Three distinct genomic landscapes define clinical outcome of pancreatic neuroendocrine tumours (pNETs)

Ben Lawrence1, Cherie Blinkiron2, Kate Parker1, Peter Tsai2, Sandra Fitzgerald2, Paula Shields2, Tamsin Robb2, Mee Ling Yeong3, Nicole Kramer2, Sarah James2, Mik Black2, Vicky Fan2, Nooryah Poonawala, Patrick Yap1, Esther Coats1, Braden Woodhouse, Reena Ramsaroop5, Masato Youzu1, Bridget Robinson1, Kimiora Henare5, Jonathan Koea2, Peter Johnston3, Richard Carroll3, Saxon Connor1, Helen Morri2, Marianne Eistor3, Christopher Jackson1, Papaaangi Reid2, John Windsor3, Andrew Mac Cormick3, Richard Babor2, Adam Barlett2, Dragan Damjanovich1, Nicholas Knowlton2, Sean Grimmond2, Michael Findlay2, Cristina Print2.

Background:

- pNETs are a poorly understood cancer with a highly variable clinical outcome.
- Genomic analysis of pNETs may provide biological insights that guide therapy.

Methods:

- 69 sporadic well-differentiated pNETs from 60 individuals along with matched normal tissues underwent deep hybridization capture DNA sequencing of 638 genes and Affymetrix RNA microarrays. More in-depth genomic analysis was undertaken for 12 pNETs including low coverage whole genome sequencing, RNASeq analysis, methylation microarray analysis and microRNA expression microarray analysis.

Careful clinical annotation was conducted for each case, then cases de-identified prior to linking with genomic findings. Clinically relevant findings were returned to the patient’s physician if deemed appropriate by an incidental findings committee, for patients who consented.

Figure 1. Copy number variation and MEN1 mutation define three groups of well differentiated pNET with distinct clinical outcome.

Results

Unsupervised clustering of copy number changes defined three groups of pNETs with differing clinical characteristics and outcomes.

pNETs in group 1 (n=11) showed a recurrent pattern of LOH affecting the same 10 chromosomes, usually in the context of somatic MEN1 mutation, and often coupled with mutations in genes affecting genome integrity (ATRX, DAXX PTEN, MSH2 and TP53). Outcomes were unfavourable in this group: 5 of the 11 tumours metastasized; three patients progressed during the study, and 10 had lymphovascular invasion.

pNETs in group 2 (n=16) also showed chromosome 11 LOH, usually in the context of MEN1 mutation, but few other chromosomal copy number changes or mutations. This group had favourable outcomes; no patients metastasized, 15 were low grade (Ki67<2%), all had low expression of proliferation-associated RNAs and only three had LVI.

By contrast, group 3 (n=13) was characterized by absence of MEN1 gene mutation, contained tumours with variable patterns of aneuploidy (ranging from none to extensive) and normal Chromosome 11 copy number. pNETs in this group had intermediate outcomes.

This figure provides a more detailed breakdown of groups formed by unsupervised clustering of copy number and mutation data, including the distinguishing clinical and genomic characteristics. The mutation rate (<1 mutation per Mb in 98% of cases) was lower than published data for adenocarcinoma of any organ.

Conclusions:

- The clinical outcome of pNETs is related to a combination of somatic MEN1 mutation, changes in copy number at a chromosomal level, and mutations in genes related to genome integrity.
- Group 2 pNETs appear to be cured by surgical resection. Given the morbidity of surgery to the head of the pancreas, pNETs in this group might be suitable for a clinical trial that tests the role of observation vs resection.
- Group 1 pNETs will often require systemic therapy. Low MGMT expression may favour the use of temozolomide in this group. A project involving retrospective testing of chromosome 11 LOH and MGMT expression in pNETs treated with temozolomide is underway.