The RODILIA pilot study for molecular screening of patients with metaplastic breast cancer

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BACKGROUND

Metaplastic breast cancer (MPBC) is a rare disease characterized by aggressive features and dismal prognosis after standard therapy. Herein, we report the molecular screening of the Milan National Cancer Institute case series for the evaluation of potentially druggable alterations.

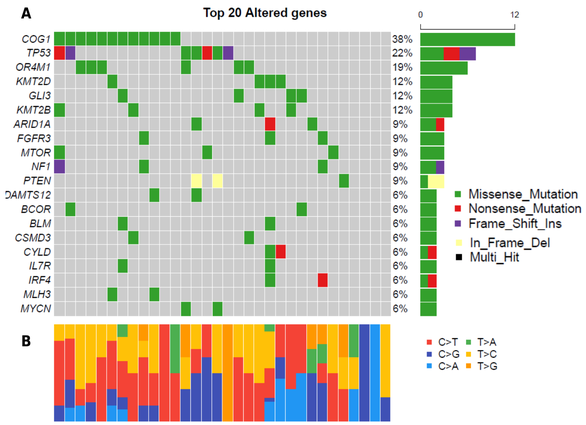
METHODS

A total of 49 MPBC cases treated with curative intent were identified. Primary tumors were profiled using Oncomine Comprehensive Assay Plus panel (Thermo Fisher Scientific) for copy number alteration (CNA), tumor mutational analyses and burden (TMB) and microsatellite instability (MSI) analyses, according to the manufacturer instructions.

STUDY PATIENT POPULATION

Herein, we report the results for the first 34 pathological reviewed cases.

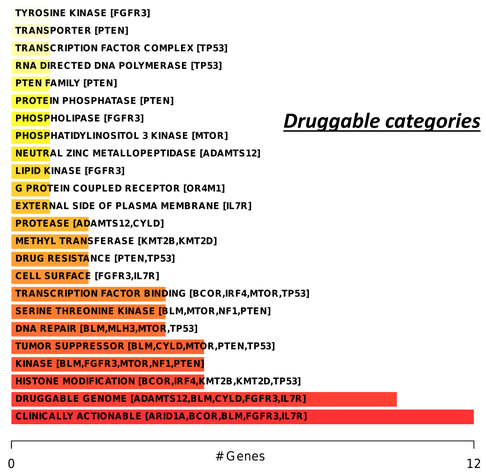
Among them, 94 unique genes harbored at least one mutation representing 24% of the panel. The median number of mutations indexed per patients was 4 (range 0-29). *COG1* (38%), *TP53* (22%) and *OR4M1* (19%). Twenty-five (25/34, 73%) cases showed actionable mutated genes, including *PTEN, mTOR, FGFR3, FGFR4* were the most commonly mutated genes.



A) The heatmap reports patients on the column and the top 20 mutated genes on the rows. B) The barplot refers to the nucleotide changes found in each case.

RESULTS

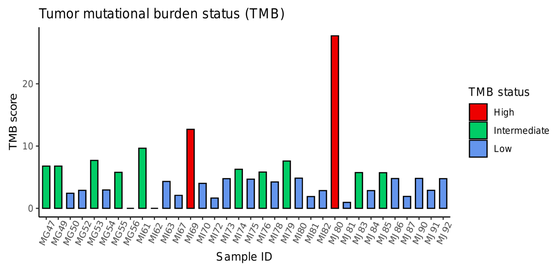
- 11 out of 17 alterated genes were included within druggable categories with different extend as reported below.



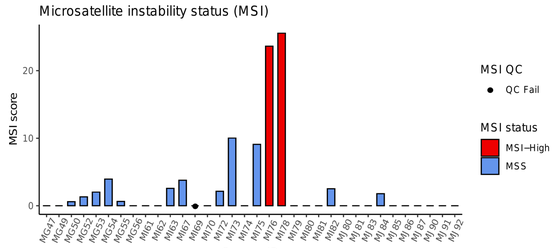
Druggable categories

The Barplot shows druggable categories where each color refers to the number of mutated genes within each category (yellow=low; red=high).

