

Molecular features of giant-cell carcinoma of the lung: a case report and literature review

Xin Li*
Zihe Zhang*
Jinghao Liu
Dan Wang
Sen Wei
Jun Chen

Department of Lung Cancer Surgery, Tianjin Key Laboratory of Lung Cancer Metastasis and Tumor Microenvironment, Tianjin Lung Cancer Institute, Tianjin Medical University General Hospital, Tianjin, People's Republic of China

*These authors contributed equally to this work

Abstract: Giant-cell carcinoma of the lung (GCCL) is a rare histological form of poorly differentiated non-small-cell lung cancer, which is classified as a subtype of pulmonary sarcomatoid carcinomas. In this case report, we describe the case of a 50-year-old Chinese male who presented with a pulmonary nodule in the right upper lobe of his lung. After thoracoscopic lobectomy, a histopathologic diagnosis of GCCL was made. He did well postoperatively, showing no local recurrence or distal disease in a 7-year follow-up period. Furthermore, for this case, we also analyzed 295 tumor-related driver genes with high-throughput sequencing technology. We found that treatment using MEK inhibitor, CDK 4/6 inhibitor, and TP53 inhibitor may provide a new therapeutic direction for GCCL. Therefore, complete tumor excision is the best choice of treatment strategy at the early stage of GCCL and gene target therapy may be a new therapeutic option for this disease.

Keywords: giant-cell carcinoma of the lung, high-throughput sequencing, gene mutation

Introduction

According to the 2004 World Health Organization (WHO) classification of lung tumors, giant-cell carcinoma of the lung (GCCL) is classified as a subtype of pulmonary sarcomatoid carcinomas (PSCs).¹ PSC accounts for 2%–3% of all lung cancers and is associated with smoking, which is more common in males. The mean age of onset is about 59 years, and generally, no specific signs or symptoms are observed.^{2–4} There are five subtypes of PSCs: polymorphic carcinoma, spindle cell carcinoma, giant-cell carcinoma, carcinosarcoma, and pulmonary blastoma.⁵ Herein, we report the case of a patient who presented with complaints of cough and bloody sputum, and received the diagnosis of GCCL followed by tumor resection in the right lung.

Case presentation

Seven years ago, a 50-year-old Chinese male with cough and expectoration (black phlegm) for about 2 weeks, sometimes accompanied with bloody sputum and breathlessness, was admitted to our hospital. These symptoms developed without apparent cause and in the absence of problems such as chest pain and/or distress, fever, nausea, or vomiting. A computed tomography (CT) scan of his chest showed a rough-edged shadow measuring nearly 32×22×10 mm in the right upper lobe of his lung, as shown in Figure 1 (A: before surgery; B: after surgery). The patient acknowledged several chronic disorders, including a 10-year history of bronchitis and emphysema, and was a smoker with a 30-pack-year history. The patient had no family history of lung cancer. There was no obvious abnormality noted in his system review. The results of a peripheral blood count, baseline serum chemistry screening, and urinalysis were normal on

Correspondence: Jun Chen
Department of Lung Cancer Surgery,
Tianjin Key Laboratory of Lung Cancer
Metastasis and Tumor Microenvironment,
Tianjin Lung Cancer Institute, Tianjin
Medical University General Hospital, 154
Anshan Rd, Heping Qu, Tianjin, 300052,
People's Republic of China
Email huntercj2004@qq.com

