

# Residents news

**Residents present their research work at USCAP 2024 (check the pictures in the next slides)**

- Dr. Dilara Akbulut wins the ISUP Stipend Award 2024 (<https://ccr.cancer.gov/laboratory-of-pathology#news>)
- Dr. Evsen Apaydin Arikan is elected Chief Resident 2024-2025
- Dr. Dilara Akbulut shares her experience as a LP clinical fellow (check the 2023/2024 Winter issue of the CCR-FYI newsletter [online here](#))
- Dr. Khaled Bin Satter presents his research work at the AACR 2024

# Evaluation of novel neuroendocrine transcription factor expressions (ASCL1, NEUROD1, POU2F3) in well differentiated neuroendocrine tumors

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## Background

- ASCL1, NEUROD1 and POU2F3 are novel transcription factors that play role in neuroendocrine differentiation.
- Their expression has been recently identified in high grade neuroendocrine carcinomas (NEC) in lung, with potential therapeutic and prognostic implications.
- A differential expression pattern with different subtypes have been shown in the tissue via immunohistochemistry.
- Different mutation profiles, hence reflecting the possible different biologic evolution between well-differentiated neuroendocrine tumors (NET) and high-grade neuroendocrine carcinomas were reported.
- In this study, we evaluate these novel markers' expression in a large group of NET, which has not been fully elucidated yet.

## Design

- Total of 270 cases were assessed in 7 multi-tissue tumor blocks.
- The cohort included 199 well differentiated NET:
  - 40 thoracic, 79 GI, 80 pancreatic NET.
- 29 NEC and 42 medullary thyroid carcinoma constituted the comparison group.
- ASCL1, NEUROD1 and POU2F3 immunostaining was performed and evaluated with external controls.
- Cases were considered positive with nuclear staining. weak to strong staining intensity. Staining percentages were also noted.

## Results

	Well differentiated NET THORACIC (n=40)	Well differentiated NET GI (n=79)	Well differentiated NET PANCREAS (n=80)	High grade NEC (n=71)
ASCL1 % (n)	23% (9)	1% (1)	1% (4)	23% (15)
NEUROD1 % (n)	0	0	4% (3)	0
POU2F3 % (n)	0	0	0	0

- ASCL1 was expressed in 14 out of 199 (7%) NET, with the following distribution:
  - 7 lung, 4 pancreatic, 2 thymic and 1 appendix NET.
- 7 of 42 (17%) medullary thyroid carcinoma and 8 of 29 (28%) NEC showed ASCL1 expression.
- Fisher's Exact Test was performed to compare ASCL1 expression between NET and NEC and showed significance with  $p=0.0025$ . (Figure 1)

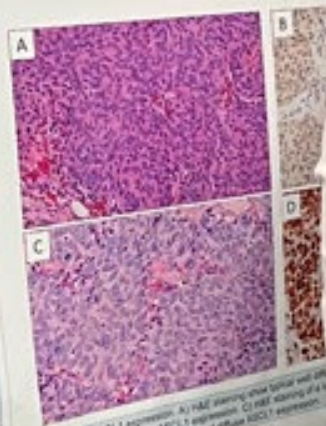


Figure 1. ASCL1 expression. A) H&E staining of typical well-differentiated NET. B) Weak and patchy ASCL1 expression in NET. C) Strong and diffuse ASCL1 expression in high-grade NET. D) Strong and diffuse ASCL1 expression in high-grade NEC.

## Results

- Staining intensity was higher in NEC compared to NET.
- Mean staining percentage for high-grade NEC was 40% and 17% for NET.
- A t-test was utilized to compare staining percentages among high-grade NEC and NET, with a p-value of  $<0.001$  (Figure 2).
- NEUROD1 was expressed in only 3 out of 80 pancreatic NET and was negative in the rest of the cases.
- POU2F3 expression was not detected in any of the cases.

Disclosure: The authors of this abstract have indicated that they have no conflicts of interest that relate to the content of this abstract.



