

## Materials and Methods

### *Case selection and tissue microarray construction*

Study approval was obtained from the University of Pittsburgh (IRB# PRO13020493) and Washington University (201404143) Institutional Review Boards. The surgical pathology archives from the Departments of Pathology at the University of Pittsburgh Medical Center and Barnes-Jewish Hospital were queried for neuroendocrine neoplasms of the pancreas between 1995 and 2014 that underwent enucleation, central pancreatectomy, pancreaticoduodenectomy or distal pancreatectomy. Cases were cross-referenced with clinical and follow-up data obtained from patient paper and/or electronic medical records. The study inclusion criteria consisted of the following: a solitary, well-differentiated neuroendocrine tumor (confirmed with positive immunolabeling for neuroendocrine markers [e.g. synaptophysin and chromogranin A]) centered within the pancreas, surveillance and survival data of >2 years, absence of a genetic syndrome associated with pancreatic neuroendocrine neoplasms (e.g. multiple endocrine neoplasia type 1 [MEN 1] syndrome, von Hippel-Lindau [VHL] syndrome, neurofibromatosis type 1 [NF1] syndrome, and tuberous sclerosis complex [TSC] syndrome), and cases with sufficient material for ancillary studies.

In total, 367 patients with a resected PanNET fulfilled the aforementioned criteria. In addition, the surgical pathology archives from the respective institutions were cross-referenced to identify corresponding distant metastases with sufficient pathologic material for ancillary studies. Among 120 patients with distant metastases, 72 patients had pathologic material available of the distant metastasis for ancillary studies. For whole-exome sequencing, 20 distant metastatic PanNETs from 20 patients were selected

Pathologic material of the surgically resected primary PanNET from the remaining 347 patients was used to create high-density tissue microarrays (TMAs) as previously described.<sup>1</sup> High-density TMAs were constructed using archival FFPE tissue blocks. Three, 1.0 mm-sized cores were punched from representative areas of each patient's tumor and collected into recipient blocks. Sufficient tissue for ancillary studies on cut sections was confirmed prior to immunohistochemical testing and fluorescence in situ hybridization. Details of both whole-exome sequencing and PanNET cohorts are discussed in detail in the Supplementary Data Section.

Clinical and demographic data were reviewed for each case. Corresponding pathology gross reports and hematoxylin-and-eosin (H&E) stained slides were also reviewed for the following pathologic features: tumor size, location, lymphovascular invasion, perineural invasion, extension outside of the pancreas and regional lymph node metastasis. Each PanNET was graded using the 2010 World Health Organization (WHO) classification system for pancreatic neuroendocrine neoplasms.<sup>2</sup> Briefly, on the basis of mitotic rate and Ki-67 immunohistochemistry, the following criteria were used: Grade 1 (G1), <2 mitoses/10 high-power fields (hpf) and Ki-67 of <3%; Grade 2 (G2), 2 to 20 mitoses/10 hpf or Ki-67 of 3% to 20%; and Grade 3 (G3), >20 mitoses/10 hpf or Ki-67 of >20%. The mitotic rate was derived from evaluation of multiple sections in 50 hpf (400x, field diameter 0.55 mm<sup>2</sup>) and expressed as mitoses/10 hpf. For Ki-67, at least 500 neoplastic nuclei were counted in the highest staining region for each case with careful exclusion of non-neoplastic cells.<sup>3</sup> A labeling index was calculated and expressed as a percentage. For cases with discordant mitotic rate and Ki-67 measurements, the highest grade was assigned. Pathologic primary tumor classification was determined according to the American Joint Committee on Cancer (AJCC) Staging Manual,

seventh edition.<sup>4</sup> Follow-up information was extracted from the patient's paper and electronic medical records to include data on surveillance, disease recurrence/distant metastasis, and survival.

*Whole-exome sequencing: sample and library preparation and next-generation sequencing*

Whole-exome sequencing was performed in the University of Pittsburgh Cancer Institute, Cancer Genomics Facility (CGF). Ten, 5  $\mu$ m unstained formalin-fixed, paraffin-embedded (FFPE) sections from both tumor and normal were used sample and library preparation. Paraffin was melted in an air incubator (60°C, 30 min), removed by submerging in 100% xylene (5 min) and rinsing in 100% ethanol three times followed by centrifugation (R5810; S4-104 rotor with slide adaptor; Eppendorf, Hamburg, Germany; 1000g; 5 min). Each unstained slide was aligned in register with its corresponding H&E and the demarcated tumor or normal phenotype domain was manually dissected with a sterile scalpel with substrate accumulated across serial slides in a 2.0 mL low retention, nuclease free tube in which the substrate underwent 2 additional xylene and ethanol washes. A stereomicroscope was utilized to assist manual microdissection (Olympus SZ61 microscope, Olympus Corp., Center Valley, PA) as needed. DNA purification was performed on all samples using the QiaAmp FFPE DNA extraction kit (Qiagen, Hilden, Germany) beginning with an overnight incubation in lysis buffer (Buffer ATL: Proteinase K; 300  $\mu$ L:100  $\mu$ L, 56°C, shaking at 600 rpm) followed by a 100  $\mu$ L proteinase spike-in and a 24 hour lysis. After the second lysis regimen, the substrate was denatured (90°C; 60 min); subjected to ethanol precipitation (2X volume and buffer AL); and QIAamp column capture was performed using a 2 mL flow-through collection tube (6000g, 1 min). The column was serially washed (buffer AW1, AW2; 6000g, 1 min) and dried (20,000g; 3 min) and the DNA eluted in low TE

buffer (53 uL Tris 10 mM; EDTA 0.1 mM, pH 8.0; 20,000g, 5 min). QA/QC analysis was performed utilizing an established pipeline including spectrophotometry for purity (NanoDrop 1000, OD 260/280 >1.8; Thermo Scientific, Grand Island, NY, USA), quantitative fluorometry for double stranded DNA yield (Qubit-High Sensitivity, >100 ng dsDNA, Thermo Scientific) and micro-capillary electrophoresis to determine DNA integrity (Bioanalyzer 2100, fragment size >500 bp, Agilent, Santa Clara, CA, USA).

The DNA samples were subjected to acoustical shearing (200ng, 50µl low TE) using a Covaris S1 (Covaris, Woburn, MA, USA) to obtain a fragment size of 150-170 bp for processing with the SureSelectXT library Prep kit (SSXT: #G9611A, Agilent). End repair was performed on individual samples (10X End Repair Buffer: 10 uL, dNTP mix: 1.6 uL, DNA polymerase: 1 uL, Klenow DNA polymerase: 2 uL, T4 Polynucleotide Kinase: 2.2 uL, nuclease free H<sub>2</sub>O: 33.2 uL; 60 min, 20°C) and the DNA captured using Agencourt AMPure beads (#A63881; Beckman-Coulter, Indianapolis, IN) with elution in nuclease free H<sub>2</sub>O. End-repaired DNA underwent 3' adenylation (10x Klenow Polymerase Buffer: 5 uL, dATP: 1uL, Exo (-) Klenow enzyme: 3 µl, NF H<sub>2</sub>O: 11 µl; 37°C, 30 min) followed by AMPure bead purification. Adapters were ligated to the paired ends (5x T4 DNA Ligase Buffer: 10 uL, T4 DNA Ligase: 1.5 uL, undiluted Adaptor Oligo Mix: 10 uL, nuclease free H<sub>2</sub>O: 15.5 uL; 20°C, 15 min) followed by AMPure bead purification and PCR amplification was performed (98°C: 2 min, 10 cycles at 98°C: 30 sec; 65°C: 30 sec; 72°C: 1 min; 72°C: 10 min) using SS primers (#G9611A) and the Herculase II Fusion DNA polymerase kit (#600679, Agilent). The DNA samples underwent QC to ensure adequate yield (>500 ng) of fragments 225 to 275 bp after PCR and AMPure bead purification.

Hybridization (SS Human All Exon V6, Agilent) was performed on individual samples (500ng DNA: 3.4 uL, SureSelect Block: 5.6 uL) which were then denatured at 95°C prior to

mixing with capture baits (hyb buffer: 13 uL, baits: 5 uL, RNase Block: 2 uL; 65°C, 24hrs). Hybridization products were then captured by incubation with streptavidin T1 beads (Dynabeads MyOne Streptavidin T1, Thermo Fisher, Waltham, MA, USA) in SS binding buffer (room temp, 30 min) followed by separation in a magnetic rack. Beads were washed (SS wash 2, 200 uL, 65°C, 10 min) and resuspended in H<sub>2</sub>O followed by amplification with indexing primers (Illumina, San Diego, CA, USA) generating unique bar codes for each sample (H<sub>2</sub>O: 18.5 uL, 5X Herculase II reaction buffer: 10 uL, 100 mM dNTP: 0.5 uL, Herculase polymerase: 1uL, indexing post-capture PCR primer: SSXT Index Reverse primers: 5 uL, DNA: 14 uL; 98°C: 2 min; 11 cycles 98°C: 30 sec; 57°C: 30 sec; 72°C: 1 min). The DNA library was recovered using AMPure beads. Sequencing was performed using the NextSeq 500 (Illumina, San Diego, CA, USA) high output flow cell kit (2 x 76 paired end, 150 cycles) with samples concentrated (660 g/mol X bp fragment size x 1X10<sup>6</sup>), pooled and titrated to 1.7 pM per sample to achieve an average base call target depth of 63x to 102x.

#### *Sequencing data processing and variant detection*

Bioinformatics analysis was performed using a custom protocol developed for tumor and paired normal analysis. First, base call (BCL) files were converted to FASTQ files using beltofastq (Illumina, San Diego, CA, USA). Per lane FASTQ files were merged into FASTQ files for each read pair (R1 & R2), as per manufacturer's recommendation. Each set of read pair FASTQs were aligned to the human reference genome (GRCh37.p13, hg19; GCF\_000001405.25) using BWA MEM and encoded into a BAM (binary sequence alignment) format using Samtools.<sup>5, 6</sup> RG (read group) tags for each sample were added at the time of sequence alignment. The raw BAM files were sorted, indexed and PCR duplicates marked using

Sambamba.<sup>7</sup> Pre-variant calling processing included concurrent local realignment around regions of known indels (COSMIC v80, dbSNPv138 and Mills gold-standard indel sets) for both tumor and normal aligned reads using GATK.<sup>8-10</sup> Subsequently, realigned BAMs were subjected to BQSR (Base Quality Score Recalibration) using GATK. Subsequently, variant calling was performed on the recalibrated BAMs using Varscan2 for SNV and short Indel detection and Scalpel for larger Indel detection.<sup>11, 12</sup> Briefly for Varscan2, recalibrated BAM files for both tumor and normal were used to generate a paired tumor-normal sequence mpileup, which was used for calling variants using Varscan2 in somatic mode. Potential false positives were marked in the VCF files using Varscan2's ffilter based on specific parameters. Variants marked as somatic and high confidence by the variant caller were prioritized. For large indel detection, Scalpel was used in somatic (paired tumor-normal) mode. Variants were represented using VCF format v4.2 (<https://samtools.github.io/hts-specs/VCFv4.2.pdf>). Variant calls from both callers were integrated, normalized and annotated using custom python modules with dependencies on ANNOVAR and HGVS python package.<sup>13, 14</sup> For FASTQ and BAM files, quality control (QC) metrics were generated by FastQC (<http://www.bioinformatics.babraham.ac.uk/projects/fastqc/>) and QualiMap, respectively.<sup>15</sup> For variant calling, sequence reads with minimum base quality score (Phred score) of 30 and minimum mapping quality score of 20 were used. Integrative Genomics Viewer (IGV, Broad Institute) was used for manual review of sequence pileups and detected variants.<sup>16</sup> Genomic data was visualized and reviewed using custom developed javascript plugin, jsComut (<https://github.com/pearcetm/jscomut>).

#### *Gene and variant prioritization*

Variants and genes were prioritized following the 2017 AMP/ASCO/CAP joint consensus guidelines for interpretation of sequence variants in cancer.<sup>17</sup> Briefly, variants that were present at a minor allele frequency greater than or equal to 1% in population databases (1000genomes, ExAC-nonTCGA and Exome server variant) were filtered out as benign/likely benign.<sup>18-20</sup> Subsequently, non-coding variants in deep intronic, intergenic and untranslated regions, and missense variants with benign/tolerated in silico predictions (SIFT and PolyPhen2) were also filtered out.<sup>21, 22</sup> Truncating variants that introduced premature stop codon (frameshift deletions and insertions, stop gain and splice site) in genes where loss of function is associated with oncogenesis, were prioritized as tier I/II and included for analysis. Similarly, missense and inframe indels in genes where gain of function is implicated in oncogenesis were prioritized as Tier I/II variants based on incidence in public somatic mutation databases (COSMIC v80 and TCGA), review of gene specific published functional studies, and damaging/deleterious in silico predictions.<sup>17, 23</sup> Germline mutation database (ClinVar) was also reviewed for prioritization of a subset of variants.<sup>24</sup> Unless supporting data for pathogenicity was available from published literature or public databases, Tier III variants (variants of uncertain clinical significance) were not prioritized.<sup>17</sup>

#### *Copy number variation analysis*

Copy number analysis was performed using Nexus Biodiscovery software (version 8.1, El Segundo, CA) designed to take into consideration the significant mosaicism, hyperploidy and normal cell heterogeneity that is present in cancer samples even after microdissection to enrich for tumor cells. Match paired next-generation sequencing analysis required 2 BAM files comprising the tumor and normal sequence for each specimen which were combined into one

result via subtraction of the  $\log_2$  ratios revealing copy number changes specific to the tumor sample. The GISTIC algorithm was used to identify aggregate regions with a statistically high frequency of copy number aberrations (gains and losses) from the global data set.<sup>25</sup> This method applies FDR (false discovery rate) correction for multiple testing and computes the Q-bound values (Q-Bound cutoff = 0.05, G-Score cut-off = 1.0). Individual gene queries employed the STAC (Significance testing for Aberrant Copy Number) algorithm using a minimum of 1000 reference reads per segment and the Nexus FASST2 (Fast Adaptive States Segmentation Technique) Segmentation algorithm with significance value =  $1 \times 10^{-6}$ .<sup>26</sup>

In addition, CNVKit (0.8.6.dev) was used as an alternate method to assess copy number changes from whole exome sequencing.<sup>27</sup> Briefly, a pool of normal reference was created using the aligned sequences from the paired normal samples. Subsequently, target and anti-target regions were created using the SureSelect exome v6 BED file. Next, the binned coverage for each of the loci in the target and the anti-target regions were computed. The binned coverage from the pool of normal reference was then used to normalize each tumor sample and correct biases (e.g. GC bias). Finally, copy number ratios were calculated and segmented using circular binary segmentation. Copy number changes were assessed manually using scatter plot visualization provided by CNVKit and compared to the calls made by the Nexus Biodiscovery software.

### *Immunohistochemistry*

TMA slides were cut at 4-um and deparaffinized with serial xylene treatments and subjected to antigen retrieval using heated citrate solution (pH 9.0) at 100°C for 10 minutes. Immunolabeling for Ki-67 (mouse monoclonal, prediluted, Ventana Medical Systems, Tucson,



AZ, USA), synaptophysin (rabbit polyclonal, prediluted, Cell Marque, Rocklin, CA, USA), chromogranin A (mouse monoclonal, prediluted, Ventana Medical Systems, Tucson, AZ, USA), DAXX (HPA008736 rabbit polyclonal, dilution 1:50, Sigma Aldrich, St Louis, MO, USA) and ATRX (HPA001906 rabbit polyclonal, dilution 1:100, Sigma Aldrich, St Louis, MO, USA), H3K36me3 (AB9050 rabbit polyclonal, dilution 1:1000, Abcam, Eugene, OR, USA), and ARID1A (AB182560 rabbit monoclonal, dilution 1:1000, Abcam, Eugene, OR, USA) were performed on the automated Ventana Benchmark XT system using the biotin-free Ventana OptiView DAB IHC Detection Kit (Ventana Medical Systems, Tucson, AZ, USA).

