Multi-Institutional Landscape of Somatic Genetic Variants in Pancreatic Neuroendocrine Tumors

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BACKGROUND AND SIGNIFICANCE

- Pancreatic Neuroendocrine Tumors (PNETs) repesent neoplasms with heterogeneous behavior and presentation, resulting in a paucity of generalizable molecular data.
- Present studies limited by single-institution analyses and small sample size
- **Using publicly-available datasets, we established a large, multi-institutional cohort of patients for additional characterization of somatic variants associated with both primary and metastatic PanNET disease.**

METHODS

- The following publicly-available genomic datasets were queried via cBioPortal: MSK-IMPACT, MSK-MET, MSK-PANET 2023, PCAWG, ARC-NET, OrigiMed, JHU PANET, Insulinoma Shanghai, and MET500.
- All documented primary and metastatic PNET tumors were included.
- Patients with known neuroendocrine carcinoma were excluded.
- For patients with multiple samples, tumor with the highest TMB was used as the representative sample.
- Somatic mutations and available clinical data were analyzed. Genes mutated at <5% frequency were not included for analysis.
- Significance testing was done by Mann-Whitney U for central tendency, Chi-square or Fisher's exact for association, Wald for logistic regression, and logrank for survival.

RESULTS

Generation of a Large, Mutli-Instiutional PNET Cohort

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Patient Characteristics by Samples Type

	Primary n=313	Metastasis n=139	All Lesions n=452	P value
Country				**p<0.0001**
Australia	29	0	29 (6%)	
China	34	19	53 (12%)	
Italy	51	0	51 (11%)	
United States	110	107	217 (49%)	
Unknown	89	13	102 (23%)	
Race				p=0.066
Asian	29	24	53 (12%)	
Black	8	9	17 (4%)	
White	161	76	237 (52%)	
Refused/Unknown	115	30	145 (32%)	
Sex				p=0.4
Female	124	58	182 (40%)	
Male	176	68	244 (54%)	
Unknown	13	13	26 (6%)	
Known Grade				
Well-Differentiated	185	2	187 (41%)	
Unknown	128	137	265 (59%)	
Dataset				
MSK-IMPACT	21	22	43 (10%)	
MSK-MET	76	90	166 (37%)	
MSK PANET	6	2	8 (2%)	
ARC-NET	93	0	93 (21%)	
OrigiMed	24	19	43 (10%)	
JHU PANET	7	2	9 (2%)	
Insulinoma Shanghai	10	0	10 (2%)	
MET500	0	4	4 (1%)	

(A) Patient Demographics by sample type. Statistical testing by association performed using Wilcox Rank Sum Test.

References

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Mutational Landscape of Primary and Metastatic Tumors

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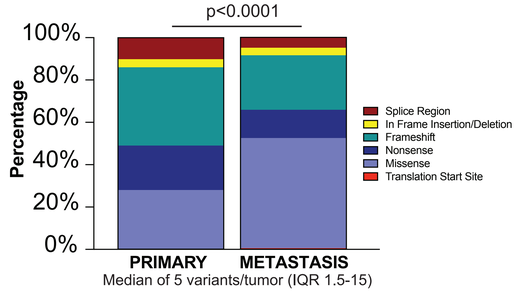

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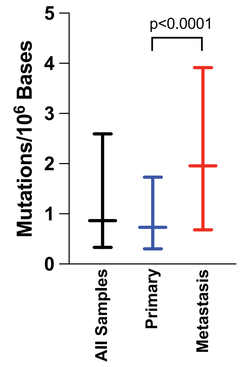

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Common Variants by Sample Type