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### Intercellular Adhesion Molecule-1 (ICAM-1) Expression in Antral Gastric Carcinoma

Lei Wang, Bao-Guang Chen, Zhong-Hua Chen, Jian-Hong Wang, Liang Wang, Hong-Hong Chen, Zhong-Hua Chen, Jian-Hong Wang, Liang Wang, Hong-Hong Chen

Background: ICAM-1 is a member of the immunoglobulin superfamily and is expressed on the surface of various cells. It plays a role in cell-cell and cell-matrix interactions. In this study, we evaluated the expression of ICAM-1 in antral gastric carcinoma and its relationship with clinicopathological parameters.

Methods: A total of 100 cases of antral gastric carcinoma were included in this study. Immunohistochemical staining was performed to detect the expression of ICAM-1. The expression was scored as 0, 1, 2, or 3 based on the intensity and percentage of positive cells.

Results: ICAM-1 expression was detected in 78 cases (78%). The expression was significantly higher in advanced stages (p < 0.05). There was no significant difference in ICAM-1 expression between different tumor locations (p > 0.05).

Conclusion: ICAM-1 expression is upregulated in antral gastric carcinoma and is associated with advanced stages. It may serve as a potential prognostic marker.

### High-Throughput Screening of Novel Therapeutic Targets in Hepatocellular Carcinoma

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death. Identifying novel therapeutic targets is crucial for improving patient outcomes. This study employed high-throughput screening (HTS) to identify potential targets in HCC cell lines.

Methods: A library of small molecules was screened against HCC cell lines. The primary screening was followed by secondary and tertiary screens to validate potential hits.

Results: Several novel compounds were identified that showed significant growth inhibition in HCC cell lines. These compounds are currently being evaluated in preclinical studies.

Conclusion: HTS is an effective strategy for identifying novel therapeutic targets in HCC. The identified compounds represent promising leads for further development.

