Case Report

A rare multiple primary sarcomatoid carcinoma (SCA) of small intestine harboring driver gene mutations: a case report and a literature review

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Abstract: Primary sarcomatoid carcinoma (SCA) is a type of rare tumor consisting of both malignant epithelial and mesenchymal components. Only 32 cases of SCA of the small bowel have been reported in the literature to date. Due to its rarity and complexity, this cancer has not been genetically studied and its diagnosis and treatment remain difficult. Here we report a 54-year-old male underwent emergency surgical resection in the small intestine due to severe obstruction and was diagnosed with multiple SCA based on postoperative pathological examination. Over 100 polypoid tumors scattered along his whole jejunum and proximal ileum. Chemotherapy (IFO+Epirubicin) was performed after surgery while the patient died two months after the surgery due to severe malnutrition. Whole-exome sequencing was performed for the tumor tissue with normal tissue as the control. Important cancer-related gene mutations, including KRAS (c.37G>T, p.G13C), TP53 (c.871A>T, p.K291*), EGFR (c.1351C>T, p.R451C), and CDKN2A (c.104_138del, p.G35fs), were found among 286 nonsynonymous somatic mutations (SNV and Indel). Copy-number amplified genes mainly gathered in chromosome 6, 7, 16 and 20. Mutation clustering analysis showed that main genetic abnormalities included DNA methylation, DNA alkylation, cellular homeostasis, and shared similarities with melanoma, glioma, prostate cancer, bladder cancer, non-small cell lung cancer, and pancreatic cancer. In summary, the genomic features of the small intestine SCA were explored at whole-exome level for the first time, and over 200 somatic mutations were identified in the tumor tissue. Key tumor driver gene mutations were revealed, as well as several aberrant functional pathways. These results contribute to further understanding of the pathogenesis and molecular mechanism of this rare tumor.

Keywords: Sarcomatoid carcinoma (SCA); small intestine; case report; KRAS; TP53

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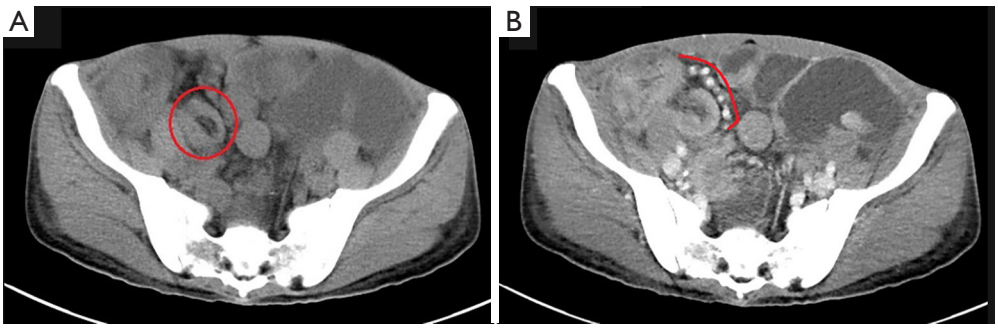

Figure 1 Abdominal contrast-enhanced computed tomography (CT) showed signs of intestinal tumors. (A) thickened intestinal wall (in red circle). (B) Multiple solid masses (along red curve).

Introduction

Primary sarcomatoid carcinoma (SCA) is a type of rare tumor consisting of both malignant epithelial and mesenchymal components (1). Tumors with sarcomatoid features have been reported to be more aggressive (2), while the pathogenesis of SCA has not been elucidated. Collision theory is a popular hypothesis suggesting that two different types of tumor cells originate from mesenchymal and epithelial origins separately (3). However, a more reasonable theory that sarcomatoid and carcinomatoid elements sharing a common clonal origin is supported by recent studies based on genomic sequencing (4,5). SCA has been reported in various organs, including lung, uterine, salivary and thyroid glands (6,7). In small intestine, SCA was described using the term enteroblastoma for the first time in 1973 (8), and other terms such as SCA, carcinosarcoma, metaplastic carcinoma, and spindle cell carcinoma, were subsequently used in other organs. Nowadays, SCA is the most accepted term used in diagnostic surgical reports (9). SCA can be discriminated from polyps by pathological examinations. SCA has both epithelioid components and sarcomatoid components with high dysplasia, and positive staining of NSE, CK and vimentin can be observed by immunohistochemistry. These features cannot be found in polyps, which are featured by hyperplasia with generally normal adenoid structure.

The most frequent types of SCA, including pulmonary SCA, sarcomatoid renal cell carcinoma, and uterine carcinosarcoma, have been characterized in terms of diagnostic classification and molecular mechanism (10-12), while intestinal SCAs are very unusual. Due to inaccessibility of routine endoscopy and nonspecific clinical symptoms, patients affected by SCA were usually diagnosed at late stages. Only dozens of cases were reported (13,14) and the patients generally had poor prognosis. We herein report a male with multiple (over 100) primary jejunum SCAs scattered along the whole jejunum and proximal ileum, which has never been reported in previous SCA studies. We also established the whole-exome mutational profile of SCA for the first time, and identified featured SNV/INDEL and CNV alterations, and revealed key tumor driver gene mutations and aberrant functional pathways. We present the following article in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2829).

Case presentation

A 54-year-old Chinese male presented with abdominal distension, fatigue and loss of weight and was diagnosed with gastro and duodenal inflammation by gastroscopy with anemia at a local hospital. Abdomen ultrasonic examination was performed with no signs of abnormality. He was referred to our hospital due to symptoms aggravated within two weeks. Preoperative contrast-enhanced computed tomography (CT) showed multiple polypoid lesions in small intestine causing intussusceptions and obstruction (*Figure 1A*,*B*). No masses were seen in lung, liver, or pancreas. Laparotomy was then performed and approximately 1,000 mL ascites in the peritoneal cavity were found. Meanwhile, many polypoid lumps in small bowel were observed with enlarged regional lymph nodes. No lesion was found in other parts of the gastrointestinal tract. Segmental resection of his whole jejunum and proximal ileum (total length of 300 cm, distal resected margin at 160 cm to the ileocecal valve) along with seven mesentery lymph nodes were performed.

