Genetic interactions in childhood cancer

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Even though the survival rate of childhood cancer has increased in the last decades to around 80% today, it is still the major cause of death in children in developed countries. Cancer develops through the acquisition of multiple mutations, and it is assumed that genetic interactions between mutated genes play an important role in cancer onset and progression. One approach to find genetic interactions in cancer is to search for pairs of mutated genes that occur more (or less) often than expected given the frequency of the individual mutated genes. Highly co-occurring mutated genes suggest a cooperative role of these altered genes in cancer development. Mutually exclusive gene pairs can be a signal of synthetic lethality and could therefore point to possible cancer treatments.
We developed a pipeline, based on two genetic interaction tests [1,2], to detect significant cases of co-occurrence and mutual exclusivity in two pediatric cancer data sets [3,4], comprising over 2,500 tumors from 24 cancer types. In total we detect twelve co-occurring and 42 mutually exclusive genetic interactions. We not only confirm previously detected genetic interactions between significantly mutated genes (SMGs), but also find many interactions that involve non-driver genes. This suggests that the inclusion of the whole set of genes instead of the set of SMGs, can lead to novel discoveries.

[1] Park & Lehner. Mol Syst Biol 11, 2015.
[2] Kim, Madan & Przytycka. Bioinformatics 33; 814–821, 2017.
[3] Gröbner et al. Nature 555;321-327, 2018.
[4] Ma et al. Nature 555;317-376, 2018.