

BEDSIDE TO BENCH REPORT



Identification of a novel metabolic-related mutation (*IDH1*) in metastatic pancreatic cancer

Jonathan R. Brody^{a,*}, Cinthya S. Yabar^{a,*}, Mahsa Zarei^{a,**}, Joseph Bender^{b,**}, Lynn M. Matrisian^c, Lola Rahib^c, Craig Heartwell^b, Kimberly Mason^b, Charles J. Yeo^a, Stephen C. Peiper^d, Wei Jiang^d, Katelyn Varieur^b, Subha Madhavan^{b,e}, Emanuel Petricoin III^b, Danielle Fortuna^d, Mark Curtis^d, Zi-Xuan Wang^d, Michael J. Pishvaian^{b,e,**}, and Jordan M. Winter^a

^aDepartment of Surgery, Jefferson Pancreas, Biliary and Related Cancer Center, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA; ^bPerthera, Inc., McLean, VA, USA; ^cThe Pancreatic Cancer Action Network, Manhattan Beach, CA, USA; ^dDepartment of Pathology, Thomas Jefferson University, Philadelphia, PA, USA; ^eLombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC, USA

ABSTRACT

Isocitrate dehydrogenase 1 (*IDH1*) is a metabolic enzyme implicated in cancer cell metabolic reprogramming. This is underscored by the detection of functional, somatic *IDH1* mutations frequently found in secondary glioblastoma. To our knowledge, there has never been a reported, validated case of an *IDH1* mutation in a pancreatic ductal adenocarcinoma (PDA). Herein, we present a case of a patient with metastatic PDA that harbored a potentially actionable, albeit rare, *IDH1* mutation. As part of the Know Your Tumor project (Pancreatic Cancer Action Network), a 48-year-old female was diagnosed with metastatic PDA and subsequently started on standard of care chemotherapy, during which her hepatic lesions progressed. Detailed molecular profiling was performed on a biopsy from a liver lesion that demonstrated an *IDH1* mutation, R132H. This mutation was confirmed by an independent sequencing reaction from the tumor sample, and by immunohistochemistry using an antibody specific for the *IDH1* R132H mutation. The patient subsequently received a mutant *IDH1* inhibitor (AG-120, Agios Pharmaceuticals, Cambridge, MA), but with no response. *IDH1* mutations are common in certain cancer types, but have not been reported in PDA. We report the first case of an *IDH1* mutation in this tumor type, perhaps providing a rare opportunity for a targeted therapy as a treatment option for PDA.

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Introduction

Isocitrate dehydrogenase 1 (*IDH1*) is the most commonly mutated metabolic enzyme in human cancer.^{1,2} The recent discovery of somatic *IDH1* mutations in diverse cancer types emphasizes the importance of metabolic pathways in cancer biology. Moreover, the discovery of small compounds that selectively target this enzyme (but spare the wild type isoenzyme) has ushered in a wave of optimism for the treatment of *IDH1* mutant tumors.³ Despite widespread molecular profiling for the purposes of targeted therapy, the FDA has approved therapies against just 12 genetic mutations,^{4–18} underscoring the infrequency of this type of discovery. Overall 25,000 new cancer diagnoses per year are associated with an *IDH1* mutation, including: secondary glioblastoma, low grade gliomas, anaplastic gliomas, central chondrosarcomas, intrahepatic cholangiocarcinomas, melanoma, and anaplastic thyroid cancer. To our knowledge, there has not been a reported *IDH1* mutation in pancreatic ductal adenocarcinoma (PDA).^{19–21}

Functionally, *IDH1* is a cytoplasmic enzyme that catalyzes the reversible interconversion of isocitrate and α -ketoglutarate. NADP is a cofactor for this reaction, and is either oxidized (with

isocitrate formation) or reduced (with α -ketoglutarate formation).²² The mutant isoenzyme typically contains a heterozygous missense substitution at arginine 132. The wild type amino acid is most commonly replaced by a histidine, but may also be replaced by a serine, cysteine, or glycine.^{23,24} The mutated enzyme diverts α -ketoglutarate into an alternative reductive pathway that produces an oncometabolite, 2-hydroxyglutarate (*D*-2HG).²⁵ The accumulation of *D*-2HG leads to increased DNA and histone methylation, which in turn drives cancer cell dedifferentiation.^{26–28} Previous studies suggest that *IDH1* mutant tumors have a more favorable prognosis compared to *IDH1* wild type tumors, and they are more vascularized. In addition, *IDH1* mutant tumors are more sensitive to both harsh metabolic conditions and chemotherapy than their wild type counterparts.^{29,30} Since PDA is characterized by a harsh and nutrient deprived microenvironment (similar to primary glioblastomas which contain wild type *IDH1*),^{31–33} it stands to reason that *IDH1* mutations may in fact be deleterious for PDA and selected against, which could account for the absence of any reported *IDH1* mutations to date. Herein, we report for the first time, a case of PDA with a bona fide and validated *IDH1* R132H mutation.

