Case Report

Primary pulmonary malignant fibrous histiocytoma: case report and literature review

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Abstract: Malignant fibrous histiocytoma (MFH) is an aggressive soft tissue sarcoma known to occur in various organs. Primary MFH arising in the lung is quite rare. Herein we report a case of a 61-year-old male with primary pulmonary MFH and explore the underlying molecular mechanisms by next-generation sequencing (NGS). Five gene mutations in TSC2, ARID1B, CDK8, KDM5C and CASP8 were detected, and the mTOR inhibitor might be an effective treatment for this patient. In addition, we reviewed the scientific literature of approximately 23 primary pulmonary MFH case reports since 1990 and summarized the clinical features and prognosis of this rare pulmonary malignant tumor.

Keywords: Malignant fibrous histiocytoma (MFH); sarcoma; surgery; sequencing

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Introduction

Malignant fibrous histiocytoma (MFH) is an aggressive soft tissue sarcoma originating from mesenchymal tissues (1). It is one of the most common soft tissue sarcomas in adults and can also affect juveniles (1). Although MFH can develop in various organs, it most commonly occurs in the extremities and the retroperitoneal space of the abdominal cavity (2). However, primary MFH arising in the lung is rare (3). Since the first case reported in 1979, there have been approximately 36 reported cases of primary pulmonary MFH. Primary pulmonary MFH is highly malignant, and there are no optimal or consensus treatment strategies (4). In order to find a better treatment and improve the survival rate, we performed next-generation DNA sequencing (NGS) of MFH tissue from a 61-year-old male with primary pulmonary MFH. In addition, we summarized the clinical features and prognosis of this rare pulmonary malignant tumor based on the published literature (4-23).

Case presentation

A 61-year-old male with a 40-year heavy smoking history was admitted with chief complaints of an intermittent cough and blood expectoration for 10 days. Computed tomography (CT) scans revealed an 8 cm × 7 cm × 5 cm mass in the right upper lobe with large lymph nodes present in the hilum and mediastinum (*Figure 1*). Subsequent physical examination revealed reduced respiratory sounds over the right upper lung field. Laboratory tests revealed a high expression of neuron-specific enolase (NSE) (19 μg/L, range: 0–16.3 μg/L), aspartate aminotransferase (AST 47 U/L, range: 15–46 U/L), creatine kinase (CK 180 U/L, range: 30–170 U/L), creatine kinase-isoenzyme (CK-MB 27 U/L, range: 0–24 U/L) and urea (8.0 mmol/L, range 2.5–7.1 mmol/L). Radiological tests revealed no