More than 100 round-like polypoid masses with diameter from 1.5 to 2.6 cm were dispersing along the resected intestinal lumen (*Figure 2*). Metastases were found in all resected lymph nodes. Microscopically, the tumor

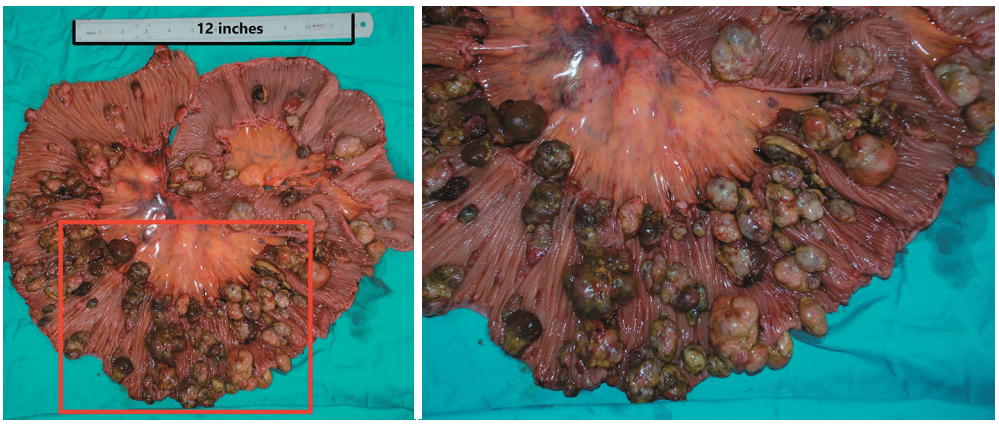

Figure 2 The resected segment of jejunum showed multiple round-like tumors in the jejunum. Part of the jejunum in red square in the left panel is amplified in the right panel to show the characteristics of the tumor.

was composed of two different components of cells, the pleomorphic cells with giant nuclei and the epithelioid cells. The two components were present in complex form without clear separation, in which approximately 30% of the lesions belonged to epithelioid components and 70% belonged to sarcomatoid components. Immunohistochemical staining showed vimentin(+), CK(+), CK8(+), CK18(+), CD34(+), CD68(+) , S-100(-), Dog-1(-), CD117(-), CD3(-), CD20(-), CD30(-), CD57(-), desmin(-), CyclinD1(-), and SMA(-), suggesting both epithelial and stromal components (*Figure 3*). The final diagnosis was confirmed as jejunal SCA with mesenteric lymph nodes metastasis, pT3N2M0, stage IV. The patient died 2 months after surgery due to severe malnutrition, cachexia and electrolyte disturbance following one cycle of postoperative chemotherapy (IFO+Epirubicin).

The tumor and its adjacent normal tissue were fixed with formalin and embedded with paraffin (FFPE). To further investigate the genomic features of this tumor, whole-exome sequencing was performed with DNA extracted from both FFPE samples. The purity and concentration of the DNA fragments were assessed using the Qubit 2.0 fluorometer and the Qubit. DNA sequencing was then performed on the Illumina Novaseq6000 system according to the manufacturer's recommendations at an average depth of 5,000×. Sequencing data were de-multiplexed and aligned to the human reference genome (hg19 or GRch37) using Burrows-Wheeler Aligner (version 0.7.15)-r1140 by default settings. Pileup files for properly paired reads with mapping quality ≥60 was generated using Samtools (http://www.htslib.org/). Thirty-five germline alterations were identified from normal tissue using a 58-gene analysis pipeline. According to the latest American College of Medical Genetics and Genomics (ACMG) guidelines, none was interpreted as pathogenic and only 3 as variant of undetermined significance (VUS) (Table S1).

Somatic variants lists were created using VarScan2 (http://varscan.sourceforge.net/). Allele frequencies were calculated for all Q30 bases. Using a custom Python script, previously identified tumor DNA mutations were intersected with a Samtools pileup file generated for each sample, and the number and frequency were then calculated for each mutation. A mutation was identified if ≥5 mutant reads were identified and ≥1 mutant read was identified on each strand. Two hundred and seventy-six single nucleotide variants (SNVs) (Table S2), 8 short deletions and 2 short insertions (Table S3) were identified in the tumor tissue, including 38 point and indel alterations in driver genes defined by previous studies (15-18) (*Table 1*). Sixty-nine copy number variations were also detected (Table S4), mainly gathered in chromosome 6, 7, 16 and 20 (*Figure 4*). The tumor mutation burden (TMB) was 7.15 mutations/Mb. Several key driver genes were revealed to harbor mutations, including KRAS (c.37G>T, 66.3%), TP53 (c.871A>T, 47.7%), EGFR (c.1351C>T, 4.2%), CDKN2A (c.104_138del, 11.1%). No alteration was found in PDGFR gene, which is usually mutated in GIST.

