



1975P - Next Generation Sequencing (NGS) for the identification of PARP inhibitors' predictive biomarkers.

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INTRODUCTION

The use of PARP inhibitors has been shown to be beneficial in tumors with *BRCA1/2* mutations and has already been approved for patients with ovarian, breast, pancreatic and prostate cancer. The aim of the study was to assess the utility of a multigene panel for the analysis of mutations in genes of the homologous recombination (HR) pathway as well as loss of heterozygosity (LOH), as predictors of treatment response.

MATERIALS AND METHODS

Tumor molecular profile analysis was performed in 939 patients with various types of solid tumors (Figure 1). An NGS methodology was used, for the analyses of more than 500 cancer-related genes. The exploration of homologous recombination deficiency was performed through the analysis of HR gene mutations (Table 1) and the measurement of %LOH at the sample level.

Table 1. Genes of the Homologous recombination pathway included in the panel

HR Genes			
<i>ATM</i>	<i>CDK12</i>	<i>FANCI</i>	<i>RAD51B</i>
<i>BAP1</i>	<i>BRIP1</i>	<i>FANCL</i>	<i>RAD51C</i>
<i>BARD1</i>	<i>FANCA</i>	<i>FANCM</i>	<i>RAD51D</i>
<i>BLM</i>	<i>FANCC</i>	<i>NBN</i>	<i>RAD52</i>
<i>BRCA1</i>	<i>FANCD2</i>	<i>MRE11A</i>	<i>RAD54L</i>
<i>BRCA2</i>	<i>FANCE</i>	<i>PALB2</i>	<i>XRCC2</i>
<i>CHEK1</i>	<i>FANCF</i>	<i>RAD50</i>	<i>XRCC3</i>
<i>CHEK2</i>	<i>FANCG</i>	<i>RAD51</i>	

