Abstract Title: Genetic determinants of response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer identified by whole exome sequencing
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Background/Objectives:

The cornerstone in the treatment of locally advanced rectal cancer (LARC) is neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision. Reliable predictors of response to nCRT in LARC remain an unmet need in colorectal cancer research. This study used high throughput DNA analysis to investigate genetic differences between highly responsive tumors and tumors resistant to nCRT.

Methods:

Whole-exome sequencing of samples from five patients with good response and two patients with resistance to nCRT was performed. An in-house developed algorithm using SQLite Database created in SQLite Expert Professional software was used to identify genetic differences between good and poor response. The interactions between the involved genes were visualised using the String tool. The consequences of mutations were analysed using the Variation Effect Prediction tool. Functional predictive scores were determined using the ProtVar.

Results:

The analysis discovered 15 InDels and 202 SNVs exclusively present in tumors with resistance to therapy, mainly in genes involved in cell cycle regulation, adhesion, and migration. On the other hand, 9 InDels and 122 SNVs were exclusively present in good response, in genes involved in extracellular matrix remodelling and immunity. Six discovered variants, mainly frameshift and nonsense mutations, had high deleterious prediction scores: CAPN2 rs17599, COL5A2 rs145404046, ROS1 rs529156, SYNM rs5030699, MAVS rs7262903 and CLIC6 rs13049028.

Conclusion:

The study has identified six variants that could be used to predict poor response to nCRT. They can be further tested in the clinical practice with the aim of identifying patients that should avoid this type of treatment.