

Research Article

Xuefei Zhang, Mo Li, Desheng Lv, Ge Sun, Yu Bai, Hui Tian, Changhong Liu*

Identification of a novel BRAF Thr599dup mutation in lung adenocarcinoma

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Abstract: BRAF mutations are known as oncogenic drivers of non-small cell lung cancer (NSCLC). BRAF inhibition has demonstrated anti-tumor activity in patients with BRAF V600E mutant NSCLC. Further molecular screening for novel BRAF thr599dup mutation is warranted. The novel BRAF Thr599dup gene mutation, for which the repeat amino acid-tyrosine is inserted between the 599th amino acid and the 600th amino acid in exon 15 of BRAF, was identified by next-generation sequencing (NGS) during routine clinical care in a lung carcinoma sample from an Asian never-smoker. Other putative driver alterations including EGFR, ALK were not found in that patient. BRAF Thr599dup gene mutation analysis was consistent with BRAF v600E gene mutation. Here we report a novel BRAF gene mutation with molecular characteristics consistent with those in BRAF-driven NSCLC. Our case expands the scope of BRAF gene mutations and provides broader molecular profiling for optimizing therapeutic options for patients with NSCLC. The new BRAF gene mutation has important clinical meaning for cancer patients.

Keywords: BRAF thr599dup gene mutation, Next-generation sequencing, Targeted therapy, Lung adenocarcinoma

1 Introduction

Lung cancer is one of the major causes of cancer mortality due to the high incidence rate, and limited treatment

strategy [1]. Most cases of lung carcinoma are NSCLC, and the 5-year survival rate remains very low [2,3], Traditional therapeutic methods for lung carcinoma are mainly based on cancer histology. Classifying NSCLC into clinically related molecular subclasses may be helpful for the cure of NSCLC. The classification is constructed depending on mutations of genes, including EGFR, HER2, KRAS, PIK3CA, BRAF, and others in frequencies of more than 1% [4-6]. In addition, the NSCLC subtypes have been successfully established with use of an overlap of genomic molecular markers and immunohistochemistry [7].

BRAF is one of RAF kinase family members and plays an important role in the mitogen-activated protein kinase signal pathways [8]. BRAF variations have been investigated in multiple cancers, such as colorectal, papillary thyroid, and ovarian cancers, as well as melanoma [9-12]. Moreover, BRAF variations have also been observed in NSCLC [13]. According to Davies et al [14], the incidence of BRAF mutation is 8% across all cancers and 3% in lung cancer. Worldwide, this means that about 35,000 patients might benefit from BRAF inhibitors, which is similar to the number of patients who might benefit from ALK inhibitors. The BRAF mutations constitutively activate the MAPK (mitogen activated protein kinase) pathway, resulting in a constant stimulation to cell growth and proliferation. Also, BRAF activating mutations are associated with MEK and ERK activation. In addition, some studies report that BRAF Thr599dup gene mutation analysis is consistent with that of BRAF v600E gene mutation, which activates MEK/ERK signaling pathways [15]. Here we describe a novel BRAF Thr599dup gene mutation.

2 Case report

A 60-year-old Chinese female never-smoker was diagnosed with stage IA NSCLC in March, 2017. A single-incision video-assisted right upper lobe radical resection was performed, and pathologic examination demonstrated invasive lung adenocarcinoma of the wall structure (Fig.1); no pleural space invasion or lymph node metastasis (T1aN0M0) was found.

*Corresponding author: Changhong Liu, Department of Thoracic Surgery, The Second Hospital of Dalian Medical University, Dalian 116023, China, E-mail: changhongliu66@163.com

Xuefei Zhang, Mo Li, Desheng Lv, Ge Sun, Yu Bai, Department of Thoracic Surgery, The Second Hospital of Dalian Medical University, Dalian 116023, China

Xuefei Zhang, Hui Tian, Department of Thoracic Surgery, Qilu Hospital of Shandong University, Ji'nan 250012, China

NGS-based comprehensive genomic profiling was performed on samples of formalin-fixed and paraffin-embedded (FFPE) tumor tissue from unstained slides at GENTALKER BIO (Dalian, China). The novel BRAF Thr599dup gene mutation was found in exon 15 of BRAF, where the repeat amino acid-tyrosine was inserted between the 599th and 600th amino acid (Fig. 2 and Fig. 3), whereas other putative oncogenic driver gene alterations including EGFR, KRAS, ERBB2, RET, ALK, MET, or ROS1 were not detected.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

Informed consent: Informed consent has been obtained from all individuals included in this study.