CONTACT Jordan M. Winter  Jordan.Winter@jefferson.edu  Department of Surgery Jefferson Pancreas, Biliary, and Related Cancer Center Thomas Jefferson University, Walnut Street, Curtis, PA, USA.

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*Contributed equally (first authors)

**Contributed equally (second authors)

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Clinical case report

A 48-year-old woman presented with stage IV PDA, and was noted to have a 7 cm liver mass, enlarged retroperitoneal lymphadenopathy, a 1.8 × 1.4 cm lesion in the uncinate process of the pancreas (likely the primary), and a 5 × 4 mm right middle lobe lung lesion. Notably, the details of her clinical presentation were not known to the study authors, since her care was performed at another institution and we were privy to just clinical information provided with biopsy material obtained for molecular profiling. The patient had a family history of prostate cancer in her father, and breast cancer in her maternal grandmother. A percutaneous biopsy of the liver lesion was presumed to be metastatic adenocarcinoma of pancreatic origin by histology.

As first line therapy, the patient received a standard combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX).³⁴ This regimen temporarily controlled the disease until progression was observed after 9 months. As second line therapy, a course of gemcitabine, nab-paclitaxel, and pembrolizumab (a PD-1 inhibitor) was given, as part of a clinical trial.³⁵ The patient had stable disease for an additional 5 months on this regimen. Upon progression, a second biopsy of the liver lesion was performed with repeat molecular profiling. Histologic evaluation revealed foci of both well and poorly differentiated tumor, including features consistent with a high grade histologic phenotype, as shown in Figs. 1A and 1C.

The biopsy specimen was sent for molecular profiling (Foundation Medicine, Cambridge, MA), which identified mutations in *KRAS*, *CDKN2A*, *CDKN2B*, *PLCG2*, and *IDH1*. Sanger sequencing and next-generation sequencing (NGS) were used to confirm the *IDH1* mutation (R132H) (Figs. 2A

and 2B) at Thomas Jefferson University (Department of Pathology). Immunohistochemistry with a mutant-*IDH1* specific antibody (Dianova, Hamburg, Germany) provided additional confirmation³⁶ (Fig. 1B and 1D). A Catalog of Somatic Mutations in Cancer (COSMIC, <http://www.sanger.ac.uk/genetics/CGP/cosmic/>) database search of *IDH1* mutations demonstrates the high prevalence of this mutation in central nervous system malignancies, as opposed to the rare occurrence in pancreatic cancers (Table 1).

The patient enrolled in a Phase I trial of an inhibitor targeted to mutant *IDH1* (AG-120, Agios Pharmaceuticals, Cambridge, MA) for advanced solid tumors,³⁷ but progressed after just 1 cycle of therapy. The patient's current clinical status is unknown.

Discussion

Somatic mutations in *IDH1* (R132H, R132G) have been reported in intraductal papillary mucinous neoplasms of the pancreas.³⁸ However, this report provides the first evidence of an intragenic *IDH1* R132H mutation in PDA.^{20,21} A close examination of the mutant and wild type *IDH1* literature hints at why *IDH1* mutations may be a rare event in PDA. While *IDH1* mutations are considered a gain of function mutation that leads to the generation of 2-hydroxyglutarate, there is also a clear element of functional loss, due to haploinsufficiency of the wild type allele. For instance, mutant *IDH1* isoenzymes are less efficient at catalyzing the reductive carboxylation of α -ketoglutarate (into isocitrate), they are more sensitive to chemotherapy, and they are more susceptible to the ill effects of hypoxia.^{1,2,29,30} Moreover, in