Assessment of DAXX, ATRX, H3K36me3 and ARID1A was done blinded to any patient data including outcome. Preserved or “positive” expression was defined as nuclear staining within tumor cells; using stromal cells as a positive internal control. Loss or “negative” staining was scored in cases where the tumor lacked nuclear immunolabeling, but preserved expression within stromal cells was still identified. Intratumoral heterogeneity or heterogeneous staining was defined as the clear presence of two distinct populations of tumor cells demonstrating preserved and loss of nuclear staining. For cases with heterogeneous staining, each component (positive or preserved and negative or loss of nuclear staining) should comprise at least 10% of the neoplastic tissue.<sup>1</sup> For subsequent statistical analysis, these cases were scored as loss or negative staining.

#### *Fluorescence in situ hybridization*

Telomere-specific FISH was performed as previously described using an Alexa-488 telomeric-C PNA probe.<sup>1</sup> In brief, 4-um TMA sections were incubated for 30 min at 55°C, washed three times for 5 min in xylene, rinsed in successive 100%, 95%, and 70% ethanol baths,

and washed in double-distilled H<sub>2</sub>O and 1% Tween before being placed in antigen unmasking solution in a boiling steamer for 30 min. Next, slides were rinsed in double-distilled H<sub>2</sub>O and dehydrated in successive ethanol washes of 70%, 95%, and 100%. Slides were incubated at 72°C for 10 min with an Alexa-488 telomeric-C PNA probe and hybridized overnight in a dark humidity chamber. Slides were washed with PNA wash buffer and PBST and incubated for 10 min in DAPI solution. After washing in double-distilled H<sub>2</sub>O, slides were mounted with prolong anti-fade mounting medium. Images were taken on a Leica fluorescent light microscope.<sup>28</sup>

Scoring for ALT was performed by assessing at least 250 nuclei from all 3 tissue cores for each case (at least 750 tumor nuclei). Using previously described criteria, ALT-positive cases were defined by the presence of large, ultrabright intranuclear foci consistent with telomere FISH signals in at least 1% of tumor nuclei and the total signal intensity for individual foci >10 fold than telomere signals from stromal cells. Of note, areas of necrosis were excluded from evaluation. Among ALT-negative PanNETs, no large, ultrabright, intranuclear signals were found in over 750 tumor nuclei that were screened.

Dual color fluorescence in situ hybridization was performed for *CDKN2A* within a Clinical Laboratory Improvement Amendments (CLIA)-accredited and College of American Pathologist (CAP)-approved laboratory as previously reported.<sup>29</sup> *CDKN2A* was assessed using a Spectrum-Orange labeled, locus-specific probe (Abbott Molecular, Des Plaines, IL, USA) with a Spectrum Green-labeled chromosome 9 centromeric (CEP9) probe. Scoring of *CDKN2A* FISH was performed on only individual and well-delineated cells; overlapping cells were excluded from the analysis. At least 60 cells were scored for each case and controls. Each tumor was assessed by the average and the maximum numbers of copies of p16 gene per cell and the average ratio of p16 gene to chromosome 9 copy numbers (CEP9). Deletion was defined if both

*CDKN2A* signals were lost in at least 20% of nuclei and showed at least one signal for the CEP9 probe.

### *Statistical analysis*

Chi-squared analysis or Fisher exact tests were used to compare categorical data, and analysis of variance was used to compare continuous variables. Survival curves were constructed using the Kaplan-Meier method and differences between groups were evaluated by the log-rank test. Disease-free survival (DFS) was calculated from the date of surgery to the date of first distant metastasis/recurrence after surgery or to the date of last follow-up (in patients without distant metastasis/recurrence) for cases without synchronous distant metastasis. Disease-specific survival (DSS) was calculated from the date of surgery to the date of death due to disease or date of last follow-up (if death did not occur). The prognostic significance of clinical and pathologic characteristics was determined using univariate Cox regression analysis. Multivariate analyses of significant risk factors by univariate analysis were performed using Cox proportional hazard regression to identify independent risk factors for both DFS and DSS. All statistical analyses were performed using the SPSS Statistical software, version 24 (IBM, Armonk, NY) and statistical significance was defined as a p value of  $< 0.05$ .

## Supplementary Data

### *Distant metastatic PanNET whole-exome sequencing cohort*

The whole-exome sequencing cohort consisted of 20 distant metastases from 20 patients with a solitary, non-syndromic PanNET. At initial presentation, patients ranged in age from 42 to 80 years (mean, 55.1 years) and included 11 females and 9 males. The patients' corresponding primary tumors were treated by either pancreaticoduodenectomy (n = 10) or distal pancreatectomy (n = 10) and pathologically confirmed to be of pancreatic origin. The primary PanNETs were distributed within the pancreas as follows: 10 in the head, 7 in the tail and 3 in the body; and ranged in size from 2.5 to 18 cm (mean, 6.2 cm). None of the PanNETs were biochemically functional.

The metastatic PanNETs consisted of 9 synchronous and 11 metachronous distant metastases, which were surgically resected from the liver (n = 19) or remnant pancreas (n = 1). Among the metachronous distant metastases, the time interval between pancreaticoduodenectomy or distal pancreatectomy and metastasectomy ranged between 1.7 to 7.8 years (mean, 4.5 years). Prior to metastasectomy, 6 of 20 (30%) patients received chemotherapy (n = 5) and/or underwent transarterial chemoembolization (TACE) to the liver (n = 2, MetaPanNET-7 and -17). All 6 patients presented with metachronous metastases. Among 5 patients that received chemotherapy, 3 patients received octreotide (MetaPanNET-10, -17 and -19) and 1 patient received everolimus (MetaPanNET-19). MetaPanNET-5 received multiple regimens of chemotherapy that included cisplatin and etoposide, carboplatin and etoposide, and irinotecan hydrochloride. Although neoadjuvant chemotherapy was documented for MetaPanNET-13, the exact regimen the patient received is unknown. While all metastatic PanNETs were morphologically well-differentiated, on the basis of mitotic rate and Ki-67

proliferation index, the tumors were classified into the following WHO grades: 1 (5%) grade 1 (G1), 13 (65%) grade 2 (G2), and 6 (30%) grade 3 (G3). Telomere-specific FISH identified ALT in 12 (60%) metastatic PanNETs and loss of nuclear expression for DAXX, ATRX or both proteins was seen in 4 (20%), 4 (20%), and 3 (15%) cases, respectively. One (5%) ALT-positive PanNET had preserved expression for DAXX/ATRX.

#### *Primary PanNET study cohort*

The study cohort consisted of 347 patients with a solitary PanNET treated by enucleation (n = 14), central pancreatectomy (n = 15), pancreaticoduodenectomy (n = 131) or distal pancreatectomy (n = 187) to include resection of identifiable metastases with curative intent. None of the patients received neoadjuvant chemotherapy, radiation or chemoembolization prior to surgical intervention. Patients ranged in age from 26 to 85 years (mean, 59 years) with a slight predominance in male gender (181 of 347, 52%). Thirty-six of 347 (10%) patients had a functional PanNET and included: 21 insulinomas, 8 gastrinomas, 5 glucagonomas, 1 somatostatinoma, 1 VIPoma and 1 ACTH-producing PanNET. The tumors were predominantly located within the pancreatic body and tail (n = 216, 62%) and ranged in size from 0.6 to 18 cm (mean, 3.4 cm). All PanNETs were morphologically well-differentiated, and, on the basis of mitotic rate and Ki-67 proliferation index, these tumors were classified into the following WHO grades: 199 (57%) grade 1 (G1), 140 (40%) grade 2 (G2), and 8 (3%) grade 3 (G3). Lymphovascular and perineural invasion were identified in 153 (44%) and 91 (26%) tumors, respectively. Using the AJCC prognostic staging system (seventh edition), the PanNETs were classified into the following pathologic tumor (pT) stages: 121 (35%) pT1, 106 (30%) pT2, and 120 (35%) pT3. Regional lymph nodes were submitted for histologic evaluation in 294 (85%)

cases with involvement of 110 (of 294, 37%) cases. At the time of surgery, 54 (16%) patients were found to have synchronous distant metastases that were resected. Of the remaining 292 patients, metachronous distant metastases were identified in 45 (of 292, 15%) cases. The DFS rates for these 292 patients were 91% at 3 years and 83% at 5 years. For all 347 patients, the DSS rates were 90% at 5 years and 76% at 10 years.

Immunohistochemistry for DAXX and ATRX and telomere-specific FISH were performed for all 347 PanNETs. Loss of nuclear expression for DAXX, ATRX, or both was identified in 37 (11%), 29 (8%), and 14 (4%) PanNETs, respectively. Of note, among the DAXX/ATRX-negative cases, heterogeneous loss of expression was seen in 1 DAXX-negative and 3 ATRX-negative PanNETs.<sup>1</sup> For these cases, the number of neoplastic nuclei lacking staining for DAXX/ATRX ranged between 65% to 80%. In addition, 94 (27%) PanNETs demonstrated large, ultrabright intranuclear foci consistent with ALT. The presence of ALT correlated with DAXX/ATRX loss ( $p < 0.001$ ), but 14 (4%) ALT-positive PanNETs had preserved expression for DAXX/ATRX. Similar to DAXX and ATRX, heterogeneous loss of expression was seen in 1 of 28 H3K36me3-negative PanNETs with lack of staining in 80% of the neoplastic nuclei, while all 10 ARID1A-negative PanNETs exhibited complete loss of nuclear expression for ARID1A.

Patients with PanNETs exhibiting loss of DAXX/ATRX, H3K36me3, or deletion in *CDKN2A* were associated with shorter DFS; while, patients with PanNETs showing loss of DAXX/ATRX, H3K36me3, ARID1A or deletion in *CDKN2A* were associated with poor DSS (Supplementary Figure 3). Disease-free survival (DFS) rates for patients with DAXX/ATRX-negative (loss of DAXX/ATRX) PanNETs were 60% at 3 years and 40% at 5 years ( $p < 0.001$ ,  $X^2 = 96.5$ ), H3K36me3-negative PanNETs were 86% at 3 years and 11% at 5 years ( $p < 0.001$ ,

$X^2 = 28.3$ ), ARID1A-negative PanNETs were 80% at 3 years and 60% at 5 years ( $p = 0.221$ ,  $X^2 = 1.50$ ), and *CDKN2A*-negative PanNETs were 53% at 3 years and 38% at 5 years ( $p < 0.001$ ,  $X^2 = 50.2$ ). In comparison, DSS rates for patients with DAXX/ATRX-negative PanNETs were 78% at 5 years and 48% at 10 years ( $p < 0.001$ ,  $X^2 = 21.5$ ), H3K36me3-negative PanNETs were 71% at 5 years and 34% at 10 years ( $p < 0.001$ ,  $X^2 = 13.9$ ), ARID1A-negative PanNETs were 80% at 5 years and 27% at 10 years ( $p < 0.001$ ,  $X^2 = 13.6$ ), and *CDKN2A*-negative PanNETs were 69% at 5 years and 35% at 10 years ( $p < 0.001$ ,  $X^2 = 18.8$ ).

Results of Cox regression analysis for DFS and DSS in relationship to various clinicopathologic features is presented in Table 1. By univariate Cox regression analysis, shorter DFS and poor DSS were associated with age ( $p = 0.008$  and  $p = 0.038$ , respectively), tumor size  $> 2.0$  cm ( $p < 0.001$  and  $p = 0.001$ ), G2-to-G3 WHO grade ( $p < 0.001$  and  $p < 0.001$ , respectively), lymphovascular invasion ( $p < 0.001$  and  $p < 0.001$ ), perineural invasion ( $p < 0.001$  and  $p < 0.001$ ), advanced tumor stage ( $p < 0.001$  and  $p < 0.001$ ) and regional lymph node (pN) metastasis ( $p < 0.001$  and  $p < 0.001$ ). A separate univariate analysis was performed for DAXX/ATRX and H3K36me3/ARID1A/*CDKN2A* status, independently. Loss of DAXX/ATRX and loss/deletion of H3K36me3/ARID1A/*CDKN2A* were associated with shorter DFS (HR = 12.08 [95% CI, 6.42 – 22.75],  $p < 0.001$ ; HR = 9.07 [95% CI, 4.99 – 16.49],  $p < 0.001$ , respectively) and poor DSS (HR = 3.67 [95% CI, 2.04 – 6.61],  $p < 0.001$ ; HR = 6.35 [95% CI, 3.52 – 11.48],  $p < 0.001$ , respectively). Multivariate analysis was used to determine the prognostic significance of H3K36me3/ARID1A/*CDKN2A* status for DFS and DSS and included tumor size  $> 2.0$  cm, WHO grade, regional lymph node metastasis and DAXX/ATRX loss. Independent prognostic factors for shorter DFS included tumor size  $> 2.0$  cm (HR = 17.08 [95% CI, 2.31 – 126.40],  $p = 0.005$ ), regional lymph node metastasis (HR = 2.03 [95% CI, 1.05 –

3.90],  $p = 0.034$ ), DAXX/ATRX loss (HR = 4.64 [95% CI, 2.39 – 9.04],  $p < 0.001$ ) and H3K36me3/ARID1A/CDKN2A loss/deletion (HR = 3.63 [95% CI, 1.93 – 6.81],  $p < 0.001$ ). In comparison, independent prognostic factors for poor DSS included tumor size  $> 2.0$  cm (HR = 9.47 [95% CI, 1.29 – 69.56],  $p = 0.027$ ), G2-to-G3 WHO grade (HR = 2.29 [95% CI, 1.09 – 4.78],  $p = 0.028$ ), regional lymph node metastasis (HR = 2.30 [95% CI, 1.14 – 4.65],  $p = 0.020$ ) and H3K36me3/ARID1A/CDKN2A loss/deletion (HR = 3.07 [95% CI, 1.65 – 5.68],  $p < 0.001$ ). Consistent with our prior study, DAXX/ATRX loss was not an independent prognostic factor for DSS.<sup>1</sup>

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### Supplementary Figure Legends

Supplementary Figure 1. Key genomic alterations identified in 20 metastatic pancreatic neuroendocrine tumors (PanNETs). (A) Each metastatic PanNET was classified based on World Health Organization (WHO) grade, timing of metastasis (synchronous versus metachronous with respect to the patient's primary PanNET), and ATRX and DAXX immunohistochemistry, and telomere-specific fluorescence *in situ* hybridization for alternative lengthening of telomeres (ALT). These findings were correlated with recurrent genomic alterations identified by whole-exome sequencing and compared to those previously published by Scarpa et al.<sup>30</sup> Somatic mutations and copy number variation are colored according to functional class. Copy number variation analysis was performed using the Nexus Biosdiscovery software (version 8.1, El Segundo, CA) and CNVKit (0.8.6.dev) comparing matched pairs of metastatic PanNETs and normal controls. (B) Recurrent copy number loss was identified within the genomic locus that includes *CDKN2A*. An example of a metastatic PanNET (MetaPanNET-3) with copy number loss at the 9p21 locus (gray dots) and a deep deletion present in *CDKN2A* (red dots).