# Moderate Posters

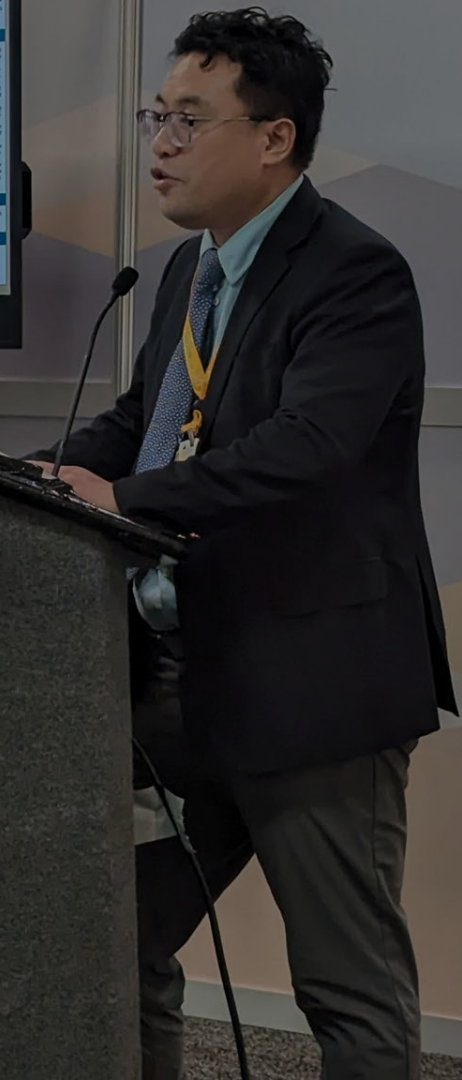
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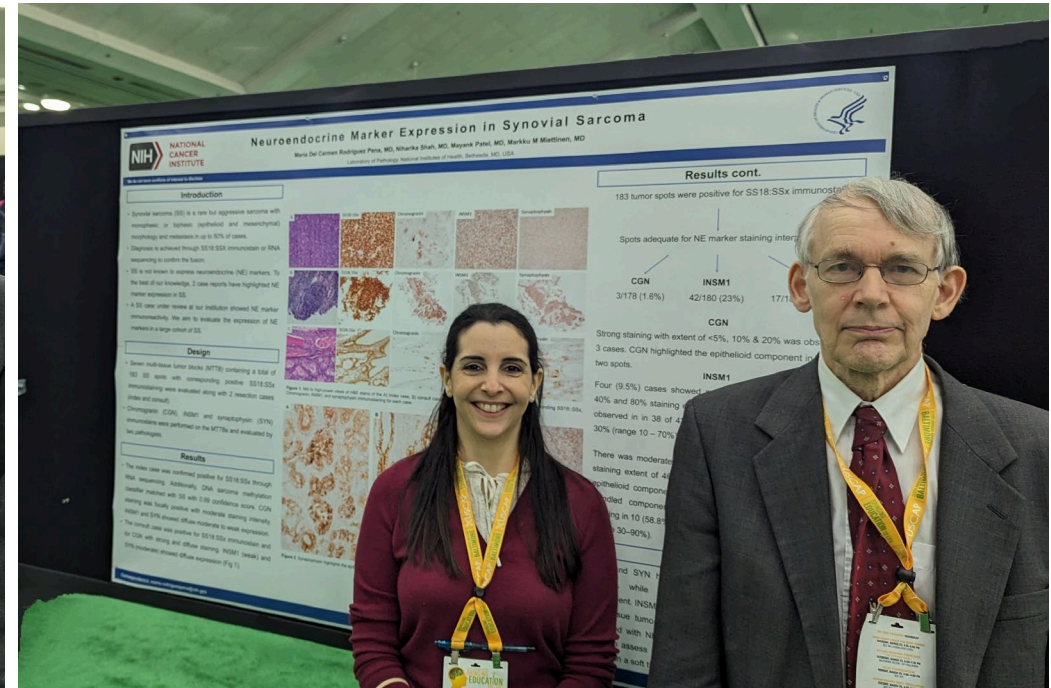
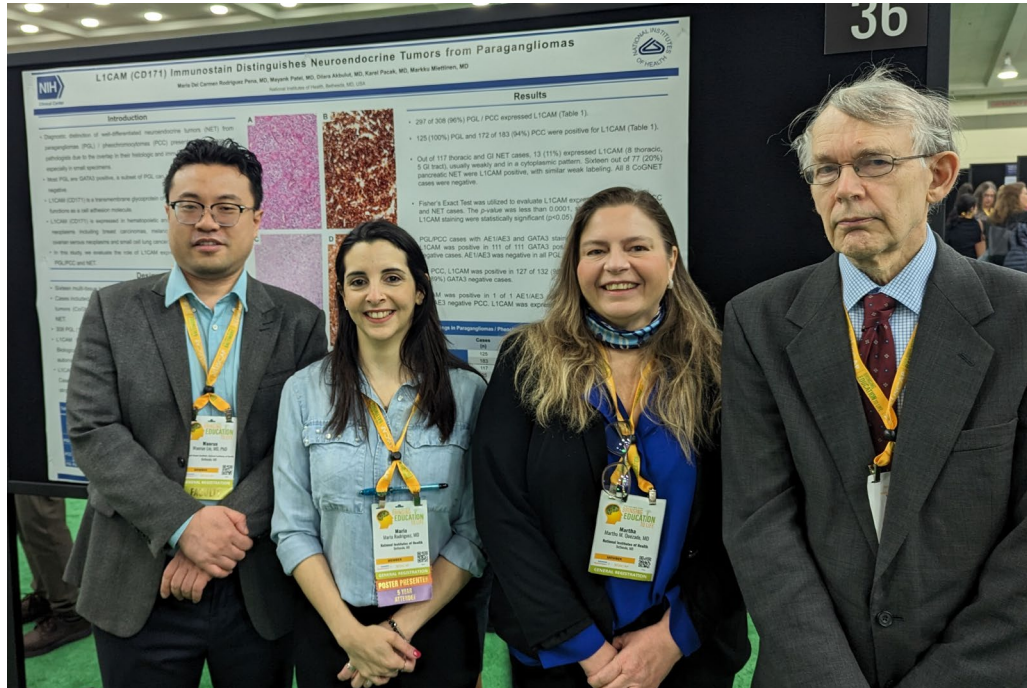
**Introduction**  
Endometrial cancer (EC) is the most common gynecologic cancer in the United States. The majority of EC cases are diagnosed at an early stage, with a 5-year survival rate of approximately 80%. However, the prognosis for advanced-stage EC is poor, with a 5-year survival rate of approximately 20%. The identification of biomarkers that predict response to treatment is critical for improving patient outcomes. POLE mutations are associated with a favorable prognosis in EC, and the presence of POLE mutations in EC is associated with a higher response rate to immunotherapy. The identification of biomarkers that predict response to immunotherapy is critical for improving patient outcomes.