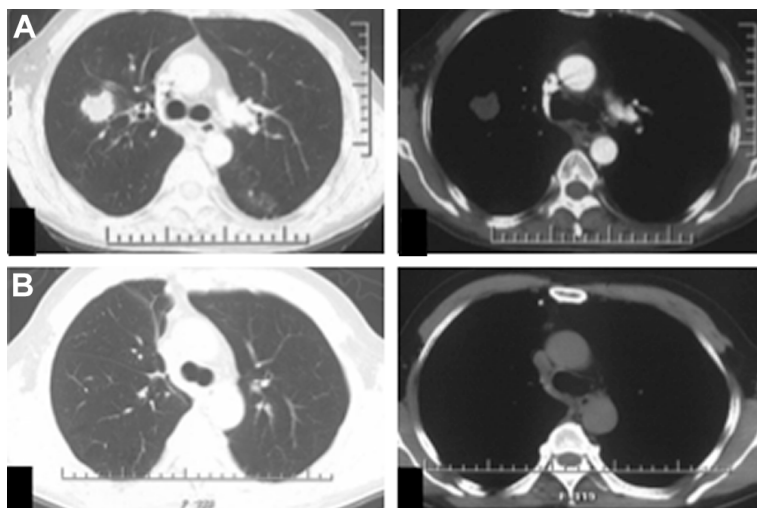


Figure 1 Computed tomography (CT) scans of the chest. (A) CT scan before surgery: tumor-like mass in the right upper lobe with blurred contour and irregular margin shown in the lung and mediastinal windows. (B) The 7-year follow-up CT scan after surgery.

admission, and tumor biomarker tests and a purified protein derivative test for tuberculosis were also negative. A rough-edged shadow of his right upper lobe was once again seen on an enhanced CT scan of his chest, although a CT scan of his abdomen, magnetic resonance imaging of his brain, and a bone scan were all normal. His right bronchial tree also appeared normal on bronchoscopic examination, with no indication of malignancy in the biopsy and washings procured.

A right-sided upper lobectomy and systematic mediastinal lymphadenectomy were performed. A tumor of his right upper lobe, roughly 3 cm in diameter, was evident at surgery, without puckering of visceral pleura. Microscopic sections showed the following findings: there were many large, multi-core, and bizarre giant cells, without special arrangement; cytoplasm was moderate to abundant, dense, and eosinophilic; nucleus was pleomorphic and phylloid; and the tumor cells appeared to have lost adhesion, and to be separated and embedded in a fibrous myxoid stroma. Histopathologic examination revealed the tumor cells were positively reactive to cytokeratin (CK) and vimentin, while immunostaining for chromogranin A (CgA) and synaptophysin (Syn) was negative, as shown in Figure 2. Diagnostically, vimentin is the major cytoskeletal component of mesenchymal cells and is often used as a marker of mesenchymally derived cells or cells undergoing an epithelial-to-mesenchymal transition during metastatic progression. Here, it was used as a sarcoma tumor marker to identify mesenchyme. Syn is often combined with CgA as a specific marker to identify tumors arising from neural and neuroendocrine tissues, such as neuroblastoma, carcinoid, and small-cell carcinoma. Therefore, the above findings supported the diagnosis of a GCCL. The detection of bronchial stump and mediastinal lymph nodes was negative,

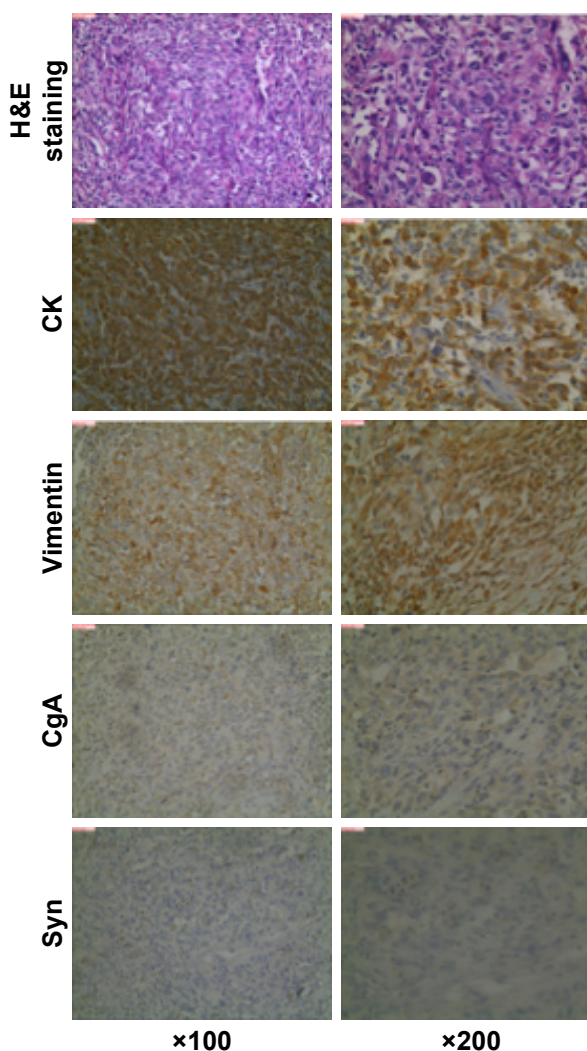


Figure 2 Pathological characteristics demonstrated by H&E staining and immunohistochemistry. CK and vimentin immunostaining was positive, while CgA and Syn immunostaining was negative.