Supplementary Figure 2. Representative examples of pancreatic neuroendocrine tumors (PanNETs) evaluated for H3K36me3 and ARID1A by immunohistochemistry and *CDKN2A* (orange) by dual-color fluorescence *in situ* hybridization (chromosome 9, green). (A) PanNET with preserved nuclear expression for both H3K36me3 (B) and ARID1A (C), and homozygous deletion of *CDKN2A* (D, loss of both orange signals, but retention of at least one green signal; white arrow, highlights a *CDKN2A* wild type stromal fibroblast). (E) PanNET with H3K36me3 loss (F), but preserved expression for ARID1A (G) and wild type *CDKN2A* (H). (I) PanNET with ARID1A loss (K), but preserved expression for H3K36me3 (J) and wild type *CDKN2A* (L).

Supplementary Figure 3. Kaplan-Meier curves comparing the cumulative probabilities of disease-free survival (DFS) and disease-specific survival (DSS) after surgical resection among 282 patients (without synchronous distant metastases) and 347 patients with PanNETs, respectively, for DAXX/ATRX, H3K36me3, ARID1A and *CDKN2A* status. Patients with PanNETs harboring loss or deletion of DAXX/ATRX, H3K36me3 or *CDKN2A* were associated with reduced time of DFS (A, B and D); while, loss or deletion of DAXX/ATRX, H3K36me3, ARID1A or *CDKN2A* was associated with reduced time of DSS (E, F, G and H), as compared to patients with wild type PanNETs.

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Variant	Specimen ID	Gene	Variant Description
3:42264742:C:A	MetaPanNET-10	TRAK1	TRAK1:NM_001042646:exon16:c.C2375A:p.S792Y
7:5607617:G:T	MetaPanNET-5	ZNF713	ZNF713:NM_182633:exon7:c.G1250T:p.R417M
11:64572033:G:A	MetaPanNET-2	MEN1	MEN1:NM_000244:exon10:c.C1621T:p.Q541A(x3bMEN1:NM_130799:exon10:c.C1606T:p.Q536A(x3bMEN1:NM_130800:exon10:c.C1621T:p.Q541A(x3bMEN1:NM_130801:e
7:112128997:A:G	MetaPanNET-11	LSMEM1	LSMEM1:NM_001134468:exon4:c.A289G:p.R97G(x3bLSMEM1:NM_182597:exon4:c.A289G:p.R97G
1:247263695:T:C	MetaPanNET-10	SNF669	SNF669:NM_001142572:exon4:c.A1118G:p.Q373R(x3bSNF669:NM_024804:exon4:c.A1376G:p.Q459R
1:36821030:C:T	MetaPanNET-7	STK40	STK40:NM_001128254:exon5:c.G362A:p.R121H(x3bSTK40:NM_001282547:exon5:c.G347A:p.R116H(x3bSTK40:NM_032017:exon6:c.G347A:p.R116H
12:57535234:C:T	MetaPanNET-14	LRP1	LRP1:NM_002332:exon3:c.C2687T:p.R90C
12:49165118:T:C	MetaPanNET-7	ADCV6	ADCV6:NM_015270:exon18:c.A3026G:p.N1009S(x3bADCV6:NM_020983:exon18:c.A2867G:p.N956S
2:207509263:C:G	MetaPanNET-6	LOC200726	LOC200726:NM_001102659:exon2:c.C303G:p.I101M
11:82892936:G:A	MetaPanNET-5	PCF11	PCF11:NM_015885:exon13:c.G4208A:p.R140Q
1:171755039:G:A	MetaPanNET-2	METTL13	METTL13:NM_001007239:exon3:c.G466A:p.E156K(x3bMETTL13:NM_014955:exon3:c.G676A:p.E226K(x3bMETTL13:NM_015935:exon3:c.G934A:p.E312K
13:24895827:G:A	MetaPanNET-4	CIQTNF9	CIQTNF9:NM_001301138:exon4:c.G923A:p.G308E(x3bCIQTNF9:NM_178540:exon4:c.G923A:p.G308E(x3bCIQTNF9:NM_001301137:exon5:c.G923A:p.G308E
7:91793825:G:A	MetaPanNET-17	LRD01	LRD01:NM_001161528:exon2:c.G692T:p.S231F
3:108072305:T:T	MetaPanNET-20	HHLA2	HHLA2:NM_001282556:exon4:c.97delC:p.P33fs(x3bHHLA2:NM_001282557:exon4:c.97delC:p.P33fs(x3bHHLA2:NM_007072:exon4:c.97delC:p.P33fs(x3bHHLA2:NM_0012825
17:17164015:T:C	MetaPanNET-11	CLDN7	CLDN7:NM_0011307:exon3:c.A419G:p.Y140C(x3bCLDN7:NM_001185022:exon4:c.A419G:p.Y140C
3:195508956:C:G	MetaPanNET-12	MUC4	MUC4:NM_018406:exon2:c.G9495C:p.Q136H
2:22570782:G:A	MetaPanNET-16	DOCK10	DOCK10:NM_001290263:exon6:c.C592T:p.R198W(x3bDOCK10:NM_0014689:exon6:c.C610T:p.R204W
2:102029529:A:G	MetaPanNET-4	RFX8	RFX8:NM_001145664:exon8:c.T566C:p.M189T
14:105417337:T:C	MetaPanNET-11	AHNAK2	AHNAK2:NM_138420:exon7:c.A4451G:p.K1484R
18:48190800:A:T	MetaPanNET-4	MAPK4	MAPK4:NM_001292040:exon2:c.A472T:p.S158C(x3bMAPK4:NM_002747:exon2:c.A472T:p.S158C
1:144621504:T:G	MetaPanNET-5	NBPFF(x3bNBPFF9	UNKNOWN
1:89448812:T:C	MetaPanNET-6	RBMX11	RBMX11:NM_019610:exon2:c.A698C:p.D233A(x3bRBMX11:NM_001162536:exon3:c.A698C:p.D233A
2:68270152:C:T	MetaPanNET-2	C15D	C15D:NM_006333:exon5:c.G295A:p.E99K(x3bC15D:NM_173177:exon5:c.G295A:p.E99K(x3bC15D:NM_001190263:exon6:c.G295A:p.E99K(x3bC15D:NM_001190265:exon6:c.G29
X:76888796:A:C	MetaPanNET-2	ATRX	ATRX:NM_138270:exon18:c.T4919G:p.V1640G(x3bATRX:NM_000489:exon19:c.T5033G:p.V1678G
3:51452107:C:A	MetaPanNET-9	VPRBP	VPRBP:NM_001171904:exon17:c.G3646T:p.G1216(x3bVPRBP:NM_014703:exon18:c.G3649T:p.G1217X
3:13368913:C:A	MetaPanNET-18	NUP210	NUP210:NM_024923:exon32:c.G4311T:p.K1437N
9:113233812:G:A	MetaPanNET-2	SVEP1	SVEP1:NM_153366:exon16:c.C2830T:p.Q944X
X:152954101:G:C:G	MetaPanNET-12	SLC6A8	SLC6A8:NM_001142805:exon1:c.73delC:p.P25fs(x3bSLC6A8:NM_005629:exon1:c.73delC:p.P25fs
3:195505925:G:A	MetaPanNET-5	MUC4	MUC4:NM_018406:exon2:c.C12526T:p.P4176S
4:17654521:T:A	MetaPanNET-16	FAM184B	FAM184B:NM_015688:exon11:c.A1213T:p.E708V
16:4745139:CAG:A:C	MetaPanNET-4	NUDT16L1	NUDT16L1:NM_032349:exon3:c.S96_598del:p.199_200del
2:233708795:C:T	MetaPanNET-17	GIGYF2	GIGYF2:NM_001103148:exon23:c.C2911T:p.0971X(x3bGIGYF2:NM_001103146:exon24:c.C2929T:p.0977Y(x3bGIGYF2:NM_001103147:exon26:c.C2992T:p.Q998X(x3bGIGYF
12:117672547:C:T	MetaPanNET-12	NOS1	NOS1:NM_001204213:exon20:c.G2050A:p.V684M(x3bNOS1:NM_001204214:exon20:c.G2050A:p.V684M(x3bNOS1:NM_000620:exon21:c.G3058A:p.V1020M(x3bNOS1:NM_
1:15694073:T:A	MetaPanNET-7	FHADI1	FHADI1:NM_052929:exon24:c.T3203A:p.V1068E
6:42236400:C:A	MetaPanNET-17	TRERF1	TRERF1:NM_001297573:exon5:c.G689T:p.G230V(x3bTRERF1:NM_001297574:exon5:c.G689T:p.G230V(x3bTRERF1:NM_033502:exon5:c.G689T:p.G230V
8:17406211:A:C	MetaPanNET-6	SLC7A2	SLC7A2:NM_001008539:exon4:c.A557C:p.E186A(x3bSLC7A2:NM_001164771:exon4:c.A677C:p.E226A(x3bSLC7A2:NM_003046:exon4:c.A677C:p.E226A
1:18809211:G:A	MetaPanNET-16	KLHD7A	KLHD7A:NM_152375:exon1:c.G1736A:p.R579Q
19:22464579:G:A	MetaPanNET-17	ZNF729	ZNF729:NM_001242680:exon4:c.G260A:p.R87H
6:52357123:G:A	MetaPanNET-14	EFHC1	EFHC1:NM_018100:exon11:c.G1907A:p.R636H(x3bEFHC1:NM_001172420:exon12:c.G1850A:p.R617H
20:1456828:C:A	MetaPanNET-5	SIRPB2	SIRPB2:NM_001122962:exon5:c.G1013T:p.S338I(x3bSIRPB2:NM_001134836:exon5:c.G719T:p.S240I
11:130319024:ACCTCATTT:A	MetaPanNET-17	ADAMTS15	ADAMTS15:NM_139055:exon1:c.157_163del:p.L53fs
9:12377490:C:A	MetaPanNET-5	C5	C5:NM_001735:exon16:c.G2046T:p.K682N
2:27361001:G:T	MetaPanNET-14	PRR30	PRR30:NM_178553:exon3:c.C197A:p.S66Y
12:40878420:T:C	MetaPanNET-2	MUC19	UNKNOWN
11:8667371:G:A	MetaPanNET-2	TRIM66	TRIM66:NM_014818:exon7:c.C586T:p.R196C
10:100154954:C:T	MetaPanNET-12	PYROXD2	PYROXD2:NM_032709:exon8:c.G784A:p.G262R
11:46908042:C:T	MetaPanNET-11	LRP4	LRP4:NM_002334:exon17:c.G2258A:p.R753H
2:179638340:A:T	MetaPanNET-7	TTN	TTN:NM_003319:exon31:c.T7305A:p.N2435K(x3bTTN:NM_133432:exon31:c.T7305A:p.N2435K(x3bTTN:NM_133437:exon31:c.T7305A:p.N2435K(x3bTTN:NM_001256850:ex
2:220439932:G:T	MetaPanNET-5	INHHA	INHHA:NM_002191:exon2:c.G785T:p.C262F
1:47904838:G:GC	MetaPanNET-2	FOXD2	FOXD2:NM_004474:exon1:c.1032dupC:p.G344fs
17:39036158:A:T	MetaPanNET-11	KRT20	KRT20:NM_019010:exon5:c.T825A:p.N275K
6:32489892:G:A	MetaPanNET-2	HLA-DRB5	HLA-DRB5:NM_002125:exon2:c.C160T:p.R54W
20:383388:C:T	MetaPanNET-1	MAVS	MAVS:NM_020746:exon3:c.C224T:p.A75V
6:117592126:G:A	MetaPanNET-2	VGLL2	VGLL2:NM_182645:exon3:c.G812A:p.G271D
13:108518557:T:G	MetaPanNET-15	FAM155A	FAM155A:NM_001080396:exon1:c.A388C:p.T130P
10:35426781:G:T	MetaPanNET-5	CREM	CREM:NM_183011:exon1:c.G187T:p.R65(x3bCREM:NM_183012:exon1:c.G187T:p.R65(x3bCREM:NM_181571:exon2:c.G187T:p.R65(x3bCREM:NM_183013:exon2:c.G187T:p.R65
6:31911738:G:A	MetaPanNET-14	C2	C2:NM_001178063:exon10:c.G1136A:p.R379Q(x3bC2:NM_001282457:exon10:c.G1040A:p.R347Q(x3bC2:NM_001145903:exon12:c.G1382A:p.R461Q(x3bC2:NM_000063:ex
11:1212792:C:T	MetaPanNET-1	MUC5AC	UNKNOWN
6:160211648:T:G	MetaPanNET-1	MRP18	MRP18:NM_0014161:exon1:c.T29G:p.L10W
1:183189964:C:T	MetaPanNET-15	LAMC2	LAMC2:NM_005562:exon5:c.C508T:p.R170X(x3bLAMC2:NM_018891:exon5:c.C508T:p.R170X
X:24329914:G:C	MetaPanNET-20	SUPT20HL2	SUPT20HL2:NM_001136233:exon1:c.C1519G:p.P507A
12:49722824:G:T	MetaPanNET-16	TROAP	TROAP:NM_005480:exon9:c.G1006T:p.G336C
14:105206086:G:A	MetaPanNET-5	ADSSL1	ADSSL1
15:32917403:C:G	MetaPanNET-14	ARHGAP11A	ARHGAP11A:NM_001286479:exon5:c.C107G:p.A36G(x3bARHGAP11A:NM_014783:exon5:c.C674G:p.A225G(x3bARHGAP11A:NM_199357:exon5:c.C674G:p.A225G(x3bARHG
1:20272217:C:T	MetaPanNET-9	KDMSB	KDMSB:NM_006518:exon12:c.G1557A:p.W519X
1:63119738:T:G	MetaPanNET-5	DOCK7	DOCK7:NM_001271999:exon3:c.G237C:p.L79F(x3bDOCK7:NM_001272000:exon3:c.G237C:p.L79F(x3bDOCK7:NM_001272001:exon3:c.G237C:p.L79F(x3bDOCK7:NM_001272
6:32489882:T:A	MetaPanNET-2	HLA-DRB5	HLA-DRB5:NM_002125:exon2:c.A170T:p.H57L
3:130873879:G:C	MetaPanNET-5	NKX11	CCDC178:NM_001105528:exon16:c.G1678A:p.E560K(x3bCCDC178:NM_198995:exon17:c.G1678A:p.E560K
18:30804879:C:T	MetaPanNET-5	CCDC178	CCDC178:NM_001105528:exon16:c.G1678A:p.E560K(x3bCCDC178:NM_198995:exon17:c.G1678A:p.E560K
3:184043280:C:A	MetaPanNET-3	EIF4G1	EIF4G1:NM_004953:exon13:c.C2389A:p.P797T(x3bEIF4G1:NM_198242:exon16:c.C428A:p.P828T(x3bEIF4G1:NM_198244:exon17:c.C2713A:p.P905T(x3bEIF4G1:NM_18291
4:5733859:C:T	MetaPanNET-4	SRP72	SRP72:NM_001267722:exon1:c.C58T:p.R20W(x3bSRP72:NM_006947:exon1:c.C58T:p.R20W
2:166618500:TTGTC:T	MetaPanNET-9	GALNT3	GALNT3:NM_004482:exon4:c.749_752del:p.R250fs
11:65810753:C:T	MetaPanNET-6	GAL3S3T3	GAL3S3T3:NM_033036:exon3:c.G521A:p.R174H
3:111312615:T:C	MetaPanNET-4	ZBED2	ZBED2:NM_024508:exon2:c.A434G:p.Q145R
6:87953192:G:A	MetaPanNET-1	ZNF292	ZNF292
14:53010244:C:T	MetaPanNET-17	TXND16	TXND16:NM_001160047:exon3:c.G32A:p.G11E(x3bTXND16:NM_0020784:exon3:c.G32A:p.G11E
11:64575139:A:C	MetaPanNET-11	MEN1	MEN1:NM_000244:exon10:c.T683G:p.L228R(x3bMEN1:NM_130799:exon10:c.T683G:p.L228R(x3bMEN1:NM_130800:exon10:c.T683G:p.L228R(x3bMEN1:NM_130801:exon10:c.T
3:195510614:T:C	MetaPanNET-10	MUC4	MUC4:NM_018406:exon2:c.A7837G:p.S2613G
5:179743775:C:T	MetaPanNET-14	GPPT2	GPPT2:NM_005110:exon12:c.G1141A:p.A381T
7:100551130:G:A	MetaPanNET-3	MUC3A	MUC3A:NM_005960:exon2:c.G1711A:p.G571S
3:195505886:C:G	MetaPanNET-2	MUC4	MUC4:NM_018406:exon2:c.G12565C:p.D4189H
18:52265084:T:C	MetaPanNET-11	DYNAP	DYNAP:NM_173629:exon3:c.T341C:p.V114A
19:20229964:C:A	MetaPanNET-16	ZNF90	ZNF90:NM_007138:exon4:c.C1601A:p.A534E
1:177899015:C:A	MetaPanNET-9	SEC16B	SEC16B:NM_033127:exon26:c.G3161T:p.R1054L
6:55406939:C:A	MetaPanNET-17	HMGCL11	HMGCL11
1:201180037:G:A	MetaPanNET-18	IGFN1	IGFN1:NM_001164586:exon12:c.G6016A:p.E2006K
11:103018514:G:C	MetaPanNET-17	DYNC2H1	DYNC2H1:NM_001080463:exon19:c.G2716C:p.D906H(x3bDYNC2H1:NM_001377:exon19:c.G2716C:p.D906H
5:14007532:G:A	MetaPanNET-17	HARS2	HARS2
7:99794868:A:G	MetaPanNET-13	STAG3	STAG3:NM_001282718:exon8:c.A857G:p.Y286C(x3bSTAG3:NM_001282716:exon10:c.A1031G:p.Y344C(x3bSTAG3:NM_001282717:exon10:c.A1031G:p.Y344C(x3bSTAG3:NM
19:9008269:C:T	MetaPanNET-7	MUC16	MUC16:NM_024690:exon41:c.G39283A:p.D1309S
3:48040176:T:A	MetaPanNET-14	MAP4	MAP4:NM_001134364:exon2:c.A175T:p.N59Y(x3bMAP4:NM_002375:exon2:c.A175T:p.N59Y(x3bMAP4:NM_030885:exon2:c.A175T:p.N59Y
1:84385413:C:T	MetaPanNET-7	TTL7	TTL7:NM_024688:exon13:c.G1469A:p.R490Q
1:93565066:G:T	MetaPanNET-17	CNN3	CNN3:NM_001286055:exon5:c.C371A:p.T124N(x3bCNN3:NM_001286056:exon6:c.C386A:p.T129N(x3bCNN3:NM_001839:exon6:c.C509A:p.T170N
3:142422729:C:T	MetaPanNET-8	PLS1	PLS1:NM_001145319:exon13:c.C1391T:p.A464V(x3bPLS1:NM_001172312:exon13:c.C1391T:p.A464V(x3bPLS1:NM_002670:exon13:c.C1391T:p.A464V
3:183824430:C:T	MetaPanNET-4	HTR3E	HTR3E:NM_001256614:exon7:c.C1298T:p.T433I(x3bHTR3E:NM_198314:exon7:c.C1220T:p.T407I(x3bHTR3E:NM_182589:exon8:c.C1265T:p.T422I(x3bHTR3E:NM_198313:ex
13:33332229:C:G	MetaPanNET-10	PDS5B	PDS5B:NM_015032:exon27:c.C3061G:p.L1021V
7:144095518:G:A	MetaPanNET-16	NOBOX	NOBOX:NM_001080413:exon9:c.C1631T:p.S544F
14:69791499:A:AGTGAAGAG	MetaPanNET-13	GALNT16	GALNT16:NM_001168368:exon3:c.A26_427insGTGAAGAG:p.T142fs(x3bGALNT16:NM_020692:exon3:c.A26_427insGTGAAGAG:p.T142fs
7:143929686:A:T	MetaPanNET-17	OR2A1(x3bOR2A42	OR2A2:NM_001001802:exon1:c.T251A:p.L84H(x3bOR2A1:NM_001005287:exon1:c.T251A:p.L84H
6:6451919:G:T	MetaPanNET-5	VCX3A	VCX3A:NM_016379:exon3:c.C428A:p.P143Q
16:2114357:C:T	MetaPanNET-4	TSC2	TSC2:NM_000548:exon15:c.C1528T:p.Q510X(x3bTSC2:NM_001077183:exon15:c.C1528T:p.Q510X(x3bTSC2:NM_00114382:exon15:c.C1528T:p.Q510X
6:69728393:T:A	MetaPanNET-4	ADGRB3	ADGRB3
16:50711373:C:A	MetaPanNET-17	SNX20	SNX20:NM_001144972:exon2:c.G65T:p.R22M(x3bSNX20:NM_153337:exon2:c.G65T:p.R22M(x3bSNX20:NM_182854:exon2:c.G65T:p.R22M
10:70644274:G:T	MetaPanNET-5	STOX1	STOX1:NM_001130161:exon3:c.G722T:p.C241F(x3bSTOX1:NM_152709:exon3:c.G722T:p.C241F
12:91449301:C:A	MetaPanNET-17	KERA	KERA:NM_007035:exon2:c.G758T:p.G253V
10:99258106:AGGCCG:C:A	MetaPanNET-2	MMS19	MMS19:NM_001289403:exon1:c.31_35del:p.A11fs(x3bMMS19:NM_022362:exon1:c.31_35del:p.A11fs(x3bMMS19:NM_001289405:exon2:c.31_35del:p.A11fs
3:195506482:G:T	MetaPanNET-5	KIZ	UNKNOWN
3:10183738:G:C:G	MetaPanNET-15	MUC4	MUC4:NM_018406:exon2:c.C11969A:p.T3990N
3:195506434:G:A	MetaPanNET-15	VHL	VHL:NM_000551:exon1:c.C208delG:p.E70fs(x3bVHL:NM_198156:exon1:c.C208delG:p.E70fs
6:168376881:T:G	MetaPanNET-1	MUC4	MUC4:NM_018406:exon2:c.C12017T:p.T4006I
2:43903409:A:G	MetaPanNET-2	HGC6.3	HGC6.3:NM_001129895:exon1:c.A452C:p.Q151P
5:15056034:C:T	MetaPanNET-10	LOC728819	LOC728819:NM_001101330:exon1:c.T53C:p.I18T
6:151671826:C:T	MetaPanNET-6	ANXA6	ANXA6:NM_001193544:exon13:c.G889A:p.G297S(x3BANXA6:NM_001155:exon14:c.G985A:p.G329S
1:68912508:G:A	MetaPanNET-16	AKAP12	AKAP12:NM_144497:exon2:c.C2006T:p.T669M(x3bAKAP12:NM_005100:exon4:c.C2300T:p.T767M
10:24874446:G:A	MetaPanNET-2	RPE65	RPE65:NM_000329:exon3:c.C130T:p.R44X
	MetaPanNET-5	ARHGAP21	ARHGAP21:NM_020824:exon26:c.A4722T:p.S1591L









