics Viewer.
Results: Library preparation protocols including DNA shearing and size selection reduced the short fragment bias. Despite the observed differences in performance of the tested analysis pipelines and SV callers on challenging variants, LRS enabled the detection of breakpoints missed by SRS, although manual reviewing was required for full characterisation.
Conclusion: LRS can be the solution for breakpoint identification in repetitive regions and for characterisation of complex SVs not exceeding their read length. Improved SV callers and optimised library preparation protocols are vital to take full advantage of LRS in genetic testing. As current LRS technologies improve, they enable an improved future for clinical sequencing.

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