Functional clustering analysis was employed on somatic mutations. Using clusterProfiler (19), we found most enriched GO term was DNA methylation or demethylation. KEGG clustering analysis (BH-corrected, $P<0.05$) showed several cancer-related pathways (*Figure 5*). These

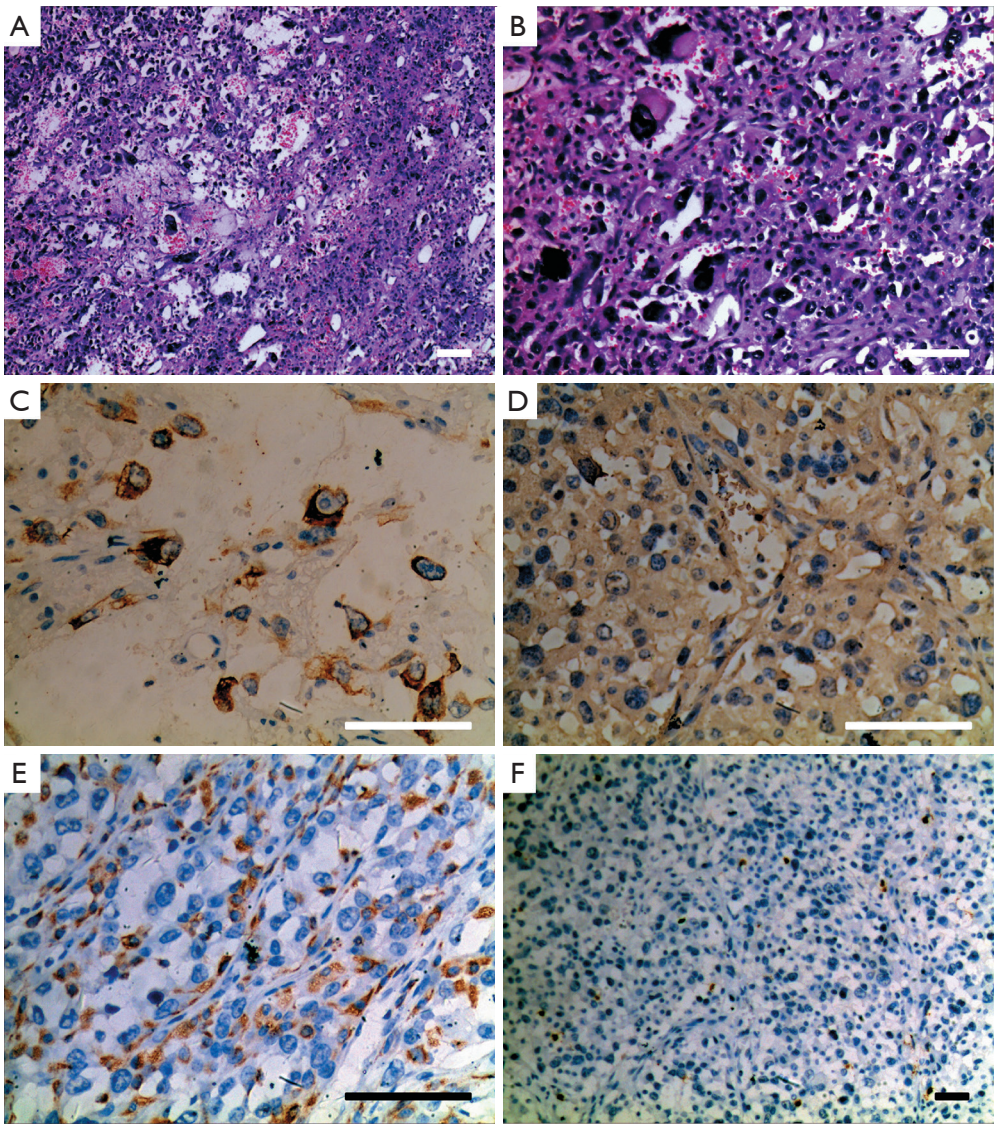

Figure 3 Postoperative pathological examination including hematoxylin and eosin (HE) staining and immunohistochemistry staining of the tumor. (A) Pleomorphic cells with giant nuclei on the left and epithelioid component on the right (HE staining, 100×). (B) Polygonal-shaped tumor cells exhibiting high dysplasia (HE staining, 200×). (C) Positive immunohistochemistry stain for cytokeratins (CK) (400×). (D) Positive immunohistochemistry stain for vimentin (400×). (E) Positive immunohistochemistry stain for CK8 (400×). (F) Negative immunohistochemistry stain for S-100 (100×). Scale bar: 100 μm.

observations suggest that the genetic abnormalities in this case were distinct from other SCA cases, and reflected the uniqueness of this case.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients.

Discussion and conclusions

Small bowel tumors are not commonly seen, accounting for less than 5% of all gastrointestinal cancers. The most common type of small bowel malignancies is adenocarcinoma, followed by neuroendocrine tumor, stromal tumor, and lymphoma (20,21). SCA is very rare. Only 32 cases of SCA in the small bowel have been reported in the literature to date (*Table 2*). The tumor mainly occurs

