Tighter diagnoses will enable not only more accurate clinical practice but also better research. While differentiation of SPN from pNET can be challenging, it is important as the diagnosis has different prognostic implications. Histological review had diagnosed these tumours as pNETs by morphological and immunohistochemical criteria but also noted uncertainty due to some variable. SPNs share some cytological features with pNETs but are genomically distinct, and have a discrete clinical course, staging and follow-up programme.

Methods

- 69 sporadic well-differentiated pNETs from 60 individuals along with matched normal tissues underwent deep hybridisation capture DNA sequencing of 637 genes and RNA expression analysis using Affymetrix microarrays.
- Cases selected had a clinical and pathological diagnosis of well-differentiated pNET, expressed at least one of the three neuroendocrine immunohistochemical protein markers (chromogranin A, synaptophysin or CD56) and were surgically resectable at initial diagnosis.
- 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 to this.

Clinical Characteristics

<table>
<thead>
<tr>
<th>Agressiveness</th>
<th>5 Year Survival</th>
<th>Treatment</th>
<th>Immunohistochemical</th>
<th>Morphological</th>
</tr>
</thead>
<tbody>
<tr>
<td>pNET</td>
<td>Variable malignant potential</td>
<td>75%(^1)</td>
<td>Surgery, chemotherapy using somatostatin analogues, mTOR inhibitor</td>
<td>Synaptophysin, chromogranin A, CD56, pan-cytokeratin, E-cadherin</td>
</tr>
<tr>
<td>SPN</td>
<td>Low-grade malignancy (local invasion / metastasis in 20%)</td>
<td>35%(^2)</td>
<td>Surgery, no chemotherapy options</td>
<td>Progesterone receptor, vimentin, CD10, nuclear β-catenin</td>
</tr>
</tbody>
</table>

In tumours from two patients initially diagnosed as pNETs, DNA, RNA and histopathological evidence contributed to re-diagnosis as SPNs.

Deep targeted DNA-seq

Revealed activating mutations\(^3\) in CTNNB1 encoding β-catenin, pathognomonic for SPNs - present in 90% of all SPN cases\(^4\).

RNA expression analysis

RNAs known to be up-regulated by β-catenin\(^5\) were highly expressed, in accord with the mutation’s activating effect.

Homoing in on precise diagnoses

- While differentiation of SPN from pNET can be challenging, it is important as the diagnosis has different prognostic implications. Genomic analysis provides a further tool for making this critical distinction. We believe that combining genomic information with traditional pathological information is likely to generate more precise diagnoses for many tumour types\(^6\).
- Tighter diagnoses will enable not only more accurate clinical practice but also better research – tighter tumour cohorts may lead to more real findings.

<table>
<thead>
<tr>
<th>Imprint</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>pNET</td>
<td>Normal</td>
</tr>
<tr>
<td>Tumour 029P</td>
<td>Normal</td>
</tr>
<tr>
<td>Tumour 048P</td>
<td>Normal</td>
</tr>
<tr>
<td>Patient 029</td>
<td>Revealed cellular relocalisation of β-catenin (brown) to the nucleus, concordant with SPN status and transcription factor function.</td>
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References:

1. Cherenfant et al. (2013) PMID 24074416
2. Ohara et al. (2016) PMID 27784972
3. Moreno-Bueno et al. (2001) PMID 11703283
4. Wikipedia.com - Michael Bonert
5. Moreno-Bueno et al. (2001) PMID 11703283
6. Wikipedia.com - Michael Bonert
7. Short et al. (2018) PMID 28780493
9. Cherenfant et al. (2013) PMID 24074416
10. Ohara et al. (2016) PMID 27784972
11. Moreno-Bueno et al. (2001) PMID 11703283
12. Wikipedia.com - Michael Bonert

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