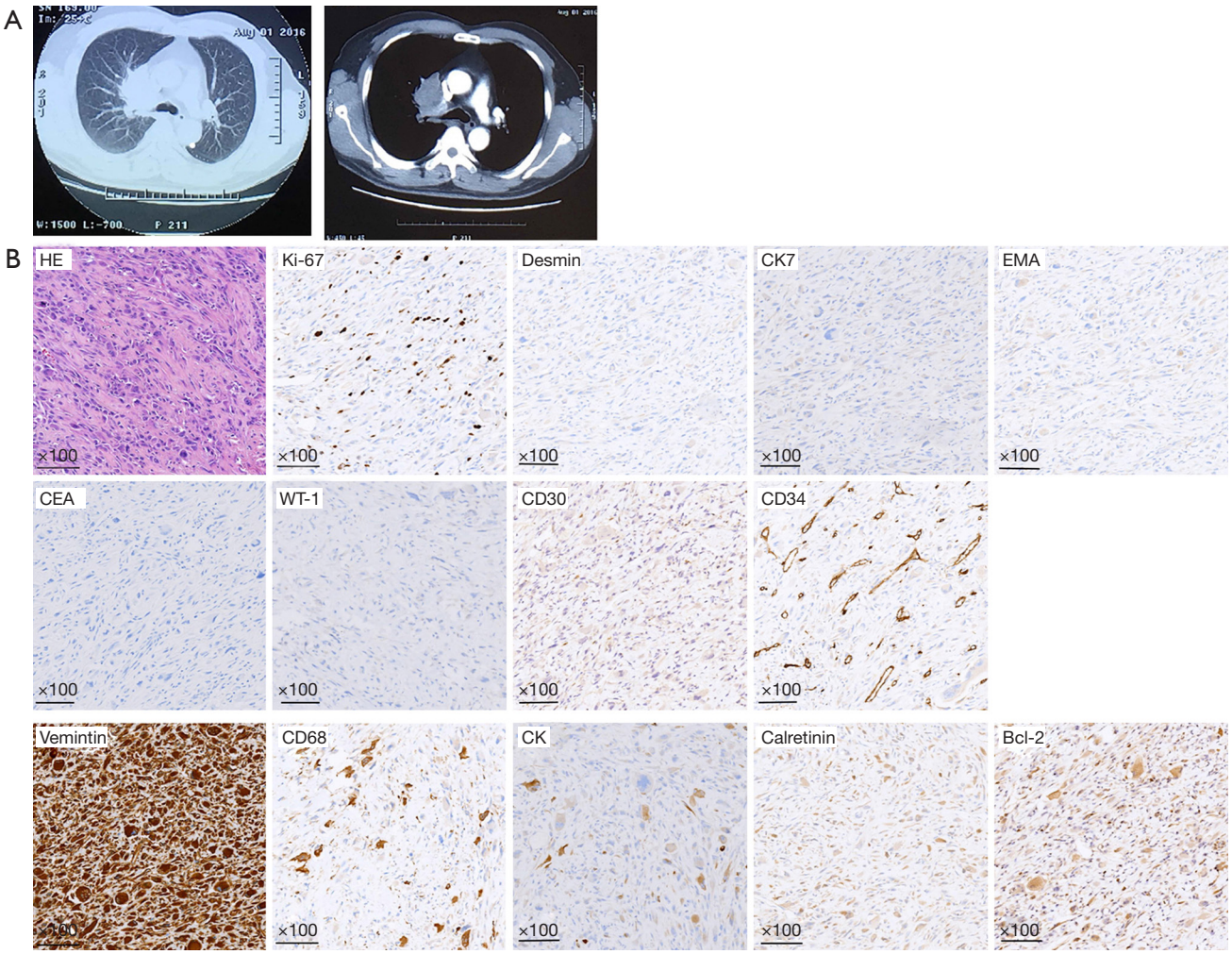

Figure 1 CT images, H&E and immunohistochemical staining results. (A) Chest CT shows an 8 cm × 7 cm × 5 cm mass in the right upper lobe with large lymph nodes present in the hilum and mediastinum; (B) H&E staining shows irregularly shaped infiltrating cells with abnormal nuclei and prominent nucleoli. IHC staining shows diffuse positivity for vimentin and partial positivity for CD68, CK, CD68, calretinin and Bcl-2 with a Ki67 index of approximately 10% and negativity for desmin, CK7, EMA, CEA, WT-1, CD34 and CD30.

significant abnormalities in the abdomen, brain or bone. A bronchoscopy was performed of the interlobar crest of the right upper lobe and rapid on-site evaluation (ROSE) revealed necrosis and morphologically heterogeneous cells. Histopathological examination further showed evidence of squamous metaplasia with moderate atypical hyperplasia, including lymphocyte and neutrophil infiltration.

Following this initial examination, the patient underwent a right upper lobectomy and systemic lymphadenectomy with bronchial sleeve resection and subsequent reconstruction of the pulmonary artery and superior vena cava. Immunohistochemical staining of tumor tissue demonstrated positivity for vimentin, CK (Cytokeratin), CD68, calretinin and Bcl-2 with a Ki-67 proliferative index of approximately 10%. In contrast, tumors were deemed negative for desmin, CK7, epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), wilm's tumor-1 (WT-1), CD34 and CD30 (*Figure 1*). Paratracheal lymph nodes were positive for metastasis, and the patient was given a diagnosis of MFH.

To explore the underlying molecular mechanisms and their potential therapeutic relevance, we utilized targeted next-generation sequencing (NGS) to detect driver mutations in tumor DNA (tDNA) with matched white blood cell (WBC) DNA as a control (sequencing depth

>1,000×; Beijing USCI Medical Laboratory Co., Ltd., China). A panel of 549 tumor-related genes was subjected to NGS (Supplementary method, *Figure S1*). The sequencing results identified five genes that each contained a single missense mutation (*Figure 2*). No copy number variation or gene translocation events were detected. Among the identified mutated genes, TSC2 was detected at the highest frequency (15.64%).