Table 1 Main SNV and indel alterations in driver genes found in this case

ID	Gene	Exon	Nucleotide	Protein	Allele frequency	Variant type
1	*AARS2*	Exon14	c.G1961T	p.G654V	31.26	Snv
2	*ATF7IP*	Exon2	c.C1154T	p.A385V	6.52	Snv
3	*ATP2B3*	Exon14	c.G2396T	p.G799V	66.67	Snv
4	*BAZ2A*	Exon9	c.C1795T	p.R599C	10.37	Snv
5	*BIRC6*	Exon10	c.G2848C	p.D950H	28.82	Snv
6	*CDKN2A*	Exon1	c.104_138del	p.G35Efs*73	11.11	Indel
7	*CEP170*	Exon13	c.C2375A	p.S792X	11.67	Snv
8	*CFH*	Exon8	c.C1126A	p.Q376K	11.83	Snv
9	*CREB3L1*	Exon3	c.C461T	p.A154V	5.94	Snv
10	*CSF3R*	Exon13	c.C1655A	p.P552H	16.74	Snv
11	*DST*	Exon24	c.A6151G	p.R2051G	38.77	Snv
12	*ECT2L*	Exon8	c.884delC	p.R296Gfs*8	50.85	Indel
13	*EGFR*	Exon12	c.C1351T	p.R451C	4.21	Snv
14	*EPB41L3*	Exon12	c.A1355T	p.Q452L	12.89	Snv
15	*EPHA7*	Exon1	c.G85T	p.A29S	58.72	Snv
16	*FAT3*	Exon23	c.G12328C	p.G4110R	19.95	Snv
17	*FBN2*	Exon38	c.C4892A	p.T1631N	55.56	Snv
18	*GNAS*	Exon1	c.C1336T	p.P446S	10.71	Snv
19	*GRIN2A*	Intron12	c.2356+1G>A	nil	29.08	Snv
20	*IRS4*	Exon1	c.G1982A	p.R661K	60.69	Snv
21	*ITGA6*	Exon13	c.C1786T	p.R596X	14.62	Snv
22	*KRAS*	Exon2	c.G37T	p.G13C	66.26	Snv
23	*LRP1B*	Exon67	c.G10481T	p.R3494L	21.88	Snv
24	*MAPK8IP1*	Exon8	c.A1697T	p.Q566L	42.38	Snv
25	*MAST2*	Exon1	c.C19T	p.R7C	26.09	Snv
26	*MKL1*	Exon12	c.C1853T	p.P618L	5.04	Snv
27	*NAV3*	Exon1	c.C170T	p.A57V	45.74	Snv
28	*NAV3*	Exon5	c.C539T	p.S180F	15.88	Snv
29	*PDGFB*	Exon4	c.G268T	p.E90X	48.46	Snv
30	*POT1*	Exon7	c.G248T	p.R83M	59.35	Snv
31	*SMARCD1*	Intron11	c.1393-1G>A	nil	16.19	Snv
32	*TP53*	Exon8	c.A871T	p.K291X	47.72	Snv
33	*TSHZ2*	Exon2	c.T1763C	p.V588A	18.81	Snv
34	*USP8*	Exon15	c.C2287T	p.R763W	14.19	Snv
35	*USP8*	Exon15	c.C2292A	p.N764K	15.44	Snv

Table 1 (*continued*)

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ID	Gene	Exon	Nucleotide	Protein	Allele frequency	Variant type
36	*USP9X*	Exon26	c.G3920A	p.S1307N	5.36	Snv
37	*ZBTB16*	Exon2	c.G1174T	p.A392S	33.64	Snv
38	*ZNRF3*	Exon8	c.G2380T	p.G794C	18.75	Snv

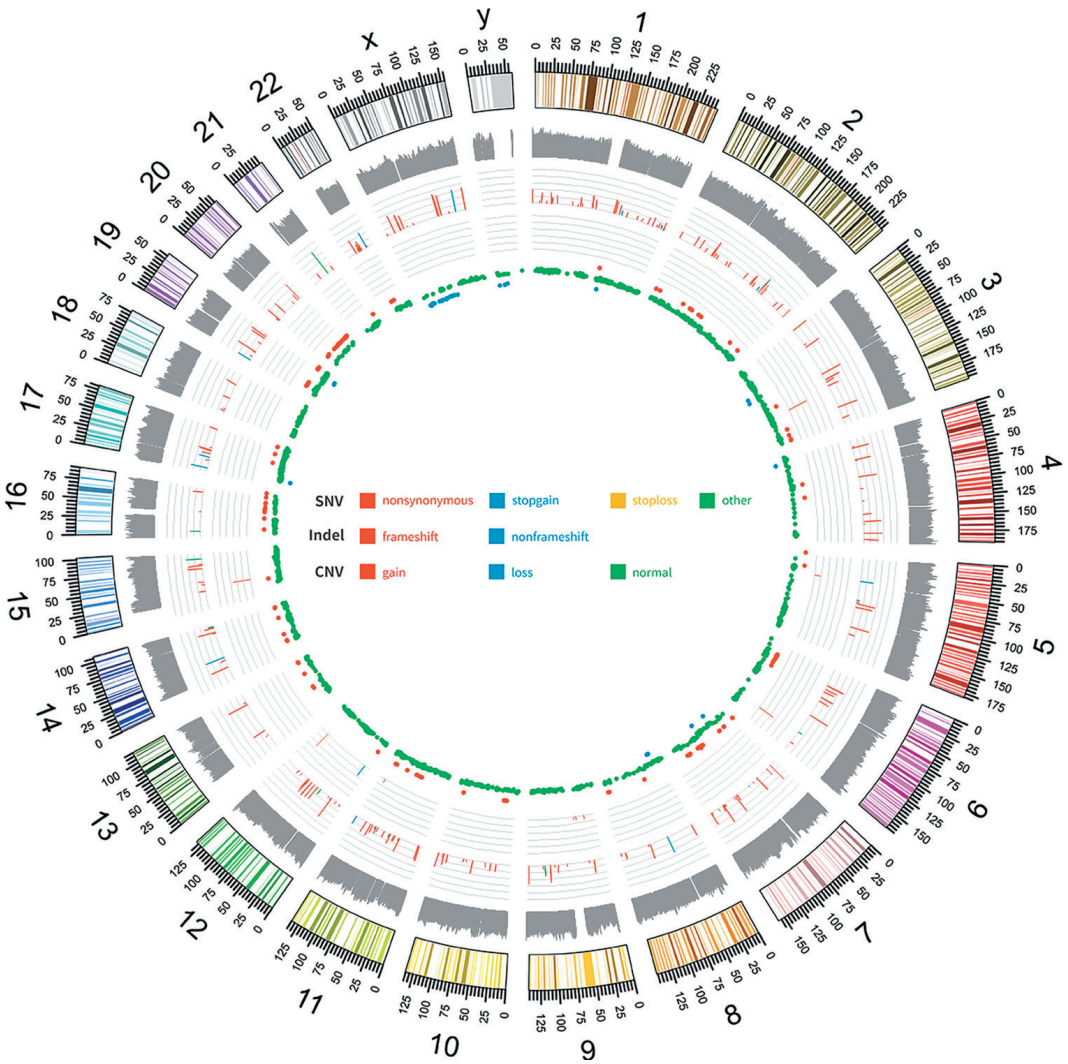

Figure 4 Circos scheme shows the whole-exome sequencing landscape of tumor tissue somatic single nucleotide variation (SNV), insertion and deletion (Indel) and copy number variation (CNV) distribution. From outer to inner rings: the outermost ring shows the human genome scheme showing 24 chromosomes, followed by log10 values of coverage depth in whole-exome sequencing (WES). The types of SNV/Indel mutations are shown by different colors, as indicated in the figure, and the position of SNV/Indel mutations is presented consecutively. The length of lines represents the variant allele frequency. The innermost ring indicates the position of the CNV change, in which red dots stand for amplification and blue dots stand for deletion, and green stands for normal CNV.