19:45565422.C:T MetaPanNET-7 CLASRP CLASRP.NM\_001278439:exon10:c.C6887:p.R230X\3bCLASRP.NM\_007056:exon11:c.C8747:p.R292X  
1:248458876.T:C MetaPanNET-12 OR21T2 OR21T2.NM\_001004692:exon11:c.A5G;p.E2G  
10:95079758.GC:G MetaPanNET-20 MYOF MYOF.NM\_133337:exon48:c.5429delG;p.G1810fs\3bMYOF.NM\_013451:exon49:c.5468delG;p.G1823fs  
13:95839003.G:T MetaPanNET-10 ABCC4 ABCC4.NM\_001301830:exon10:c.C1272A;p.Y424X\3bABCC4.NM\_001105515:exon11:c.C1497A;p.Y499X\3bABCC4.NM\_001301829:exon11:c.C1497A;p.Y499X\3bABCC4.N  
17:40280352.G:A MetaPanNET-2 RAB5C RAB5C.NM\_004583:exon4:c.C368T;p.A123V\3bRAB5C.NM\_001252039:exon5:c.C4677;p.A156V\3bRAB5C.NM\_201434:exon5:c.C368T;p.A123V  
2:86434409.A:T MetaPanNET-16 MRPL35 MRPL35.NM\_016622:exon3:c.A3377;p.R113V\3bMRPL35.NM\_145644:exon3:c.A3377;p.R113V  
MetaPanNET-5 EVLP EVLP.NM\_001988:exon17:c.G2058T;p.Q686H  
3:197726165.A:G MetaPanNET-14 LMLN LMLN.NM\_001136049:exon11:c.A1184G;p.Q395R\3bLMLN.NM\_033029:exon11:c.A1184G;p.Q395R  
19:794697.C:G MetaPanNET-20 MAP2K7 MAP2K7.NM\_0219755:exon2:c.C182G;p.S61C\3bMAP2K7.NM\_145185:exon2:c.C182G;p.S61C\3bMAP2K7.NM\_001297555:exon3:c.C2309:p.S77C  
3:13467084.G:A MetaPanNET-14 EPFB1 EPFB1.NM\_000441:exon3:c.G755A;p.R252Q  
16:84346700.C:G MetaPanNET-6 WFDC1 WFDC1.NM\_001282466:exon2:c.G278C;p.R93P\3bWFDC1.NM\_001282467:exon2:c.G278C;p.R93P\3bWFDC1.NM\_021197:exon2:c.G278C;p.R93P  
9:13095165.A:G MetaPanNET-7 CIZ1 CIZ1.NM\_001257976:exon3:c.T32C;p.L11P\3bCIZ1.NM\_001131015:exon4:c.T335C;p.L112P\3bCIZ1.NM\_001131016:exon4:c.T335C;p.L112P\3bCIZ1.NM\_001131017:exon  
3:191888300.T:C MetaPanNET-12 FGF12 FGF12.NM\_021032:exon4:c.A560G;p.N187S\3bFGF12.NM\_004113:exon5:c.A374G;p.N125S  
12:40897325.T:C MetaPanNET-9 MUC19 MUC19  
20:35390932.T:A MetaPanNET-11 DSN1 DSN1.NM\_001145317:exon5:c.A201T;p.E67D\3bDSN1.NM\_001145318:exon5:c.A474T;p.E158D\3bDSN1.NM\_001145319:exon6:c.A522T;p.E174D\3bDSN1.NM\_00114531  
6:33288213.G:A MetaPanNET-4 DAXX DAXX.NM\_001254717:exon3:c.C970T;p.Q324X\3bDAXX.NM\_001141969:exon4:c.C1195T;p.Q399X\3bDAXX.NM\_001141970:exon4:c.C1231T;p.Q411X\3bDAXX.NM\_0013  
8:52320716.G:T MetaPanNET-5 PXDNL PXDNL.NM\_144651:exon17:c.C3468A;p.F1156L  
1:109860574.C:T MetaPanNET-17 SORT1 SORT1.NM\_001205228:exon16:c.G1631A;p.R544H\3bSORT1.NM\_002959:exon16:c.G2042A;p.R681H  
16:15501896.G:A MetaPanNET-11 MPV17L MPV17L.NM\_001128423:exon4:c.G518A;p.G173D  
11:797701.C:T MetaPanNET-15 PANO1 PANO1.NM\_001293167:exon11:c.C76T;p.L26F  
5:140503232.T:G MetaPanNET-18 PCDBH4 PCDBH4.NM\_0018938:exon11:c.T1652G;p.L551R  
13:25670797.C:G MetaPanNET-6 PABPC3 PABPC3.NM\_0030979:exon11:c.C461G;p.A154G  
6:154743710.C:T MetaPanNET-15 CNKSR3 CNKSR3.NM\_173515:exon9:c.G875A;p.R292H  
1:110740127.T:C:T MetaPanNET-14 SLC6A17 SLC6A17.NM\_001010898:exon11:c.1722delC;p.F574fs  
8:131149247.C:T MetaPanNET-6 ASAP1 ASAP1.NM\_018482:exon14:c.G1118A;p.C373Y\3bASAP1.NM\_001247996:exon15:c.G1097A;p.C366Y  
6:155450721.G:A MetaPanNET-5 TIAM2 TIAM2.NM\_0012454:exon3:c.G364A;p.E122K  
6:35773651.C:A MetaPanNET-2 LHFPL5 LHFPL5.NM\_182548:exon11:c.C204A;p.C68X  
2:10095207.G:A MetaPanNET-16 GRHL1 GRHL1.NM\_198182:exon2:c.G184A;p.G62S  
6:29911928.C:G MetaPanNET-12 HLA-A HLA-A.NM\_001242758:exon4:c.C649G;p.P217A\3bHLA-A.NM\_002116:exon4:c.C649G;p.P217A  
20:61050103.A:T MetaPanNET-17 GATAS GATAS.NM\_080473:exon2:c.T475A;p.F159I  
10:71684726.G:A MetaPanNET-4 COL13A1 COL13A1.NM\_008005:exon21:c.G1106A;p.R369H\3bCOL13A1.NM\_080800:exon21:c.G1106A;p.R369H\3bCOL13A1.NM\_080800:exon21:c.G1106A;p.R369H\3bCOL13A1.N  
1:247655327.G:T MetaPanNET-18 OR2W5 OR2W5.NM\_001004698:exon11:c.G898T;p.D300Y  
1:248525639.A:T MetaPanNET-6 OR2T4 OR2T4.NM\_001004696:exon11:c.A7577;p.L253F  
3:195510182.C:T MetaPanNET-7 MUC4 MUC4.NM\_018406:exon2:c.G8269A;p.D2757N  
12:11506264.C:G MetaPanNET-8 PRB1 PRB1.NM\_199353:exon4:c.G374C;p.G125A\3bPRB1.NM\_199354:exon4:c.G314C;p.G105A  
11:1212966.C:A MetaPanNET-1 MUC5AC MUC5AC  
7:104753293.C:T MetaPanNET-5 KMT2E KMT2E.NM\_018682:exon2:c.C5090T;p.S1697F\3bKMT2E.NM\_182931:exon27:c.C5090T;p.S1697F  
10:120828968.C:T MetaPanNET-2 EIF3A EIF3A.NM\_003750:exon6:c.G940A;p.E314K  
6:29911931.A:G MetaPanNET-12 HLA-A HLA-A.NM\_001242758:exon4:c.A652G;p.I218V\3bHLA-A.NM\_002116:exon4:c.A652G;p.I218V  
18:2771569.C:T MetaPanNET-11 SMCHD1 SMCHD1.NM\_015295:exon4:c.C5005T;p.R1669X  
17:8926124.C:T MetaPanNET-13 NTN1 NTN1.NM\_004822:exon2:c.C434T;p.T145I  
11:46456487.G:T MetaPanNET-18 AMBRA1 AMBRA1.NM\_001300731:exon12:c.C2553A;p.S851R\3bAMBRA1.NM\_001267783:exon13:c.C2376A;p.S792R\3bAMBRA1.NM\_017749:exon14:c.C2463A;p.S821R\3bAMBR  
1:205056819.G:A MetaPanNET-9 RBP85 RBP85.NM\_001193272:exon12:c.C1387T;p.P463S\3bRBP85.NM\_001193273:exon12:c.C1006T;p.P336S\3bRBP85.NM\_005057:exon12:c.C1387T;p.P463S  
16:28989327.T:C MetaPanNET-4 SPNS1 SPNS1.NM\_001142449:exon2:c.T340C;p.S114P\3bSPNS1.NM\_001142451:exon3:c.T406C;p.S136P\3bSPNS1.NM\_032038:exon3:c.T406C;p.S136P\3bSPNS1.NM\_00114244  
1:204511951.C:T MetaPanNET-16 MDM4 MDM4.NM\_001204171:exon8:c.C551T;p.S184F\3bMDM4.NM\_002939:exon8:c.C551T;p.S184F  
18:3253408.G:A MetaPanNET-5 MYL12A MYL12A.NM\_001303048:exon2:c.G163A;p.D55M\3bMYL12A.NM\_001303049:exon2:c.G181A;p.D61N\3bMYL12A.NM\_006471:exon2:c.G163A;p.D55M\3bMYL12A.NM\_00  
2:220107975.G:T MetaPanNET-1 GLB1L1 GLB1L1.NM\_001286427:exon2:c.C134A;p.P450\3bGLB1L1.NM\_001286423:exon3:c.C134A;p.P450\3bGLB1L1.NM\_024506:exon3:c.C134A;p.P450  
14:21560642.G:A MetaPanNET-5 ZNF219 ZNF219.NM\_001101672:exon3:c.C814T;p.P272S\3bZNF219.NM\_001102454:exon3:c.C814T;p.P272S\3bZNF219.NM\_016423:exon3:c.C814T;p.P272S  
3:174815077.T:A MetaPanNET-20 NALALD12 NALALD12.NM\_207015:exon2:c.T541A;p.F181I  
7:6889133.C:T MetaPanNET-10 ATRX ATRX.NM\_138270:exon17:c.G4763A;p.C1588Y\3bATRX.NM\_000489:exon18:c.G4877A;p.C1626Y  
3:195508548.C:G MetaPanNET-4 MUC4 MUC4.NM\_018406:exon2:c.G9903C;p.E3301D  
7:76918958.A:T MetaPanNET-11 ATRX ATRX.NM\_138270:exon11:c.3918delA;p.K1306fs\3bATRX.NM\_000489:exon12:c.4032delA;p.K1344fs  
16:2131647.C:G MetaPanNET-2 TSC2 TSC2.NM\_001077183:exon30:c.C3530G;p.S1177V\3bTSC2.NM\_000548:exon31:c.C3662G;p.S1221W\3bTSC2.NM\_00114382:exon31:c.C3662G;p.S1221W  
17:41477501.C:G MetaPanNET-1 ARL4D ARL4D.NM\_001661:exon2:c.C401G;p.A134G  
11:46903429.C:T MetaPanNET-17 LRP4 LRP4.NM\_002334:exon20:c.G2638A;p.A880T  
2:133540288.T:A MetaPanNET-2 NCKAP5 NCKAP5.NM\_207363:exon14:c.A4096T;p.S1366C  
21:45165993.G:A MetaPanNET-17 PDXK PDXK.NM\_003681:exon5:c.G365A;p.G122D  
3:5315559.C:A MetaPanNET-7 RFT1 RFT1.NM\_052859:exon4:c.G2877;p.W96L  
12:29494741.G:A MetaPanNET-16 ERGIC2 ERGIC2.NM\_016570:exon13:c.C997T;p.H333Y  
10:135020720.C:T MetaPanNET-9 KNDC1 KNDC1.NM\_152643:exon20:c.C3659T;p.T1220M  
1:15987738.G:T MetaPanNET-5 RSC1A1 RSC1A1.NM\_006511:exon11:c.G1375T;p.G459C  
12:56579985.A:G MetaPanNET-13 SMARCC2 SMARCC2.NM\_001130420:exon3:c.T271C;p.C91R\3bSMARCC2.NM\_003075:exon3:c.T271C;p.C91R\3bSMARCC2.NM\_139067:exon3:c.T271C;p.C91R  
13:43659911.T:A MetaPanNET-11 DNAI1 DNAI1.NM\_0013238:exon5:c.A379T;p.K127X  
8:196247.G:C MetaPanNET-13 ZNF596 ZNF596.NM\_001042415:exon6:c.G1400C;p.R467T\3bZNF596.NM\_001042416:exon6:c.G1400C;p.R467T\3bZNF596.NM\_001287254:exon6:c.G1400C;p.R467T\3bZNF596.N  
22:39909758.C:G MetaPanNET-11 MIEF1 MIEF1.NM\_001304564:exon6:c.C822G;p.I274M\3bMIEF1.NM\_019008:exon6:c.C822G;p.I274M  
7:4839014.G:A MetaPanNET-13 RADIL RADIL.NM\_018059:exon15:c.C3223T;p.L1075F  
19:10254467.T:C MetaPanNET-7 DNMT1 DNMT1.NM\_001379:exon28:c.A3043G;p.K015E\3bDNMT1.NM\_001130823:exon29:c.A3091G;p.K031E  
1:186008969.G:C MetaPanNET-11 HMCN1 HMCN1.NM\_031935:exon39:c.G6138C;p.L2046F  
3:47032902.G:A MetaPanNET-2 NBEAL2 NBEAL2.NM\_0015175:exon8:c.G649A;p.G217R  
16:30616673.G:A MetaPanNET-14 ZNF689 ZNF689.NM\_138447:exon3:c.C415T;p.R139X  
11:213159.C:A MetaPanNET-3 MUC5AC MUC5AC  
11:46786718.C:A MetaPanNET-5 CKAP5 CKAP5.NM\_001008938:exon28:c.G3500T;p.G1167V\3bCKAP5.NM\_014756:exon28:c.G3500T;p.G1167V  
4:95204305.G:A MetaPanNET-18 SMARCAD1 SMARCAD1.NM\_001254949:exon14:c.G1470A;p.M490\3bSMARCAD1.NM\_001128429:exon22:c.G2766A;p.M921\3bSMARCAD1.NM\_001128430:exon22:c.G2766A;p.M9  
19:56736055.T:C MetaPanNET-15 ZSCAN5A ZSCAN5A.NM\_024303:exon2:c.A361G;p.N121D  
4:79387478.G:C MetaPanNET-17 FRAS1 FRAS1.NM\_025074:exon50:c.G7146C;p.Q2382H  
12:40897323.C:T MetaPanNET-9 MUC19 MUC19  
15:43023149.C:T MetaPanNET-17 CDAN1 CDAN1.NM\_138477:exon13:c.G1981A;p.D661N  
20:20552231.C:A MetaPanNET-17 RALGAPA2 RALGAPA2.NM\_020343:exon23:c.G3027T;p.K1009N  
12:6601487.G:A MetaPanNET-15 MRPL51 MRPL51.NM\_016497:exon3:c.C3377;p.R113C  
2:172809497.A:G MetaPanNET-17 HAT1 HAT1.NM\_003642:exon4:c.A287G;p.D96G  
14:23548793.C:T MetaPanNET-6 ACIN1 ACIN1.NM\_001164815:exon5:c.G1805A;p.R602H\3bACIN1.NM\_001164814:exon6:c.G1925A;p.R642H\3bACIN1.NM\_014977:exon6:c.G1925A;p.R642H  
5:140563608.C:T MetaPanNET-5 PCDBH16 PCDBH16.NM\_020957:exon11:c.C1474T;p.P492S  
3:195506798.C:G MetaPanNET-4 MUC4 MUC4.NM\_018406:exon2:c.G11653C;p.D3885H  
16:31153157.C:T MetaPanNET-16 PRSS36 PRSS36.NM\_001258290:exon11:c.G1631A;p.W544X\3bPRSS36.NM\_001258291:exon11:c.G1646A;p.W549X\3bPRSS36.NM\_173502:exon11:c.G1646A;p.W549X  
3:18336898.C:T MetaPanNET-14 KHLH24 KHLH24.NM\_017644:exon3:c.C454T;p.R152C  
18:29054302.G:A MetaPanNET-5 DSG3 DSG3.NM\_001944:exon15:c.G2320A;p.G774R  
12:40884757.C:G MetaPanNET-12 MUC19 MUC19  
7:107638828.A:C MetaPanNET-18 LAMB1 LAMB1.NM\_002291:exon4:c.T323G;p.L108R  
6:7249073.C:T MetaPanNET-14 RREB1 RREB1.NM\_001003698:exon12:c.C4936T;p.Q1646X\3bRREB1.NM\_001003700:exon12:c.C4303T;p.Q1435X\3bRREB1.NM\_001168344:exon12:c.C4936T;p.Q1646X\3bRREB  
10:121652454.G:A MetaPanNET-11 SEC23IP SEC23IP.NM\_007190:exon11:c.G160A;p.G54R  
5:35591599.T:A MetaPanNET-17 HUWE1 HUWE1.NM\_00131407:exon5:c.A6965T;p.E2322V  
13:61985445.C:A MetaPanNET-17 PCDH20 PCDH20.NM\_002843:exon2:c.G2787T;p.Q929H  
14:23057888.C:A MetaPanNET-5 DAD1 DAD1.NM\_001344:exon11:c.G176T;p.G59V  
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MetaPanNET-5 VAMP7  
MetaPanNET-8 EDEM2  
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18:11689658:C:CG MetaPanNET-8 GNAL GNAL:NM\_182978:exon1:c.97dupG:p.P32fs  
 3:121351328:G:GGCTCAGGCTCAG MetaPanNET-7 HCL51 HCL51:NM\_001292041:exon11:c.979\_980insCTGACGCTCAGC:p.P327delinsPEPEPv3bHCL51:NM\_005335:exon12:c.1090\_1091insCTGAGCTGAGC:p.P364delinsPEPEP  
 3:47142949:C:A MetaPanNET-17 SETD2 SETD2:NM\_014159:exon8:c.G5014T:p.G1672X  
 3:112358744:C:G MetaPanNET-5 CCDC80 CCDC80:NM\_199511:exon2:c.G9C:p.W3Cv3bCCDC80:NM\_199512:exon2:c.G9C:p.W3C  
 19:45888874:C:A MetaPanNET-5 PPR1R3L PPR1R3L:NM\_001142502:exon11:c.G2194T:p.E732Xv3bPPR1R3L:NM\_006663:exon11:c.G2194T:p.E732X  
 19:9021161:C:T MetaPanNET-7 MUC16 MUC16:NM\_024690:exon19:c.G37162A:p.V12388I  
 9:37518180:T:C MetaPanNET-17 FBOY10 FBOY10:NM\_012166:exon9:c.A2456G:p.N819S  
 1:103352377:G:T MetaPanNET-7 COL11A1 COL11A1:NM\_080630:exon61:c.C4496A:p.P1499Hv3bCOL11A1:NM\_001190709:exon62:c.C4727A:p.P1576Hv3bCOL11A1:NM\_001854:exon63:c.C4844A:p.P1615Hv3bCOL  
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 19:55174472:T:C MetaPanNET-13 LILRB4 LILRB4:NM\_001278429:exon1:c.T110C:p.L37P  
 5:126676229:T:G MetaPanNET-11 MEGF10 MEGF10:NM\_001256545:exon4:c.T226G:p.Y76Dv3bMEGF10:NM\_032446:exon5:c.T226G:p.Y76D  
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 7:93516654:C:A MetaPanNET-10 TFPF2 TFPF2:NM\_001271003:exon4:c.G517T:p.D173Yv3bTFPF2:NM\_006528:exon4:c.G550T:p.D184Y  
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 8:145639801:G:T MetaPanNET-5 SLC39A4 SLC39A4:NM\_017767:exon5:c.C919A:p.L307Mv3bSLC39A4:NM\_130849:exon6:c.C994A:p.L332M  
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 15:23685913:G:C MetaPanNET-7 GOLGA6L2 GOLGA6L2:NM\_001304388:exon8:c.C1709G:p.A570G  
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 3:130427138:G:A MetaPanNET-4 PIK3R4 PIK3R4:NM\_014602:exon10:c.C2530T:p.R844W  
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 16:81242149:T:C MetaPanNET-17 PKD1L2 PKD1L2:NM\_01076780:exon4:c.A707G:p.N236S  
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13:73482676:C:T MetaPanNET-16 PIBF1 PIBF1:NM\_006346:exon12:c.C1496T:p.T499I