Discussion

Since the first introduction in 1979, and the origin of MFH was always an enigma. Until 2012 MFH was declassified as a formal diagnostic entity and renamed as an undifferentiated pleomorphic sarcoma by the World Health Organization (WHO). This new terminology has been supported by a compelling body of evidence over the last decade to suggest that MFH is an aggressive soft tissue sarcoma originating from mesenchymal cells (1). MFH most frequently occurs in the extremities or retroperitoneal abdominal cavity (2), whereas pulmonary MFH is uncommon, accounting for less than 0.2% of pulmonary tumors (3).

We provide a literature review of primary pulmonary MFH patients as summarized in *Table 1*. Since 1990 there have been 20 published case reports of 23 primary pulmonary MFH patients (4-23). We have retrieved this literature and summarized the clinical features of these cases together with the case reported in the current study (*Table 1*). Coughing, hemoptysis and dyspnea were the most common symptoms, whereas shortness of breath, chest pain and weight loss were less frequently reported. In addition, 3 patients (13.04%) were asymptomatic such that MFH was discovered by CT scan during the course of a regular examination. There were more male MFH patients than female patients (14 *vs.* 9), and patient age ranged from 9 to 86 years old with a mean age of 52.87; 73.91% of these patients were between 40 and 80 years old at the time of diagnosis. Of these 23 patients, 3 were smokers, 5 were nonsmokers, and the remaining 15 had no specific record of smoking history. Thus, there is no obvious correlation of cigarette smoking with pulmonary MFH morbidity. There was no significant difference between the left and right lungs for MFH morbidity (30 *vs.* 31).

The documented information regarding tumor size is variable. One MFH patient with a tumor diameter of 1.7 cm lived for 108 months and still had no disease symptoms (3), while another patient with a tumor diameter of 11 cm died six months after diagnosis (19). This comparison suggests that MFH patients with smaller tumors have a relatively good prognosis, although the overall prognosis for the disease is poor.

In general, the overall survival of reported cases ranged from 0 to more than 168 months. For these 23 patients, 5 patients did not receive any treatment and 2 patients received only chemotherapy or radiotherapy. In total, 15 patients underwent surgical resection, including 11 lobectomies, 3 pneumonectomies and 1 tumorectomy. In these 15 surgeries, 6 combined resection with neoadjuvant or adjuvant chemotherapy. Of these, 4 patients survived less than 12 months, 2 patients survived more than 12 months. Complete resection of tumors with systematic lymph node dissection is thought to contribute to the survival of patients with primary pulmonary MFH (4).

The diagnosis of primary pulmonary MFH is typically a multi-step process. First, a complete extrathoracic evaluation is made to confirm that MFH originated in the lung. Imaging techniques such as PET-CT are also utilized to arrive at a diagnosis of pulmonary MFH, which must be ultimately confirmed by histological examination. Histological sections can be obtained from preoperative puncture, tracheoscopic biopsy or postoperative tumor tissue. Maeda *et al.* (4) report that histological analysis for preoperative diagnosis is rare and only 4% of reported cases were histologically diagnosed before surgery. There are no specific immunohistochemical markers for MFH, however, other sarcomas with similar microscopic findings have be excluded with immunohistochemical staining. Desmin, actin, vimentin, keratin, and neurogenic tumors are commonly stained for the differential diagnosis. In the current case, no abnormalities other than the pulmonary mass were found by brain MRI, enhanced CT of abdomen and bone ECT examinations. The patient was then subjected to surgical resection, and subsequent immunohistochemical staining confirmed the diagnosis of MFH.

Molecular mechanisms responsible for primary pulmonary MFH formation and progression are mainly unknown. To explore possible underlying mechanisms, we performed NGS on postoperative tumor tissue. The resulting profiling data revealed five mutations in the *TSC2* , *ARID1B*, *CDK8*, *KDM5C* and *CASP8* genes. The mutation distribution diagrams of these genes from TCGA and highlighted in *Figure 2*. Among these, the mutation frequency of TSC2 was 15.64%, which encodes a M280V missense mutation. The *TSC2* gene encodes tuberin, which is known to form heterodimers with hamartin (24). The tuberin/hamartin

