

392P Candidate markers of homologous recombination deficiency for triple negative breast cancer

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Background: Nowadays many researchers are focused on a study of genes involved in the repair of double-strand breaks (DSB) by homologous recombination (HR) to identify new predictive markers of cancer therapy. Patients with triple negative breast cancer (TNBC) without mutations of BRCA genes (BRCAmut), which are the well-known markers of HR deficiency and targets for DNA-damaging therapy, have a heterogeneous response to treatment and as a result high mortality rate. Therefore, the aim of this study was to evaluate a Mre11-NBN-RAD50 complex which plays a key role in DSB repair as a potential predictive marker of HR deficiency among TNBC patients.

Methods: In silico analysis of the Mre11, RAD50 and NBN gene copy number alterations (CNAs) was performed utilizing the genomic profiles and clinical data of 2509 breast cancers (METABRIC, Nature 2012 & Nat Commun 2016 studies). Alterations (mutations, deep deletions (del) and amplifications (ampl)) of 41 key genes involved in DSB pathways and/or tumorigenesis excluding patients with BRCA1/2 alterations were used to separate a TNBC patients cohort (n = 399) into groups: with conditionally "breached HR" (n = 157) and with "normal HR" (n = 242). For this a median alterations amount across the patients was used as a threshold. Statistical analysis (chi-squared test, logistic regression, ROC curve) was performed using RStudio.

Results: The NBN gains and ampl occurred in 41,9%, RAD50 del – in 38,1%, MRE11 del - 21,8% of TNBC patients. TNBC patients with "breached HR" had higher frequency (p-value < 0,01) of RAD50 (64,5%) and MRE11 (34,4%) del, as well as NBN (72%) ampl and gains than patients with "normal HR" (20,7%,13,6% and 22,3% correspondingly). Based on the above-mentioned CNAs the model for prediction of HR deficiencies with – 60,5% sensitivity and 84,3% specificity (area under the ROC curve – 0,85) was created.

Conclusions: Thus Mre11-NBN-RAD50 complex could be considered as potential HR deficiency marker in tumors of TNBC patients which could predict response to DNA damaging therapy. Model will be cross-validated and optimized in future.

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