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13:21357994:G:C MetaPanNET-11 XPO4 XPO4:NM\_022459:exon23:c.G3323C:p.R1108T

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12:68647197:A:G MetaPanNET-15 IL22 IL22:NM\_020525:exon1:c.T32C:p.F115

10:93773506:A:G MetaPanNET-14 BTAF1 BTAF1:NM\_003972:exon31:c.A4394G:p.Y1465C

11:7110515:C:T MetaPanNET-14 RBMXL2 RBMXL2:NM\_014469:exon1:c.C164T:p.T55I

19:53572327:C:T MetaPanNET-12 ZNF160 ZNF160:NM\_033288:exon6:c.G1460A:p.S487N;x3bZNF160:NM\_001102603:exon7:c.G1460A:p.S487N;x3bZNF160:NM\_198893:exon7:c.G1460A:p.S487N

16:22086951:G:T MetaPanNET-17 C16orf52 C16orf52:NM\_001164579:exon2:c.G250T:p.G84C

5:75428011:G:A MetaPanNET-2 SV2C SV2C:NM\_001297716:exon2:c.G436A:p.G1465;x3bSV2C:NM\_014979:exon2:c.G436A:p.G1465

13:25670801:T:G MetaPanNET-6 PABPC3 PABPC3:NM\_030979:exon1:c.465\_466insG:p.I555f

19:9086088:A:T MetaPanNET-5 MUC16 MUC16:NM\_024690:exon1:c.T572A:p.H1909Q

2:131976077:C:A MetaPanNET-17 POTE1 POTE1:NM\_001083538:exon1:c.C102A:p.C34X

22:40042787:G:A MetaPanNET-7 CACNA11 CACNA11:NM\_001003406:exon8:c.G1363A:p.G455S

17:56833466:A:ACCCGAA PPM1E PPM1E:NM\_001490:exon1:c.108\_109insCCGAA:p.E36delinsEPE

19:22171651:C:T MetaPanNET-5 ZNF208 ZNF208:NM\_007153:exon2:c.G64A:p.D22N

1:247201695:C:A MetaPanNET-5 ZNF670 ZNF670:NM\_001204220:exon4:c.G223T:p.E75Y;x3bZNF670:NM\_033213:exon4:c.G226T:p.E76X

10:7772046:G:A MetaPanNET-17 ITIH2 ITIH2:NM\_002216:exon12:c.G1411A:p.G471R

11:40136012:CTG:C MetaPanNET-1 LRRc4C LRRc4C:NM\_020929:exon5:c.1828\_1830del:p.610\_610del;x3bLRRc4C:NM\_001258419:exon7:c.1828\_1830del:p.610\_610del

6:33287320:A:T MetaPanNET-12 DAXX DAXX:NM\_001254717:exon5:c.1551delA:p.Q517fs;x3bDAXX:NM\_001141969:exon6:c.1776delA:p.Q592fs;x3bDAXX:NM\_001141970:exon6:c.1812delA:p.Q604fs;x3bDAXX:NI