Parameter	POLE Mutated (%)	POLE Wild-Type (%)	P-value
Overall Survival	8.0	10.7	0.027
Response Rate	7.0	10.0	0.03
Progression-Free Survival	7.0	10.0	<0.001
Time to Next Treatment	21.0	16.0	<0.001
Quality of Life	10.0	15.0	<0.001
Healthcare Costs	10.0	15.0	<0.001

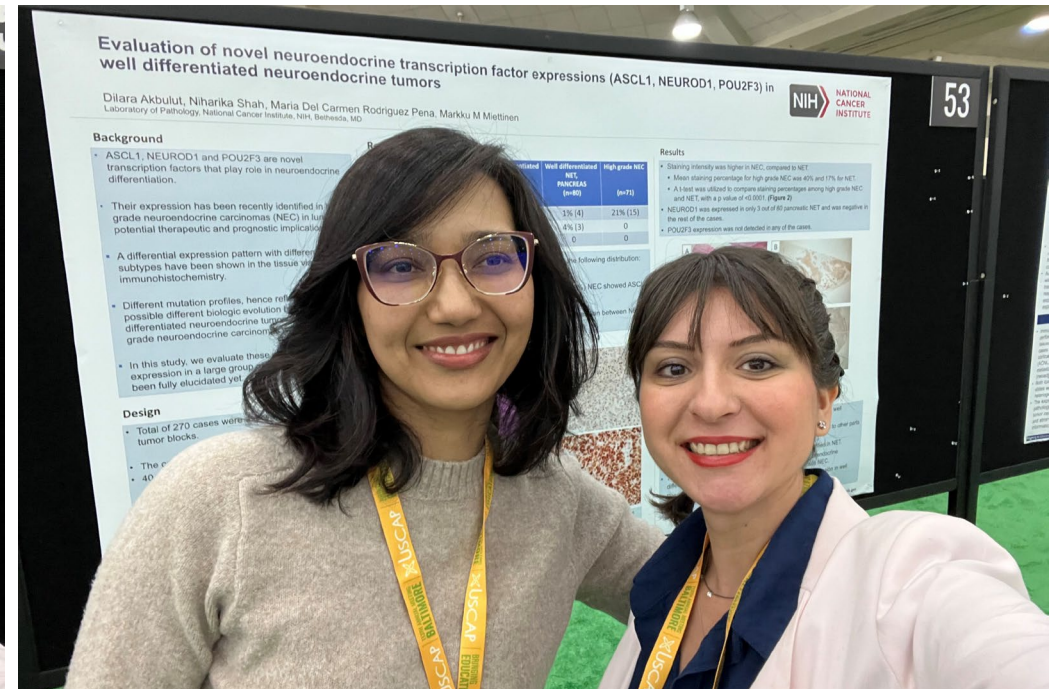
**Conclusion**  
Finding markers and nuclear protein expression that effectively use as pathologic POLE mutation in EC. These biomarkers and immunohistochemical features can serve as prognostic markers, potentially enhancing the response rate to immunotherapy. This research suggests efficacy and resource allocation. This research may, particularly, benefit regions with limited healthcare resources, such as developing countries. However, additional validation through larger-scale studies is imperative to facilitate their clinical application.