Gene	Amino acid change	Frequency(%)
TSC2	M280V missense mutation	15.64
ARIDIB	A329G missense mutation	3.28
CDK8	A68E missense mutation	2.17
KDM5C	R614Q missense mutation	1.94
CASP8	D217E missense mutation	1.68

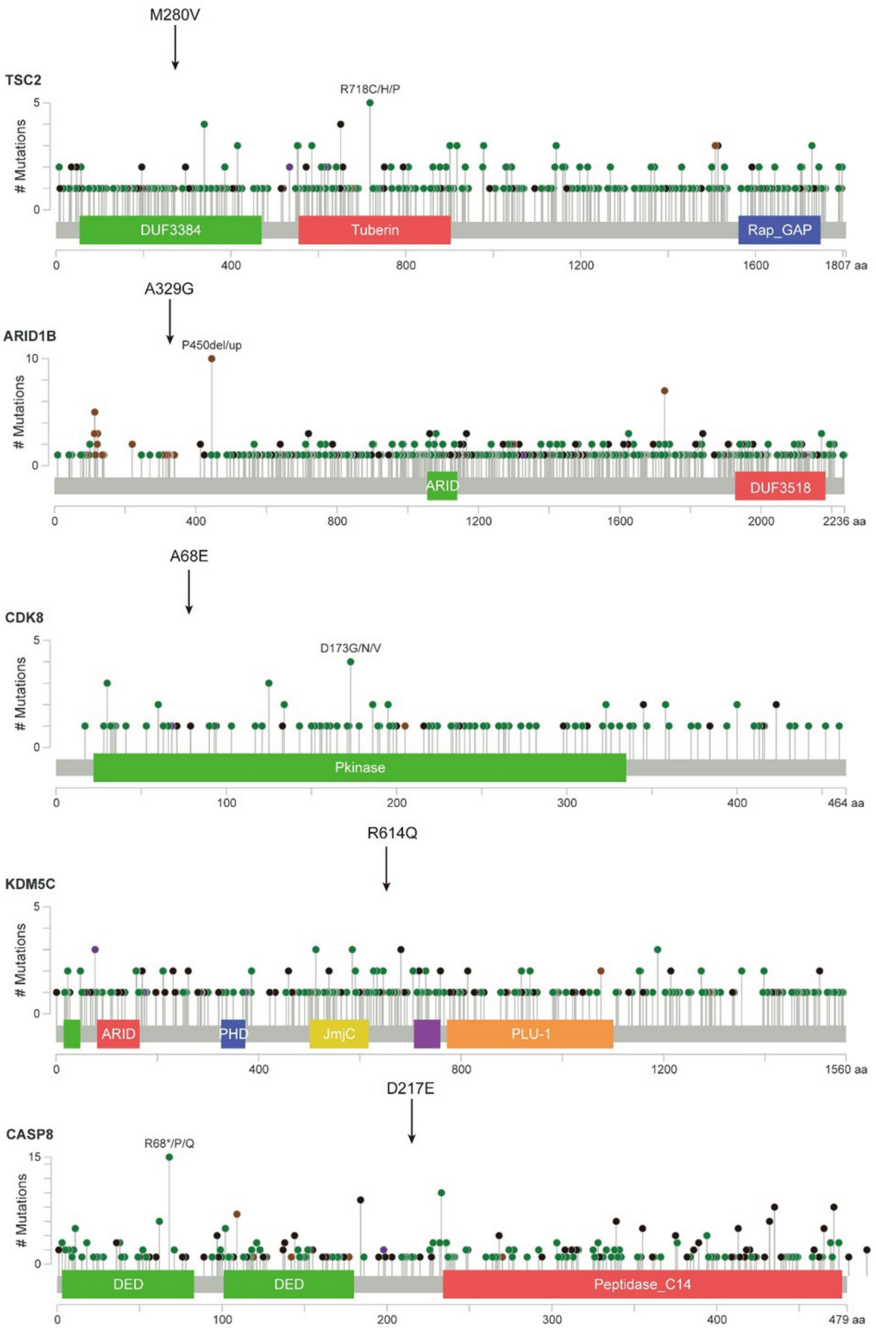

Figure 2 Gene mutation analysis results and corresponding data from The Cancer Genome Atlas (TCGA). The identified missense mutations in TSC2, ARID1B, CDK8, KDM5C and CASP8 are overlaid with the mutation distribution diagrams of these genes from TCGA and highlighted with black arrows.

