Abstract #844

Blood-, Urine-, and Tissue-Based Detection of MTAP Gene Loss in Bladder Cancer and Other Solid Tumors

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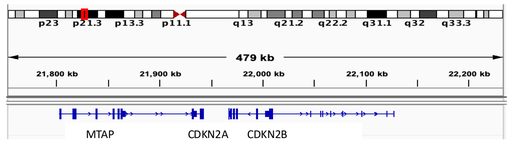
BACKGROUND

MTAP, located on chromosome 9p21.3 adjacent to CDKN2A/B, is frequently co-deleted with CDKN2A in multiple cancers. Homozygous 9p21 deletions (encompassing CDKN2A and MTAP) occur in approximately 15% of all cancers, while MTAP homozygous deletion is observed in about 30% of bladder cancers. MTAP loss creates a therapeutic vulnerability through dependence on the PRMT5/MAT2A pathway, which is being targeted by emerging synthetic-lethal therapies. A non-invasive liquid biopsy assay capable of detecting MTAP loss could enable biomarker-driven patient selection in clinical drug development.

METHODS

Tumor tissue, blood, and urine samples from patients with non–muscle-invasive bladder cancer (NMIBC) and advanced solid tumors (including PDAC, NSCLC, CRC, prostate, bladder, H&N, and kidney cancers) were analyzed using the PredicineCARE 200-gene NGS assay. This assay covers the coding regions of MTAP and CDKN2A and incorporates a genome-wide SNP backbone, enabling detection of MTAP gene deletion events independently of CDKN2A. PredicineCARE can detect copy number loss down to 7.5% tumor fraction (TF) using coverage-based approach, the sensitivity can be down to 1% TF using breakpoint-based copy loss detection method.

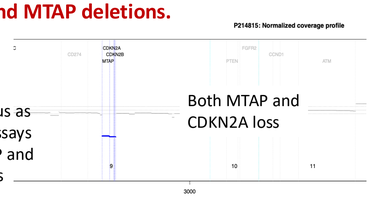
Figure 1. MTAP gene location and prevalence of MTAP loss

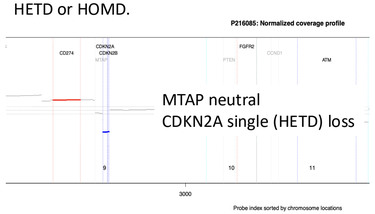


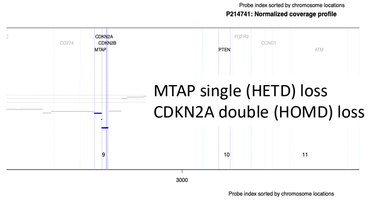
Homozygous deletion of the chromosomal region 9p21.3 (9p21 loss) is one of the most frequent copy number variations (CNVs) across human cancers, occurring in ~15% of all cancers and in ~30% of bladder cancers.

Figure 2. Representative cases of CDKN2A and MTAP deletions.

MTAP-targeted therapeutic strategies are generally effective in MTAP-null cancers, making it critical to differentiate heterozygous deletions (HETD) from homozygous deletions (HOMD) when using MTAP status as a biomarker. The PredicineCARE and PredicineATLAS assays can distinguish copy number variations (CNVs) in MTAP and CDKN2A, as well as accurately classify deletion types as HETD or HOMD.







RESULTS

Figure 3. Oncoplot of NMIBC urine samples showing CDKN2A and/or MTAP deletions.

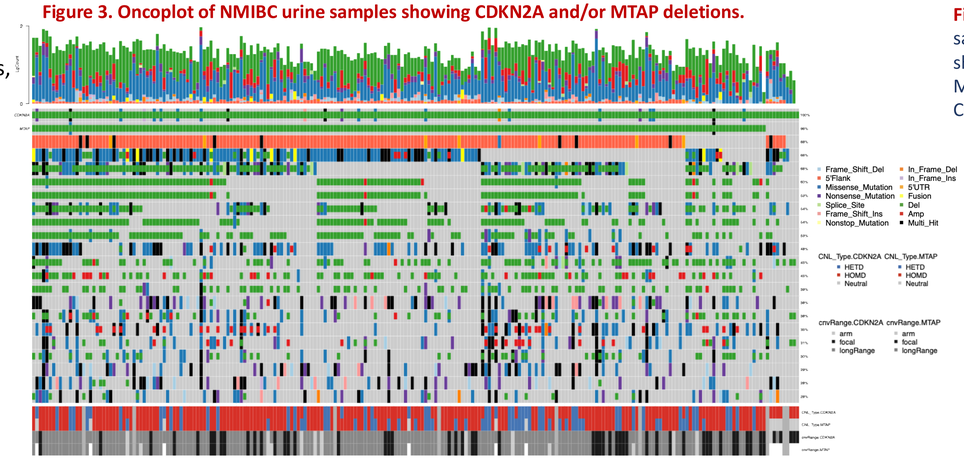


Figure 4. Genomic span of CDKN2A and MTAP deletions.