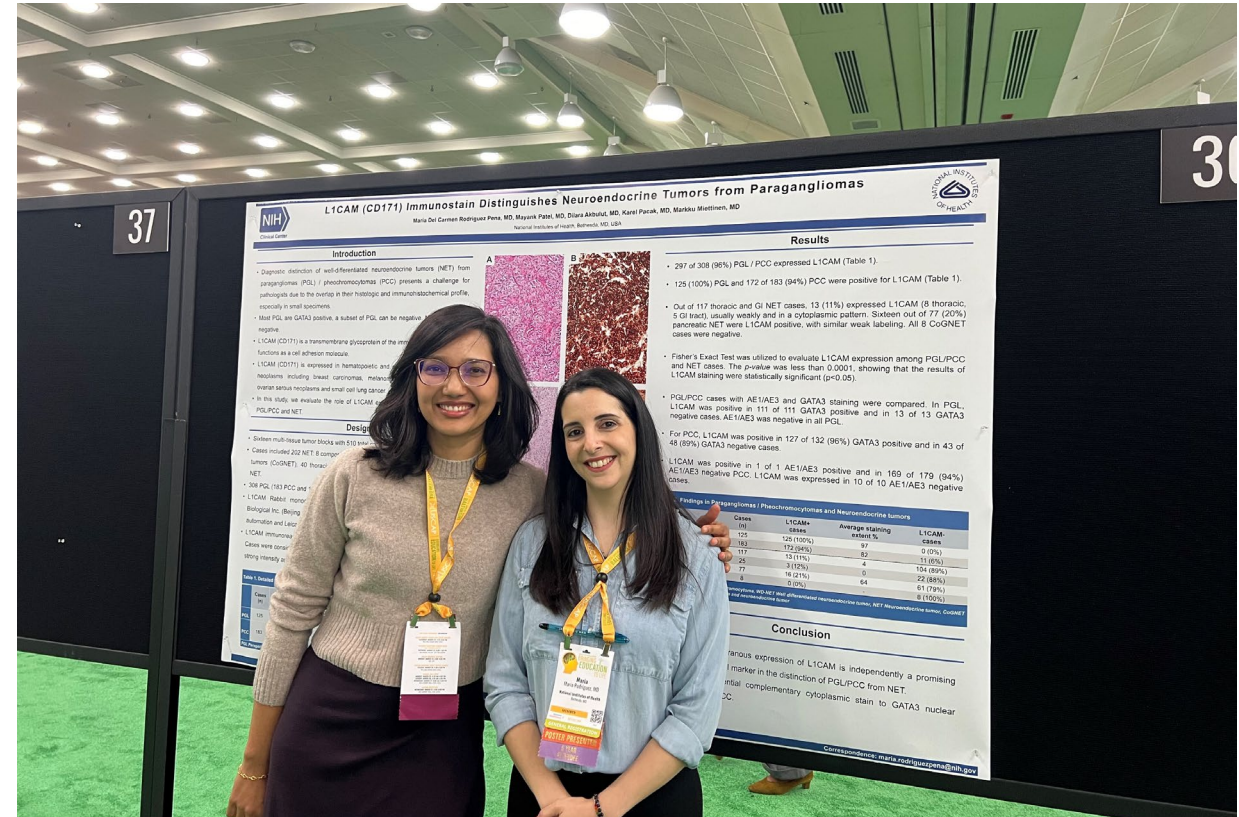
# Poster presentation



# Poster presentation



# Poster presentation



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EXHIBIT HALL HOURS

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9:30 AM-5:00 PM

Tuesday, March 26  
9:30 AM-5:00 PM

Wednesday, March 27  
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# Poster presentation