- Most of the cases showed low TMB, the median value being 4.5 (range 0-28). MSI status was high only in 2 cases. 2 cases (6%) showed high TMB status while 22 (64%) and 10 (34%) cases were characterized by low and intermediate status respectively.
- MSI status was detected as high and stable in 2 and 31 cases respectively. Only 1 samples was not evaluable for MSI (QC fail).

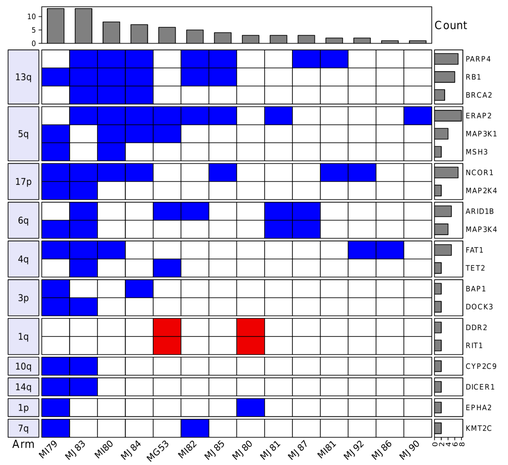


Tumor mutational burden status for each case. Red, green and blue colors refer to TMB high, intermediate and low status respectively.



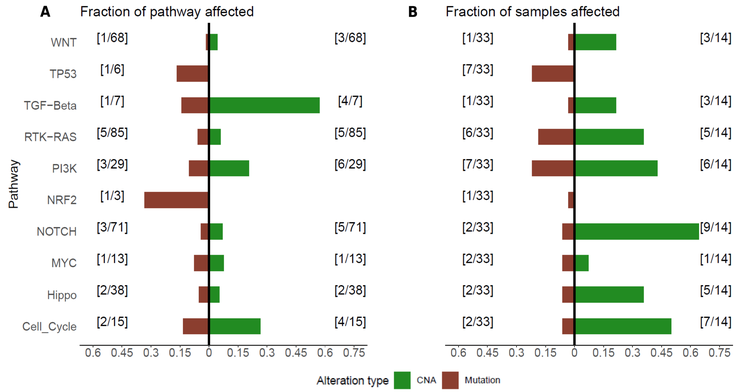
Microsatellite instability status for each case. Red and blue colors refer to MSI-High and MSS status respectively. Black dot refers to QC of MSI analysis

- Common CNAs included 13q (10%), 5q (9%) and 17p (6%), with the top 3 altered genes represented by *ERAP2* (57%), *NCOR* and *PARP4* (50%). Only *DDR2* and *RIT1* genes showed amplification (14%).



The heatmap reports patients on the column and the top 20 altered genes on the rows divided by chromosomal arms. Red and blue colors refer to amplification and deletion events respectively.

- Eight out of ten canonical cancer pathways (cell cycle, Hippo, MYC, NOTCH, PI3K, RTK-RAS, TGFβ and β-catenin/WNT) were altered by both mutational and CNA events occurring at different proportions, with mutational events involving up to 33%, and CNA involving up to 42% of genes of the altered pathway.
- In the Hippo and RTK-RAS pathways the two types of alterations were instead equally represented whereas the remaining pathways (β-catenin/WNT, TGFβ, PI3K, NOTCH, MYC and Cell cycle) were more affected by CNA than mutations. NRF2 and TP53 signaling pathways were instead activated by mutational events only.



Comparison between 10 canonical cancer pathway (Vega F.S. et. al., Cell 2018) enriched by mutational and/or CNA events. Fraction of pathway affected (A) and fraction of samples affected by mutational and CNA events were reported in brown and green respectively. "Fraction of pathway" and "fraction of samples" affected refer to the number of altered genes present in a specific pathway and to the number of cases showing the altered pathway, respectively.

CONCLUSIONS

Mutational and copy number alterations conveyed complementary information in MPBC cooperating in activation of cancer pathways. These findings suggest to further study the value of CNAs in MPBC biological processes, especially immunogenicity, which cannot be explained by the low TMB and MSI found.

DISCLOSURES

None

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