7:75130916:C:G MetaPanNET-5 SPDYE5 SPDYE5:NM\_001099435:exon6:c.C791G:p.S264C

1:152800275:C:A MetaPanNET-5 LCE1A LCE1A:NM\_178348:exon1:c.C327A:p.C109X

18:24442266:C:G MetaPanNET-5 AQP4 AQP4:NM\_004028:exon1:c.G261C:p.K87N;x3bAQP4:NM\_001650:exon2:c.G327C:p.K109N

3:52469819:C:T MetaPanNET-18 SEMA3G SEMA3G:NM\_020163:exon16:c.T1429A:p.A717T

7:44047183:G:C MetaPanNET-5 SPDYE1 SPDYE1:NM\_175064:exon5:c.G949C:p.E317Q

10:106982894:C:T MetaPanNET-14 SORCS3 SORCS3:NM\_014978:exon20:c.C2755T:p.L919F

16:72923651:T:A MetaPanNET-14 ZFXH3 ZFXH3:NM\_001164766:exon3:c.A685T:p.R229W;x3bZFXH3:NM\_006885:exon4:c.A3427T:p.R1143W

17:7705319:C:A MetaPanNET-4 DNAH2 DNAH2:NM\_020877:exon58:c.C8956A:p.L2986M

15:72020908:C:T MetaPanNET-8 THSD4 THSD4:NM\_001286429:exon3:c.C298T:p.R100C;x3bTHSD4:NM\_024817:exon8:c.C1378T:p.R460C

X:51075941:C:T MetaPanNET-18 NUDT10 NUDT10:NM\_001304963:exon1:c.C124T:p.P425;x3bNUDT10:NM\_153183:exon2:c.C124T:p.P425

15:79586392:G:A MetaPanNET-5 ANKRD34C ANKRD34C:NM\_001146341:exon2:c.G766A:p.G256S

8:53045633:C:G MetaPanNET-2 ST18 ST18:NM\_014682:exon21:c.G2428C:p.E810Q

1:36563637:C:T MetaPanNET-10 COL8A2 COL8A2:NM\_001294347:exon4:c.G1450A:p.G4845;x3bCOL8A2:NM\_005202:exon4:c.G1645A:p.G549S

21:38852962:G:A MetaPanNET-14 DYRK1A DYRK1A:NM\_001396:exon4:c.G350A:p.R1170;x3bDYRK1A:NM\_130436:exon4:c.G323A:p.R108Q;x3bDYRK1A:NM\_130438:exon4:c.G350A:p.R117Q;x3bDYRK1A:NM\_1001395

7:139662031:A:G MetaPanNET-10 TBXAS1 TBXAS1:NM\_001061:exon9:c.A1136G:p.H379R;x3bTBXAS1:NM\_030984:exon9:c.A1136G:p.H379R;x3bTBXAS1:NM\_001166253:exon10:c.A1274G:p.H425R;x3bTBXAS1:NM\_C

5:149546722:C:T MetaPanNET-13 CDX1 CDX1:NM\_001804:exon1:c.C283T:p.P95S

3:172163142:A:T MetaPanNET-2 GHRN GHRN:NM\_198407:exon2:c.T910A:p.C3045

9:78686749:G:T MetaPanNET-18 PCSK5 PCSK5:NM\_001190482:exon7:c.G829T:p.D277Y;x3bPCSK5:NM\_006200:exon7:c.G829T:p.D277Y

11:64577329:TAGACT:C MetaPanNET-7 MEN1 MEN1:NM\_000244:exon2:c.249\_252del:p.L83fs;x3bMEN1:NM\_130800:exon2:c.249\_252del:p.L83fs;x3bMEN1:NM\_1300

22:36682805:T:A MetaPanNET-16 MYH9 MYH9:NM\_002473:exon35:c.A5020T:p.K1674X

2:201873697:G:A MetaPanNET-10 MFM12B MFM12B:NM\_173822:exon7:c.C529T:p.R177W

1:201176138:G:A MetaPanNET-14 IGFN1 IGFN1:NM\_001164586:exon12:c.G2117A:p.G706E

8:124141459:G:A MetaPanNET-12 TBC1D31

16:74443490:C:T MetaPanNET-16 CLEC18B

1:145298247:C:T MetaPanNET-15 NBPFF10 NBPFF10:NM\_001039703:exon5:c.C659T:p.S220F;x3bNBPFF10:NM\_001302371:exon5:c.C659T:p.S220F

3:195508654:G:T MetaPanNET-3 MUC4 MUC4:NM\_018406:exon2:c.C9797A:p.P3266H

11:118361922:C:T MetaPanNET-5 KMT2A KMT2A:NM\_001197104:exon14:c.C4708T:p.P1570S;x3bKMT2A:NM\_005933:exon14:c.C4708T:p.P1570S

12:531858087:G:A MetaPanNET-14 KRT3 KRT3:NM\_057088:exon7:c.C1438T:p.R480W

19:37835599:C:T MetaPanNET-1 HKR1 HKR1:NM\_181786:exon3:c.C137T:p.H5Y

8:126075778:C:T MetaPanNET-5 KIAA0196 KIAA0196:NM\_014846:exon11:c.G1394A:p.R465K

1:100133298:A:C MetaPanNET-14 PALMD PALMD:NM\_017734:exon3:c.A227C:p.Q76P

3:47163437:GAGTT:G MetaPanNET-13 SETD2 SETD2:NM\_014159:exon3:c.2685\_2688del:p.L895fs

6:160509083:C:T MetaPanNET-2 IGF2R IGF2R:NM\_000876:exon42:c.C6224T:p.T2075M

2:70047943:C:T MetaPanNET-14 ANXA4 ANXA4:NM\_001153:exon12:c.C896T:p.S299L

3:195506761:G:A MetaPanNET-14 MUC4 MUC4:NM\_018406:exon2:c.C11690T:p.A3897V

1:117142707:G:A MetaPanNET-12 IGSF3 IGSF3:NM\_001072377:exon7:c.C1885T:p.R629C;x3bIGSF3:NM\_001542:exon7:c.C1945T:p.R649C

11:64083293:G:T MetaPanNET-9 ESRR4 ESRR4:NM\_001282450:exon7:c.G1127T:p.R376L;x3bESRR4:NM\_001282451:exon7:c.G1124T:p.R375L;x3bESRR4:NM\_004451:exon7:c.G1127T:p.R376L

4:190878608:C:A MetaPanNET-15 FRG1 FRG1:NM\_004477:exon6:c.G488A:p.G163E

22:22036804:A:T MetaPanNET-9 PPI2 PPI2:NM\_014337:exon8:c.A466T:p.I156F;x3bPPI2:NM\_148175:exon8:c.A466T:p.I156F

11:34904971:A:T MetaPanNET-16 AP1P AP1P:NM\_015957:exon6:c.T542A:p.M181K

15:23685920:A:C MetaPanNET-17 GOLGA6L2 GOLGA6L2:NM\_001304388:exon8:c.T1702G:p.S568A

12:40879080:C:T MetaPanNET-17 MUC19 UNKNOW

16:27476823:G:T MetaPanNET-5 GTF3C1 GTF3C1:NM\_001286242:exon33:c.C5113A:p.L1705I;x3bGTF3C1:NM\_001520:exon33:c.C5113A:p.L1705I

2:71840511:G:T MetaPanNET-14 DYSF DYSF:NM\_001130976:exon39:c.G4339T:p.D1447Y;x3bDYSF:NM\_001130977:exon39:c.G4339T:p.D1447Y;x3bDYSF:NM\_001130984:exon39:c.G4342T:p.D1448Y;x3bDYSF:NM

3:9424966:T:C MetaPanNET-12 THUMPD3 THUMPD3:NM\_00114092:exon8:c.T1208C:p.I403T;x3bTHUMPD3:NM\_015453:exon8:c.T1208C:p.I403T

18:52895577:G:T MetaPanNET-17 TCF4 TCF4:NM\_001243234:exon12:c.C1415A:p.P472Q;x3bTCF4:NM\_001243235:exon12:c.C1403A:p.P468Q;x3bTCF4:NM\_001243236:exon12:c.C1403A:p.P468Q;x3bTCF4:NM\_00

17:7319307:C:CT MetaPanNET-13 NLGN2 NLGN2:NM\_020795:exon6:c.1516dupT:p.P505fs

8:52733102:G:A MetaPanNET-9 PCMTD1 PCMTD1:NM\_001286782:exon4:c.C655T:p.L219F;x3bPCMTD1:NM\_001286783:exon6:c.C355T:p.L119F;x3bPCMTD1:NM\_052937:exon6:c.C883T:p.L295F

13:77459959:C:T MetaPanNET-5 KCTD12 KCTD12:NM\_138444:exon1:c.G325A:p.E109K

1:52289446:G:A MetaPanNET-6 NRD1 NRD1:NM\_001101662:exon7:c.C1049T:p.T350M;x3bNRD1:NM\_001242361:exon9:c.C857T:p.T286M;x3bNRD1:NM\_002525:exon9:c.C1253T:p.T418M

6:24289090:G:C MetaPanNET-13 DCDC2 DCDC2:NM\_016356:exon6:c.C749G:p.S250C;x3bDCDC2:NM\_001195610:exon7:c.C749G:p.S250C

16:2301430:C:T MetaPanNET-5 EC11 EC11:NM\_001178029:exon2:c.G53A:p.G18E;x3bEC11:NM\_001919:exon2:c.G53A:p.G18E

22:32100659:G:C MetaPanNET-8 PRR14L PRR14L:NM\_173566:exon5:c.C5810G:p.T1937S

12:40884121:C:A MetaPanNET-19 MUC19 UNKNOW

3:195508903:G:A MetaPanNET-19 MUC4 MUC4:NM\_018406:exon2:c.C9548T:p.T3183M

1:169580892:CTT MetaPanNET-19 SELP SELP:NM\_003005:exon7:c.984\_985insAA:p.A329fs

9:42410368:T:C MetaPanNET-19 ANKRD20A2;x3bANKRD20A3 ANKRD20A3:NM\_001012419:exon15:c.T2357C:p.M786T;x3bANKRD20A2:NM\_001012421:exon15:c.T2357C:p.M786T

15:51735781:G:A:G MetaPanNET-19 RNF11 RNF11:NM\_014372:exon2:c.278delA:p.E93fs

3:10018733:G:C MetaPanNET-19 EMC3 EMC3:NM\_018447:exon3:c.C215G:p.S72C

15:74174052:G:A MetaPanNET-19 TBC1D21 TBC1D21:NM\_001286434:exon2:c.C128A:p.S43Y;x3bTBC1D21:NM\_153356:exon3:c.C236A:p.S79Y

14:103429476:C:T MetaPanNET-19 CDC42BPB CDC42BPB:NM\_006035:exon20:c.G2743A:p.E91SK

8:7320252:G:T MetaPanNET-19 SPAG11B SPAG11B:NM\_016512:exon2:c.C191A:p.P640;x3bSPAG11B:NM\_058200:exon2:c.C191A:p.P640;x3bSPAG11B:NM\_058201:exon2:c.C191A:p.P640;x3bSPAG11B:NM\_058202

19:15273370:T:A MetaPanNET-19 NOSH2C NOSH2C:NM\_000435:exon32:c.A5819T:p.K1940I

7:100550696:C:T MetaPanNET-19 MUC3A MUC3A:NM\_005960:exon2:c.C1277T:p.T426I

15:23685904:G:A MetaPanNET-19 GOLGA6L2 GOLGA6L2:NM\_001304388:exon8:c.T1718C:p.V573A

6:32713061:C:A MetaPanNET-19 HLA-DQA2 HLA-DQA2:NM\_020056:exon2:c.C208A:p.Q70K

3:195506844:G:C MetaPanNET-19 MUC4 MUC4:NM\_018406:exon2:c.C11607G:p.H3869Q

1:4772582:G:GCCA AJA1 AJA1:NM\_001042478:exon2:c.652\_653insCCA:p.A218delinsAT;x3bAJA1:NM\_018836:exon2:c.652\_653insCCA:p.A218delinsAT

5:140953360:G:C MetaPanNET-19 DIAPH1 DIAPH1:NM\_001079812:exon15:c.G2030C:p.R677Y;x3bDIAPH1:NM\_005219:exon16:c.G2057C:p.R686T

**Supplementary Table 2. Pathologic findings and immunohistochemical/FISH status of 347 pancreatic neuroendocrine tumors.**

Patient	Tumor size (cm)	Histologic grade	ALT status	ATRX expression	DAXX expression	H3K36me3 expression	ARID1A expression	<i>CDKN2A /CEP9</i> ratio
1	0.6	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
2	0.6	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.18 (Wild type)
3	0.6	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.96 (Wild type)
4	0.6	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.05 (Wild type)
5	0.6	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.06 (Wild type)
6	0.7	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.03 (Wild type)
7	0.7	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.97 (Wild type)
8	0.7	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
9	0.7	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.96 (Wild type)
10	0.7	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
11	0.8	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.96 (Wild type)
12	0.8	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.02 (Wild type)
13	0.8	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
14	0.8	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.12 (Wild type)
15	0.8	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
16	0.9	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
17	0.9	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.02 (Wild type)
18	0.9	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
19	0.9	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.13 (Wild type)
20	0.9	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.02 (Wild type)
21	1.0	G1	Positive	Loss	Preserved	Preserved	Preserved	1.11 (Wild type)
22	1.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.02 (Wild type)
23	1.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
24	1.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.97 (Wild type)
25	1.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.01 (Wild type)
26	1.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.89 (Wild type)
27	1.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.02 (Wild type)
28	1.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.01 (Wild type)
29	1.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)



30	1.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.02 (Wild type)
31	1.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
32	1.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
33	1.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
34	1.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.96 (Wild type)
35	1.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
36	1.1	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.98 (Wild type)
37	1.1	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.02 (Wild type)
38	1.1	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
39	1.1	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.98 (Wild type)
40	1.1	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
41	1.1	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.01 (Wild type)
42	1.2	G2	Positive	Loss	Preserved	Loss	Preserved	1.00 (Wild type)
43	1.2	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
44	1.2	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.03 (Wild type)
45	1.2	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.93 (Wild type)
46	1.2	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.05 (Wild type)
47	1.2	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.91 (Wild type)
48	1.2	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.95 (Wild type)
49	1.3	G1	Negative	Preserved	Preserved	Loss	Preserved	1.07 (Wild type)
50	1.3	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.11 (Wild type)
51	1.3	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.96 (Wild type)
52	1.3	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.01 (Wild type)
53	1.3	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.01 (Wild type)
54	1.3	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.04 (Wild type)
55	1.3	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.06 (Wild type)
56	1.3	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.98 (Wild type)
57	1.3	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.02 (Wild type)
58	1.3	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
59	1.3	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.06 (Wild type)
60	1.4	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.96 (Wild type)
61	1.4	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
62	1.4	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.92 (Wild type)

63	1.4	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
64	1.4	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.98 (Wild type)
65	1.4	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.02 (Wild type)
66	1.4	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
67	1.5	G2	Negative	Preserved	Preserved	Loss	Preserved	1.00 (Wild type)
68	1.5	G1	Positive	Preserved	Loss	Preserved	Preserved	0.95 (Wild type)
69	1.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.88 (Wild type)
70	1.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
71	1.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
72	1.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.98 (Wild type)
73	1.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.02 (Wild type)
74	1.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.05 (Wild type)
75	1.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.06 (Wild type)
76	1.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.04 (Wild type)
77	1.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.97 (Wild type)
78	1.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.03 (Wild type)
79	1.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.07 (Wild type)
80	1.5	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.22 (Wild type)
81	1.5	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.01 (Wild type)
82	1.5	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.06 (Wild type)
83	1.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
84	1.5	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.96 (Wild type)
85	1.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.03 (Wild type)
86	1.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
87	1.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.05 (Wild type)
88	1.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
89	1.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.98 (Wild type)
90	1.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.95 (Wild type)
91	1.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.19 (Wild type)
92	1.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.04 (Wild type)
93	1.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
94	1.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.98 (Wild type)
95	1.6	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.08 (Wild type)