Deletions are categorized as focal (<3 Mb), long-range (≥3 Mb), or arm-level.

CDKN2A	Arm	Focal	Long Range
HETD	2	5	42
HOMD	8	50	114

MTAP	Arm	Focal	Long Range
HETD	8	10	46
HOMD	5	40	99

Figure 5. Concordance of MTAP loss between matched tissue and urine samples from 25 NMIBC patients undergoing pre–repeat TURBT.

CDKN2A	HETD	HOMD	Total
Tissue	4	6	10
Urine	3	8	11

MTAP	HETD	HOMD	Total
Tissue	4	6	10
Urine	3	7	10

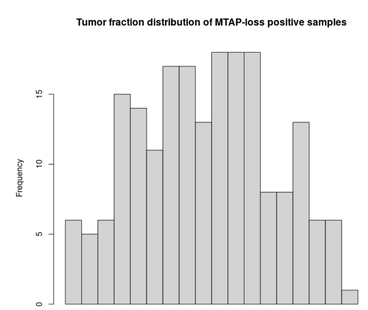
RESULTS

Differentiating heterozygous (HETD) from homozygous deletions (HOMD) is critical for establishing MTAP as a clinically useful biomarker. Among 516 urine samples with tumor fraction ≥0.1, MTAP loss was detected in 40.3% (208/516), including 27.9% (144/516) with HOMD. CDKN2A loss was observed in 42.8% (221/516) of samples, with 33.3% (172/516) showing HOMD.

Predicine cfDNA platform distinguished MTAP-specific deletions from CDKN2A deletions despite their close genomic proximity (<30 kb). Notably, 13 patients had CDKN2A deletions with neutral MTAP, and 22 cases showed CDKN2A HOMD with MTAP HETD, indicating a higher rate of focal HOMD in CDKN2A than MTAP. High concordance of MTAP loss was observed in 25 matched pre-repeat TURBT tissue and urine samples.

Analysis of plasma samples from advanced solid tumors showed a similar HETD-to-HOMD pattern, supporting the broader applicability of liquid biopsy for MTAP loss detection

Figure 6. Prevalence of CDKN2A and MTAP loss in NMIBC urine samples. Among 516 urine samples with tumor fraction ≥0.1, 64/516 (12.4%) showed MTAP HETD and 144/516 (27.9%) showed MTAPHOMD. Among 416 urine samples with tumor fraction ≥0.2, 52/416 (12.5%) showed MTAP HETD and 126/416 (30.3%) showed MTAP HOMD. All detected MTAP losses co-occurred with CDKN2A deletions.



MTAP Loss

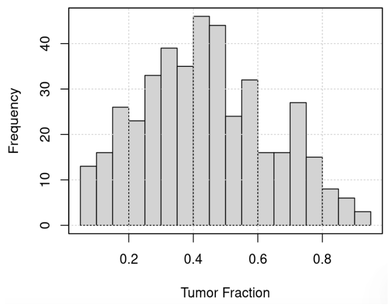
Among 516 samples with TF > 0.1

CKDN2A Loss	HETD	HOMD	Neutral
HETD	42	1	6
HOMD	22	143	7

Among 416 samples with TF > 0.2

CKDN2A Loss	HETD	HOMD	Neutral
HETD	36	1	5
HOMD	16	125	3

Figure 7. Prevalence of CDKN2A and MTAP loss in advanced solid tumors. Among 1,829 plasma samples with tumor fraction ≥0.1 from patients with pancreatic, lung, bladder, prostate, head and neck, and other advanced solid tumors, 108/1,829 (5.9%) exhibited MTAP HETD and 285/1,829 (15.6%) showed MTAP HOMD.



MTAP Loss

CKDN2A Loss	HETD	HOMD	Neutral	Total
HETD	72	3	13	88
HOMD	35	280	10	325
Neutral	1	2	0	3
Total	108	285	23	416

CONCLUSION

This study demonstrates the feasibility of urine- and blood-based detection of MTAP gene loss in NMIBC and other advanced solid tumors, respectively, and the ability to differentiate MTAP deletions from adjacent CDKN2A losses, while resolving both heterozygous (HETD) and homozygous (HOMD) deletion events using Predicine cfDNA assays. These findings highlight the potential of liquid biopsy–based diagnostics for patient selection and therapy monitoring in clinical drug development and personalized cancer care.