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# Novel *MET* exon 14 skipping analogs characterized in non-small cell lung cancer patients: A case study

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ABSTRACT

*MET* exon 14 skipping (*MET*ex14) is a validated oncogenic driver in lung cancer and *MET* tyrosine kinase inhibitors are now available as effective clinical treatments. The majority of known *MET*ex14 alterations are typical donor/acceptor splicing or ubiquitination site mutations. Herein, two new *MET*ex14 variants were detected in two patients with lung adenocarcinoma by targeted next generation sequencing (NGS). Reverse transcription (RT)-based analysis confirmed that these mutations led to *MET* exon 14 skipping. Our analysis provided evidence for possible targeted therapy options for patients carrying these *MET* mutations or similar *MET*ex14 analogs.

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## Introduction

The *MET* gene, located at chromosome 7q21-q31, encodes the widely expressed receptor of hepatocyte growth factor (HGF), which is involved in various cellular processes, including cell growth, proliferation, survival, migration, and differentiation [1]. Gain-of-function alteration in *MET* is known as a primary oncogenic driver and a major factor for resistance to tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC) treatment [2–4].

The exon 14 of *MET* encodes the intracellular juxtamembrane domain of MET. Tyrosine 1003 (Y1003) in the juxtamembrane domain is a binding site for c-Cbl, an ubiquitin protein ligase (E3). The binding process plays a role in ubiquitination, receptor endocytosis, and degradation of MET [5,6]. Somatic alterations of the splicing sites of *MET* exon 14 would cause exon skipping, which increases MET stability and enhances signaling by hepatocyte growth factor stimulation, and therefore drives oncogenesis. Mutations that cause *MET* exon 14 skipping (*MET*ex14) occur in approximately 3~4% of NSCLC [8,9] and they rarely co-exist with other known drivers of NSCLC [10] except for *MET* amplification [11]. However, some studies reported co-occurrence of *MET*ex14 and genomic alterations such as mutations in *EGFR* and *CDK4* etc. [6,12]. NSCLC patients carrying *MET*ex14 may benefit from MET tyrosine kinase inhibitors including crizotinib, cabozantinib, and clumetinib [13–16]. Capmatinib (Tabrecta, Novartis) that specifically targets *MET*ex14 has been granted accelerated approval by the Food and Drug Administration (FDA) for treating metastatic NSCLC [17].

*MET*ex14 variations are a diverse group of DNA mutations, including nucleotide substitutions (SNV), insertions/deletions (indels), and complex events [6]. Based on the mutation type and chromosomal localization, *MET*ex14 is currently categorized into several subsets, such as polypyrimidine tract (PPT), acceptor splicing site, donor splicing donor site, D1010, Y1003X, PPT+ SA and DNA level whole exon deletion [18]. Besides afore mentioned categories, emerging data has shown that other rare mutations falling within or neighboring the Y1003 motif might also impair receptor degradation. These rare missense and in-frame indels do not induce *MET* exon 14 skipping at RNA level and were first referred to as functional analogs [19,20].

*MET*ex14 alterations display a remarkably diverse sequence composition. Over 120 distinct point mutations and indels have been reported [2]. *MET* exon 14 skipping mutations can be detected using DNA/RNA-based hybrid capture NGS, quantitative re-

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**Table 1**
Clinical characteristics of patients in this study.

| Variable | Patient1(Sample1) | Patient2 (Sample2) |
|---|---|---|
| Age | 77 | 57 |
| Sex | Female | Male |
| Histology | Lung Adenocarcinoma | Lung Adenocarcinoma |
| TNM stage | Ia | Ia |
| *MET* exon 14 Mutation (NM_000245.2) | c.3003_3023delinsTACAAGCCTATCCAAATG (VAF = 3.72%) | c.3023_3027delinsT (VAF = 25.2%) |

Abbreviations:VAF = variant allele frequency.

verse transcription polymerase chain reaction (RT-qPCR) or other less common techniques [7, 21–23]. In DNA-based analysis, alterations at splicing sites (or the whole exon deletion) are classified as *MET* exon 14 skipping mutation, while in RNA-based analysis, fusion transcripts, observed as exon 13–15 "fusion", serve as the standard to identify *MET* exon skipping [21]. Therefore, RNA-based confirmatory assays should be carried out for novel variants detected by DNA-based analysis.

Herein, we reported two novel *MET*ex14 variants identified in patients with stage Ia NSCLC. These two small indels are located near the donor splicing site. Although one of them impairs the Y1003 motif, both variants are analogous to canonical *MET*ex14 alterations, which lead to exon 14 skipping. By analyzing these two variants, we provided possible targeted therapy options for patients who carry these two or other similar *MET*ex14 analogs.