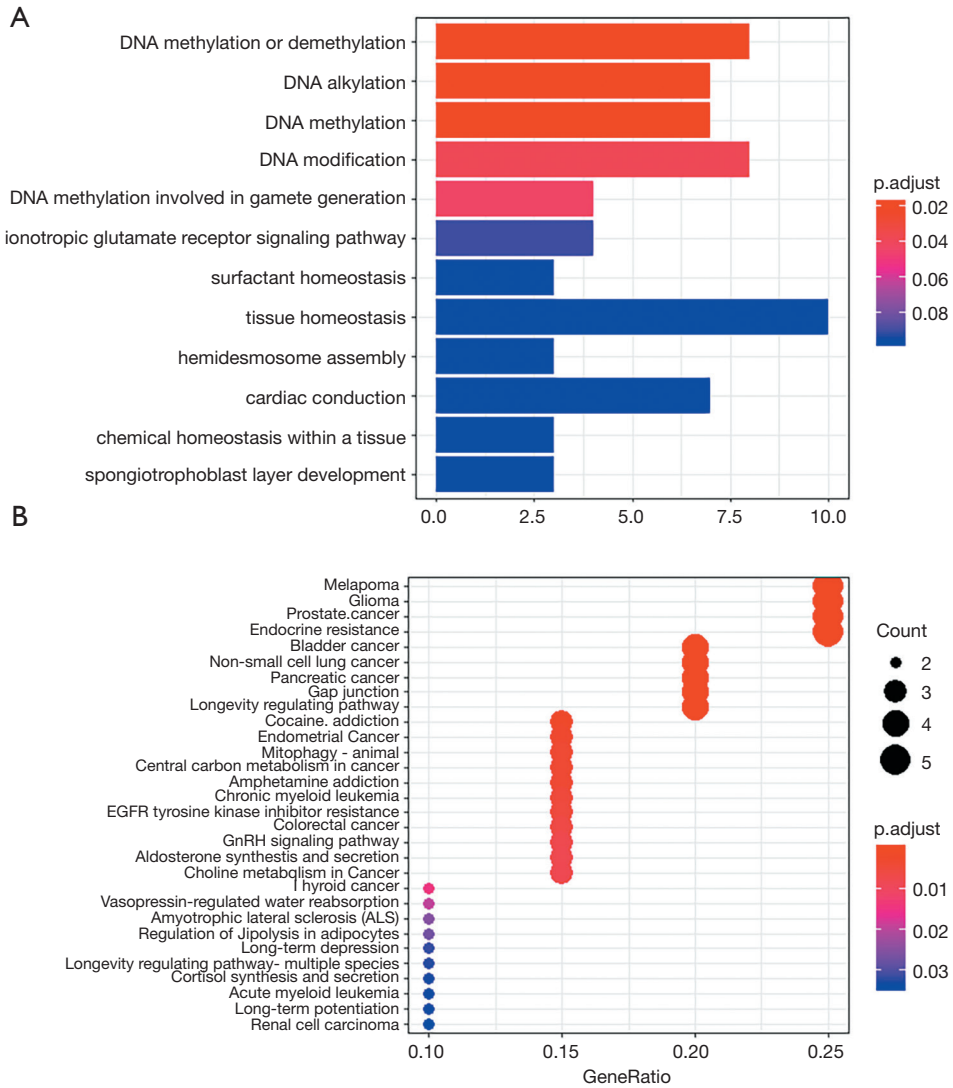

Figure 5 The pathway clustering analysis on the tumor tissue of this study. (A) Gene ontology (GO) term clustering analysis of somatic mutated genes. (B) Kyoto encyclopedia of Genes and Genome (KEGG) pathway clustering analysis of mutated somatic genes. Colors represent the statistical significance of the analysis, and length of bar (A) represents the ratio of mutated genes in all genes of certain pathways. The size of dots (B) represents the number of mutated genes in the analysis and the generatio (X axis) represents the ratio of mutated genes in all genes of certain pathways for amplification and blue dots stand for deletion, and green stands for normal CNV.

in elder patients with a mean age of 60 years old (ranged from 35 to 85, *Figure 6A*) and a male-female ratio of 1.46:1 (19 male *vs.* 13 female). The most frequent primary location is jejunum (17/32, 53.1%) followed by ileum (14/32, 43.8%), and duodenum SCA is very rare (1/32, 3.1%). Mesenteric lymph nodes metastasis was present in 56.3% (18/32) of the reported cases. Macroscopically, SCA can be divided into five types, including the endophytic (33.3%), the polypoid (29.6%), the ulcerating (18.5%), the nodular (11.1%) and the exophytic (7.4%) (*Table 2*, *Figure 6B*). The case in this study belonged to the polypoid type. Microscopically, SCA tumors are composed of two or three cells components: polygonal, anaplastic and spindle, and basically exhibited positive expression for both cytokeratin (CK) (27 positives in 30 patients) and vimentin (21 positives in 21 patients) in immunohistochemistry staining (*Table 2*).

