

# Landscape of IDH1/2 mutations in Chinese patients with solid tumors: a pan-cancer analysis

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## Abstract

Isocitrate dehydrogenase (IDH) is an enzyme family involved in cell aerobic metabolism of tricarboxylic acid cycle. However, the landscape of IDH mutations in pan-cancer has not been fully characterized. Tissue or blood samples were subjected to next-generation sequencing (NGS) for detection the IDH mutation. A total of 28,868 patients from more than 20 solid tumor species were analyzed. 374 cases (1.30%) with IDH mutations were identified. Among all the IDH mutations cases, 80 (21.4%) were biliary tract cancer, 80 (21.4%) were lung cancer, 57 (15.2%) were liver cancer and 42 (11.2%) were colorectal cancer. The most common IDH variant were IDH1 and IDH2 which were discovered in 0.81% cases and 0.47% cases, respectively. TP53, PBRM1 and BAP1 were the most significantly mutated genes in biliary tract cancer which were different from others cancer. Moreover TMB were significantly higher in lung cancer, colorectal cancer and gastric cancer than biliary tract cancer ( $p=0.0164$ ,  $p<0.0001$ ,  $p=0.0067$ , respectively) and biliary tract cancer patients with IDH mutation had lower TMB compared with wild-type IDH. Somatic IDH mutation was found in multiple solid tumors and IDH would be a driver gene in biliary tract cancer.

## Introduction

Isocitrate dehydrogenase (IDH) is an enzyme family involved in cell aerobic metabolism of tricarboxylic acid cycle, where *IDH1* and *IDH2* are commonly mutated metabolic genes in human cancers such as glioma and hematologic malignancies [1,2]. Since a missense mutation of *IDH1* was first identified in progressive glioblastoma in 2008 [3], numerous studies have been conducted to describe this genetic mutation and to understand its biological impact on tumors [4]. And it has been confirmed *IDH1/2* mutations have been associated with prognostic and predictive values as biomarkers [5].

The understanding of the role of *IDH1/2* mutations in tumorigenesis and early occurrence has led to the development of *IDH1/2* mutation inhibitors. IDH inhibitors have shown promising efficacy not only in hematologic malignancies, but also in cholangiocarcinoma patients harboring *IDH1* mutations, such as AG-120 (NCT02073994), AG-881 (NCT02481154) and BAY1436032 (NCT02746081) [6-8]. However, the landscape of *IDH1/2* mutations in pan-cancer has not been fully characterized. In this study, we invested the *IDH1/2* pathologic or likely pathologic mutations landscape in pan-cancer.

## Material and Methods

### Clinical Specimens

Formalin-Fixed Paraffin-Embedded (FFPE) tumor sample or biopsy (n=28,868) of pan-cancer patients were enrolled in this study, including biliary carcinoma (1377 cases), liver cancer (2148 cases), lung cancer (11614 cases) and colorectal cancer (4056 cases), etc. The following clinical characteristics were abstracted: age, sex, and tumor histology.

## NGS Sequencing

Tumor tissue samples (self-blood negative control) of pan-cancer were subjected to NGS for detection the *IDH1/2* mutation with 800× sequencing depth in a College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) certified laboratory of 3D Medicines Inc. All pathologic or likely pathologic mutations of *IDH1/IDH2* were considered. In addition, the TMB was defined as the total number of nonsynonymous mutation in coding region. This study was conducted under the approval of the ethics committees of the hospitals and informed consents were obtained from patients.

## Results

### Patient Characteristics

From January 01, 2017 to October 30, 2019, a total of 28,868 cases of Chinese solid tumor types were included in this study, including biliary carcinoma (4.77%), liver cancer (7.44%), lung cancer (40.23%) and colorectal cancer (14.05%). 374 cases (1.30%) with *IDH* mutations were identified. Patients with *IDH* mutation < 60 years old were 49.7% (n=186). Among all the *IDH* mutations cases, 80 (21.4%) were biliary tract cancer, 80 (21.4%) were lung cancer, 57 (15.2%) were liver cancer, and 42 (11.2%) were colorectal cancer (**Table 1**).