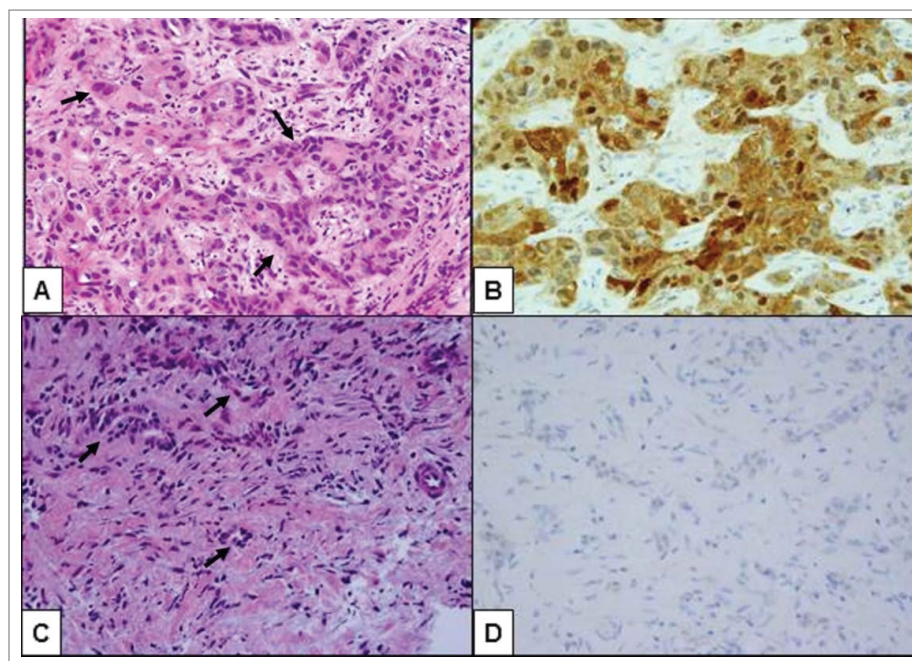


Figure 1. Histologic review of the second biopsy showed high grade pancreatic ductal adenocarcinoma (PDA), metastatic to the liver throughout the tissue cores (original magnification 400X). (A) Areas of undifferentiated tumor cells containing markedly pleomorphic nuclei were arranged in highly cellular nests and clusters of malignant cells (arrows) within a relatively scarce fibrotic stroma. (B) These undifferentiated tumor cells were positive by immunohistochemistry for *IDH1* (R132H) mutation. (C) Distinct areas of the tumor biopsy demonstrated less tumor pleomorphism that was more characteristic of conventionally tubular morphology (arrows). (D) In contrast to high grade foci, the well-differentiated foci were negative by immunohistochemical stain for *IDH1* (R132H) mutation, consistent with *IDH1* wild type status of tumor cells in these areas.

