Building the foundations for cancer genomic analysis for research and clinical diagnostics

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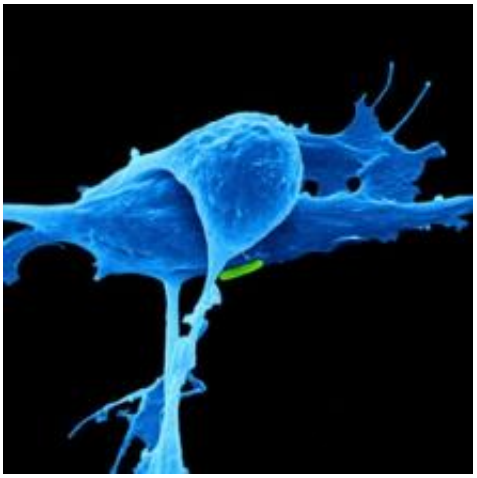

An eye-opening article from the International Cancer Genome Consortium (ICGC) was published today in the prestigious journal *Nature Communications*. It lays a foundation for the coming era of research in cancer genomics. The project, led by the Centro Nacional de Analisis Genómico (CNAG-CRG) and the German Cancer Research Center (DKFZ) is the result of an effort to create reliable standards to obtain accurate results in the detection of somatic mutations, which are a hallmark of cancer genomes. Somatic mutations are genetic alterations spontaneously acquired by a cell that can be passed to the progeny of the mutated cell in the course of cell division and tumour growth. Somatic mutations differ from germline variants, which are inherited from

parents to children.

The study, involving 83 researchers from 78 research institutions participating in the International Cancer Genomics Consortium, identified big differences in procedures and quality of cancer genome sequencing between sequencing centres. This led to dramatic discrepancies in the number and types of gene mutations detected when using the same cancer genome sequences for analysis. Out of >1,000 confirmed somatic single-base mutations in the cancer genome analyzed, only 40 per cent were unanimously identified by all participating teams. Small insertions or deletions in the DNA sequence were even more challenging - only a single somatic insertion/deletion mutation out of 337 was identified in all centres (0.3 per cent). As a consequence, the Consortium has established a reference mutation dataset to assess analytical procedures. The 'gold-set' reference database has helped the ICGC community to improve procedures for identifying more true somatic mutations in cancer genomes while making fewer false positive calls.

As whole genome sequencing of cancer genomes is increasingly being used as a clinical tool, full understanding of the variables affecting sequencing analysis output quality is required. The key points to consider and the necessary tools for improvement are provided here. "The findings of our study have far-reaching implications for cancer genome analysis. We have found many inconsistencies in both the sequencing of cancer genomes and the data analysis at different sites. We are making our findings available to the scientific and diagnostic community so that they can improve their systems and generate more standardized and consistent results," says Ivo Gut, senior author of the publication and director of the CNAG-CRG in Barcelona.

David Jones, a Senior Scientist at the DKFZ who co-led the study, commented that "as the latest technological advances in cancer genome

analysis become more widely available to support personalized cancer medicine, it is vitally important that rigorous quality testing is applied to ensure accuracy and consistency of results. We hope that our study can provide a framework for this process, to help researchers in providing the best possible analysis of patients' samples."

Tom Hudson, President and Scientific Director of the Ontario Institute for Cancer Research (OICR) declared that "At the founding of the ICGC, members of the Consortium agreed that the guidelines for "best practices" could be revised as needed to adapt to new technologies and knowledge. This benchmarking exercise gives the research community gained confidence in calling and verifying somatic mutations - a step forward to improve clinical decisions based on genomic analyses."

"The promise of cancer genomics relies on accurate and robust detection of mutations affecting DNA," said Dr. Jared Simpson, Principal Investigator in OICR's Informatics and Bio-computing Program. "This paper helps us track progress on this important problem by both identifying the strengths of our current approaches and where further work is needed."

"This project really demonstrates that while new technologies can bring challenges in data quality and data analysis, when the international community comes together in a collaborative way these can rapidly become results," said Dr. Paul Boutros, Principal Investigator in OICR's Informatics and Bio-computing Program. "The results of this collaboration are going to significantly improve the quality of sequencing and data analysis we do here at OICR, for example as part of the Canadian Prostate Cancer Genome Network."

More information: Tyler S. Alioto et al. A comprehensive assessment of somatic mutation detection in cancer using whole-genome sequencing, *Nature Communications* (2015). DOI:

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