## Materials and methods

### *Sample information*

Formalin-fixed, paraffin-embedded (FFPE) tissue sections were obtained from two patients with stage Ia NSCLC at Nanjing Drum Tower Hospital in March and July, 2020, respectively.

FFPE tissue from a 65-year-old female harboring *MET* c.3017_3028+15del mutation which disrupts the 3′ donor splicing site and leads to exon 14 skipping was used as a positive control, while the 293T cell line and a tissue sample without *MET* variations were employed as negative controls.

### *Targeted NGS and data analysis*

Both DNA preparation and NGS testing were conducted at 3D Medicines Inc., a College of American Pathologists (CAP)-accredited and Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. Genomic DNA was extracted using the QIAamp DNA FFPE Tissue Kit (Qiagen) and quantified by the PicoGreen fluorescence assay (Invitrogen) for each tissue sample. DNA extracts (50–200 ng) were fragmented to around 200 bp by sonication (Covaris), and libraries were prepared using the KAPA Hyper Prep Kit (Kapa Biosystems) according to the manufacturer's protocol. The libraries were then subjected to hybridization with probes targeting a panel of 381 cancer-related genes panel was to capture the targeted genomic regions, followed by sequencing on an Illumina NextSeq 550 instrument.

Sequencing reads were mapped against the human reference genome (hg19/GRCh37) with BWA version 0.7.12 and SAMtools version 1.3. Duplicate reads were removed using Picard version 1.130. Variant calling in targeted regions was performed using an in-house developed algorithm, with the filtering model containing background error correction, strand bias, base quality, mapping quality, short tandem repeat regions and low-quality mapping ratio 25.

We used a Bayesian methodology to detect novel somatic mutations and the de Bruijn approach to detect indels. In-house developed BIC-seq (Bayesian information criterion) algorithm was applied to detect copy number variations (CNVs). The reliability of NGS detection has been validated in reference to conventional molecular diagnostic methods. The sensitivity and specificity of SNV and indel detection are 100%. The concordance of CNV detection between NGS and fluorescence *in situ* hybridization (FISH) was up to 93.3% [24].

### *Sanger sequencing and quantitative reverse transcription PCR*

Total RNA was isolated from FFPE samples using the ReliaPrep™ FFPE Total RNA Miniprep System (Promega) according to the manufacturer's protocol. For cDNA preparation, 100 ng of total RNA from each sample was reverse-transcribed using the SuperScript™ VILO™ cDNA Synthesis Kit (Invitrogen). The primers for Sanger sequencing and RT-qPCR in validation of *MET* exon 14 skipping were as follows: forward primer for exon 13 of *MET* (13F), 5′- TTGGGTTTTTCCTGTGGCTG -3′; reverse primer for exon 15 of *MET* (15R), 5′- GCATGAACCGTTCTGAGATGAATT -3′. DNA fragments separated in agarose gel were excised and subjected to PCR amplification, followed by Sanger sequencing. RT-PCR was performed on the Applied Biosystems 7500 Real-Time PCR Machine under the following cycling conditions: 95°C for 2 min, 45 cycles of 95°C for 15 s, 54°C for 15 s, 72°C for 1 min.

## Results

### *Patient characteristics*

The FFPE tissue sections of the two patients with stage Ia NSCLC were subjected to genomic profiling using a 381-gene panel (3D Medicines). Their clinical characteristics and gene alteration profiles are shown in Table 1. For Patient 1, *MET* variant was the only detected somatic mutation. For Patient 2, other somatic mutations were detected in addition to MET, such as *RB1* c.381-2A>*G*, *TP53* p.L194R and *RBM10* p.Q277Rfs*31. Copy number variations were not detected in either sample.

### *Two rare variations in* MET *exon 14 in two NSCLC samples*

In Patient 1, the *MET* variant near the 3′ end of exon 14 is named as c.3003_3023delinsTACAAGCCTATCCAAATG (NM_000245), which includes an indel and a SNV. This variant introduces a new stop codon in exon 14 and causes the loss of Y1003 (Fig. 1B). In Patient 2, another rare *MET* variant, c.3023_3027delinsT (NM_000245), was detected. This variant is located at the 3′ end of exon 14, and is comprised of a deletion and a SNV. Typically, this variation would be annotated as a frame-shift mutation and predicted to trigger premature termination of translation. Of note, the two variants were also described as c.3057_3077delinsTACAAGCCTATCCAAATG and c.3077_3081delinsT, respectively, using NM_001127500. Since *MET* alterations were the only drivers in these two patients and may affect splicing efficiency, we carried out the following experiments to verify whether these variants can cause exon 14 skipping.