Table 2 Summary of diagnostic information for all SCA cases reviewed in this study

ID	Age	Gender	Diagnosis	Tumor Site	No of lesion(s)	Maximal Diameter (cm)	Morphology	Metastasis	CK	Vimentin	OS (months)	Ref
1	44	M	Enteroblastoma	Ileum	1	N/A	Polypoid	Yes	N/A	N/A	N/A	(22)
2	35	F	Anasplastic and SCA	Jejunum	1	7.5	Endophytic	Yes	–	N/A	36	(2)
3	38	F	Anasplastic and SCA	Jejunum	1	16	Endophytic	Yes	+	N/A	8	(2)
4	48	F	Anasplastic and SCA	Jejunum	1	6	Endophytic	Yes	+	N/A	29	(2)
5	65	M	Anasplastic and SCA	Jejunum	1	5	Endophytic	Yes	+	N/A	5	(2)
6	54	F	Anasplastic and SCA	Ileum	1	4.5	Endophytic	No	–	N/A	12*	(2)
7	62	M	Anasplastic and SCA	Ileum	1	5	Endophytic	Yes	–	N/A	20	(2)
8	52	F	Pleomorphic CA	Jejunum	2	8	Nodular	Yes	+	+	7	(23)
9	56	M	Pleomorphic CA	Jejunum	2	8	Nodular	Yes	+	+	8	(23)
10	45	M	Pleomorphic CA	Ileum	1	3	Endophytic	No	+	+	0.2	(24)
11	57	M	Pleomorphic CA	Ileum	1	14	Endophytic	No	+	+	6*	(24)
12	63	M	Pleomorphic CA	Ileum	1	6	Endophytic	No	+	+	39*	(24)
13	68	F	SCA	Ileum	1	N/A	N/A	No	N/A	N/A	N/A	(25)
14	75	M	SCA	Ileum	1	N/A	N/A	No	+	+	N/A	(25)
15	77	M	SCA	Duodenum	1	N/A	N/A	Yes	+	+	N/A	(25)
16	76	F	SCA	Jejunum	N/A	N/A	N/A	No	+	+	2	(26)
17	76	F	SCA	Ileum	1	5	Ulcerating	NA	+	+	2	(27)
18	53	M	Anasplastic and SCA	Ileum	N/A	N/A	Polypoid	Yes	+	+	N/A	(28)
19	56	M	SCA	Ileum	1	9.2	Ulcerating	Yes	+	+	3	(29)
20	55	M	SCA	Jejunum	1	7.5	Polypoid	Yes	+	+	11	(1)
21	55	M	SCA	Jejunum	N/A	N/A	N/A	Yes	+	N/A	9.4	(30)
22	51	F	SCA	Jejunum	1	8	Polypoid	Yes	+	+	1.9	(31)
23	85	F	SCA	Jejunum	1	10.1	Polypoid	No	+	N/A	3	(32)
24	70	F	SCA	Jejunum	1	NA	Polypoid	No	+	+	7*	(33)
25	56	F	SCA	Jejunum	1	6.7	Ulcerating	Yes	+	+	6	(34)
26	62	M	SCA	Ileum	1	15	Ulcerating	No	+	+	3*	(35)
27	69	M	N/A	Jejunum	1	6	Polypoid	No	+	+	41*	(36)
28	78	M	SCA	Jejunum	N/A	N/A	Exophytic	NA	+	+	N/A	(37)
29	60	M	N/A	Ileum	N/A	N/A	Nodular	Yes	+	N/A	N/A	(38)
30	60	M	SCA	Jejunum	6	5	Ulcerating	Yes	+	+	0.33	(17)
31	62	M	SCA	Jejunum	1	12	Exophytic	Yes	+	+	1	(39)
32	58	F	SCA	Ileum	1	3	Polypoid	No	+	+	0.36	(15)
This study	54	M	SCA	Jejunum	>100	2.6	Polypoid	No	+	+	3	This study

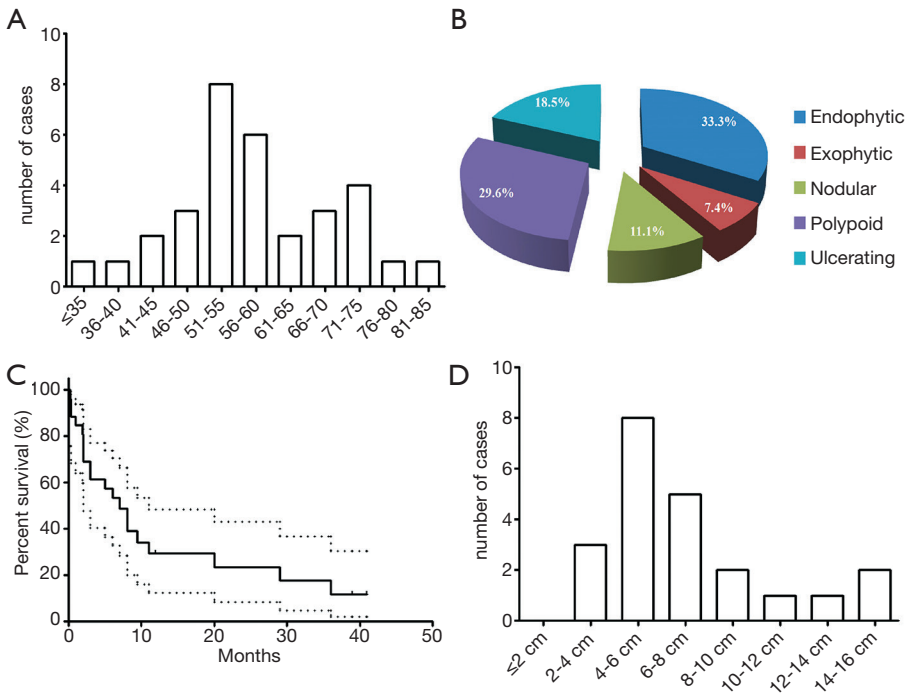

Figure 6 Analysis on the distribution of age, tumor size, macroscopic tumor type and survival analysis of 32 reported sarcomatoid carcinoma (SCA) cases. (A) The age distribution shows that patients aged from 51 to 60 represent the highest frequency of SCA morbidity. (B) Tumors with maximal diameter at 4–6 and 6–8 cm represents the highest frequency of tumor size. (C) Endophytic, polypoid and ulcerating are the three most common type of SCA. (D) Survival analysis shows that the prognosis of SCA was generally poor with a median overall survival of 7 months.