Table 1 Literature review of primary pulmonary MFH

Case	Reference	Age (years)	Sex	Smoke status	Site	Size (cm)	Symptoms at the admission	Treatment	LN	F/U	Survival (m)
1	Patel *et al.* (5)	86	M	NA	RLL	9.6×8.9 ×7.6	Cough, dyspnea, and increasing weakness	Lobectomy	NEG	NED	6
2	Li *et al.* (7)	80	F	NA	RUL	8	Cough	None	NA	DOD	1.5
3	Jeon *et al.* (8)	55	M	NA	LLL	NA	Cough and chest pain	Pneumonectomy/ chemotherapy/XRT	NEG	NED	9
4	Thomas *et al.* (6)	47	M	No	RUL	NA	Swelling on the gingiva	Chemotherapy/ XRT	POS	DOD	2
5	Tsangaridou *et al.* (9)	54	M	Yes	LUL/ LLL	NA	NA	Pneumonectomy	POS	AWD	168
6	Maitani *et al.* (10)	18	F	NA	LUL	2.2	Asymptomatic	Partial lobectomy	NA	NED	36
7	Maeda *et al.* (4)	62	M	Yes	LUL	4.5×4	Asymptomatic	Lobectomy	POS	DNED	24
8	Noh *et al.* (11)	58	F	No	RUL	5×4	NA	Lobectomy/XRT	NEG	NED	5
9	Wang *et al.* (12)	86	M	No	LLL	9×15	Exertional dyspnea and poor appetite	None	NA	DOD	2
10	Alhadab *et al.* (13)	56	M	NA	LUL/ LLL	NA	Cough and shortness of breath	None	NA	DOD	4
11	Herrmann *et al.* (14)	57	M	No	RUL	13×8	Car accident	Lobectomy	NA	NED	12
12	Fujita *et al.* (15)	65	F	NA	LL	12×12	Cough, yellow sputum and exertional dyspnea	None	NA	DOD	6
13	Barbas *et al.* (17)	37	M	Yes	RML/ RLL	10×6×3	Cough, hemoptysis and weight loss	Pneumonectomy	NEG	DNED	6
14	Shah *et al.* (18)	9	M	NA	LUL	6	Cough, hemoptysis and weight loss	Lobectomy/XRT/ chemotherapy	NA	NED	36
15	Nistal *et al.* (16)	12	F	No	LUL	7×6×5	Chest pain, fatigue, non-productive cough and weight loss	Lobectomy/ chemotherapy	NA	AWD	5
16	Gómez-Román *et al.* (20)	61	M	NA	RUL	3	NA	Tumorectomy	NA	NED	9

Table 1 (*continued*)

Table 1 (*continued*)

Case	Reference	Age (years)	Sex	Smoke status	Site	Size (cm)	Symptoms at the admission	Treatment	LN	F/U	Survival (m)
17	Halyard *et al.* (19)	51	F	NA	LLL	10×8	Pleuritic chest pain	Lobectomy/XRT	NEG	NED	60
18		77	M	NA	RML	2.2	Asymptomatic	lobectomy	NEG	NED	36
19		40	M	NA	LLL	11×9×8	Cough, pain in the left posterior rib cage, weight loss, fatigue	Lobectomy/XRT/ chemotherapy	POS	DOD	6
20		57	F	NA	LUL	7.5×6×4	Ataxia, headache, and left homonymous hemianopsia	Lobectomy	NA	DOD	1
21	Kamath *et al.* (21)	56	M	NA	RLL	10	Blurred vision in the right eye	None	NA	DOD	3
22	Higashiyama *et al.* (22)	49	F	NA	RLL	6	Dry cough	Pneumonectomy	POS	NED	NA
23	In *et al.* (23)	43	F	NA	RLL	NA	Chest pain	Chemotherapy/ XRT	NA	NA	NA

MFH, malignant fibrous histiocytoma; LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; NA, not available; XRT, radiotherapy; F/U, follow up; DOD, dead of MFH disease; AWD, alive with MFH disease; NED, no evidence of MFH disease; DNED, dead no evidence of MFH disease; m, month.

heterodimer inhibits the Rheb GTPase, leading to inactivation of the Rheb/mTOR/p70S6K pathway, which is a major regulator of cell growth and proliferation (24) Thus, deleterious mutations in TSC2 result in activation of the mTOR pathway, abnormal cell growth and increased proliferation. In non-small cell lung cancer, a previous study reported that targeting TSC2 can inhibit cancer cell growth (25). Therefore, we postulate that the TSC2 mutation identified here might be functionally involved in primary pulmonary MFH occurrence or progression, and mTOR inhibitors, such as everolimus, might be efficacious for some MFH patients.

