Quantification of within-sample genetic heterogeneity from SNP-array data - DTU Orbit (20/12/2018)

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Intra-tumour genetic heterogeneity (ITH) fosters drug resistance and is a critical hurdle to clinical treatment. ITH can be well-measured using multi-region sampling but this is costly and challenging to implement. There is therefore a need for tools to estimate ITH in individual samples, using standard genomic data such as SNP-arrays, that could be implemented routinely. We designed two novel scores S and R, respectively based on the Shannon diversity index and Ripley's L statistic of spatial homogeneity, to quantify ITH in single SNP-array samples. We created in-silico and in-vitro mixtures of tumour clones, in which diversity was known for benchmarking purposes. We found significant but highly-variable associations of our scores with diversity in-silico (p <0.001) and moderate associations in-vitro (p = 0.015 and p = 0.085). Our scores were also correlated to previous ITH estimates from sequencing data but heterogeneity in the fraction of tumour cells present across samples hampered accurate quantification. The prognostic potential of both scores was moderate but significantly predictive of survival in several tumour types (corrected p = 0.03). Our work thus shows how individual SNP-arrays reveal intra-sample clonal diversity with moderate accuracy.

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