A novel classification of pancreatic neuroendocrine tumours (pNETs) guided by genomics

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Background

- NET outcomes differ by primary site. Yet pNETs are classified using a generic GI grading system.
- Genomics may assist prognostication of pNET behaviour in the clinic.

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. Tumours found not to be pNETs based on combined evidence from genomic and histopathological analysis were removed from this cohort (see ENETS 2018 Poster B14)

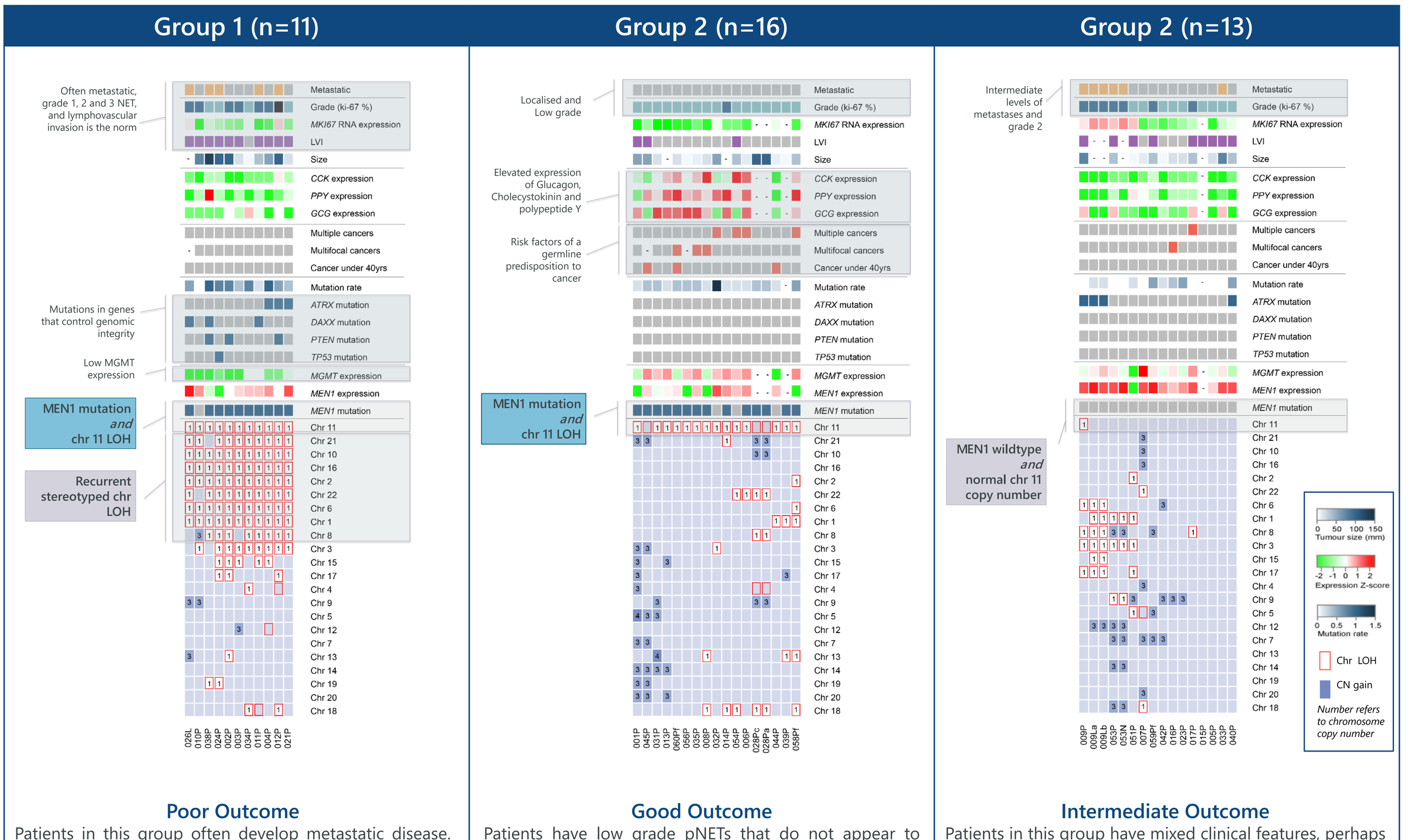
Results

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

- Group 1 (n=11): pNETs 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; 5 of the 11 tumours metastasised, three patients progressed during the study, and 10 had lymphovascular invasion.
- Group 2 (n=16): pNETs 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 (Ki-67 <2%), all had low expression of proliferation-associated RNAs and only three had LVI.
- 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. These pNETs had intermediate outcomes.

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

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.



Poor Outcome

Patients in this group often develop metastatic disease. The low MGMT expression may make temozolomide-based therapy appropriate. Low MGMT expression may be caused by MGMT haploinsufficiency (loss of 1 copy of chromosome 10), as there was no evidence of MGMT promoter hypermethylation.

Good Outcome

Patients have low grade pNETs that do not appear to metastasise. They undergo surgical resection without relapse. They may have a germline tendency to cancer, as they are more likely to develop second cancer, have multifocal NETs, and develop NETs at a young age. Systemic therapy is not required. Is surgical resection required, in light of lack of metastasis?

Intermediate Outcome

Patients in this group have mixed clinical features, perhaps because the group remains heterogenous outside the defining wild-type *MEN1* and normal copy number of chromosome 11. Approximately half of tumours were aneuploid.

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 temozolamide is underway.
- We plan to validate the proposed pNET classifications in a larger tumour set.

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