Ductal, Acinar and Neuroendocrine Carcinomas of the Prostate: A Comparative Comprehensive Genomic Profiling Study

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ABSTRACT

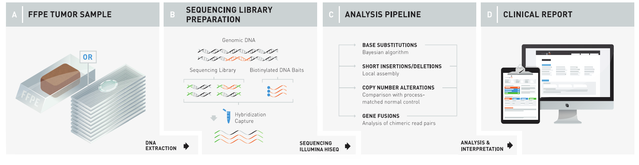
Background: Prostate ductal carcinoma (PDC), prostate acinar carcinoma (PAC) and prostate neuroendocrine carcinoma (PNC) are histologic subtypes of prostate cancer (PC). We queried whether these subsets would share similar genomic alterations (GA) reflecting their disease biology and clinical features.

Methods: CGP was performed using a hybrid capture-based assay on 61 PDC, 4,132 PAC and 217 PNC. Tumor mutational burden (TMB) was determined on 0.83-1.14 Mbp of sequenced DNA and microsatellite instability (MSI) was determined on 114 loci.

Results: The age, GA per tumor and *TP53* GA of PDC, PAC and PNC were similar (Table). *RB1* GA were predominant in PNC. *TMPRSS2:ERG* fusions were most frequent in PNC, intermediate in PAC and lowest in PDC. *AR* GA were more often identified in PAC than PDC or PNC whereas *PTEN* GA were most frequent in PDC than PAC or PNC. Targetable GA were identified in all 3 groups when focused on *BRCA2* (PARP inhibitors) and *PIK3CA* (MTOR inhibitors). *ATM* GA (PARP inhibitors) were more common in PAC than PDC or PNC. *BRAF* GA (BRAF/MEK inhibitors) were more frequent in PDC and PAC than PNC. *CDK12* GA potentially associated with immunotherapy (IO) benefit were similar in PDC and PAC and low in PNC. Low frequencies of MSI-High and low median TMB levels were similar in all 3 groups.

Conclusions: The pathologic features of PDC, PAC and PNC have been classically maintained as representative of 3 different tumor types with potentially contrasting histogenesis. In the current CGP based study, all 3 tumor types did not display significant differences in genomic signatures other than the high RB1 GA. CGP may reveal biomarkers that could direct patients to targeted (PARP, MTOR and BRAF/MEK inhibitors) or immunotherapies (*CDK12* GA, MSI-High or high TMB status) especially in PDC and PAC.

MATERIALS AND METHODS

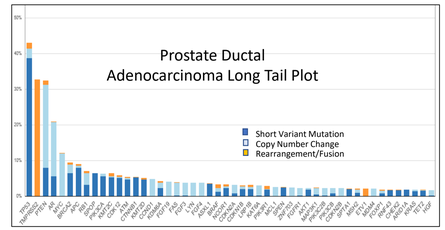


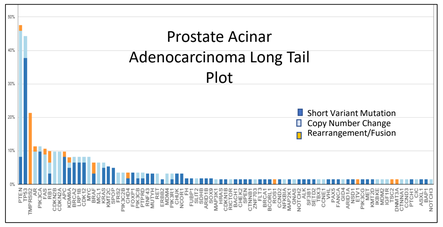
- ≥50 ng DNA extracted from 40 µm of FFPE sections
- Sequencing performed for up to 315 cancer-related genes and introns from 28 genes commonly rearranged in cancer
- Hybrid capture-based sequencing using adaptor ligation-based libraries
- Mean coverage depth >600X
- Base substitutions, insertions and deletions (short variants; SV), rearrangements, and copy number changes were assessed
- Tumor mutational burden (TMB) calculated from 0.83-1.14 Mb sequenced DNA

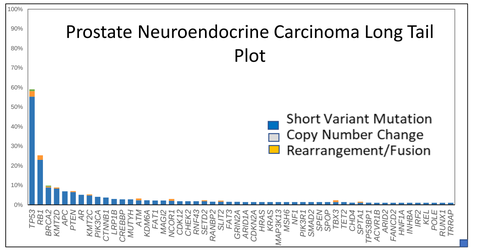
RESULTS

- Ages, GA per tumor and *TP53* GA of PDC, PAC and PNC were similar
- *RB1* GA were predominant in PNC
- *TMPRSS2:ERG* fusions were most frequent in PNC, intermediate in PAC and lowest in PDC
- *AR* GA were more often identified in PAC than PDC or PNC whereas *PTEN* GA were most frequent in PDC than PAC or PNC
- Targetable GA were identified in all 3 groups when focused on *BRCA2* (PARP inhibitors) and *PIK3CA* (MTOR inhibitors)
- *ATM* GA (PARP inhibitors) were more common in PAC than PDC or PNC
- *BRAF* GA (BRAF/MEK inhibitors) were more frequent in PDC and PAC than PNC
- *CDK12* GA potentially associated with immunotherapy (IO) benefit were similar in PDC and PAC and low in PNC
- Low frequencies of MSI-High and low median TMB levels were similar in all 3 groups