### IDH Mutation of Pan-Cancer

The prevalence of *IDH1/IDH2* mutations in 28,868 patients with different cancer types is summarized in **Figure 1**, with biliary tract cancer patients having the highest levels of *IDH1/IDH2* mutations (80/1377). Across all 28,868 patients, the mutational frequencies of *IDH1* and *IDH2* were 0.81% and 0.47%, respectively.

We further investigated the genetic variation profile of *IDH* mutated patients (Figure 2). Targeted therapies have been successfully developed to treat lung cancer harboring driver gene mutations. In lung cancer, driver gene mutations *EGFR* and *KRAS* were the most significantly mutated genes, whereas *TP53*, *PBRM1* and *BAP1* were more frequently observed in biliary tract cancer (**Fig. 2A, C**). In addition, *TP53*, *PBRM1* and *BAP1* were high frequency mutated gene in liver cancer (**Fig. 2B**). *APC*, *TP53* and *KRAS* were among the top mutated genes in colorectal cancer, while *TP53*, *SPTA1* and *ACVR2A* were more in *IDH* mutated gastric cancer (Fig. 2D,E).

### Associate with TMB and IDH mutation

We also analyzed the association between *IDH1/IDH2* mutations and TMB in five type of cancer. As shown in **Figure 2F**. The TMB were significantly higher in lung cancer, colorectal cancer and gastric cancer than biliary tract cancer ( $p = 0.0164$ ,  $p < 0.0001$ ,  $p = 0.0067$ , respectively). In addition, we also analyzed the relationship between *IDH* mutation/wild-type with TMB in biliary tract cancer in **Figure 2G**. Patients with *IDH* mutation had lower TMB compared with patients with wild-type *IDH* ( $p = 0.0236$ ).

## Discussion

From a cohort of 28,868 patients with different types of solid tumors, a high frequency of *IDH1/IDH2* mutations were observed not only in biliary tract cancer, but also liver cancer, lung cancer, colorectal cancer and others. The reprogramming of cellular metabolism is a fundamental characteristic of cancer, and *IDH1/2* mutations represent key therapeutic targets in this arena. Somatic *IDH1/2* mutations are found in multiple solid tumors, and mounting evidence indicates that they contribute to premalignant disorders as well as early and late cancers. And then, another interesting point, we found that TMB was higher in other gastrointestinal tumors. However, in biliary tract cancer, *IDH* mutation accompanied by low TMB indicates that *IDH* would be a driver gene in biliary tract cancer. With the continuous emergence of *IDH* inhibitors, a considerable

number of patients with solid tumors carrying *IDH1/2* gene mutations may be more likely to benefit from IDH inhibitors, which is worth further expectation and exploration in clinical studies.

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## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Ethics approval and consent to participate

Tumor tissue samples (self-blood negative control) of pan-cancer were subjected to NGS in a College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) certified laboratory of 3D Medicines Inc. This study was conducted under the approval of the ethics committees of the hospitals and informed consents were obtained from patients.

## Consent for publication

Not applicable.

**Conflict of Interest** Drs Junling Zhang, Jing Zhao, Zhengyi Zhao, Longgang Cui, Yuzi Zhang, Guoqiang Wang, Shangli Cai, Yuezhong Bai are employees of 3D Medicines Inc. Other authors declare no conflict of interest.

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**Figure legends**

**Figure 1** Prevalence of *IDH1/IDH2* mutations in 28,868 patients with pan-cancer.

**Figure 2** Top 20 significantly mutated genes in *IDH1/2* mutated patients of biliary tract cancer (A), liver cancer (B), lung cancer (C), colorectal cancer (D) and gastric cancer (E). Genes were ranked by mutation frequencies (right panel). Age and gender are annotated in the top panel. Tumor mutational load among *IDH1/2* mutated pan-cancers (F) and in biliary tract cancer (G).

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