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**L1CAM (CD171) Immunostain Distinguishes Neuroendocrine Tumors from Paragangliomas**  
 Maria Del Carmen Rodriguez Pena, MD, Mayank Patel, MD, Dilara Akbulut, MD, Karol Pacak, MD, Markku Mattinen, MD  
 National Institutes of Health, Bethesda, MD, USA

**Introduction**

- Diagnostic distinction of well-differentiated neuroendocrine tumors (NET) from paragangliomas (PGL) / pheochromocytomas (PCC) presents a challenge for pathologists due to the overlap in their histologic and immunohistochemical profile, especially in small specimens.
- Most PGL are GATA3 positive, a subset of PGL can be negative. NET are GATA3 negative.
- L1CAM (CD171) is a transmembrane glycoprotein of the immunoglobulin group that functions as a cell adhesion molecule.
- L1CAM (CD171) is expressed in hematopoietic and epithelial cells, and various neoplasms including breast carcinomas, melanomas, neuroblastomas, PGL, ovarian serous neoplasms and small cell lung cancer.
- In this study, we evaluate the role of L1CAM expression in a diverse group of PGL/PCC and NET.

**Design**

- Sixteen multi-tissue tumor blocks with 510 total cases were assessed.
- Cases included 202 NET, 8 composite gangliocytoma/neuroma and neuroendocrine tumors (CoGNET), 40 thoracic, 77 gastrointestinal (GI) tract, and 77 pancreatic NET.
- 308 PGL (183 PCC and 125 extra-adrenal PGL) formed the comparison group.
- L1CAM Rabbit monoclonal antibody (10140-R014) was obtained from Sino Biological Inc. (Beijing, China). Immunostaining performed with the Leica Bond-Max automation and Leica Refine detection kit (Leica Biosystems, Bannockburn, IL).
- L1CAM immunoreactivity in peripheral nerves served as internal positive control. Cases were considered L1CAM positive with focal (at least 10%) to diffuse, weak to strong intensity and membranous / cytoplasmic staining.

**Results**

- 297 of 308 (96%) PGL / PCC expressed L1CAM (Table 1).
- 125 (100%) PGL and 172 of 183 (94%) PCC were positive for L1CAM (Table 1).
- Out of 117 thoracic and GI NET cases, 13 (11%) expressed L1CAM (5 GI tract), usually weakly and in a cytoplasmic pattern. Six pancreatic NET were L1CAM positive, with similar weak cytoplasmic staining. All other NET cases were negative.
- Fisher's Exact Test was utilized to evaluate L1CAM expression in PGL/PCC and NET cases. The p-value was less than 0.0001, showing L1CAM staining were statistically significant (p<0.05).
- PGL/PCC cases were L1CAM positive and in 13% of NET cases, L1CAM was positive and in 15% of NET cases, L1CAM was negative.
- L1CAM was positive in 48 (89%) GATA3 positive cases.

**Table 1. Detailed immunohistochemical findings in Paragangliomas / Pheochromocytomas**

Cases (n)	L1CAM +	Staining Extent		Staining Pattern		Staining Intensity	Weak
		50-100%	49-10%	Cytoplasmic	Membranous		
PGL	125 (100%)	122 (97.6%)	3 (2.4%)	0	123 (97.6%)	0	3 (2.4%)
PCC	183 (94%)	172 (93.9%)	11 (6.1%)	172 (100%)	0	165 (90.2%)	7 (4%)

**Table 2. Findings by Tumor Type**

Tumor Type	L1CAM Positive (%)	L1CAM Negative (%)
PGL/PCC	96%	4%
NET	11%	89%

**Figure 1. L1CAM expression in representative tumors from the study.** A: NET showing strong cytoplasmic staining pattern in a pheochromocytoma with CD171. B: PGL showing strong membranous staining in a paraganglioma with CD171. C: NET showing weak cytoplasmic staining in a neuroendocrine tumor with CD171. D: PGL showing strong membranous staining in a paraganglioma with CD171. E: NET showing weak cytoplasmic staining in a neuroendocrine tumor with CD171. F: PGL showing strong membranous staining in a paraganglioma with CD171.

