Genomic Classification of Clinically Advanced Solid Tumors Based on Methylthioadenosine Phosphorylase (MTAP) Genomic Loss

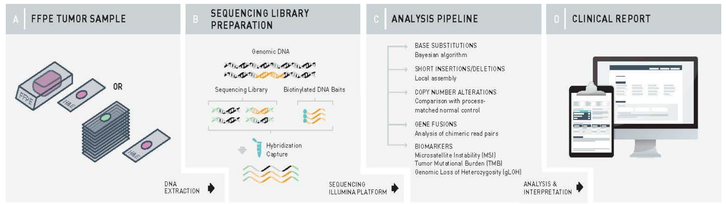
Andrea Necchi, Antonio Cigliola, Valentina Tateo, Chiara Mercinelli, Jeffrey S Ross, Dean C Pavlick

IRCCS San Raffaele Hospital and Scientific Institute, Milan, Italy, Upstate Medical University, Syracuse, NY, Foundation Medicine Inc., Boston, MA

Background

MTAP genomic loss, often but not exclusively a bi-allelic homozygous deletion, has recently emerged as important biomarker guiding a novel synthetic lethality mechanism for drugs in the class of PRMT5 and MAT2A inhibitors. In the current study, we studied the nature and distribution of *MTAP* complete and partial loss in a series of more than 540,000 clinical samples.