In conclusion, based on the published literature reviewed here, MFH is insensitive to both chemotherapy and radiotherapy. Thus, once the diagnosis is confirmed, complete surgical resection is necessary. Targeted therapy using mTOR inhibitors might be a promising future treatment for this rare disease.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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Supplementary method

Next-generation sequencing

The panel was used to sequence all exons of 549 tumor-related genes mutations simultaneously (*Figure S1*). The concentration of the DNA samples was measured with the Qubit dsDNA assay to make sure that genomic DNA was 100 ng. Adjust the volume to a total of 100 µL using 1× TE (low EDTA) and transfer to a Covaris microTUBE for fragmentation. Fragment the gDNA so that the average DNA fragment size is 180–220 bp, followed by hybridization with the capture probes baits, hybrid selection with magnetic beads, and PCR amplification. A bioanalyzer high-sensitivity DNA assay was then used to assess the quality and size range. Available indexed samples were then sequenced on a Nextseq (Illumina, San Diego, CA, USA) with pair-end reads. Raw data from the NEXT SEQ 500 runs were processed with flexbar software (version 2.7.0, https://sourceforge.net/projects/flexbar/) to generate clean fastq data, trim adapter sequences, and filter and remove poor quality reads. Then clean fastq data were aligned to hg19 (GRCH37) assembly by using BWA-sampe (Burrows Wheeler Aligner software version 0.7.12-r1039, https://sourceforge.net/projects/bio-bwa/files/), and PCR (polymerase chain reaction) duplicates were removed by MarkDuplicates tool in Picard Tools (version 1.124, http://broadinstitute.github.io/picard/). All variants were annotated using ANNOVAR (version 20160201, http://annovar.openbioinformatics.org/en/latest/). Variation frequency (>0.5%) was used to eliminate erroneous base calling and generate final mutations, and a manual verification was performed using IGV (Intergrative Genomics Viewer version 2.3.72, http://software.broadinstitute.org/software/igv/).