96	1.6	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.23 (Wild type)
97	1.6	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
98	1.6	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.10 (Wild type)
99	1.7	G2	Positive	Preserved	Loss	Preserved	Loss	1.07 (Wild type)
100	1.7	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.16 (Wild type)
101	1.7	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
102	1.7	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.05 (Wild type)
103	1.7	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.03 (Wild type)
104	1.7	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.98 (Wild type)
105	1.7	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.85 (Wild type)
106	1.8	G2	Positive	Preserved	Preserved	Preserved	Preserved	0.95 (Wild type)
107	1.8	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.04 (Wild type)
108	1.8	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
109	1.8	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.08 (Wild type)
110	1.8	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
111	1.8	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.04 (Wild type)
112	1.8	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.23 (Wild type)
113	1.9	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.96 (Wild type)
114	2.0	G2	Positive	Loss	Preserved	Preserved	Preserved	0.46 (Deletion)
115	2.0	G2	Positive	Loss	Loss	Preserved	Preserved	0.65 (Deletion)
116	2.0	G2	Negative	Preserved	Preserved	Loss	Preserved	1.01 (Wild type)
117	2.0	G2	Positive	Preserved	Loss	Preserved	Preserved	0.98 (Wild type)
118	2.0	G1	Positive	Loss	Loss	Preserved	Preserved	1.04 (Wild type)
119	2.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.04 (Wild type)
120	2.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
121	2.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.10 (Wild type)
122	2.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
123	2.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.15 (Wild type)
124	2.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.03 (Wild type)
125	2.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.04 (Wild type)
126	2.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.01 (Wild type)
127	2.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.01 (Wild type)
128	2.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.96 (Wild type)

129	2.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.07 (Wild type)
130	2.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.01 (Wild type)
131	2.1	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.96 (Wild type)
132	2.1	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.97 (Wild type)
133	2.1	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.94 (Wild type)
134	2.1	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.03 (Wild type)
135	2.1	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.05 (Wild type)
136	2.1	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.98 (Wild type)
137	2.1	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.11 (Wild type)
138	2.2	G1	Positive	Preserved	Loss	Preserved	Preserved	1.02 (Wild type)
139	2.2	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
140	2.2	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.17 (Wild type)
141	2.2	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.96 (Wild type)
142	2.2	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.94 (Wild type)
143	2.2	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.02 (Wild type)
144	2.2	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.01 (Wild type)
145	2.2	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
146	2.3	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.98 (Wild type)
147	2.3	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.15 (Wild type)
148	2.4	G1	Positive	Preserved	Loss	Preserved	Preserved	0.97 (Wild type)
149	2.4	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.04 (Wild type)
150	2.4	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.97 (Wild type)
151	2.4	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
152	2.4	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.97 (Wild type)
153	2.4	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.19 (Wild type)
154	2.4	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.16 (Wild type)
155	2.5	G1	Positive	Loss	Preserved	Preserved	Preserved	0.66 (Deletion)
156	2.5	G2	Positive	Preserved	Preserved	Preserved	Preserved	0.55 (Deletion)
157	2.5	G2	Negative	Preserved	Preserved	Preserved	Loss	0.46 (Deletion)
158	2.5	G1	Positive	Preserved	Loss	Loss	Preserved	1.00 (Wild type)
159	2.5	G2	Positive	Preserved	Loss	Preserved	Preserved	1.00 (Wild type)
160	2.5	G2	Positive	Loss	Loss	Preserved	Preserved	1.06 (Wild type)
161	2.5	G2	Positive	Loss	Loss	Preserved	Preserved	0.96 (Wild type)

162	2.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.02 (Wild type)
163	2.5	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.10 (Wild type)
164	2.5	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.88 (Wild type)
165	2.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
166	2.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.04 (Wild type)
167	2.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
168	2.5	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.13 (Wild type)
169	2.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
170	2.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.96 (Wild type)
171	2.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.04 (Wild type)
172	2.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.97 (Wild type)
173	2.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.98 (Wild type)
174	2.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.08 (Wild type)
175	2.5	G3	Negative	Preserved	Preserved	Preserved	Preserved	1.04 (Wild type)
176	2.6	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
177	2.7	G1	Negative	Preserved	Preserved	Loss	Preserved	0.67 (Deletion)
178	2.7	G1	Positive	Loss	Loss	Preserved	Preserved	0.96 (Wild type)
179	2.7	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.96 (Wild type)
180	2.7	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
181	2.7	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.19 (Wild type)
182	2.8	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.59 (Deletion)
183	2.8	G2	Positive	Loss	Loss	Loss	Preserved	1.06 (Wild type)
184	2.8	G1	Positive	Loss	Preserved	Preserved	Preserved	1.01 (Wild type)
185	2.8	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
186	2.8	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
187	2.8	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
188	2.8	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
189	2.8	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
190	2.8	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
191	2.9	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.05 (Wild type)
192	3.0	G2	Positive	Loss	Preserved	Preserved	Preserved	0.35 (Deletion)
193	3.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.70 (Deletion)
194	3.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.43 (Deletion)

195	3.0	G2	Positive	Loss	Loss	Loss	Preserved	1.11 (Wild type)
196	3.0	G2	Positive	Loss	Preserved	Preserved	Preserved	1.01 (Wild type)
197	3.0	G2	Positive	Preserved	Loss	Preserved	Preserved	1.00 (Wild type)
198	3.0	G1	Positive	Loss	Loss	Preserved	Preserved	1.01 (Wild type)
199	3.0	G2	Positive	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
200	3.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.08 (Wild type)
201	3.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
202	3.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.89 (Wild type)
203	3.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
204	3.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.96 (Wild type)
205	3.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.06 (Wild type)
206	3.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
207	3.1	G1	Positive	Loss	Preserved	Preserved	Preserved	1.00 (Wild type)
208	3.1	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
209	3.2	G1	Positive	Loss	Preserved	Preserved	Preserved	1.11 (Wild type)
210	3.2	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.92 (Wild type)
211	3.2	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.01 (Wild type)
212	3.3	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.84 (Wild type)
213	3.4	G2	Positive	Preserved	Preserved	Preserved	Preserved	1.02 (Wild type)
214	3.5	G1	Positive	Loss	Preserved	Loss	Preserved	0.65 (Deletion)
215	3.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.74 (Deletion)
216	3.5	G1	Positive	Preserved	Loss	Preserved	Loss	1.02 (Wild type)
217	3.5	G2	Positive	Preserved	Loss	Loss	Preserved	0.97 (Wild type)
218	3.5	G2	Negative	Preserved	Preserved	Loss	Preserved	1.12 (Wild type)
219	3.5	G1	Negative	Preserved	Preserved	Loss	Preserved	0.99 (Wild type)
220	3.5	G1	Negative	Preserved	Preserved	Loss	Preserved	1.10 (Wild type)
221	3.5	G2	Positive	Loss	Loss	Preserved	Preserved	1.01 (Wild type)
222	3.5	G2	Positive	Preserved	Loss	Preserved	Preserved	1.00 (Wild type)
223	3.5	G2	Positive	Loss	Preserved	Preserved	Preserved	1.02 (Wild type)
224	3.5	G2	Positive	Loss	Preserved	Preserved	Preserved	1.14 (Wild type)
225	3.5	G1	Positive	Loss	Preserved	Preserved	Preserved	1.02 (Wild type)
226	3.5	G2	Positive	Loss	Preserved	Preserved	Preserved	1.19 (Wild type)
227	3.5	G1	Positive	Preserved	Preserved	Preserved	Preserved	0.98 (Wild type)

228	3.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.07 (Wild type)
229	3.5	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.06 (Wild type)
230	3.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.01 (Wild type)
231	3.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.97 (Wild type)
232	3.6	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.97 (Wild type)
233	3.6	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.95 (Wild type)
234	3.6	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.03 (Wild type)
235	3.7	G1	Positive	Loss	Preserved	Preserved	Preserved	0.65 (Deletion)
236	3.7	G3	Positive	Preserved	Loss	Preserved	Preserved	0.97 (Wild type)
237	3.8	G2	Positive	Preserved	Loss	Preserved	Preserved	0.97 (Wild type)
238	3.8	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
239	3.8	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.09 (Wild type)
240	4.0	G1	Positive	Preserved	Loss	Loss	Preserved	0.98 (Wild type)
241	4.0	G1	Positive	Preserved	Preserved	Loss	Preserved	1.08 (Wild type)
242	4.0	G2	Negative	Preserved	Preserved	Preserved	Loss	1.06 (Wild type)
243	4.0	G1	Positive	Preserved	Loss	Preserved	Preserved	1.08 (Wild type)
244	4.0	G2	Positive	Preserved	Loss	Preserved	Preserved	0.97 (Wild type)
245	4.0	G2	Positive	Preserved	Loss	Preserved	Preserved	0.85 (Wild type)
246	4.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.02 (Wild type)
247	4.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.92 (Wild type)
248	4.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.90 (Wild type)
249	4.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.06 (Wild type)
250	4.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.17 (Wild type)
251	4.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.97 (Wild type)
252	4.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.89 (Wild type)
253	4.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.03 (Wild type)
254	4.2	G2	Positive	Loss	Loss	Preserved	Preserved	0.29 (Deletion)
255	4.2	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.03 (Wild type)
256	4.2	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
257	4.2	G3	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
258	4.2	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.98 (Wild type)
259	4.4	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.04 (Wild type)
260	4.5	G3	Negative	Preserved	Preserved	Preserved	Preserved	0.67 (Deletion)

261	4.5	G2	Negative	Preserved	Preserved	Preserved	Loss	0.53 (Deletion)
262	4.5	G2	Positive	Loss	Preserved	Loss	Preserved	0.96 (Wild type)
263	4.5	G3	Negative	Preserved	Preserved	Preserved	Loss	1.01 (Wild type)
264	4.5	G2	Positive	Loss	Preserved	Preserved	Preserved	0.93 (Wild type)
265	4.5	G2	Positive	Preserved	Loss	Preserved	Preserved	0.98 (Wild type)
266	4.5	G2	Positive	Preserved	Loss	Preserved	Preserved	0.99 (Wild type)
267	4.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.95 (Wild type)
268	4.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.97 (Wild type)
269	4.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.96 (Wild type)
270	4.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
271	4.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
272	4.5	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.86 (Wild type)
273	4.6	G2	Positive	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
274	4.6	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.98 (Wild type)
275	4.6	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
276	4.8	G1	Positive	Loss	Loss	Preserved	Preserved	0.97 (Wild type)
277	4.9	G2	Positive	Preserved	Loss	Preserved	Preserved	0.69 (Deletion)
278	5.0	G2	Negative	Preserved	Preserved	Loss	Preserved	1.01 (Wild type)
279	5.0	G2	Positive	Preserved	Loss	Preserved	Preserved	1.00 (Wild type)
280	5.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.01 (Wild type)
281	5.0	G3	Negative	Preserved	Preserved	Preserved	Preserved	1.01 (Wild type)
282	5.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.96 (Wild type)
283	5.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
284	5.1	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.96 (Wild type)
285	5.3	G2	Positive	Preserved	Loss	Preserved	Preserved	1.03 (Wild type)
286	5.5	G2	Positive	Loss	Preserved	Preserved	Preserved	0.95 (Wild type)
287	5.5	G2	Positive	Loss	Loss	Preserved	Preserved	0.97 (Wild type)
288	5.5	G2	Positive	Preserved	Loss	Preserved	Preserved	0.99 (Wild type)
289	5.5	G2	Positive	Preserved	Loss	Preserved	Preserved	0.99 (Wild type)
290	5.5	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.88 (Wild type)
291	5.6	G2	Positive	Loss	Preserved	Preserved	Preserved	1.01 (Wild type)
292	5.7	G1	Positive	Loss	Preserved	Preserved	Preserved	0.95 (Wild type)
293	5.8	G1	Positive	Preserved	Preserved	Preserved	Preserved	0.90 (Wild type)



294	6.0	G2	Positive	Preserved	Loss	Preserved	Preserved	0.77 (Deletion)
295	6.0	G2	Negative	Preserved	Preserved	Preserved	Loss	0.95 (Wild type)
296	6.0	G2	Negative	Preserved	Preserved	Loss	Preserved	1.00 (Wild type)
297	6.0	G2	Negative	Preserved	Preserved	Loss	Preserved	1.00 (Wild type)
298	6.0	G2	Negative	Preserved	Preserved	Loss	Preserved	0.89 (Wild type)
299	6.0	G2	Positive	Preserved	Loss	Preserved	Preserved	0.97 (Wild type)
300	6.0	G2	Positive	Loss	Preserved	Preserved	Preserved	0.98 (Wild type)
301	6.0	G1	Positive	Loss	Preserved	Preserved	Preserved	1.02 (Wild type)
302	6.0	G2	Positive	Preserved	Loss	Preserved	Preserved	0.99 (Wild type)
303	6.0	G1	Positive	Preserved	Loss	Preserved	Preserved	0.96 (Wild type)
304	6.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.96 (Wild type)
305	6.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.94 (Wild type)
306	6.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.84 (Wild type)
307	6.4	G2	Negative	Preserved	Preserved	Loss	Preserved	0.48 (Deletion)
308	6.5	G3	Positive	Loss	Loss	Preserved	Preserved	0.66 (Deletion)
309	6.5	G2	Positive	Preserved	Loss	Loss	Preserved	0.98 (Wild type)
310	6.5	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.03 (Wild type)
311	6.5	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
312	6.5	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.91 (Wild type)
313	6.8	G2	Positive	Preserved	Loss	Preserved	Preserved	0.98 (Wild type)
314	7.0	G2	Positive	Preserved	Loss	Preserved	Preserved	1.01 (Wild type)
315	7.0	G1	Positive	Loss	Preserved	Preserved	Preserved	0.93 (Wild type)
316	7.0	G2	Positive	Loss	Preserved	Preserved	Preserved	0.95 (Wild type)
317	7.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.97 (Wild type)
318	7.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.98 (Wild type)
319	7.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.92 (Wild type)
320	7.5	G2	Positive	Preserved	Loss	Preserved	Preserved	0.24 (Deletion)
321	7.5	G2	Positive	Preserved	Preserved	Preserved	Preserved	0.72 (Deletion)
322	7.5	G2	Positive	Preserved	Loss	Preserved	Loss	0.97 (Wild type)
323	7.5	G2	Positive	Preserved	Preserved	Preserved	Preserved	0.98 (Wild type)
324	7.5	G2	Negative	Preserved	Preserved	Preserved	Preserved	1.00 (Wild type)
325	7.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.95 (Wild type)
326	7.5	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.95 (Wild type)