3 Discussion

Targeted therapy has been proven to be a successful strategy in patients with NSCLC harboring oncogenic driver mutations. For example, EGFR tyrosine kinase inhibitors induce both a high overall response ($\approx 70\%$) and a durable response (9.7- to 11.0-month median PFS) in treatment-naïve patients with activating EGFR mutations [16, 17]. Similarly, Met/ALK/ROS inhibitor crizotinib (Xalkori®) has shown outstanding clinical effects in patients with corresponding mutations. BRAF mutations are primarily and most frequently identified in melanoma [18]. The most common type is V600E, where a glutamate is substituted

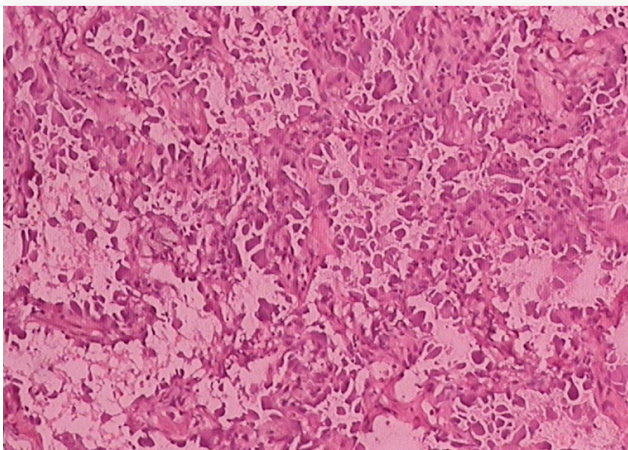


Figure 1: Histopathologic examination of formalin-fixed and paraffin-embedded tumor tissue with BRAF Thr599dup gene mutation.

with a valine at codon 600 [19]. BRAF V600E mutations are less frequently reported in lung cancer than those in melanoma. However, there is a possibility that the incidence of V600E mutation in lung cancer might be underestimated, and, besides sequencing, sensitive methods should be used to evaluate V600E mutation status [20, 21]. Although the prognostic implications of BRAF V600E mutations in NSCLC remain unclear [22-25], the V600E inhibitor vemurafenib has been reported to be effective in V600E-harboring lung cancers in some cases [26, 27]. Recruitment of NSCLC patients with BRAF mutations for targeted therapies should be encouraged in clinical trials, because that would contribute to improved knowledge about those rare mutations, resulting in targeted therapies with enhanced effectivity and reduced toxicity. Meanwhile, emphasizing BRAF mutation status at diagnosis may help to personalize therapeutic decisions.

In this study we identified a novel BRAF gene mutation in an Asian never-smoker patient with NSCLC. Compared to the traditional genomic profiling method

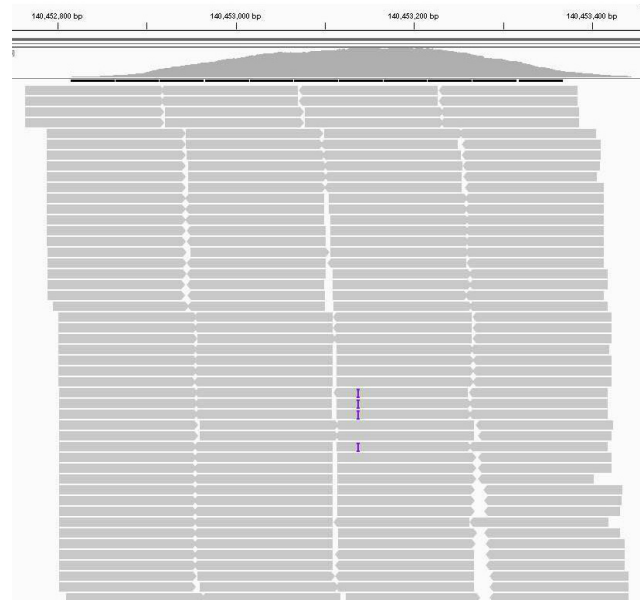


Figure 2: Next-generation sequencing data demonstrating a somatic genomic mutation in BRAF gene.

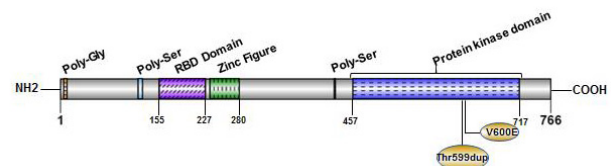


Figure 3: Schematic representation of the BRAF Thr599dup gene mutation.

of reverse transcriptase-polymerase chain reaction (RT-PCR), NGS provides more information about comprehensive breakpoints and structural variations on genes and accelerates the identification of novel structure variants. The newly discovered BRAF mutation provides immediate clinical significance.

Conflict of interest statement: Authors state no conflict of interest.

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