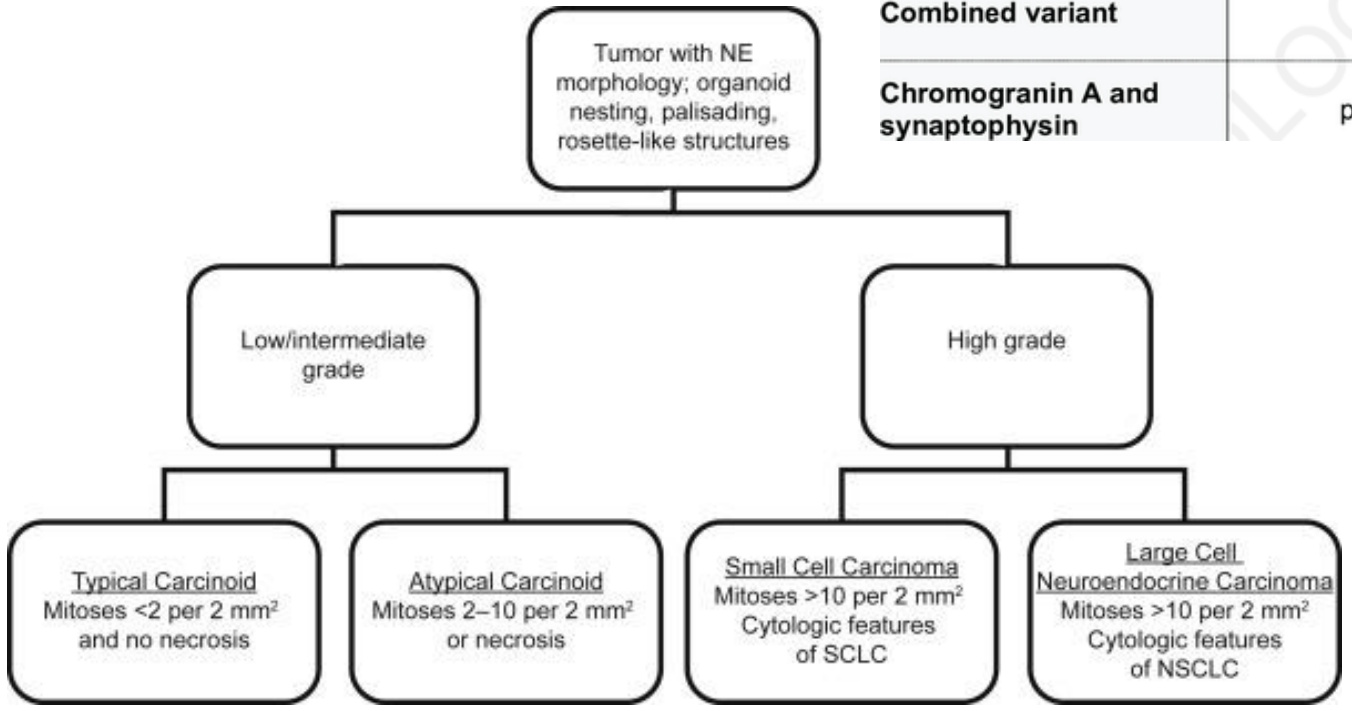
Atypical Lung Neuroendocrine Tumors

ANNA KOYMAPIANOY

Take home messages

Variable	Typical carcinoid	Atypical carcinoid	Large-cell neuroendocrine carcinoma	Small-cell carcinoma
Neuroendocrine morphology	yes (organoid)	yes (organoid)	yes (organoid)	yes (nuclear features)
Cytological criteria	no	no	yes	yes
Mitoses/2 mm^2	1	2-10	≥ 11	≥ 11
Necrosis	no	punctate	extensive	extensive
Use of immunohistochemistry	recommended	recommended	defining	recommended
Combined variant	no	no	yes	yes
Chromogranin A and synaptophysin	positive	positive	positive 80-90%	positive 80-90%



Pelosi, G. et al. Most high-grade neuroendocrine tumours of the lung are likely to secondarily develop from pre-existing carcinoids: innovative findings skipping the current pathogenesis paradigm. *Virchows Arch.* **472**, 567–577 (2018).