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**Microlesions and  $\beta$ -Catenin Predict POLE Mutation-Driven Endometrial Cancer: A Pathway to More Cost-Effective Diagnostic Procedures**  
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 Department of Pathology, UT Southwestern Medical Center, Dallas, TX, USA

**Introduction**

Endometrial cancer (EC) is the most common gynecologic malignancy with variable survival rates dependent on the stage at diagnosis [1]. Recent genome-wide analyses have identified four microRNA signatures of endometrial carcinomas: DNA polymerase epsilon (POLE) mismatch repair-deficient (MMRd), MMRd, MMRd, and non-specific molecular profile (NSMP). POLE-mutated endometrial cancer is characterized by a high degree of genomic instability, resulting in a high frequency of copy number alterations, including gains of 12q and losses of 18q [2]. The NSMP signature is associated with a high degree of genomic instability, resulting in a high frequency of copy number alterations, including gains of 12q and losses of 18q [2].

**AIM**

The study investigates the correlation between distinct morphological features, specifically squamous metaplasia and SO, as well as  $\beta$ -catenin expression, with POLE mutation status in EC. The aim is to streamline diagnostic procedures and enhance time and cost-efficiency in identifying POLE-mutated status in EC patients.

**Method**

Our study included 36 POLE-mutated (POLEmut) EC and 388 non-POLEmut (EC) cases. Immunohistochemical features were assessed, including squamous metaplasia, SO, and  $\beta$ -catenin expression. Statistical analysis was performed using Fisher's exact test and logistic regression. Representative images of POLEmut EC are shown in Figure 1, morphology of POLEmut EC in EC and  $\beta$ -catenin expression is displayed in Figure 2.

**RESULTS**

Microlesions were absent in all POLEmut cases, while SO was present in 20% in non-POLEmut cases. Squamous metaplasia and SO were significantly associated with POLEmut status (P=0.028). POLEmut ECs showed higher performance in identifying EC cases compared to non-POLEmut ECs. Clinical cases are summarized in Table 1.

**CONCLUSION**

Microlesions and squamous metaplasia are not reliable and nuclear  $\beta$ -catenin expression is not a reliable marker for identifying POLEmut ECs. These morphological features, including squamous metaplasia and SO, are more reliable and cost-effective diagnostic procedures. This research may benefit regions with limited healthcare resources and improve diagnostic accuracy. Further large-scale studies are imperative to validate these findings.

**REFERENCE**

1. American Cancer Society. Cancer Facts and Figures 2020. Atlanta, GA: American Cancer Society; 2020. 2. Sun J, Wang H, Wang Y, et al. Genomic instability in endometrial cancer: a high-throughput analysis of copy number alterations. *J Clin Oncol*. 2014;32(27):2921-2928.





# L1CAM (CD171) Immunostain Distinguishes Neuroendocrine Tumors from Paragangliomas

Maria Del Carmen Rodriguez Pena, MD, Mayank Patel, MD, Dilara Akbulut, MD, Karel Pacak, MD, Markku Miettinen, MD  
National Institutes of Health, Bethesda, MD, USA



## Introduction

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- L1CAM immunoreactivity in peripheral nerves served as internal positive control. Cases were considered L1CAM positive with focal (at least 10%) to diffuse, weak to strong intensity and membranous / cytoplasmic staining.

