Göteborg, 2019

Computational exploration of cancer genomes

Akademisk avhandling
Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Academicum, Medicinaregatan 3, den 30 januari, klockan 13:00

av Joakim Karlsson

Fakultetsopponent:
Dr. Anders Jacobsen Skanderup
Genome Institute of Singapore, Singapore

Avhandlingen baseras på följande delarbeten

I. **Mutational signature and transcriptomic classification analyses as the decisive diagnostic tools for a cancer of unknown primary**
*Olofsson Bagge R, *Demir A, *Karlsson J, Alaei-Mahabadi B, Einarsdottir BO, Jespersen H, Lindberg MF, Muth A, Nilsson LM, Persson M, Svensson JB, Söderberg EMV, de Krijger RR. Nilsson O, Larsson E, Stenman B and Nilsson JA.
JCO Precision Oncology. 2018.

II. **FocalScan: Scanning for altered genes in cancer based on coordinated DNA and RNA change**
Karlsson J and Larsson E.
Nucleic Acids Research. 2016; 44 (19): e150.

III. **Molecular profiling of driver events and infiltrating T-cells in metastatic uveal melanoma**
Karlsson J, Nilsson LM, Forsberg EMV, Mitra S, Alsén S, Stierner U, All-Eriksson C, Green L, Einarsdottir B.O, Jespersen H, Belgrano V, Nilsson Wassen O, Ny L, Lindnér P, Larsson E, Olofsson Bagge R and Nilsson J.A.
Manuscript

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICIN

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Computational exploration of cancer genomes

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Abstract

Cancer evolves due to changes in DNA that give a cell an advantage at the expense of the remaining organism. These alterations range from individual base substitutions to broad losses or duplications of chromosomal material. This thesis explores how DNA and RNA sequencing can guide discovery of altered genes responsible for cancer development, profile the immune landscapes of tumors and support the diagnosis of difficult cases.

In the first of three studies, we examined DNA and RNA from the tumors of a patient with metastatic cancer but an uncertain diagnosis. We discovered that these tumors harbored a mutational signature associated with ultraviolet radiation. This restricted the possible sites of origin to those that can be exposed to sunlight. To confirm this, gene expression estimates were then compared to a large database of multiple cancer types. This gave a perfect match to cutaneous melanoma, thus enabling a certain diagnosis.

The second study established a method for searching candidate cancer genes that are altered by genomic copy number changes. The method integrates estimates of copy number changes with gene expression to prioritize genes concurrently and consistently altered with respect to both, putting greater emphasis on copy number changes comprising smaller chromosomal regions, which tend to exclude unselected genes from consideration. This system was able to retrieve known cancer genes as top candidates in several cancer types. In addition, this method also implemented a way to examine regions of DNA where genes are currently not known to exist.

In the final study, we molecularly profiled metastatic uveal melanoma (UM), a rare but difficult to treat eye cancer. We reintroduced a functional version of the tumor suppressor *BAP1* into one deficient tumor, resulting in a global transcriptional shift towards a less metastatic subtype. We also found one tumor harboring a specific mutational signature that has not previously been observed in UM, and which might suggest a new risk factor. Next, we narrowed down a set of candidate genes potentially influencing tumor behavior via broad copy number changes, which could possibly be drug targets. Finally, we transcriptomically profiled tumor-infiltrating T-cells and found these to be in exhausted states, possibly explaining the failures of immunotherapy in UM. Despite this, they were in several cases capable of tumor recognition. In conclusion, this thesis explores molecular data of cancers from a number of different angles. The results should have relevance for diagnostic principles and may suggest candidate genes for future functional studies.

Keywords: Cancer genomics, transcriptomics, driver genes, copy number changes, immunogenomics, cancer of unknown primary, uveal melanoma.

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