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.

### 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.

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 genes
- **Group 2 (n=16)**: pNETs showed chromosome 11 LoH, usually in the context of MEN1 mutation
- **Group 2 (n=13)**: pNETs showed chromosome 11 LoH, in the context of MEN1 mutation, but few other chromosomal copy number changes or mutations.

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.

### 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 CHROMsome 11 LOH and MGMT expression in pNETs treated with temozolomide is underway.
- We plan to validate the proposed pNET classifications in a larger tumour set.

### Table

<table>
<thead>
<tr>
<th>Group 1 (n=11)</th>
<th>Group 2 (n=16)</th>
<th>Group 2 (n=13)</th>
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<tbody>
<tr>
<td>Localised and low grade</td>
<td>Metastatic</td>
<td>Intermediate</td>
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<td>Distant</td>
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<td>Elevated expression</td>
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<td>Increased expression</td>
<td>Reduced expression</td>
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<tr>
<td>Mutations in genes that control genomic integrity</td>
<td>Low MGMT expression</td>
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<td></td>
<td>MEN1 mutation</td>
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<td>chr 11 LOH</td>
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</table>

**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 heterogeneous outside the defining wild-type MEN1 and normal copy number of chromosome 11. Approximately half of tumours were anaplastic.