Abbreviations: CgA, chromogranin A; CK, cytokeratin; H&E, hematoxylin and eosin; Syn, synaptophysin.

and it indicated that there was no lymph node metastasis in this patient.

Since 2 months after surgery, the patient was treated with combined chemotherapy using gemcitabine (1,000 mg/m² on days 1 and 8) and cisplatin (75 mg/m² on day 1) every 3 weeks for four cycles, and then whole-body radiography examinations were carried out every year in a local hospital. He was still alive 7 years after surgery, free from disease progression. Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Follow-up and outcomes

Until now, the therapeutic result of this case is satisfactory. With the development of high-throughput sequencing technology, more and more genomes have been successfully sequenced. Recently, in order to explore the molecular structure of this tumor, mutations of 295 tumor-related driver genes were detected by a high-throughput sequencing test (Burning Rock Biotechnology Inc., Guangzhou, People's Republic of China). All the 295 genes are listed in Table S1. We analyzed normal and tumor tissues of this patient, after ruling out genetic variations; nine tumor-related somatic mutations were confirmed, of which six were missense variants and three were synonymous variants. The high-throughput screening results of the patient are shown in Table S2. The six missense mutations included *KRAS*, *KMT2D*, *TP53*, *SETD2*, *TET2*, and *MAP3K*. As a hotspot mutation, *KRAS* gene mutation on chromosome 12, exon 2 p.G12D, with a mutant abundance of about 26.7%, indicated the tumor may be sensitive to MEK inhibitor and CDK 4/6 inhibitor like trametinib and abemaciclib. *TP53* gene mutation on chromosome 17, exon 7 p.R249K, with a mutant abundance of about 8.30%, indicated the tumor cell may be sensitive to some novel compound that can reverse the *TP53* mutation like APR-246. For the other four somatic mutations, including *KMT2D*, *SETD2*, *TET2*, and *MAP3K*, there was no sufficient evidence to show their correlation with target drugs known so far in clinical use.

Discussion and review of the literature

GCCL is a rare malignant form of large-cell lung carcinoma, a subtype of PSCs. Nash and Stout first described this tumor in 1958.⁶ For the past 25 years, the WHO has been under constant pressure to change the classification of sarcomatoid tumors of the lung, and this has been driven by our evolving understanding of their histogenetic origins. In the second revision (1981) of the WHO classification, GCCL was

considered as a subtype of large-cell carcinomas.⁷ In the third revision (1999) of the WHO classification, it was placed within a subtype called “carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements”, along with pleomorphic carcinoma, spindle cell carcinoma, carcinosarcoma, and pulmonary blastoma, which are related variants.⁸ The rules for classifying PSC under WHO classification in 2004 were identified as more improved than in the past, for now accurate classification of a pulmonary carcinoma as a GCCL requires that the entire tumor consists only of malignant giant cells. Therefore, complete sampling of the entire tumor obtained via a surgical resection is absolutely necessary for a precise diagnosis of GCCL to be made.⁹

Due to the lack of accurate data from a large sample, the incidence and mortality of GCCL is generally unclear until now. It is known to be a very rare tumor variant of all races. Travis et al described in their study of a database of more than 60,000 patients in the US that GCCL comprised about 0.3%–0.4% of primary lung cancers, with an incidence of about three new cases per million persons per year.¹⁰ However, the GCCL incidence was much lower than other four PSC subtypes, in a series of 4,212 lung cancer cases, in which only one (0.024%) case was confirmed to be a pure giant-cell component after complete sectioning of all tumor samples.¹¹ Like other non-small-cell lung cancers (NSCLCs), GCCL can invade in any lung lobes, but it is observed much more frequently in the upper lobes and always at periphery.¹² Usually, patients with GCCL complain of no specific signs or symptoms, but experience cough or hemoptysis, or may be asymptomatic just like other NSCLC patients. GCCL is a poorly differentiated tumor with early metastasis through lymph and blood circulation to the brain, bone, adrenal gland, and liver, similar to other NSCLCs, but uncommon metastasis to the gastrointestinal tract, kidney, and heart is reported constantly.^{2,13,14}