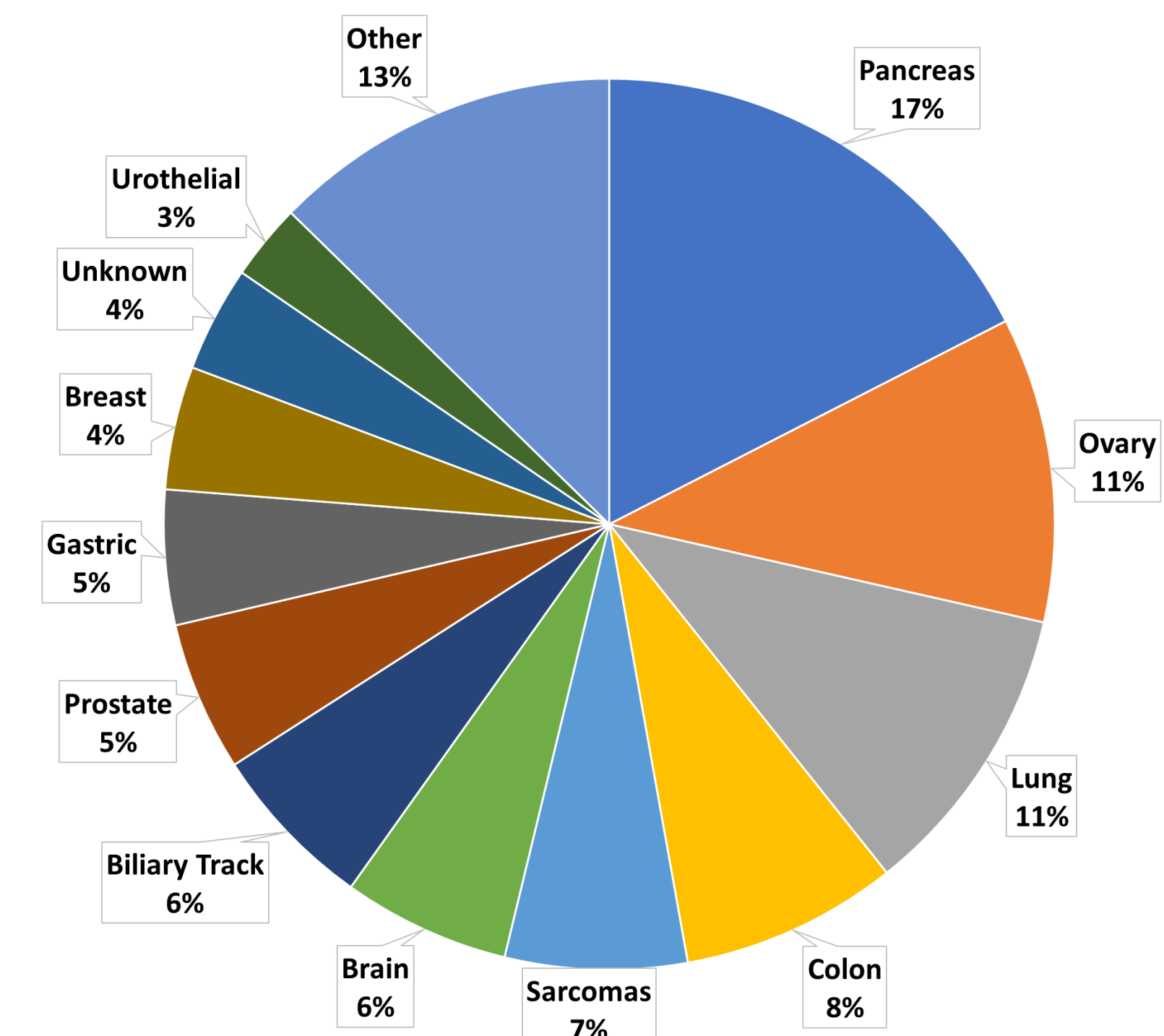


Figure 1. Percentage of various tumor histology types among the 939 patients included in the study

RESULTS

Mutations in the *BRCA1/2* genes were detected in 3.09% of patients, while mutations in other HR genes were found in 10.65% of the cases (Figure 2). In prostate, ovarian, breast, and pancreatic cancers with approved PARP inhibitors available, the rates of HR mutation detection were significantly increased: 40% (14/35), 26.83% (22/82), 15.85% (13/82), and 10% (14/140) respectively (Figure 3). Furthermore, in 201 patients the %LOH value was also calculated. The median LOH value obtained was 19.22% (min 0%; max 99%), with 88 samples (43.78%) showing an LOH value higher than the median and 113 (56.22%) samples with a lower than the median value. Increased LOH rates were observed for breast (68.18%) and ovarian cancer (52.63%). While in prostate and pancreatic cancer the % of samples with high LOH rates was lower, 0% and 35.71% of tumors respectively. HR mutations were highly correlated with high %LOH in ovarian cancer patients since 50% of the cases with a high-risk HR gene mutation (*BRCA1/2*, *PALB2*, *RAD51C*) had increased LOH values, while 22% of the cases in the low LOH population, carried a mutation in a low-risk HR gene (*RAD51B*, *FANCA*). Apart from ovarian cancer, the detection of HR mutations was not always accompanied by increased %LOH in the rest of the tumor types analyzed, since 52.63% (10/19) of *BRCA1/2* positive tumors and 60% (18/30) of HR-positive tumors had a low LOH value (Table2, Figure 4).