Variant	Primary Mutational Frequency	Metastatic Mutational Frequency	P value
MEN1	38.34%	35.97%	0.643
DAXX	19.81%	22.30%	0.293
ATRX	15.34%	10.79%	0.444
SETD2	**7.03%**	**10.07%**	**0.017**
PTEN	6.07%	5.76%	0.8277
TSC2	**5.11%**	**13.67%**	**<0.0001**
TP53	**3.19%**	**16.55%**	**<0.0001**
ARID1A	**3.19%**	**7.91%**	**0.024**
NOTCH1	**1.28%**	**5.04%**	**<0.0001**
KRAS	**0.32%**	**7.19%**	**0.023**
BRAF	**0%**	**5.04%**	**0.015**

D

Genomic Correlates of Metastases

Variant	P value	OR	95% CI
TP53	**0.00001**	**6.53**	**2.80, 15.25**
TSC2	**0.00339**	**3.60**	**1.53, 8.49**
ATRX	0.20935	0.62	0.30, 1.31
SETD2	0.28177	1.57	0.69, 3.57
DAXX	0.41426	0.76	0.39, 1.48
MEN1	0.52881	1.19	0.70, 2.02
PTEN	0.73463	1.19	0.44, 3.18

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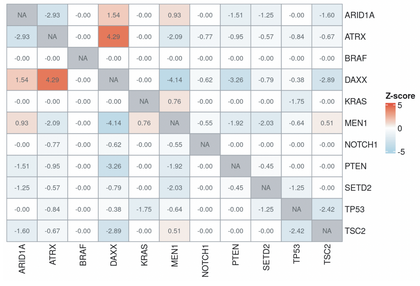

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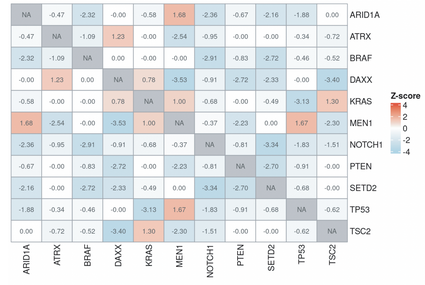

(A) Distribution of variant classes of primary and metastatic samples. Statistical testing by association performed using Chi-Square.
(B) Total Mutation Burden (TMB) of primary and metastatic lesions. Median and quartiles are denoted. Statistical testing performed by Wilcoxon Rank Sum Test
(C) Most common variants observed in primary and metastatic lesions. Statistical testing by association performed using Chi-Square.
(D) Variants with the strongest correlation with metastasis by logistic regression. Statistical testing by Wald's Test for logistic regression.
(E) Mutual exclusivity of common variants within primary lesions. Statistical testing by Fischer's Exact test.
(F) Mutual exclusivity of common variants within metastatic lesions. Statistical testing by Fischer's Exact test.

Association Testing suggests Different Patterns of Somatic Variants

- *ATRX* and *DAXX* mutations are mutually exclusive in primary tumors, exclusivity is lost in metastatic tumors, reflecting convergence of these genes on the same pathway.
- *MEN1* mutations demonstrates co-occurrence with both *DAXX* and *ATRX* mutations separately.
- Compared to *ATRX* mutations, *DAXX* mutations co-occur with other variants (*TSC2, PTEN*), suggesting other implicated pathways in *DAXX*-mutant tumors.
- *TP53* and *KRAS* demonstrate co-occurrence in metastatic lesions, potentially illustrating a unique tumor subgroup evolution within metastases.

ATRX and DAXX Mutations are associated with Nodal Involvement

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Genomic Correlates of Regional Nodal Metasatasis

Variant	P value	OR	95% CI
ATRX	**0.00093**	**7.98**	**2.33, 27.28**
DAXX	**0.00569**	**3.44**	**1.43, 8.28**
SETD2	0.12554	0.35	0.07, 1.73
MEN1	0.23980	0.64	0.30, 1.35
PTEN	0.32624	1.97	0.51, 7.66
TTN	0.53374	1.51	0.41, 5.55

