Non-ductal pancreatic tumor classification by whole genome DNA prolfiling

Anna Vera D. Verschuur  
Florine Westerbeke  
Wenzel M. Hackeng  
Christoph Geisenberger  
Lodewijk A.A. Brosens

# Abstract

*Background and aim:* Histopathological diagnosis of acinar cell carcinoma’s (ACC), solid pseudopapillary neoplasm (SPN) and pancreatic neuroendocrine neoplasms (PanNETs) may be challenging in daily clinical practice. As the cancer methylome harbors characteristics reflecting the cell of origin allowing identification of tumor origin, here we build a methylation profiling based classifier in order to facilitate differentiation between ACC, SPN and PanNETs.  
*Methods:  
Results:  
Conclusion:*

# Introduction

Acinar cell carcinoma’s (ACC), solid pseudopapillary neoplasm (SPN) and pancreatic neuroendocrine neoplasms (PanNETs) comprise 1%, 2% and 5% of all pancreatic neoplasms respectively and are the most commonly occurring neoplasms that arise from non-ductal structures of the pancreas in adults [1, 2]. Behavior varies widely, where SPNs are predominantly indolent, while ACCs and PanNETs come close to the aggressiveness of their ductal counterpart pancreatic ductal adenocarcinoma (PDAC) [3-6]. ACC, SPN and PanNETs resemble in histomorphology and immunophenotype [1, 2]. Increased use of immunohistochemistry and genetics have contributed to better classification of these tumors. Despite, differentiation sometimes remains challenging while it is crucial for therapeutic decision making and prognosis.  
  
Whole genome methylation based tumor classification is increasingly used for tumor classification [7]. DNA methylation is an epigenetic mechanism regulating gene expression. Hypermethylation of specific gene promotor regions can lead to transcriptional suppression and thereby inactivation of certain genes, including tumor suppressor genes [8, 9]. Besides somatically acquired DNA methylation changes, the cancer methylome harbors characteristics reflecting the cell of origin allowing for identification of tumor origin. Based on this rationale numerous classifiers have been developed for cancer classification and some are routinely used in daily practice [10-15]. Similarly Hackeng et al developed a classifier for distinguishing different neuroendocrine tumors, including PanNETs [16]. Additionally, Jäkel et al. compared methylomes of ACCs, PanNETs and PDAC and showed that tumor types could be distinguished on methylation profiles [17]. Together, these data suggest potential applicability of methylation profiling for classification of non-ductal pancreatic tumors.

To facilitate differentiation between three non-ductal pancreatic tumors ACC, SPN and PanNET, here we build a methylation profiling based prediction model. To this end we used three different machine and deep learning algorithms and selected the best performing classifier based on the accuracy in predicting ACC, SPN and PanNET primaries.

1. Dhillon, J., *Non-Ductal Tumors of the Pancreas.* Monogr Clin Cytol, 2020. **26**: p. 92-108.

2. Hackeng, W.M., et al., *Surgical and molecular pathology of pancreatic neoplasms.* Diagn Pathol, 2016. **11**(1): p. 47.

3. Papavramidis, T. and S. Papavramidis, *Solid pseudopapillary tumors of the pancreas: review of 718 patients reported in English literature.* J Am Coll Surg, 2005. **200**(6): p. 965-72.

4. Schmidt, C.M., et al., *Acinar cell carcinoma of the pancreas in the United States: prognostic factors and comparison to ductal adenocarcinoma.* J Gastrointest Surg, 2008. **12**(12): p. 2078-86.

5. Sonbol, M.B., et al., *Survival and Incidence Patterns of Pancreatic Neuroendocrine Tumors Over the Last 2 Decades: A SEER Database Analysis.* Oncologist, 2022. **27**(7): p. 573-578.

6. Wisnoski, N.C., et al., *672 patients with acinar cell carcinoma of the pancreas: a population-based comparison to pancreatic adenocarcinoma.* Surgery, 2008. **144**(2): p. 141-8.

7. Pan, Y., et al., *DNA methylation profiles in cancer diagnosis and therapeutics.* Clin Exp Med, 2018. **18**(1): p. 1-14.

8. Shen, H. and P.W. Laird, *Interplay between the cancer genome and epigenome.* Cell, 2013. **153**(1): p. 38-55.

9. Ehrlich, M., *DNA methylation in cancer: too much, but also too little.* Oncogene, 2002. **21**(35): p. 5400-13.

10. Capper, D., et al., *DNA methylation-based classification of central nervous system tumours.* Nature, 2018. **555**(7697): p. 469-474.

11. Jurmeister, P., et al., *Machine learning analysis of DNA methylation profiles distinguishes primary lung squamous cell carcinomas from head and neck metastases.* Sci Transl Med, 2019. **11**(509).

12. Koelsche, C., et al., *Sarcoma classification by DNA methylation profiling.* Nat Commun, 2021. **12**(1): p. 498.

13. Leitheiser, M., et al., *Machine learning models predict the primary sites of head and neck squamous cell carcinoma metastases based on DNA methylation.* J Pathol, 2022. **256**(4): p. 378-387.

14. Maas, S.L.N., et al., *Integrated Molecular-Morphologic Meningioma Classification: A Multicenter Retrospective Analysis, Retrospectively and Prospectively Validated.* J Clin Oncol, 2021. **39**(34): p. 3839-3852.

15. Moran, S., et al., *Epigenetic profiling to classify cancer of unknown primary: a multicentre, retrospective analysis.* Lancet Oncol, 2016. **17**(10): p. 1386-1395.

16. Hackeng, W.M., et al., *Genome Methylation Accurately Predicts Neuroendocrine Tumor Origin: An Online Tool.* Clin Cancer Res, 2021. **27**(5): p. 1341-1350.

17. Jakel, C., et al., *Genome-wide genetic and epigenetic analyses of pancreatic acinar cell carcinomas reveal aberrations in genome stability.* Nat Commun, 2017. **8**(1): p. 1323.