	Age Median range	GA/ tumor	Top Un-targetable GA	Top Targetable GA	CDK12 GA	MSI High	Median TMB	TMB ≥ 10 mut/Mb	TMB ≥ 20 mut/Mb
PDC 61 cases	66 (51-86)	4.1	*TP53* 46% *TMPRSS2* 21% *FAS* 11% *RB1* 10%	*PTEN* 48% *AR* 11% *PIK3CA* 11% *BRCA2* 9% *BRAF* 7% *RET* 4% *ATM* 0%	8.2%	1.9%	2.6	3.3%	1.6%
PAC 4,132 cases	66 (34-88)	4.4	*TP53* 43% *TMPRSS2* 32% *MYC* 12% *RB1* 7%	*PTEN* 32% *AR* 21% *BRCA2* 10% *PIK3CA* 7% *ATM* 6% *BRAF* 4%	6.0%	2.6%	2.6	3.8%	0.7%
PNC 217 cases	67 (30-86)	5.0	*TP53* 64% *RB1* 55% *TMPRSS2* 42% *MYC* 11%	*PTEN* 33% *BRCA2* 12% *AR* 11% *PIK3CA* 5% *ATM* 3% *BRAF* 1%	1.8%	1.0%	3.5	8.8%	2.8%



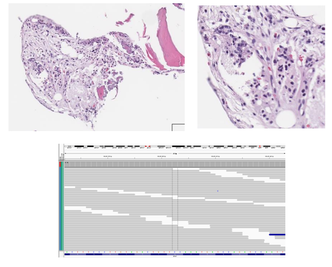




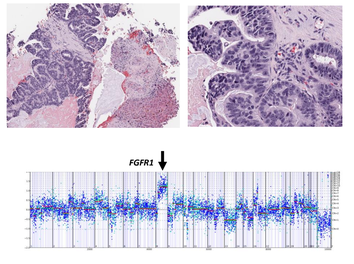
CONCLUSIONS

- In the current CGP based study, the PDC, PAC and PNC tumor types did not display significant differences in genomic signatures other than the high RB1 GA in PNC
- CGP may reveal biomarkers that could direct patients to targeted (PARP, MTOR and BRAF/MEK inhibitors) or immunotherapies (*CDK12* GA, MSI-High or high TMB status) especially in PDC and PAC

CASES



Bone biopsy in a 68 year old Caucasian man with metastatic ductal adenocarcinoma of the prostate. CGP revealed short variant mutations in *BRAF, BRCA2, KDM6A* and *RB1*. Alterations that activate BRAF kinase activity, such as in the G469A *BRAF* mutation lead to hyperactivation of the downstream MEK-ERK signaling pathway and may confer sensitivity to BRAF and/or MEK inhibitors. *BRAF* mutations have been reported in 1% of prostate adenocarcinomas. For ductal prostate cancer, the frequency and significance of *BRAF* mutations has not been previously considered. *BRCA2* mutations in prostate cancer such as were found in this patient are linked to defective DNA damage repair and have been widely associated with potential sensitivity to PARP inhibitors.



Metastatic prostatic ductal adenocarcinoma to the liver in a 75 year old Caucasian man. CGP revealed amplifications of *FGFR1, AR, MYC, LYN* and *ZNF703;* losses of *PTEN* and *MAP3K1;* and short variant mutations in *PIK3CA, ABL1* and *TP53*. *FGFR1* encodes the protein fibroblast growth factor receptor 1, which plays key roles in regulation of the cell cycle and angiogenesis and is an upstream regulator of the RAS, MAPK, and AKT signaling pathway. Amplification of *FGFR1* has been correlated with protein expression and may predict pathway activation and sensitivity to therapies targeting this pathway. Putative high-level amplification of *FGFR1* has been found in 1-4.7% of prostate adenocarcinomas in several sequencing datasets and has been reported to be higher in hormone refractory prostate cancer . Tumors with alterations that activate FGFR1 may be sensitive to FGFR family inhibitors including pazopanib and ponatinib. Other inhibitors of FGFR1, such as AZD4547, BGJ398, Debio 1347, INCB054828, JNJ-42756493, TAS-120, and the multikinase inhibitors lenvatinib and lucitanib, are under clinical investigation.