Methods

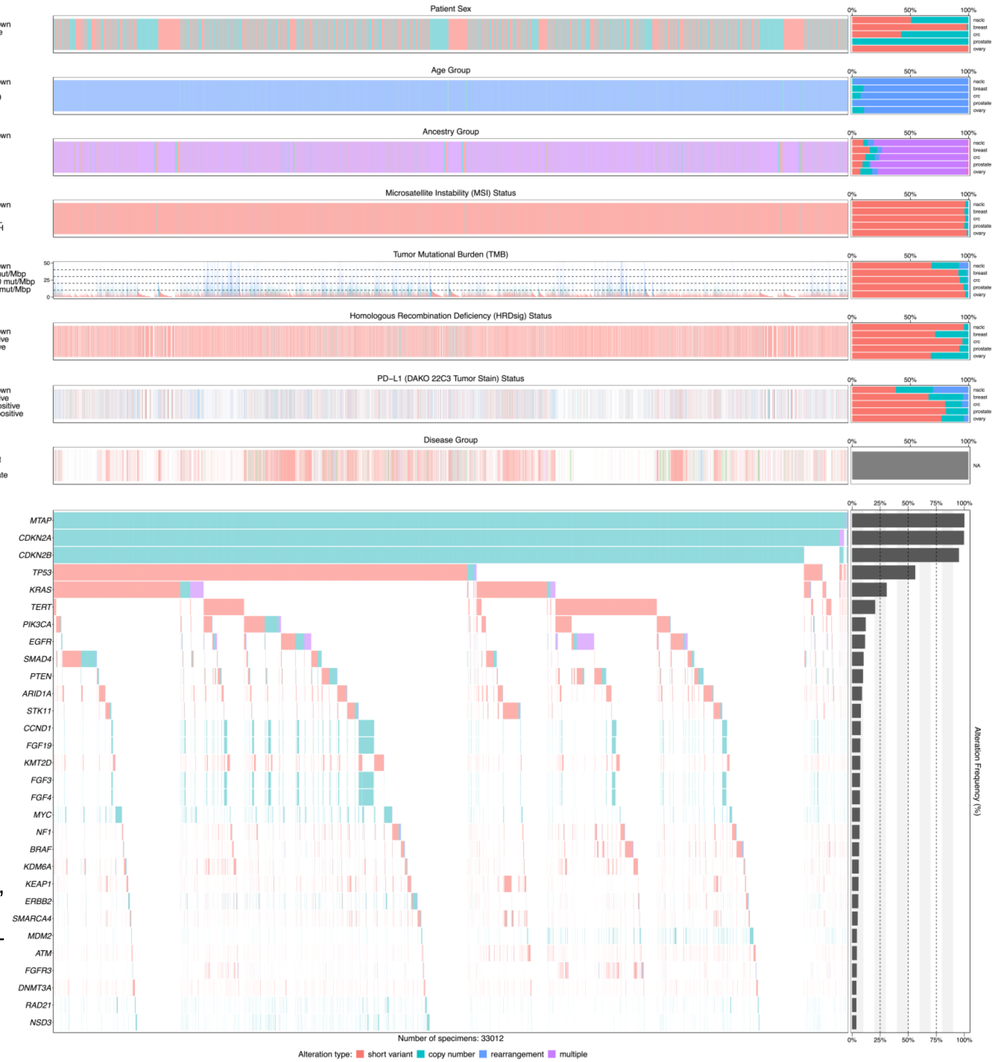


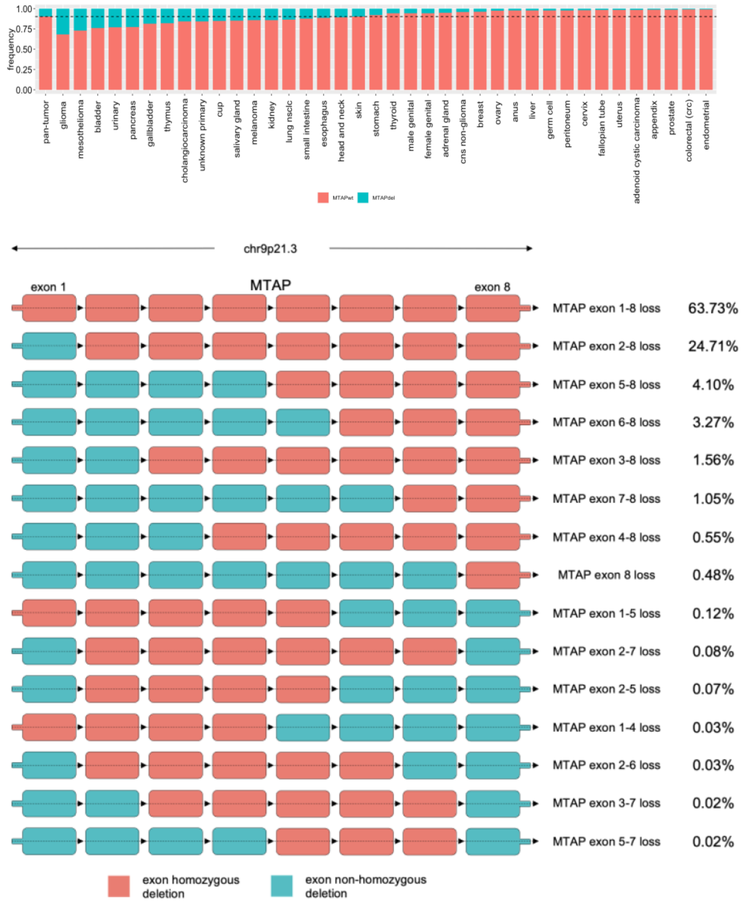
- ≥50 ng DNA extracted from 40 µm of FFPE sections
- Sequencing performed on 324 cancer-related genes and introns from 28 genes commonly rearranged in cancer
- FDA-approved (F1CDx) hybrid capture-based sequencing using adaptor ligation-based libraries
- Mean coverage depth >600X
- Base substitutions, insertions and deletions (short variants; SV), rearrangements, and copy number changes were assessed
- TMB calculated from 0.80 Mb sequenced DNA

Results

- *MTAP* genomic loss pan-cancer is 9.3%
- Most frequent *MTAP* loss included: 42.6% glioblastoma (GBM), 13.4% non-small cell lung cancer (NSCLC), 22.3% pancreatic and 24.9% bladder
- *CDKN2A* (99.7%), *CDKN2B* (95.1%), *TP53* (55.4%), *KRAS* (30.1%), *TERT* (20.5%) and *PIK3CA* (12.0%) were the most frequent co-GA
- Short variant mutations in *EGFR*, *ERBB2*, *BRAF*, *FGFR2-3* and *MET* and fusions involving *ALK*, *RET*, *ROS1* and *NTRK1-3* were not decreased in *MTAP* loss cases
- MSI high status was 0.3% and TMB ≥ 10 mutations per Mb was 17.0 in *MTAP* loss cases
- 63.7% of the *MTAP* loss cases involved deletion of all 8 *MTAP* exons (complete loss) with partial loss accounting for 36.3% of cases
- All partial loss cases involved loss of multiple exons (35.8%) except for loss of only exon 8 (0.5%)
- The multiple exon loss frequencies included exons 2-8 loss in 24.7%, exons 5-8 loss in 4.1%, exons 6-8 loss in 3.3%, exons 3-8 loss in 1.6%, exons 7-8 in 1.1%, exon 4-8, 1-5, 2-7,2-5, 1-4, 2-6, 3-7 and 5-7 all at less than 1%
- No impact of *MTAP* loss status on genomic ancestry or HRD score

Results





Conclusions

- *MTAP* loss is a frequent GA of emerging clinical importance as the trials using PRMT5 and MTA-2 inhibitors progress
- *MTAP* loss is frequent in common cancers of the brain, lung, pancreas and bladder and not associated with diminishment of other targetable driver mutations
- Although one-third of *MTAP* loss is a partial loss, the partial loss cases involve near total (exons 2-8) loss and may well also be indicative of PRMT5/MAT2A inhibitor benefit
- This study strengthens the opportunity to consider a tumor-agnostic approach to targeted therapies