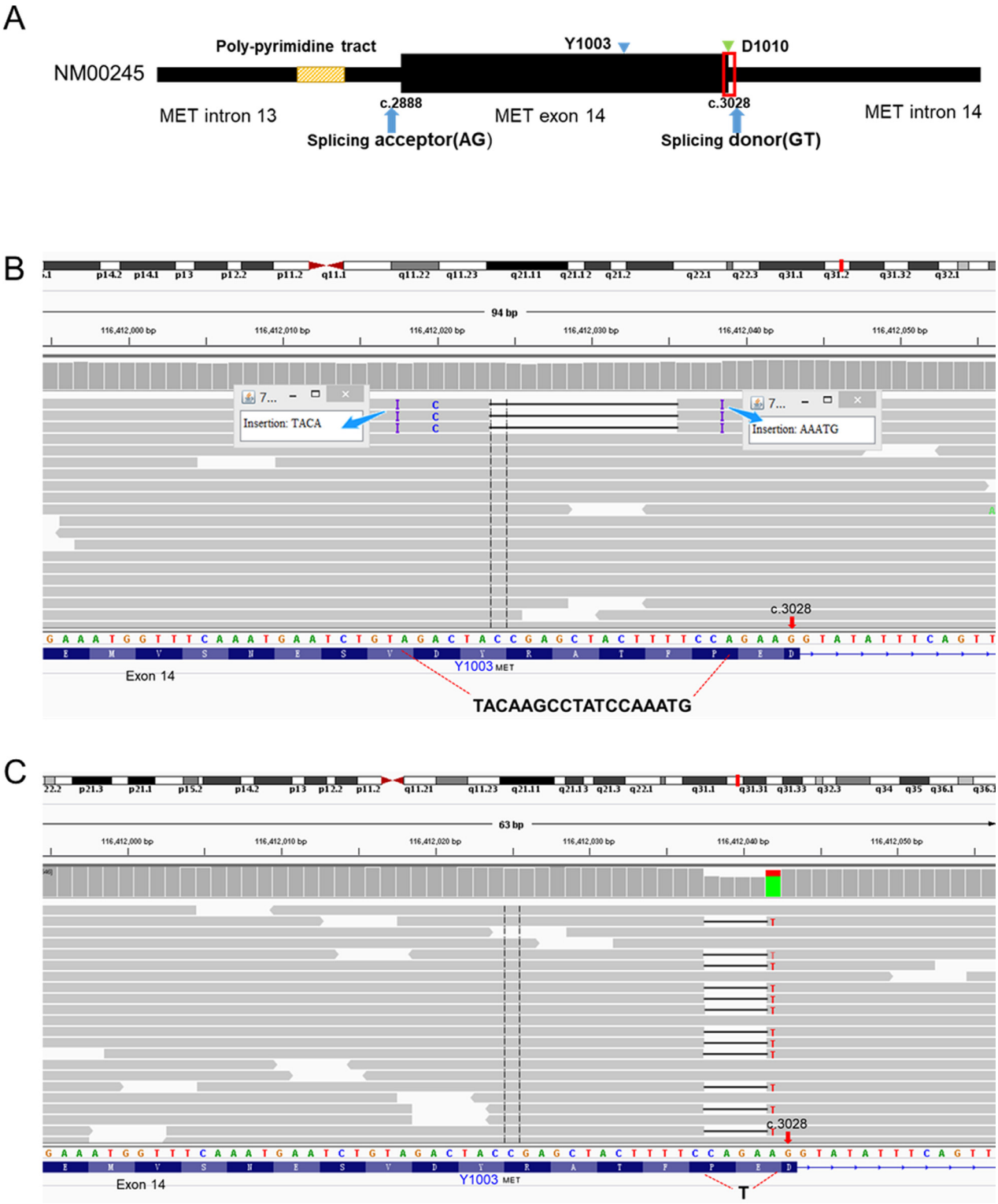


**Fig. 1.** Schematic diagram of the chromosomal sites and types of the two *MET* mutations. (A) Characterize potential differences across various *MET* exon 14 alteration subsets. (B) grey bars depict NGS reads, and an insertion within a read is noted with a purple line, blank regions with black lines for deleted sequence. c.3028 is the last position of *MET* exon 14. c.3003_3023delinsTACAAGCCTATCCAAATG, contains insertion, deletion and base substitution. (C) c.3023_3027delinsT contains deletion and base substitution. The resulting sequence generated through the variants are shown in black bold. Y1003 is shown in blue.