Most patients had surgical resection but only survived for several months. The median overall survival (OS) was 7 months (*Table 2*, *Figure 6C*).

In our case, aggressive development was observed following the appearance of symptoms in gastrointestinal tract. Tumor location identification was difficult and ambiguous. A very distinct clinical feature of our case is that many lesions scattered in jejunum and proximal ileum. Compare to the single, large tumors (average diameter was 7.75 cm) in most reported cases (*Table 2*, *Figure 6D*), our patient had multiple smaller tumors (1.5 to 2.6 cm), which is characteristic from those previous reported.

Immunohistochemistry, in combination with H&E staining, is the golden standard for diagnosis of SCA. A wide panel of markers has been used for SCA pathological diagnosis. SCA usually presents positive for CK, vimentin, EMA, and negative for desmin, S-100, and DOG-1. C-kit negativity is the key to differentiate SCA from GIST, which has similar morphology with SCA (9,40). Certain cases may also exhibit focal positivity for neuroendocrine and neuron-specific markers (1).

Exploration in genetic alterations of small intestine SCA had not been conducted. We exploited next generation sequencing (NGS) technique to study the whole-exome genetic profile of this case. Among 35 germline alterations, none was interpreted as known pathogenic mutation and only 3 were interpreted VUS according to ACMG guidelines. This might suggest the carcinogenesis of the tumor in our case was driven by some acquired factors.

In TCGA data and other large-scale analysis of various types of sarcoma, the top frequently mutated genes include *TP53*, *TTN*, *ATRX*, *PIK3CA*, *MUC16*, *RB1*, and *PTEN* (12,41,42). PI3K signal pathway is undoubtedly a hotspot pathway in this disease based on previous studies. Aberrances on driver genes in this pathway are involved in the progression of cancer. However, the mutated profile of our case did not show that PI3K signal pathway was the dominant abnormality. We identified cetuximab-resistant mutation in KRAS gene (c.37G>T, p.G13C), which is in upstream of PI3K signal pathway. This mutation could lead to activation of the downstream signal pathways (12,41-43). The specific alteration in TP53 (c.871A>T, p.K291*) is only described in a few

cancer studies, including those on transitional cell (urothelial) carcinoma (44), large intestine adenocarcinoma (22), laryngeal squamous cell carcinoma (23), and melanoma (45). CDKN2A gene encodes tumor suppressor proteins which act as negative regulator in the proliferation of normal cells and induce cell cycle arrest in G1 and G2 phases. The CDKN2A mutation (c.104_138del, p.G35fs) is a frameshift mutation which could lead to malfunctioned truncated protein. Many amplified genes were found in our study, but their roles were not clarified. It is possible that the combination of multiple aberrances in key driver genes with other genetic alterations led to the characteristics of the tumor, but the key factors in its pathogenesis still needs further investigation.

Small intestinal cancers mainly include adenocarcinoma, carcinoid, malignant lymphoma and sarcoma, which account for 2–3% of all gastrointestinal cancers. It was reported that 55–80% of them are adenocarcinoma and carcinoid, while lymphoma and sarcoma are rarely seen (46,47). The mechanism of small intestine adenocarcinoma has been suggested to be similar to that of the colorectal cancer, including APC, TP53 and KRAS mutations, aberrancies of the Wnt pathway and abnormal mismatch repair (48). The mechanism of carcinoid was suggested to be related to TGF-β pathway (49) and Chromosome X inactivation (50). SCA is the rarest type of small intestine carcinoma, and most reports so far are case reports without systematic investigation on its molecular mechanism. Our study provided the first piece of evidence on the possible molecular mechanism of small intestine SCA.

There is still no official treatment guideline for SCA. Palliative segment resection was the main treatment in most cases. Adjuvant chemotherapy, such as 5-FU and/or cisplatin or radiotherapy, was performed in some patients, but no report identified improvements in survival. In conclusion, diagnosis and treatment of SCA are still clinical challenges. Our sequencing results revealed the genomic feature of a rare SCA case, providing further understanding on molecular pathogenesis of this specific cancer.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at http://dx.doi.org/10.21037/tcr-20-2829

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients.

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Table S1 Germline alterations identified and interpretated based on ACMG guidelines