B

(A) Variants with the strongest correlation with N1 status. Statistical testing by Wald's Test for logistic regression.
(B) Mutual exclusivity of variants with at least 5% mutational frequency in N0 or N1 disease. Statistical testing by Fischer's Exact test.
(C-F) Kaplan-Meier plot displaying survival analysis stratified by ATRX and DAXX mutational status. Statistical testing by logrank.
(G-H) Kaplan-Meier plot displaying survival analysis stratified by regional nodal involvement. Statistical testing by logrank

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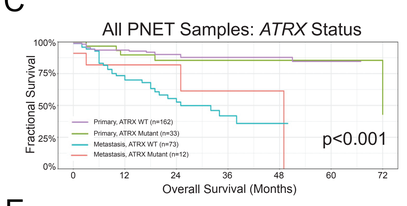

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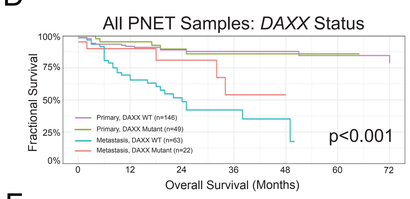

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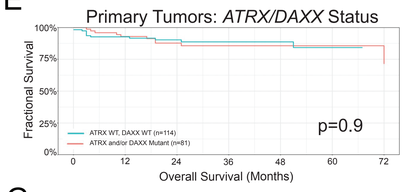

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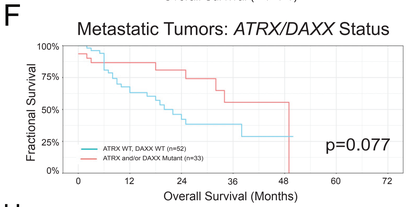

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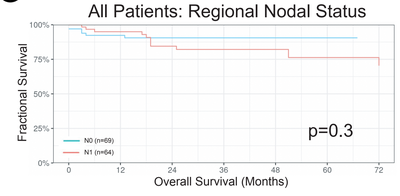

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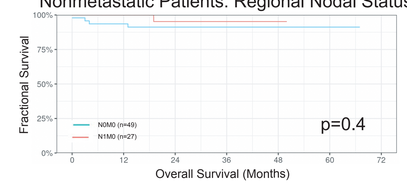

Gene-Specific Survival Analyses

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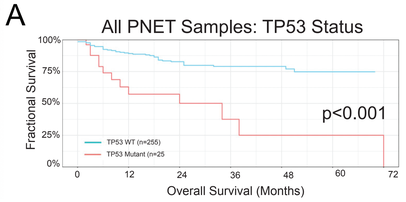

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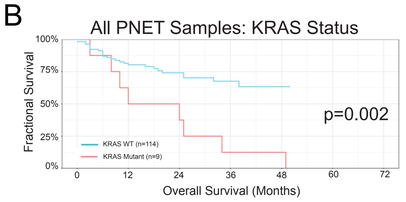

(A) Kaplan-Meier plot displaying survival analysis stratified by *TP53* mutational status. Statistical testing by logrank.
(B) Kaplan-Meier plot displaying survival analysis stratified by *KRAS* mutational status. Statistical testing by logrank.

SUMMARY

- **Largest aggregate landscape of somatic mutations of PNETs utilizing multiple publicly-available datasets.**
- ***MEN1* remained most commonly mutated gene in 38.3% of primaries and 36.0% metastases, and was found to co-occur with *ATRX* and *DAXX* mutations, indicating a shared molecular pathway.**
- ***ATRX* and *DAXX* variants are nearly mutually exclusive in primary tumors and loss this mutual exclusivity in metastatic lesions, implicating their shared pathway in tumorigenesis.**
- ***ATRX/DAXX* variants correlate with regional but not distant disease and correlate with improved survival in those with *ATRX/DAXX* mutated metastatic disease.**
- **In the subset of patients with available correlative clinical data, regional nodal involvement does not associate with a decrement in survival.**
- ***TP53* mutations are highly correlated with metastases and co-occur with *KRAS* mutations, both mutations are associated with poor overall survival, possibly indicating a unique tumor subgroup of aggressive disease.**