*Identification of the transcripts confirm* MET*ex14*

RT-PCR and Sanger sequencing were performed to verify whether the two new *MET* variants affect mature mRNA structure. The primer positions and amplicon sizes are shown in Fig. 2A. Compared with the negative (without *MET* mutation) and the positive (known *MET*ex14) controls, two bands representing DNA products of different lengths were observed on the gel: a shorter fragment corresponding to a *MET*ex14 transcript (77 bp), and a longer fragment corresponding to the wild-type product (218 bp). The dis-

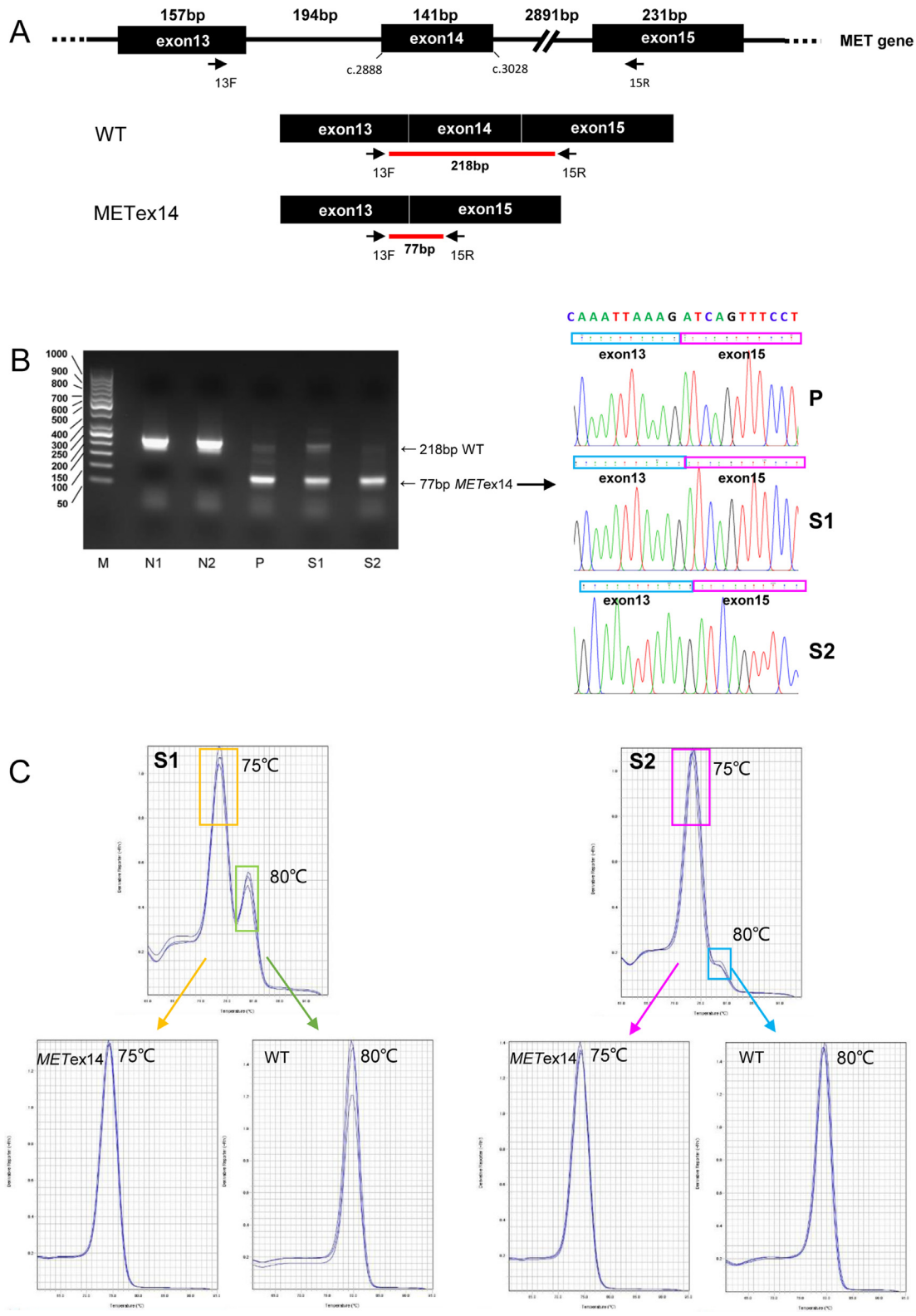


**Fig. 2.** Sanger sequencing and RT-PCR for *MET* exon 14 skipping testing. (A) The schematic diagram of the primer locations and amplicon sizes. A fragment of 218 bp indicts WT *MET* transcript; and a fragment of 77 bp, *MET*ex14. (B) Two cDNA samples and negative, positive control were amplified with 13F-15R primer, and result were analysis by polyacrylamide gel electrophoresis. The corresponding Sanger sequencing diagram for WT and *MET*ex14 DNA fragments cut from gel was shown on the right. (C) Top melt curve was acquired by amplifying total cDNA from Sample 1 or Sample 2, while bottom melt curve from WT and *MET*ex14 DNA fragments (cut from gel) amplification. Wild-type = WT; *MET* exon 14 skipping = *MET*ex14; 293T = N1; Negative = N2; Positive = *P*; Sample1 = S1; Sample2 = S2.

tance between the bands was longer than the size of the deleted DNA fragment but was similar to the length of exon 14 of the *MET* gene. The result showed that both the wild-type and the *MET*ex14 transcripts were expressed in the patients' tumor tissues. Sanger sequencing also confirmed exon 14 deletion. Fig. 2B showed the junction between the last nucleotide of exon 13 and the first nucleotide of exon 15, namely *MET* exon 13–15 "fusion". Furthermore, the RT-PCR results of both samples showed two melt peaks at 75 and 80 °C (Fig. 2C). The small melt peak at 80 °C represented the longer non-mutated wild-type transcript (Supplementary Fig. S1A), and the major peak at 75 °C represented the *MET*ex14 transcript (Supplementary Fig. S1B). Collectively, the two novel *MET* variants were confirmed by both Sanger sequencing and RT-PCR to result in *MET* exon 14 skipping.

## Discussion

In this study, we detected two *MET*ex14 analogs in NSCLC patients. The *MET*ex14 analog was first defined as genomic alterations located in the exon 14 of the *MET* gene without affecting acceptor splicing site or donor splicing site. Bioinformatics algorithms annotate these variants as C-terminal truncated proteins (P1008Lfs*20 in Patient 1 and D1002Tfs*5 in Patient 2). Since *MET* mutation is a well-characterized oncogenic driver in NSCLC [25,26] and these two cases lacked other known oncogenic factors, we further analyze the potential oncogenicity of rare *MET* alterations.