Rekhtman, N. et al. Next-generation sequencing of pulmonary large cell neuroendocrine carcinoma reveals small cell carcinoma-like and non-small cell carcinoma-like subsets. *Clin. Cancer Res.* **22**, 3618–3629 (2016).

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molecular profiles through integrative analysis of transcriptome and methylome data, using both machine learning (ML) techniques and multi-omics factor analyses (MOFA)

ARTICLE

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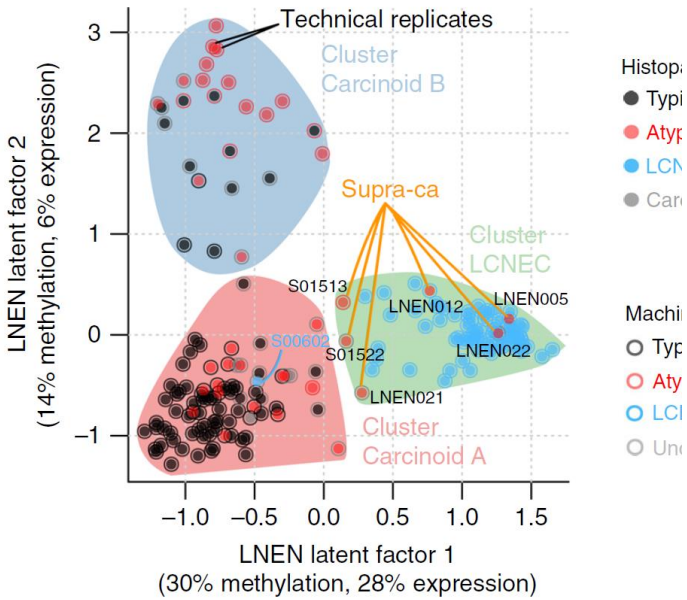
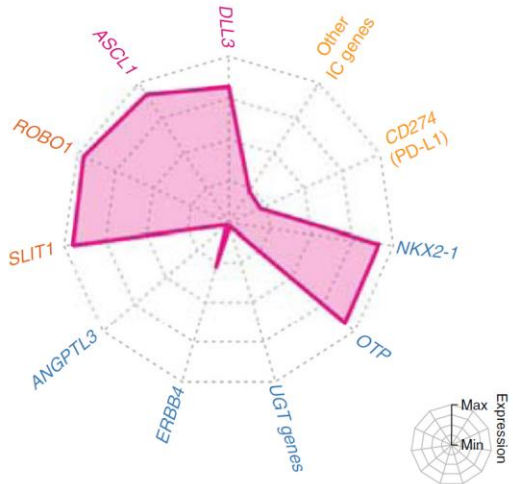
Integrative and comparative genomic analyses identify clinically relevant pulmonary carcinoid grc

N. Alcala et al.#

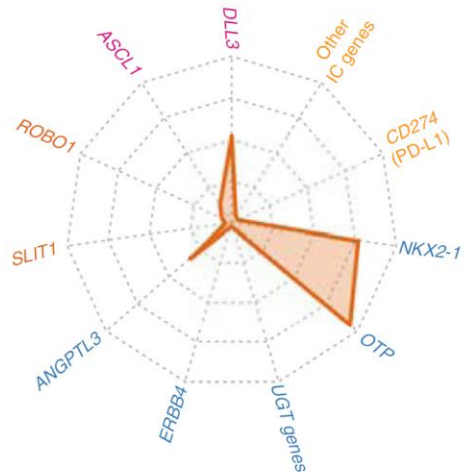
The worldwide incidence of pulmonary carcinoids is increasing, but little is known about their molecular characteristics. Through machine learning and multi-omics factor analysis, we compare and contrast the genomic profiles of 116 pulmonary carcinoids (including 35 atypical), 75 large-cell neuroendocrine carcinomas (LCNEC), and 66 small-cell lung cancers. Here we report that the integrative analyses on 257 lung neuroendocrine neoplasms stratify atypical carcinoids into two prognostic groups with a 10-year overall survival of 88% and 27%, respectively. We identify therapeutically relevant molecular groups of pulmonary carcinoids, suggesting DLL3 and the immune system as candidate therapeutic targets; we confirm the value of *OTP* expression levels for the prognosis and diagnosis of these diseases, and we unveil the group of supra-carcinoids. This group comprises samples with carcinoid-like morphology yet the molecular and clinical features of the deadly LCNEC, further supporting the previously proposed molecular link between the low- and high-grade lung neuroendocrine neoplasms.