GCCL is essentially undifferentiated and usually appears as a bulky necrotic mass, having no distinct architectural pattern. Under microscope, the background of GCCL contains plenty of neutrophils and lymphocytes. The tumor cells are big, multi-core, and bizarre, and the size of the tumor cells varies by more than fivefold. The tumor cells have an abundant, thick, and well-demarcated cytoplasm. The nucleus is oval or irregular and centrifugal. Multinucleated giant cells are observed more often than uninuclear cells. The size of nucleus is more than five times that of normal lymphocytes. The nuclear membrane is thin, and nuclear chromatin is coarsely granular, while the nucleolus is single and round. In cytological preparations, giant cells typically appear as single cells or in flat loose clusters, and occasionally

in fascicles.¹⁵ Another specific feature known about this malignancy is the presence of a phenomenon called emperipolesis: collections of polymorphonuclear leukocytes within the giant cells, apparently phagocytosing cytoplasmic contents.⁶ However, the etiology of emperipolesis in GCCL is unclear. Some exocrine features of GCCL are also analyzed under electron microscope. The immunohistochemical features of GCCL are also nondistinct. In Rossi et al's study, CK7 was positive in two of three (67%) GCCL samples, thyroid transcription factor-1 was negative in one of three (33%) GCCL samples, and CK20 was negative in all three samples (100%).¹⁶

GCCL does not have specific radiologic characteristics. Only Park et al described in their paper that on positron emission tomography scanning, GCCL was found to have exceedingly high standardized uptake values for radioactive glucose, values that were statistically significantly higher than other histological variants of lung cancer, and so it was difficult to diagnose with only radiologic imaging such as CT and magnetic resonance imaging.

For limited-stage GCCL, surgical resection is an effective treatment and provides adequate local control.¹⁷ However, most cases of GCCL are quite advanced at the time of diagnosis (50% of patients present with metastasis situation),^{13,18} and even after surgery, most patients experience tumor recurrence or death within 16–18 months.¹⁹ Platinum-based chemotherapy has been used to treat GCCL by most clinicians, but plenty of studies demonstrate the poor response of GCCL to chemotherapy in general.^{13,19–22} There is no study in the literature showing the efficacy of radiotherapy in the treatment of GCCL until now.

Because of the higher rate of resistance to conventional chemotherapy than other NSCLCs, we need more treatment options like molecular targeted therapy for patients with GCCL. However, molecular structure features of GCCL are still mysterious. A clinical trial involving 42 pleomorphic carcinomas was conducted to investigate the somatic mutations of EGFR and TP53. EGFR mutations were detected in 23.8% (10 of 42) of cases, including the exon 19 and 21 mutations. TP53 mutations were found in 28.6% (12 of 42) of cases. This indicated pleomorphic carcinomas are likely to benefit from treatment with EGFR tyrosine kinase inhibitors.²³ Liu et al performed a next-generation sequencing (NGS) of 36 PSC patients (excluding carcinosarcoma and blastoma). They defined a broad mutation spectrum for PSC, including several known oncogenes and tumor suppressor genes (*MET*, *KRAS*, *TP53*, *PIK3CA*, *STK11*, *NOTCH1*, *SMARCA4*, *RBI*, and *MLL2*), and six novel mutated genes, including *RASA1*, *CDH4*, *CDH7*, *LAMB4*,