Coding-region nucleotide changes within exonic splicing enhancers (ESEs, a purine-rich DNA sequence and often within 30 base pairs of the exon boundary) may affect the patterns or efficiency of mRNA splicing [27,28], which cause skipping of constitutive exons. Coding-region nucleotide changes, including deletions and substitutions, are sometimes incorrectly annotated as nonsense, missense or silent mutations [27–33]. When the two variants were annotated as premature termination, the c-terminal truncated MET product would be interpreted as functional loss. However, considering these variants might change mRNA splicing efficiency, exon skipping product would cause MET activation. The two *METex14* analogs cause MET exon 14 skipping by changing the ESE region.

RNA-based confirmation demonstrated that the two non-classical mutations cause exon 14 deletion of *MET*. The major peak in melt curves indicated the *MET*ex14 RNA transcript and the small peak next to it corresponded to the wild-type *MET* transcript. For Patient 2, mature RNA of the mutant allele was detected at much higher abundance than the wild-type allele, given the much smaller wild-type peak in the melting curves. This phenomenon indicated that *MET*ex14 carriers tend to have a lower expression level of non-truncated *MET*. This is consistent with previous findings by The Cancer Genome Atlas project [34].

The efficacy of MET-targeting therapies varies due to the patients' clinical complexity as well as the interpretation of *MET* genomic alterations. Potential oncogenic variants identified by any diagnostic approach should not be ignored. Combining DNA-based and RNA-based techniques will better inform treatment decision. Based on the presented evidence, the patients may be eligible for *MET*-targeting therapies upon disease recurrence.

## Declaration of Competing Interest

All authors declare that they have no conflicts of interest.

## CRediT authorship contribution statement

**Minke Shi:** Writing – original draft. **Jing Ma:** Formal analysis, Visualization, Writing - original draft. **Meilin Feng:** Formal analysis, Visualization, Writing - original draft. **Lei Liang:** Investigation. **Hongyuan Chen:** Investigation. **Tao Wang:** Writing – review & editing. **Zhenghua Xie:** Writing – review & editing.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cancergen.2021.04.005.

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