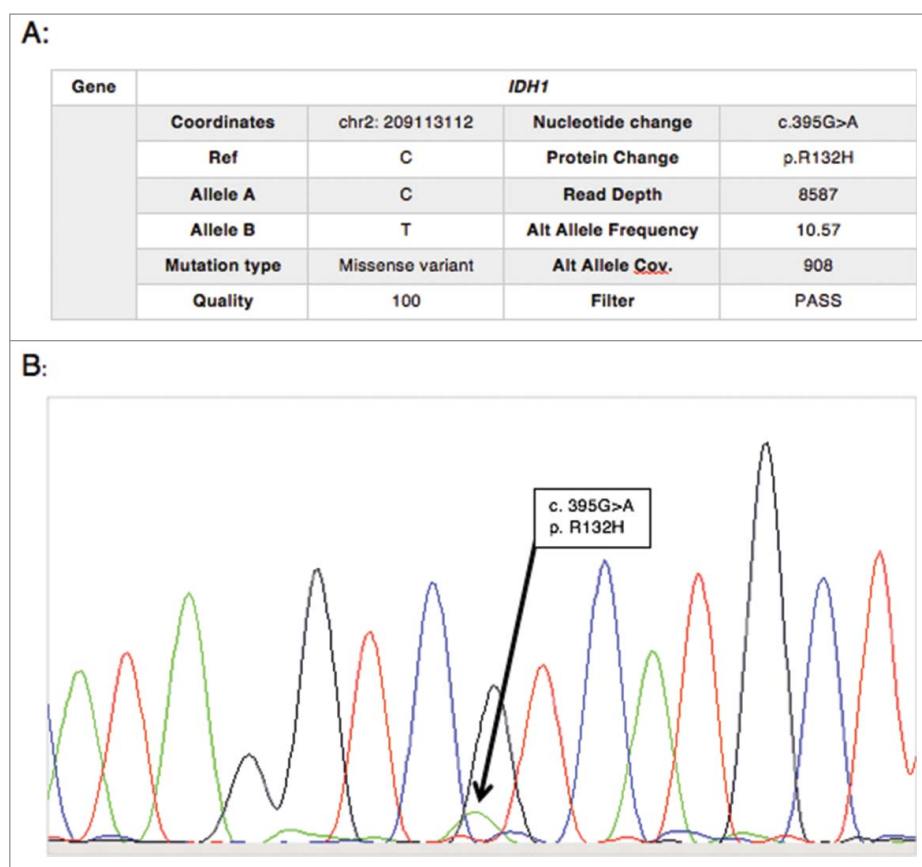


Figure 2. (A) NGS results, and (B) chromatogram from Sanger sequencing confirming the *IDH1* mutation (R132H) in the pancreatic tumor sample.

glioblastoma multiforme, tumors with biallelic wild type *IDH1* are more aggressive and associated with worse outcomes than their mutant counterparts.¹ Thus, PDA may in fact be maladapted for *IDH1* mutations due to the harsh tumor microenvironment that is a hallmark of the disease.³¹

This particular example of PDA reported herein was notable for having a mixed histology of both differentiated and undifferentiated components (Fig. 1). A prior study of noncohesive PDA (defined as tumors having any foci lacking infiltrating glands, including anaplastic and undifferentiated PDA) revealed that this phenotype is a common finding at autopsy, but rare in resected specimens. This finding suggests that an epithelial-to-mesenchymal transition (EMT) occurs at a very late stage in many PDAs.³⁹ The authors noted a hypermethylation phenotype in some tumors with undifferentiated foci, and frequent loss of E-cadherin associated with high grade morphology. It is notable that *IDH1* mutations result in a hypermethylation phenotype due to enhanced 2-HG, and are believed

to drive neomorphic dedifferentiation in affected tumors.^{40,41} Based on this connection, we tested the index tumor for E-cadherin expression and observed that the differentiated foci lacked expression, while high grade foci paradoxically had intact expression (data not shown). Thus, E-cadherin loss cannot explain the dedifferentiated phenotype in this sample. Still, the labeling pattern observed in this metastatic lesion leaves open the possibility that a late *IDH1* mutation is responsible for the observed morphologic findings and a driver of EMT in at least this case of advanced PDA.

In conclusion, we describe the first validated case of an *IDH1*-mutant PDA. The mutant *IDH1* inhibitor proved to be ineffective in this patient. It is not known if the lack of inactivity was due to polyclonality and heterogeneity of the tumor (e.g., the *IDH1* mutation was likely a late event), the advanced stage of the cancer, poor performance status of the patient, or some other reason. As noted, at the time of submission the KYT program identified the same *IDH1* mutation in a PDA patient (data not shown), we are hopeful this patient identified earlier in the disease process may have a better chance to respond to targeted therapy. These case studies were identified under the auspices of the “Know Your Tumor” program led by the Pancreatic Cancer Action Network (PanCAN) wherein multi-omic broad-scale molecular profiling is performed for all eligible pancreatic cancer patients. To date, 285 patients in this program have undergone NGS analysis. Such systematic molecular screening initiatives are extremely useful to identify patients with rare or infrequent molecular alterations that would be eligible for targeted therapy-based clinical trials and/

Table 1. COSMIC database search of *IDH1* mutation frequencies in various malignancies.

Tissue	Overall <i>IDH1</i> Mutation Frequency	Frequency of <i>IDH1</i> R132 Mutations
Central nervous system	6,975/20,299 (34.4%)	6,956/6,975 (99.7%)
Bone	357/1,775 (20.1%)	340/357 (95.2%)
Biliary tract	93/1,097 (8.48%)	91/93 (97.8%)
Pancreas	4/1,712 (0.23%)	2/4* (50%)

*The 2 R132 mutations were in intraductal papillary neoplasms, while the 2 non-R132 mutations were synonymous variants.

or off-label therapy for existing FDA approved therapies. Future studies are required to better understand the role of IDH1 mutations in this small subset of PDAs, and the susceptibility of these tumors to “metabolic” targeted therapy.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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