Reviewer Report

Title: 16GT: a fast and sensitive variant caller using a 16-genotype probabilistic model

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Reviewer Comments to Author:

Luo, R. etc described a new 16GT variant caller optimized for Illunima sequencing data that uses a new 16-genotype probabilistic model to unify SNP and indel calling. They demonstrated the improved sensitivity for SNPs and comparable accuracy for indels comparing to GATK HaplotypeCaller, using genome of NA12878 in GIAB project. 16GT more comprehensively models 16 genotypes to unify SNP and indel calling in the same algorithm. 16GT appears to be a useful alternative tool for analyzing germline sequencing using Illumina platform.A few comments:1. Need to emphasize that at least at the moment, 16GT can only be applied to germline sequencing using Illumina sequencing platform, and not appropriate for cancer genome sequencing, especially clinical cancer samples, where tumor cellularity varies greatly and not fit those models.2. Can authors comment on whether increased sensitivity of SNPs is due to incorporation of indels into the model, or are those additional SNPs called have indel as the 2nd allele?3. Can authors discuss the limitations of 16GT? What's the indel size limit? Should sex chromosomes be treated differently if gender is known?4. I'm not keen to highlight better indel performance over GATK's UnifiedGenotyper, as it's known to be not a good indel caller, and not widely used for indels nowadays.5. Given the run time in Table 2, I'm not sure "16GT ran faster" should be in the abstract.

Level of Interest

Please indicate how interesting you found the manuscript: An article whose findings are important to those with closely related research interests

Quality of Written English

Please indicate the quality of language in the manuscript: Acceptable

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I have developed an NGS variant caller, VarDict, for cancer research and was published in Nucleic Acids Research in 2016.

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