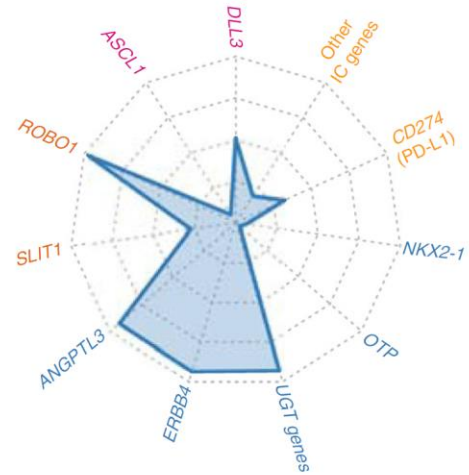
Cluster Carcinoid A1
- 10-year overall survival = 88%
- Median *MKI67* = 0.7 FPKM
- *DLL3*↑ *ASCL1*↑



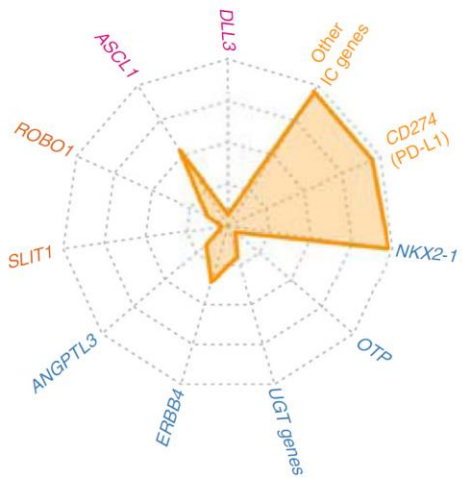
Cluster Carcinoid A2
- 10-year overall survival = 83%
- Median *MKI67* = 0.3 FPKM
- *EIF1AX* mutations
- *ROBO1*↓ *SLIT1*↓



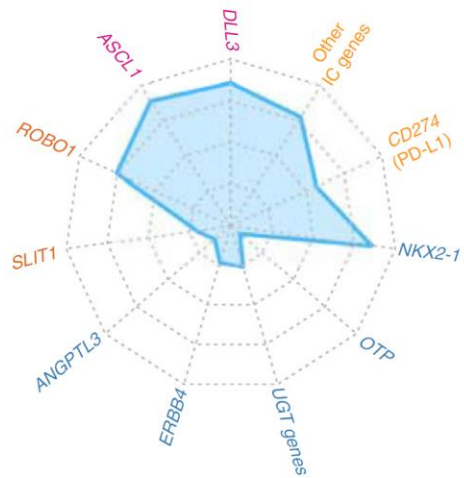
Cluster Carcinoid B
- 10-year overall survival = 60%
- Median *MKI67* = 0.4 FPKM
- *MEN1* mutations
- *ANGPTL3*↑ *ERBB4*↑ *UGT*↑ *OTP*↓ *NKX2-1*↓



Supra-ca
- 10-year overall survival = 33%
- Median *MKI67* = 2.6 FPKM
- IC receptors and ligands
- High neutrophil content



LCNEC
- 10-year overall survival = 21%
- Median *MKI67* = 10.3 FPKM



SCLC
- 10-year overall survival = 11%
- Median *MKI67* = 11.2 FPKM