327	8.0	G2	Positive	Preserved	Loss	Preserved	Preserved	0.88 (Wild type)
328	8.5	G2	Negative	Preserved	Preserved	Loss	Preserved	1.01 (Wild type)
329	8.5	G2	Positive	Loss	Preserved	Preserved	Preserved	0.95 (Wild type)
330	8.5	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.97 (Wild type)
331	9.0	G2	Positive	Loss	Loss	Loss	Preserved	0.99 (Wild type)
332	9.0	G3	Positive	Preserved	Preserved	Loss	Preserved	0.84 (Wild type)
333	9.0	G1	Negative	Preserved	Preserved	Preserved	Loss	0.95 (Wild type)
334	9.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.98 (Wild type)
335	9.5	G2	Positive	Preserved	Preserved	Loss	Preserved	0.88 (Wild type)
336	10.0	G2	Positive	Preserved	Loss	Preserved	Preserved	0.56 (Deletion)
337	10.0	G2	Positive	Preserved	Preserved	Preserved	Preserved	0.53 (Deletion)
338	10.0	G2	Positive	Loss	Preserved	Loss	Preserved	0.94 (Wild type)
339	10.0	G1	Negative	Preserved	Preserved	Preserved	Preserved	0.96 (Wild type)
340	10.0	G2	Negative	Preserved	Preserved	Preserved	Preserved	0.99 (Wild type)
341	12.0	G2	Positive	Loss	Preserved	Preserved	Preserved	1.00 (Wild type)
342	12.2	G2	Positive	Preserved	Loss	Preserved	Preserved	0.96 (Wild type)
343	14.0	G1	Positive	Preserved	Loss	Preserved	Preserved	0.19 (Deletion)
344	15.0	G2	Positive	Loss	Preserved	Preserved	Preserved	0.95 (Wild type)
345	15.0	G2	Positive	Loss	Preserved	Preserved	Preserved	0.95 (Wild type)
346	17.0	G2	Negative	Preserved	Preserved	Preserved	Loss	0.94 (Wild type)
347	18.0	G2	Positive	Preserved	Preserved	Loss	Preserved	0.93 (Wild type)

*Abbreviations: ALT, alternative lengthening of telomeres*

ACCE

**Supplementary Table 3. Clinical and pathologic comparison of DAXX/ATRX, H3K36me3, ARID1A and CDKN2A status in non-syndromic well-differentiated PanNETs.**

Patient or Tumor Characteristics	DAXX/ATRX		<i>p</i>	H3K36me3		<i>p</i>	ARID1A		<i>p</i>	CDKN2A		<i>p</i>	DAXX/ATRX/H3K36me3/ARID1A/CDKN2A		<i>p</i>
	Preserved	Loss		Preserved	Loss		Preserved	Loss		Wildtype	Deletion		Preserved/Wildtype	Loss/Deletion	
Gender															
Female	139 (84%)	27 (16%)	0.005	155 (93%)	11 (7%)	0.431	161 (97%)	5 (3%)	1.000	154 (93%)	12 (7%)	1.000	124 (75%)	42 (25%)	0.008
Male	128 (71%)	53 (29%)		164 (91%)	17 (9%)		176 (97%)	5 (3%)		168 (93%)	13 (7%)		111 (61%)	70 (39%)	
Mean age (range), years	58.3 (26 - 85)	61.3 (31 - 83)	0.057	59.1 (26 - 85)	57.6 (32 - 82)	0.546	59.1 (26 - 83)	57.3 (37 - 85)	0.679	58.8 (26 - 85)	61.8 (37 - 80)	0.241	58.4 (26 - 83)	60.4 (31 - 85)	0.162
Mean tumor size (range), cm	3.0 (0.6 - 18.0)	5.0 (1.0 - 15.0)	< 0.001	3.3 (0.6 - 17.0)	5.3 (1.2 - 18.0)	< 0.001	3.3 (0.6 - 18.0)	6.0 (1.7 - 17.0)	0.002	3.3 (0.6 - 18.0)	4.9 (2.0 - 14.0)	0.004	2.6 (0.6 - 10.0)	5.2 (1.0 - 18.0)	< 0.001
Functional*	33 (92%)	3 (8%)	0.034	36 (100%)	0 (0%)	0.096	36 (100%)	0 (0%)	0.607	36 (100%)	0 (0%)	0.091	33 (92%)	3 (8%)	0.001
Insulinoma	21 (100%)	0 (0%)		21 (100%)	0 (0%)		21 (100%)	0 (0%)		21 (100%)	0 (0%)		21 (100%)	0 (0%)	
Gastrinoma	7 (88%)	1 (12%)		8 (100%)	0 (0%)		8 (100%)	0 (0%)		8 (100%)	0 (0%)		7 (88%)	1 (12%)	
Glucagonoma	4 (100%)	0 (0%)		4 (100%)	0 (0%)		4 (100%)	0 (0%)		4 (100%)	0 (0%)		4 (100%)	0 (0%)	
Somatostatinoma	0 (0%)	1 (100%)		1 (100%)	0 (0%)		1 (100%)	0 (0%)		1 (100%)	0 (0%)		0 (0%)	1 (100%)	
VIPoma	1 (100%)	0 (0%)		1 (100%)	0 (0%)		1 (100%)	0 (0%)		1 (100%)	0 (0%)		1 (100%)	0 (0%)	
ACTH-producing	0 (0%)	1 (100%)		1 (100%)	0 (0%)		1 (100%)	0 (0%)		1 (100%)	0 (0%)		0 (0%)	1 (100%)	
Location															
Head and uncinate	104 (79%)	27 (21%)	0.432	113 (86%)	18 (14%)	0.004	128 (98%)	3 (2%)	0.748	120 (92%)	11 (8%)	0.526	88 (67%)	43 (33%)	0.906
Body and tail	163 (75%)	53 (25%)		206 (95%)	10 (5%)		209 (97%)	7 (3%)		202 (94%)	14 (6%)		147 (68%)	69 (32%)	
WHO grade															
Low (G1)	175 (88%)	24 (12%)	< 0.001	191 (96%)	8 (4%)	0.004	197 (99%)	2 (1%)	0.026	190 (95%)	9 (5%)	0.033	165 (83%)	34 (17%)	< 0.001
Intermediate (G2)	86 (61%)	54 (39%)		121 (86%)	19 (14%)		133 (95%)	7 (5%)		126 (90%)	14 (10%)		67 (48%)	73 (52%)	
High (G3)	6 (75%)	2 (25%)		7 (88%)	1 (12%)		7 (88%)	1 (12%)		6 (75%)	2 (25%)		3 (38%)	5 (62%)	
Lymphovascular invasion	93 (61%)	60 (39%)	< 0.001	133 (87%)	20 (13%)	0.003	143 (93%)	10 (7%)	< 0.001	131 (86%)	22 (14%)	< 0.001	67 (44%)	86 (56%)	< 0.001
Perineural invasion	59 (65%)	32 (25%)	0.002	77 (85%)	14 (15%)	0.006	86 (95%)	5 (5%)	0.136	78 (86%)	13 (14%)	0.004	42 (46%)	49 (54%)	< 0.001
Primary tumor (pT) stage															
T1	115 (95%)	6 (5%)	< 0.001	118 (98%)	3 (2%)	0.001	120 (99%)	1 (1%)	0.001	120 (99%)	1 (1%)	< 0.001	113 (93%)	8 (7%)	< 0.001
T2	80 (75%)	26 (25%)		99 (93%)	7 (7%)		106 (100%)	0 (0%)		99 (93%)	7 (7%)		74 (70%)	32 (30%)	
T3	72 (60%)	48 (40%)		102 (85%)	18 (15%)		111 (93%)	9 (7%)		103 (86%)	17 (14%)		48 (40%)	72 (60%)	
Lymph node metastases (n = 294)**	62 (56%)	48 (44%)	< 0.001	98 (89%)	12 (11%)	0.397	103 (94%)	7 (6%)	0.044	94 (85%)	16 (15%)	0.003	45 (41%)	65 (59%)	< 0.001
Synchronous metastases	28 (51%)	27 (49%)	< 0.001	44 (80%)	11 (20%)	0.002	50 (91%)	5 (9%)	0.011	45 (82%)	10 (18%)	0.002	14 (25%)	41 (75%)	< 0.001
Metachronous metastases (n = 282)***	17 (38%)	28 (62%)	< 0.001	36 (80%)	9 (20%)	< 0.001	42 (93%)	3 (7%)	0.027	33 (73%)	12 (27%)	< 0.001	5 (11%)	40 (89%)	< 0.001
Presence of ALT (n = 94)	14 (15%)	80 (85%)	< 0.001	79 (84%)	15 (16%)	0.003	91 (97%)	3 (3%)	0.734	78 (83%)	16 (17%)	< 0.001	7 (7%)	87 (93%)	< 0.001
Loss of DAXX/ATRX (n = 80)				69 (86%)	11 (14%)	0.058	77 (96%)	3 (4%)	0.702	67 (84%)	13 (16%)	0.001			
Loss of H3K36me3 (n = 28)	17 (61%)	11 (39%)	0.058				28 (100%)	0 (0%)	1.000	25 (89%)	3 (11%)	0.440			
Loss of ARID1A (n = 10)	7 (70%)	3 (30%)	0.702	10 (100%)	0 (0%)	1.000				8 (80%)	2 (20%)	0.157			
Deletion in CDKN2A (n = 25)	12 (48%)	13 (52%)	0.001	22 (88%)	3 (12%)	0.440	23 (92%)	2 (8%)	0.157						

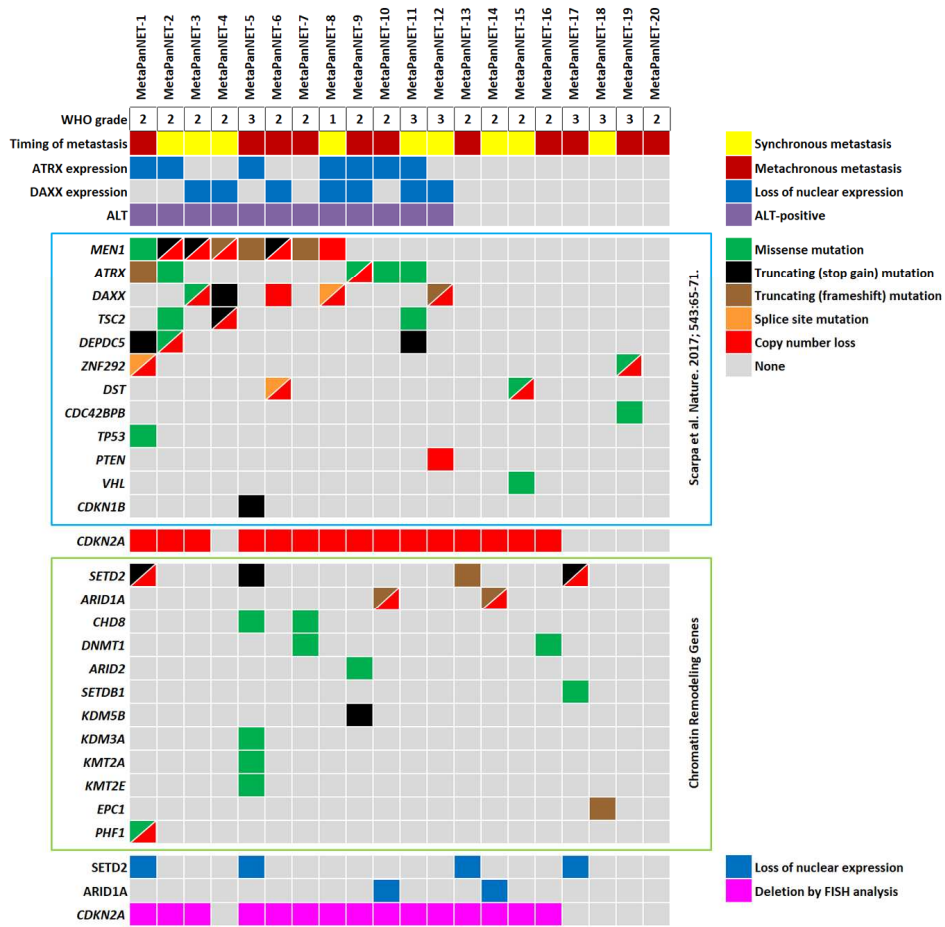
Abbreviations: ALT, alternative lengthening of telomeres

\*Statistical analysis as reported is based on the presence or absence of functionality and not functional subtype.

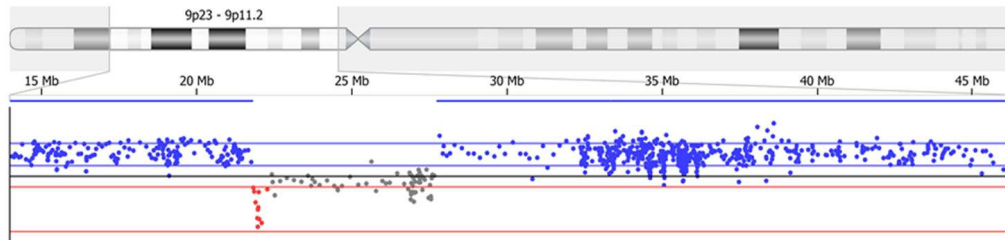
\*\*Regional lymph nodes were present for evaluation in 294 cases.

\*\*\*The presence of metachronous metastasis was evaluated in patients that had not presented with synchronous metastases (n = 282).

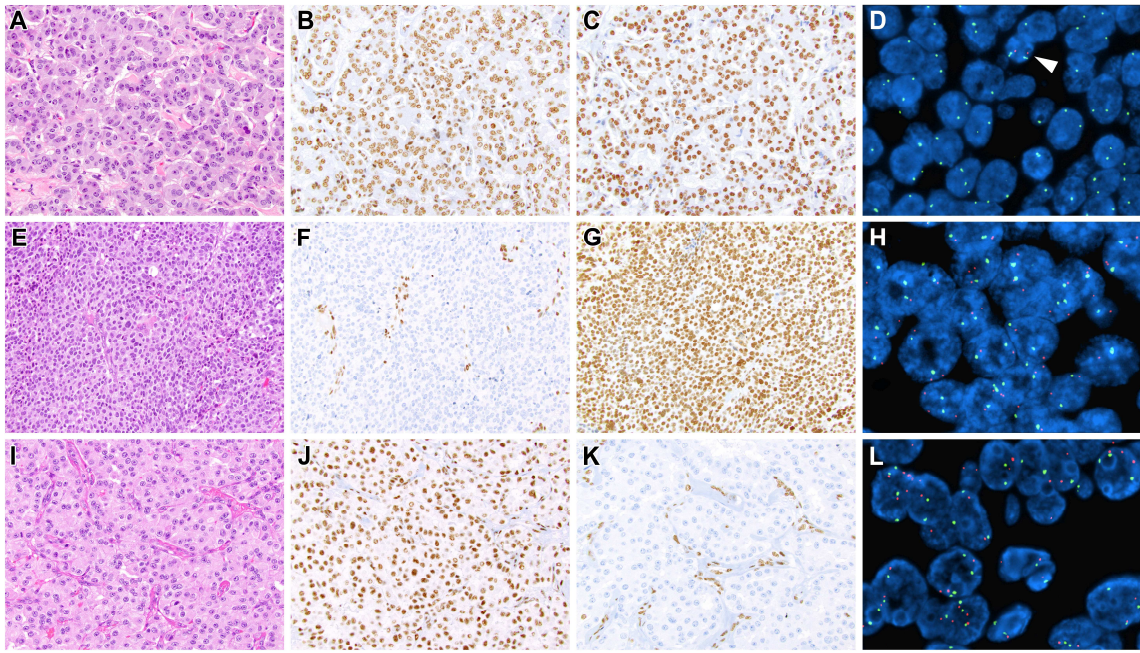
A



B



ACC



ACCEPTED MANUSCRIPT