SCAF1, and *LMTK2*. From the results, they found a distinctly high frequency of splice-site somatic mutations leading to MET exon 14 skipping (8 of 36, 22%), mutually exclusive with known driver mutations like *KRAS*, *EGFR*, *BRAF*, and *ALK*. Further experiments indicated that ablation of MET-driven signaling inhibited cell growth in H596 and Hs746T cell lines with MET exon 14 skipping.²⁴ A few months ago, we reported the NGS result of seven pleomorphic carcinomas. A total of 136 putative somatic variants and one gene fusion were identified, of which 16 variants were considered as hotspot mutations, including *EGFR*, *EML4-ALK*, *MET*, *BRAF*, *PIK3CA*, and *TP53*. All cases were pleomorphic carcinomas, including mixed components (giant cells, spindle cells, and/or adenocarcinoma cells). *EGFR* mutation was found in one pleomorphic carcinoma sample with more than 10% adenocarcinoma components, which indicated that point mutation may occur in adenocarcinoma area. However, *EML4-ALK* gene fusion was discovered in one sample comprising entirely spindle cells and giant cells, and no *KRAS* gene mutation was found in any sample.²⁵ In this case, the tumor comprised pure giant cells, and missense mutation of the *KRAS*, *TP53*, *KMT2D*, *SETD2*, *TET2*, and *MAP3K* was detected. This result was similar to the finding of Terra et al. They reported 10 of 33 PSCs harbored *KRAS* mutations, and 19 cases had *TP53* mutations.²⁶ There are no relevant target drugs or clinical trials on *KMT2D*, *SETD2*, *TET2*, and *MAP3K* mutations until now. A selective allosteric inhibitor of MEK1/MEK2, trametinib, showed similar progression-free survival and response rates as docetaxel in patients with previously treated *KRAS*-mutation-positive NSCLC in clinical trial GSK1120212.²⁷ The JUNIPER study (NCT02152631) with abemaciclib, an inhibitor of *CDK4* and *CDK6*, showed a safety profile allowing continuous dosing to achieve sustained target inhibition. The first-in-human experience demonstrates single-agent activity for patients with advanced breast cancer, NSCLC, and other solid tumors.²⁸ The *TP53* molecule is a nuclear protein with a tumor suppressor function related to sequence-specific DNA binding and repair of damaged DNA. Generally, mutant *TP53*-carrying tumors reveal poorer sensitivity to conventional chemotherapy and have worse prognosis than wild-type tumors. This is a possible reason for chemotherapy resistance of GCCL. The high incidence of *TP53* mutation in human tumors made it a potential target for new-concept cancer therapy. APR-246 is an effective compound which can reverse the *TP53* mutation in tumor cells by synergizing with many DNA-damaging cytotoxic drugs and has little toxicity on normal cells.²⁹ However, the effect of APR-246 on GCCL needs more experimental confirmation.

Conclusion

GCCL is a poorly differentiated non-small-cell lung cancer. Throughout the decades, the classification and concepts pertaining to the histogenesis have been controversial before the five subtypes of PSCs were established by the WHO. GCCL has exceptionally aggressive characteristics, and its prognosis is much poorer than other NSCLCs. Although complete tumor excision and chemotherapy are often adopted in clinical use, the tumor seems to have a poor response to any currently known treatment modality, including platinum-based chemotherapy and radiotherapy. More studies are needed to deeply understand the molecular structure of GCCL, and target therapy using MEK inhibitor, CDK 4/6 inhibitor, and TP53 mutation reversal drugs may be a potent treatment option for this disease in future.

Acknowledgments

This research was partially supported by grants from the National Natural Science Foundation of China (81773207 and 61573251), the Tianjin Natural Science Foundation (16PTSYJC00160 and 16JCZDJC34200), and the Tianjin Medical University General Hospital Young Incubation Foundation (ZYYFY2015027). The funders had no role in study design, data collection and analysis, decision to publish, or in the preparation of the manuscript.

Author contributions

Xin Li and Jun Chen wrote the manuscript and analyzed all of the data. Xin Li, Ziheng Zhang, Jinghao Liu, and Sen Wei provided medical care for the patients and collected the data. Dan Wang assisted in the pathological analysis. All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Cancer-related 295-gene panel