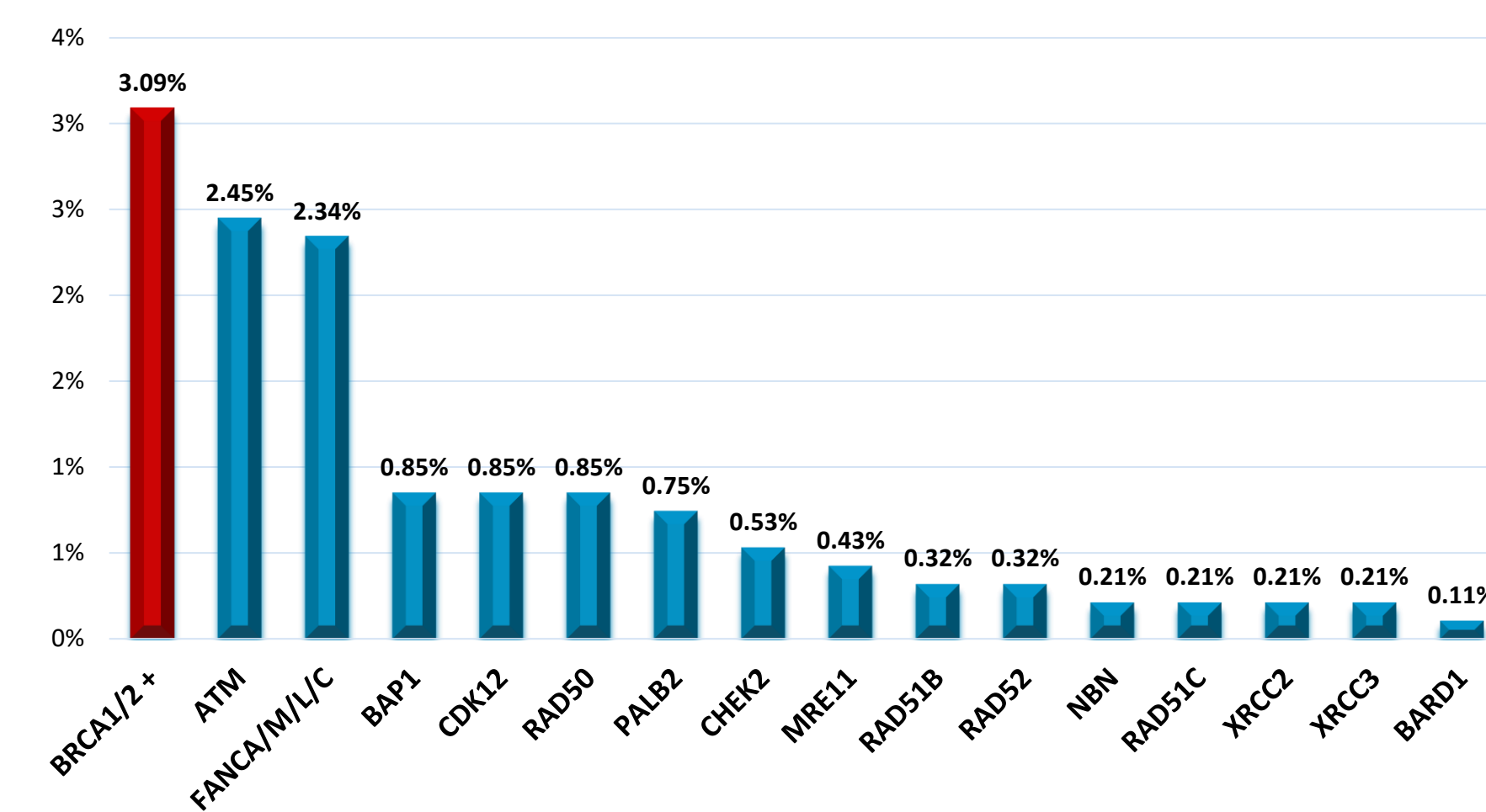


Figure 2. Mutation rates in the HR genes in all tumors analyzed

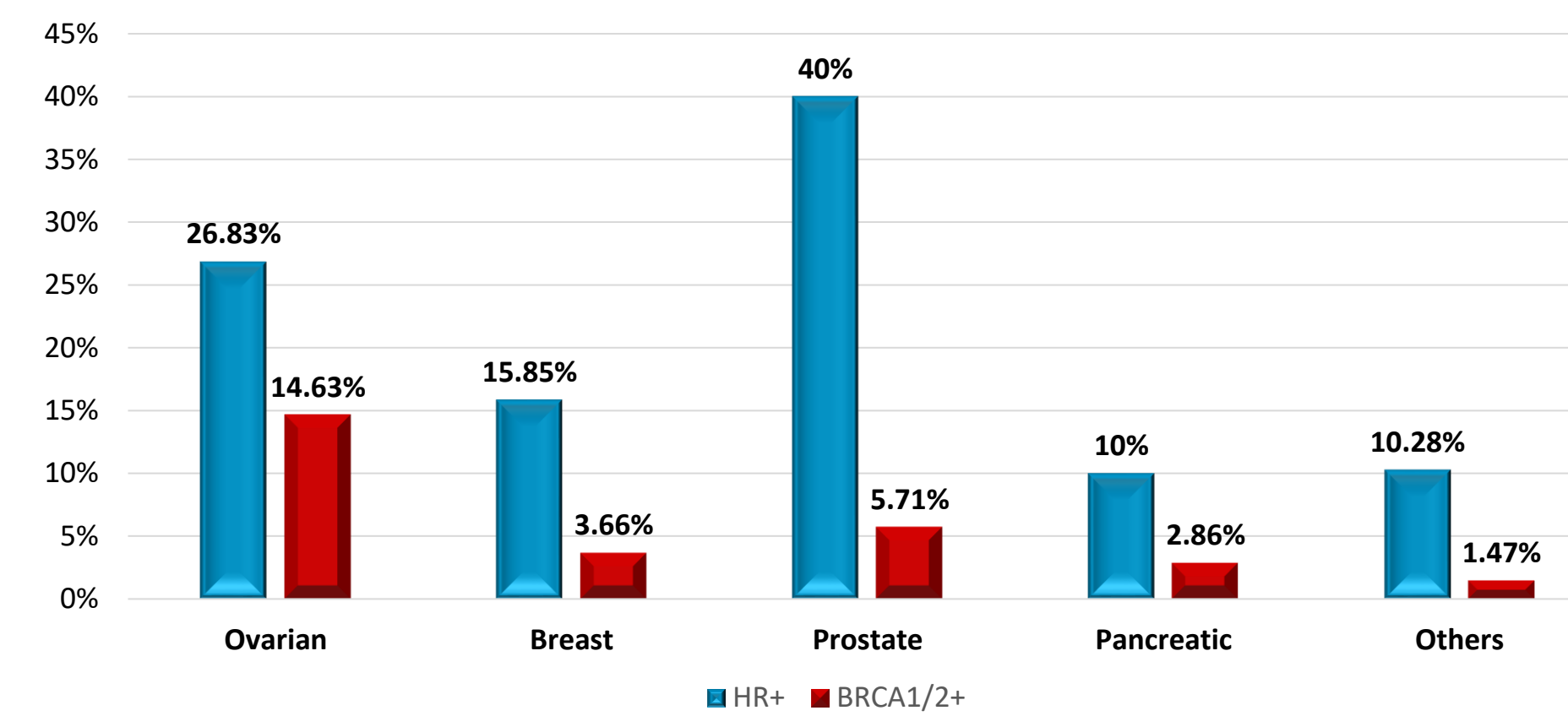


Figure 3. HR mutation rates in tumor histological types with PARP inhibitors approved

Table 2. HR genes mutation rate and correlation to the LOH value

TUMOR TYPE	% OF HR+ TUMORS	% OF LOH+ PATIENTS	<i>BRCA+ /LOH+ PATIENTS</i>	HR+ /LOH- PATIENTS
OVARIAN	27%	55%	0%	22%
OTHERS	12%	44%	53%	60%

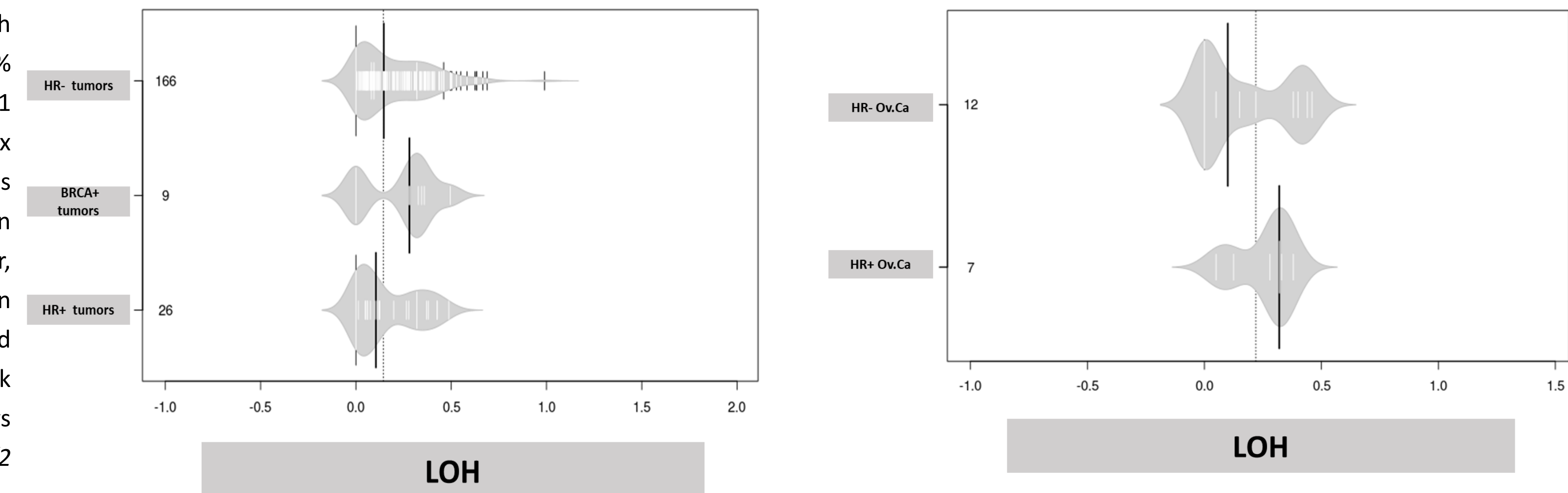


Figure 4. A. Bean Plots showing the distribution of LOH in HR+, *BRCA1/2+*, and HR- tumor. B. Bean Plots showing the distribution of LOH in HR+ and HR- in ovarian cancer

CONCLUSIONS

- A total of 13.74% of the cases carried a mutation in a gene involved in the HR pathway.
- The use of large gene panels permitted the identification of more mutations in the HR genes, while allowing us to get insight of the genomic instability of the tumor by measuring LOH.

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