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CDCOCA: a statistical method to define complexity dependent co-occurring chromosomal aberrations

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Background

Copy number alterations (CNA) play a key role in cancer development and progression. In general, more than one CNA can be detected in any given tumor; therefore co-occurring genetic CNA may point to co-operating cancer related genes. Existing methods for co-occurrence evaluation so far have not considered the overall heterogeneity of CNAs per tumor, resulting in a preferential detection of frequent changes with limited specificity for each association owing to the frequently high genetic instability of the samples.

Results

We hypothesize that in cancer some linkage-independent CNAs might display a statistically non-random co-occurrence, and that these CNAs could be of pathogenetic relevance for the respective cancer. We also hypothesize that two CNAs co-occurring in samples with overall few changes (low complexity samples) represent a stronger association then coming from samples with a high number of changes. To verify our hypothesis, we here present a simulation based algorithm CDCOCA (complexity dependent co-occurring chromosomal aberrations). For an initial modeling approach, CNA data for bladder cancer and mantle cell lymphoma at cytogenetic band resolution was obtained from our Progenetix reference database (www.progenetix.net) and the CDCOCA was applied to them. A display of ~50 most frequent co-occurrences obtained after p value cut off along with selected cancer associated genes are shown here (Figure 1).

Conclusions

Our CDCOCA algorithm has constitutes a new approach to establish statistically significant co-occurring regional genomic imbalances from for example CGH data sets containing at least hundreds of individual copy number profiles. Along with finding CNAs from low/intermediate complexity samples, our algorithm points towards a generally low statistical specificity for

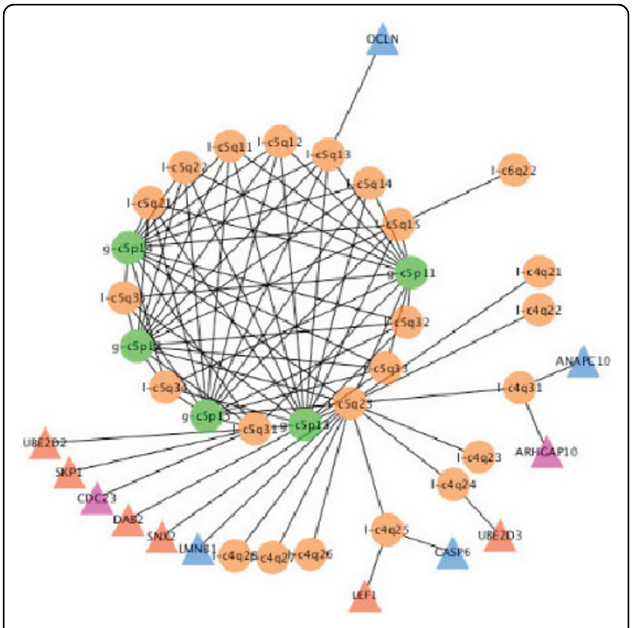

Figure 1 50 most frequent associations obtained after p value cut off of 0.02. 50 most frequent associations plotted using cytoscape. Green circles represent gains, orange represent losses. Red triangles represent apoptotic signaling genes and blue triangles represent TGF-beta receptor signaling genes located to these associations. Magenta triangles represent overlapping genes between both signaling pathways.

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co-occurrence of regional CNAs in a CNA rich samples, with a negative impact on pathway modeling approaches based on genomic copy number screening analyses derived from such data.

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