ABL1	BRAF	CHEK2	ETV4	FGFR4	JAK2	PAK3	PALB2	RAD51D	STAG2
AKT1	BRCA1	CHUK	ETV5	FLT1	JAK3	PAK7	PARP1	RAD52	STAT4
AKT2	BRCA2	CIC	ETV6	FLT3	JUN	MRE11A	PARP2	RAD54L	STK11
AKT3	BRIP1	CRBN	EWSR1	FLT4	KDM5A	MSH2	PARP3	RAFI	SUFU
ALK	BTGI	CREBBP	EZH2	FOXL2	KDM5C	MSH6	PARP4	RARA	SYK
ALOX12B	BTK	CRKL	FAM123B	GATA1	KDM6A	MTOR	PAX5	RBI	TBX3
APC	C11ORF30	CRLF2	FAM46C	GATA2	KDR	MUTYH	PBRM1	REL	TET2
APCDD1	C17ORF39	CSF1R	FANCA	GATA3	KEAP1	MYC	PDGFRA	RET	TGFBR2
AR	CARD11	CTCF	FANCC	GNA11	KIT	MYCL1	PDGFRB	RICTOR	TIPARP
ARAF	CASP8	CTNNA1	FANCD2	GNA13	KLHL6	MYCN	PDK1	RNF43	TMPRSS2
ARFRP1	CBFB	CTNNB1	FANCE	GNAQ	KRAS	MYD88	PIK3C2G	RPA1	TNFAIP3
ARID1A	CBL	CUL4A	FANCF	GNAS	LMO1	MYST3	PIK3C3	RPTOR	TNFRSF14
ARID2	CCND1	CUL4B	FANCG	GPR124	LRP1B	NBN	PIK3CA	ROSI	TOPI
ASXL1	CCND2	CYP17A1	FANCI	GRIN2A	MAP2K1	NCOR1	PIK3CG	RUNX1	TP53
ATM	CCND3	DAXX	FANCL	GSK3B	MAP2K2	NF1	PIK3R1	RUNX1T1	TRRAP
ATR	CCNE1	DDR2	FANCM	HGF	MAP2K4	NF2	PIK3R2	SETD2	TSC1
ATRX	CD79A	DIS3	FAT3	HLA-A	MAP3K1	NFE2L2	PMS2	SF3B1	TSC2
AURKA	CD79B	DNMT3A	FBXW7	HRAS	MAP3K13	NFKBIA	PNRC1	SH2B3	TSHR
AURKB	CDC73	DOT1L	FGF10	IDH1	MCL1	NKX2-1	PPP2R1A	SMAD2	VHL
AXL	CDH1	EGFR	FGF12	IDH2	MDM2	NOTCH1	PRDM1	SMAD4	WISP3
BACH1	CDK12	EP300	FGF13	IGF1	MDM4	NOTCH2	PRKARIA	SMARCA4	WT1
BAP1	CDK4	EPHA3	FGF19	IGF1R	MED12	NOTCH3	PRKDC	SMARCB1	XPO1
BARD1	CDK6	EPHA5	FGF23	IGF2	MEF2B	NOTCH4	PRSS8	SMARCD1	XRCC3
BCL2	CDK8	EPHB1	FGF3	IKBKE	MEN1	NPM1	PTCH1	SMO	ZNF217
BCL2L2	CDKN1B	ERBB2	FGF4	IKZF1	MET	NRAS	PTEN	SOC1	ZNF703
BCL6	CDKN2A	ERBB3	FGF6	IL7R	MITF	NSD1	PTPNI1	SOX10	
BCOR	CDKN2B	ERBB4	FGF7	INHBA	MLH1	NTRK1	RAD50	SOX2	
BCORL1	CDKN2C	ERG	FGFR1	IRF4	MLL	NTRK2	RAD51	SPEN	
BCR	CEBPA	ESR1	FGFR2	IRS2	MLL2	NTRK3	RAD51B	SPOP	
BLM	CHEK1	ETV1	FGFR3	JAK1	MPL	NUP93	RAD51C	SRC	

Table S2 High-throughput sequencing results of the patient

chr:posi	ref>alt	Type	Gene name	Amino acid change	Effect	Impact	Mutant abundance
12:253982849	C>T	SNP	KRAS	p.G12D	Missense_variant	Moderate	26.7%
12:49420858	C>T	SNP	KMT2D	p.R4964H	Missense_variant	Moderate	34.0%
17:7577535	C>T	SNP	TP53	p.R249K	Missense_variant	Moderate	8.30%
3:47147512	T>C	SNP	SETD2	p.Y1605C	Missense_variant	Moderate	16.60%
4:106164796	G>A	SNP	TET2	p.E1222K	Missense_variant	Moderate	48.50%
5:56177065	A>T	SNP	MAP3K1	p.T779S	Missense_variant	Moderate	41.40%
12:49434520	A>G	SNP	KMT2D	p.L2345=	Synonymous_variant	Low	66.10%
17:78882693	C>T	SNP	RPTOR	p.D828=	Synonymous_variant	Low	6.40%
2:209106734	C>T	SNP	IDH1	p.S278=	Synonymous_variant	Low	42.60%

Abbreviations: alt, gene alteration; chr, chromosome; posi, position; ref, reference genome; SNP, single-nucleotide polymorphism.

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