Table 1. Detailed immunohistochemical findings in Paragangliomas / Pheochromocytomas

Cases (n)	L1CAM +	Staining Extent			Staining Pattern		Staining Intensity	
		50-100%	48-10%	0-4%	Cytoplasmic	Membranous	Strong	Weak
PGL	125	125 (100%)	122 (97.6%)	3 (2.4%)	0	125 (100%)	0	122 (97.6%)
PCC	183	172 (94%)	154 (89.5%)	15 (8.7%)	3 (1.7%)	172 (100%)	0	165 (95.9%)

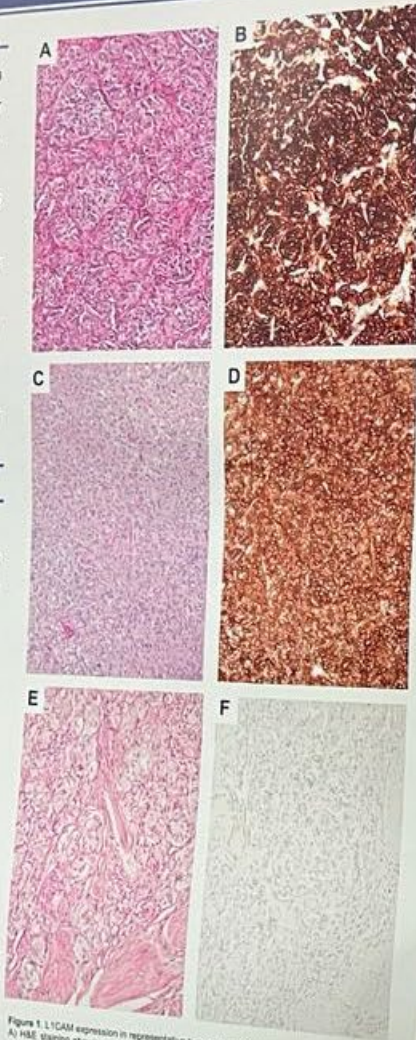


Figure 1. L1CAM expression in representative tumors from the study. A) H&E staining showing typical "zellballer" pattern in a pheochromocytoma with B) strong diffuse L1CAM expression. C) H&E staining on a pancreatic neuroendocrine tumor with D) strong and diffuse L1CAM expression. E) H&E staining on a composite gangliocytoma/paraganglioma neuroendocrine tumor with F) L1CAM expression. G) H&E staining on a composite gangliocytoma/paraganglioma neuroendocrine tumor with E) lack of L1CAM expression. All images at 20x magnification.

## Results

- 297 of 308 (96%) PGL / PCC expressed L1CAM (Table 1).
- 125 (100%) PGL and 172 of 183 (94%) PCC were positive for L1CAM (Table 1).
- Out of 117 thoracic and GI NET cases, 13 (11%) expressed L1CAM (8 thoracic, 5 GI tract), usually weakly and in a cytoplasmic pattern. Sixteen out of 77 (20%) pancreatic NET were L1CAM positive, with similar weak labeling. All 8 CoGNET cases were negative.
- Fisher's Exact Test was used to compare L1CAM expression among PGL/PCC and NET cases. The p-value was 0.0001, showing that the results of L1CAM staining were statistically significant (p < 0.05).
- PGL/PCC cases with L1CAM expression were compared. L1CAM was positive in 100% of PGL and in 13 of 13 (100%) PCC negative cases. All cases were negative.
- For PCC, L1CAM was positive in 94% (172/183) GATA3 positive and 48 (89%) GATA3 negative cases.
- L1CAM was positive in 100% (125/125) GATA3 positive and in 169 of 177 (95.5%) GATA3 negative PCC. L1CAM was positive in 10 of 10 AE1/AE3 negative PCC.

Table 2. Findings in Paragangliomas / Pheochromocytomas

Tumor type	L1CAM +	L1CAM -
PGL	125 (100%)	0
PCC	172 (94%)	11 (6%)
WD	125 (100%)	0
NET	13 (11%)	104 (89%)
CoGNET	0	8 (100%)
Pancreatic NET	16 (20%)	61 (80%)
Thoracic NET	8 (11%)	64 (89%)
GI NET	5 (11%)	40 (89%)