A								
ABCB1	*ABCC4*	*ABL1*	*ACVR1B*	*AKT3*	*APC*	*ARFRP1*	*ARID2*	*ATIC*
ABCC1	*ABCC6*	*ABL2*	*AKT1*	*ALK*	*AR*	*ARID1A*	*ASXL1*	*ATM*
ABCC2	*ABCG2*	*AKT2*	*AMER1*	*ARAF*	*ARID1B*	*ATF7IP*	*ATP7A*	*ATR*
AURKB	*ATRX*	*AXIN1*	*AURKA*	*AXL*				
B								
B2M	*BARD1*	*BCL2L2*	*BCORL1*	*BLK*	*BRAF*	*BRD4*	*BSG*	*BAP1*
BAIAP3	*BCL2*	*BCL6*	*BCR*	*BLM*	*BRCA1*	*BRIP1*	*BTG1*	*BCL2L1*
BCOR	*BIRC5*	*BMPR1A*	*BRCA2*	*BTK*				
C								
C11orf30	*CAMKK2*	*CBFB*	*CBR3*	*CCND3*	*CD19*	*CD33*	*CD52*	*CD79B*
C18orf56	*CARD11*	*CBL*	*CCND1*	*CCNE1*	*CD22*	*CD38*	*CD74*	*CDA*
CAMK2G	*CASP8*	*CBR1*	*CCND2*	*CCR4*	*CD274*	*CD3EAP*	*CD79A*	*CDC73*
CDH1	*CDK2*	*CDK6*	*CDK9*	*CDKN2A*	*CEBPA*	*CHEK1*	*CIC*	*CREBBP*
CDK1	*CDK4*	*CDK7*	*CDKN1A*	*CDKN2B*	*CHD2*	*CHEK2*	*CK1*	*CRKL*
CDK12	*CDK5*	*CDK8*	*CDKN1B*	*CDKN2C*	*CHD4*	*CHST3*	*COMT*	*CRLF2*
CSF1R	*CTCF*	*CTNNA1*	*CUL3*	*CYLD*	*CYP1A1*	*CYP1B1*	*CYP2B6*	*CYP2C8*
CSK	*CTLA4*	*CTNNB1*	*CYBA*	*CYP19A1*	*CYP1A2*	*CYP2A6*	*CYP2C19*	*CYP2C9*
CYP2D6	*CYP2E1*	*CYP3A4*	*CYP3A5*	*CYP4B1*				
D								
DAXX	*DDR1*	*DDR2*	*DNMT1*	*DNMT3A*	*DOT1L*	*DPYD*	*DSCAM*	*DAXX*
E								
E2F1	*EGFR*	*EML4*	*EPCAM*	*EPHA3*	*EPHA7*	*EPHB2*	*ERBB2*	*ERCC1*
EGF	*EGR1*	*ENOSF1*	*EPHA1*	*EPHA4*	*EPHA8*	*EPHB3*	*ERBB3*	*ERCC2*
EGFL7	*EMC8*	*EP300*	*EPHA2*	*EPHA5*	*EPHB1*	*EPHX1*	*ERBB4*	*ERG*
ERRFI1	*ESR1*	*ETV1*	*ETV4*	*ETV5*	*ETV6*	*EWSR1*	*EXT1*	*EXT2*
EZH2								
F								
FAM46C	*FANCE*	*FAS*	*FGF10*	*FGF3*	*FGFR2*	*FH*	*FLT3*	*FRK*
FANCA	*FANCF*	*FAT1*	*FGF14*	*FGF4*	*FGFR3*	*FKBP1A*	*FLT4*	*FRS2*
FANCC	*FANCG*	*FBXW7*	*FGF19*	*FGF6*	*FGFR4*	*FLCN*	*FOXL2*	*FUBP1*
FANCD2	*FANCL*	*FCGR3A*	*FGF23*	*FGFR1*	*FGR*	*FLT1*	*FOXP1*	*FYN*
FZD7								
G								
GABRA6	*GATA1*	*GATA3*	*GATA6*	*GID4*	*GLI1*	*GNA11*	*GNAQ*	*GPC3*
GALNT14	*GATA2*	*GATA4*	*GCK*	*GINS2*	*GLI3*	*GNA13*	*GNAS*	*GPR124*
GRIN2A	*GRM3*	*GSK3B*	*GSTM1*	*GSTM3*	*GSTP1*	*GSTT1*		
H								
H3F3A	*HCK*	*HGF*	*HIF1A*	*HIST1H3B*	*HNF1A*	*HRAS*	*HSD3B1*	*HSP90AA1*
I								
IDH1	*IGF-1*	*IGF2*	*IKBKB*	*IKZF1*	*INHBA*	*INSR/IR*	*IRF2*	*IRS2*
IDH2	*IGF1R*	*IGF2R*	*IKBKE*	*IL7R*	*INPP4B*	*IQGAP3*	*IRF4*	*ITIH5*
ITK								
J								
JAK1	*JAK2*	*JAK3*	*JUN*					
K								
KAT6A	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLC3*
KLHL6	*KMT2A*	*KMT2B*	*KMT2C*	*KMT2D*	*KRAS*			
L								
