Next-Generation Sequencing (NGS) in Pancreatic Neuroendocrine Tumors (panNETs): Defining Differentiation and Grade Genetically

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Background

- Advances in tumor sequencing technology have improved our understanding of the genetic basis of panNETs, a heterogeneous group of tumors demonstrating indolent to highly aggressive behavior.
- Whole exome sequencing in well differentiated (WD) panNETs demonstrated increased mutations in chromatin remodeling genes.
- Targeted sequencing of poorly differentiated neuroendocrine carcinomas (PDNEC) demonstrates a genetic profile distinct from WD panNETs, with mutations observed largely in TP53 and RB1.
- We sought to validate and build on these observations in clinical practice, using a comprehensive institutional NGS platform.

Methods

- Our institutional NGS platform, MSK-IMPACT (Memorial Sloan Kettering Integrated Mutation Profiling for Actionable Cancer Targets) was used.
- This platform provides full coverage of 410 cancer related genes, detecting base substitutions, small indels, copy number changes, select gene rearrangements.
- After written consent, testing was performed on FFPE-embedded tumor samples and matched blood.
- Genetic alterations were catalogued.

Results

Table 1. Patient characteristics

Number of patients/samples	67/77
Age (mean)	53
Sex	58% female
Grade (G1/G2/G3, %)	27 (35%) / 30 (39%) /20 (26%)
Stage (locally advanced/metastatic, %)	9 (13%) / 58 (87%)
Received systemic therapies	59 (88%)
Somatostatin analogs	43 (64%)
Everolimus	20 (30%)
Sunitinib	5 (7%)
Platinum agents	20 (30%)
Alkylating agents	37 (55%)
Peptide receptor radiotherapy (PRRT)	9 (13%)

WD/G2 tumors with TP53 alterations:

#1: TP53 truncating mutation, also with MEN1/DAXX/SETD2 and TSC2 alterations, clinically aggressive behavior with progression through all approved therapies

#2: TP53 missense mutation R248Q (hotspot), also with MEN1/ ATRX alterations, clinically indolent behavior (on octreotide LAR for many years for low-volume liver disease)

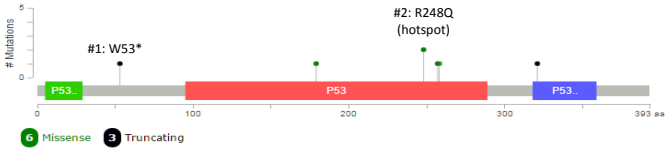
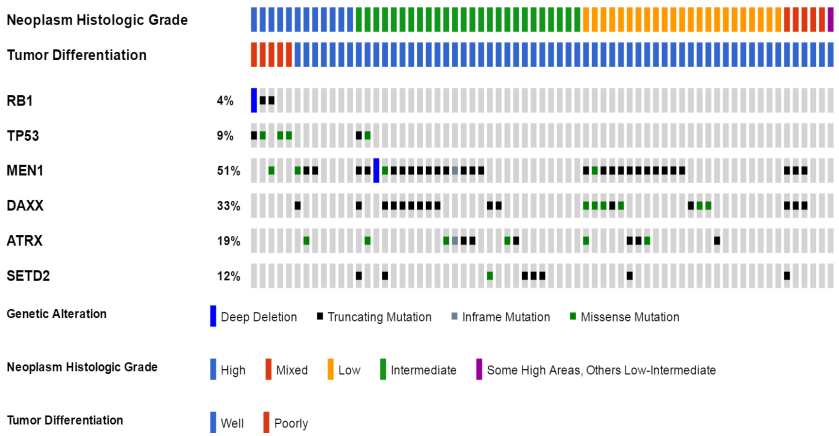


Table 2. Summary of findings

panNETs	WD G1	WD G2	WD G3	PDNEC
RB1	-	-	-	+
TP53	-	+	-	+
MEN1	+	+	+	+
DAXX	+	+	+	-
ATRX	+	+	+	-
SETD2	+	+	-	-

Figure 1. Gene alterations based on grade and differentiation



Conclusions

- Tumor grade and differentiation can be characterized through NGS.
- Changes in chromatin remodeling genes are exclusive to WD tumors.
- RB1 loss is seen only in PDNEC.
- Changes in TP53 are seen in WD and PD tumors.

  *TP53-alterated WD tumors also harbor changes in chromatin remodeling genes.