Göteborg, 2022

Genomic mutational heterogeneity in cancer

Improved models and tools for driver gene detection

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal **Arvid Carlsson**, Akademicum, Medicinaregatan 3, Göteborg, den **11:e februari 2022**, klockan **09:00**.

av Martin Boström

Fakultetsopponent:
Dr. Jason Wong
University of Hong Kong, Kina

Avhandlingen baseras på följande delarbeten

I. Elliott K*, Boström M*, Filges S, Lindberg M, Van den Eynden J, Ståhlberg A, Clausen A, Larsson E. **Elevated pyrimidine dimer formation at distinct genomic bases underlies promoter mutation hotspots in UV-exposed cancers.**
PLOS Genetics 2018, 14(12)
* Dessa författare bidrog likvärdigt

II. Lindberg M, Boström M, Elliott K, Larsson E. **Intragenomic variability and extended sequence patterns in the mutational signature of ultraviolet light**
PNAS 2019, 116 (41) 20411-20417

III. Boström M, Larsson E. **Mutation distribution skew in patient cohorts provides a novel signal for positive selection in cancer**
Manuskript

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Improved models and tools for driver gene detection

Martin Boström

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Abstract

Cancer is a disease that is strongly related to evolution, as mutations that confer a benefit to individual cells face positive selection and eventually lead to tumorigenesis. As such, the search for genes that drive cancer development entails distinguishing positive selection from other sources of increased mutation rates, which requires detailed knowledge of how normal mutation rates vary across the genome. This thesis aims to improve that knowledge, as well as to provide novel methods of driver detection.

In cutaneous melanoma, there are mutational hotspots in promoters that coincide with the sequence motif "TTCCG". These hotspots could easily be misinterpreted as cancer drivers, but in the first paper of this thesis we show that they are in fact caused by increased UV damage susceptibility upon transcription factor binding, with some contribution from impaired DNA repair.

In the second paper, we study how the UV mutational signature varies between different genomic regions and show that the main difference is caused by the level of cytosine methylation, owing to its effect on UV damage formation. We also improve the traditional trinucleotide mutational signature by incorporating longer patterns, capturing the effect of TTCCG-related promoter mutations.

In the third paper, we demonstrate a novel method for driver detection that ignores recurrence signals, instead testing the likelihood of observing a particular combination of mutated tumours in a patient cohort. In addition to providing an orthogonal perspective on driver detection, this method is less sensitive to flaws in modelling some forms of mutational heterogeneity, such as the TTCCG hotspots.

In summary, this thesis improves our knowledge of mutational heterogeneity in cancer, in addition to describing a new driver detection test that is less sensitive to situations where that knowledge falls short. Both of these advances contribute to the search for genes that drive cancer development.

Keywords: Cancer, genomics, ultraviolet light, mutational heterogeneity

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