LCK	*LIMK1*	*LMO1*	*LRP1B*	*LRP2*	*LYN*	*LZTR1*	*LCK*	*LIMK1*
M								
MAGI2	*MAP3K1*	*MAPK10*	*MAPKAPK2*	*MDM2*	*MEN1*	*MKNK2*	*MRC2*	*MSH6*
MAP2K1	*MAP4K4*	*MAPK14*	*MARK1*	*MDM4*	*MERTK*	*MLH1*	*MRE11A*	*MTDH*
MAP2K2	*MAP4K5*	*MAPK8*	*MAX*	*MED12*	*MET*	*MLH3*	*MS4A1*	*MTHFR*
MAP2K4	*MAPK1*	*Mapk9*	*MCL1*	*MEF2B*	*MITF*	*MPL*	*MSH2*	*MTOR*
MTRR	*MUTYH*	*MYC*	*MYCL1*	*MYCN*	*MYD88*			
N								
NAT1	*NBN*	*NCF4*	*NCOR1*	*NF1*	*NFE2L2*	*NKX2-1*	*NOTCH1*	*NOTCH3*
NAT2	*NCAM1*	*NCOA3*	*NEK11*	*NF2*	*NFKBIA*	*NOS3*	*NOTCH2*	*NPM1*
NQO1	*NRAS*	*NSD1*	*NTRK1*	*NTRK2*	*NTRK3*	*NUP93*		
P								
PAK1	*PARP2*	*PDGFRA*	*PIGF*	*PIK3R1*	*PLCG2*	*POLE*	*PRDX4*	*PRKCI*
PAK3	*PAX5*	*PDGFRB*	*PIK3C2B*	*PIK3R2*	*PLK1*	*PPARD*	*PRKAA1*	*PRKDC*
PALB2	*PBRM1*	*PDK1*	*PIK3CA*	*PPP1R13L*	*PMS1*	*PRRT2*	*PRKAR1A*	*PRSS8*
PARK2	*PDCD1*	*PHF6*	*PIK3CB*	*PKCγ*	*PMS2*	*PPP2R1A*	*PRKCA*	*PTCH1*
PARP1	*PDCD1LG2*	*PHKA2*	*PIK3CG*	*PRKCE*	*POLD1*	*PRDM1*	*PRKCB*	*PTEN*
PTK2	*PTPN11*	*PTPRD*	*PTK6*					
Q								
QKI								
R								
RAC1	*RAD50*	*RAD51C*	*RAF1*	*RARA*	*RBM10*	*RHPN2*	*RMDN2*	*ROCK1*
RAC2	*RAD51*	*RAD51D*	*RANBP2*	*RB1*	*RET*	*RICTOR*	*RNF43*	*MST1R*
ROS1	*RPL13*	*RPS6KA1*	*RPS6KB1*	*RPTOR*	*RRM1*	*RUNX1*	*RUNX1T1*	
S								
KITLG	*SDHD*	*SKP2*	*SLC22A6*	*SMAD4*	*SOD2*	*SPOP*	*STAT1*	*STAT6*
SDHA	*SETD2*	*SLC10A2*	*SLCO1B1*	*SMARCA4*	*SOX10*	*SPTA1*	*STAT2*	*STEAP1*
SDHAF1	*SF3B1*	*SLC15A2*	*SLCO1B3*	*SMARCB1*	*SOX2*	*SRC*	*STAT3*	*STK11*
SDHAF2	*SGK1*	*SLC22A1*	*SLIT2*	*SMO*	*SOX9*	*SRD5A2*	*STAT4*	*STK3*
SDHB	*SHH*	*SLC22A16*	*SMAD2*	*SNCAIP*	*SPEN*	*SRMS*	*STAT5A*	*STK4*
SDHC	*SIK1*	*SLC22A2*	*SMAD3*	*SOCS1*	*SPG7*	*STAG2*	*STAT5B*	*SUFU*
SULT1A1	*SULT1A2*	*SULT1C4*	*SYK*					
T								
TAF1	*TCF7L2*	*TNF*	*TNFRSF8*	*TET2*	*TK1*	*TOP1*	*TPMT*	*TSC1*
TBX3	*TEK*	*TNFAIP3*	*TNFSF11*	*TGFBR1*	*TMEM127*	*TOP2A*	*TPX2*	*TSC2*
TCF7L1	*TERT*	*TNFRSF14*	*TNFSF13B*	*TGFBR2*	*TMPRSS2*	*TP53*	*TYRO3*	*TYMS*
TSHR	*TNK2*	*TNFRSF10B*	*TNFRSF10A*					
U								
U2AF1	*UBE2I*	*UGT1A1*	*UGT2B15*	*UGT2B17*	*UGT2B7*	*UMPS*	*U2AF1*	*UBE2I*
V								
VEGFA	*VEGFB*	*VHL*						
W								
WEE1	*WISP3*	*WNK3*	*WT1*					
X								
XPC	*XPO1*	*XRCC1*	*XRCC4*					
Y								
YES1								
Z								
ZAP70	*ZBTB2*	*ZC3HAV1*	*ZNF217*	*ZNF703*				

Figure S1 Next-generation sequencing to identify mutations in 549 tumor-related genes.