Gene	exon	base	AA	dbSNP138	Zygosity	Classification
APC	exon16	c.T5465A	p.V1822D	rs459552	Heterozygous	Benign
ATM	exon40	c.A5948G	p.N1983S	rs659243	Homozygous	Benign
AXIN2	exon2	c.C148T	p.P50S	rs2240308	Heterozygous	Benign
BARD1	exon4	c.G1134C	p.R378S	rs2229571	Heterozygous	Benign
BARD1	exon1	c.C70T	p.P24S	rs1048108	Heterozygous	Benign
BARD1	exon6	c.G1519A	p.V507M	rs2070094	Heterozygous	Benign
BLM	exon13	c.C2603T	p.P868L	rs2227935	Heterozygous	Benign
BLM	exon21	c.G3961A	p.V1321I	rs7167216	Heterozygous	Benign
BMPR1A	exon3	c.C4A	p.P2T	rs3182217	Homozygous	Benign
BRCA1	exon10	c.A3113G	p.E1038G	rs16941	Heterozygous	Benign
BRCA1	exon15	c.A4837G	p.S1613G	rs1799966	Heterozygous	Benign
BRCA1	exon10	c.A3548G	p.K1183R	rs16942	Heterozygous	Benign
BRCA1	exon10	c.C2612T	p.P871L	rs799917	Heterozygous	Benign
BRCA2	exon15	c.G7522A	p.G2508S	rs80358978	Heterozygous	VUS
BRCA2	exon14	c.T7397C	p.V2466A	rs169547	Homozygous	Benign
BRIP1	exon19	c.T2755C	p.S919P	rs4986764	Homozygous	Benign
EPCAM	exon3	c.T344C	p.M115T	rs1126497	Heterozygous	Benign
FLCN	exon8	c.G907A	p.G303R	rs3744124	Heterozygous	Benign
MEN1	exon10	c.A1636G	p.T546A	rs2959656	Homozygous	Benign
MLH3	exon2	c.A2476G	p.N826D	rs175081	Homozygous	Benign
MSH2	exon7	c.C1255A	p.Q419K	rs63750006	Heterozygous	Likely benign
MSH2	exon12	c.A1886G	p.Q629R	rs61756468	Heterozygous	Likely benign
NBN	exon5	c.G553C	p.E185Q	rs1805794	Heterozygous	Benign
PALB2	exon4	c.A1676G	p.Q559R	rs152451	Heterozygous	Benign
PMS2	exon11	c.C1454A	p.T485K	rs1805323	Heterozygous	Benign
PMS2	exon15	c.G2570C	p.G857A	rs1802683	Heterozygous	Likely benign
PMS2	exon11	c.C1408T	p.P470S	rs1805321	Heterozygous	Benign
PMS2	exon10	c.A1103G	p.N368S	NA	Heterozygous	VUS
PMS2	exon11	c.A1621G	p.K541E	rs2228006	Homozygous	Benign
PTEN	intron1	c.154+1T>-	NA	rs71022512	Homozygous	Benign
PTEN	exon1	c.G10A	p.G4R	rs12573787	Heterozygous	Benign
PTEN	exon2	c.G194C	p.C65S	rs2943772	Homozygous	Benign
RAD51D	exon6	c.G494A	p.R165Q	rs4796033	Heterozygous	Benign
TP53	exon4	c.C215G	p.P72R	rs1042522	Heterozygous	Benign
TSC2	exon18	c.G1939A	p.D647N	rs45509392	Heterozygous	VUS
TP53	exon4	c.C215G	p.P72R	rs1042522	Heterozygous	Benign

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Table S2 List of SNV mutations in this case

Chr	Position	Ref	Alt	Func.refGene	Gene	Transcript	Region	Nucleotide	Protein	Tumor_AF
chr1	887940	G	T	stopgain	NOC2L	NM_015658	exon10	c.C1043A	p.S348X	33.98
chr1	1535029	G	C	nonsynonymous	C1orf233	NM_001242659	exon1	c.C367G	p.R123G	40.74
chr1	13497715	G	C	nonsynonymous	PRAMEF17	NM_001099851	exon3	c.G1012C	p.E338Q	5.45
chr1	17668486	C	A	nonsynonymous	PADI4	NM_012387	exon7	c.C701A	p.P234H	30.37
chr1	26801075	G	A	nonsynonymous	HMGN2	NM_005517	exon5	c.G154A	p.V52I	6.35
chr1	34677947	C	T	nonsynonymous	C1orf94	NM_032884	exon6	c.C1091T	p.P364L	31.95
chr1	36933744	G	T	nonsynonymous	CSF3R	NM_156039	exon13	c.C1655A	p.P552H	16.74
chr1	37324743	C	T	nonsynonymous	GRIK3	NM_000831	exon7	c.G1070A	p.R357H	16.16
chr1	46269586	C	T	nonsynonymous	MAST2	NM_015112	exon1	c.C19T	p.R7C	26.09
chr1	75037154	C	T	nonsynonymous	ERICH3	NM_001002912	exon14	c.G4240A	p.E1414K	10.95
chr1	75055708	C	A	stopgain	ERICH3	NM_001002912	exon12	c.G1783T	p.E595X	9.02
chr1	75055726	G	T	nonsynonymous	ERICH3	NM_001002912	exon12	c.C1765A	p.P589T	10.09
chr1	84946676	G	A	nonsynonymous	RPF1	NM_025065	exon2	c.G266A	p.R89K	5.94
chr1	89401904	C	T	nonsynonymous	CCBL2	NM_001008661	exon14	c.G1327A	p.E443K	28.28
chr1	89845996	G	A	nonsynonymous	GBP6	NM_198460	exon6	c.G677A	p.R226H	9.18
chr1	92811452	G	C	nonsynonymous	RPAP2	NM_024813	exon11	c.G1669C	p.A557P	9.71
chr1	111439320	C	A	nonsynonymous	CD53	NM_000560	exon6	c.C469A	p.P157T	37.5
chr1	111439321	C	A	nonsynonymous	CD53	NM_000560	exon6	c.C470A	p.P157Q	37.98
chr1	111742343	C	A	nonsynonymous	DENND2D	NM_024901	exon2	c.G145T	p.G49W	11.01
chr1	117699283	C	A	nonsynonymous	VTCN1	NM_024626	exon3	c.G358T	p.V120L	25.55
chr1	152277258	G	C	nonsynonymous	FLG	NM_002016	exon3	c.C10104G	p.H3368Q	14.43
chr1	152586336	C	A	nonsynonymous	LCE3B	NM_178433	exon1	c.C50A	p.P17H	40.82
chr1	154685979	C	G	nonsynonymous	KCNN3	NM_002249	exon7	c.G1860C	p.K620N	35.14
chr1	155178627	G	A	nonsynonymous	MTX1	NM_198883	exon1	c.G32A	p.R11H	5
chr1	161953743	G	T	nonsynonymous	OLFML2B	NM_015441	exon8	c.C1975A	p.Q659K	28.97
chr1	166990343	G	T	stopgain	MAEL	NM_032858	exon11	c.G1063T	p.G355X	15.05
chr1	176526264	G	T	nonsynonymous	PAPPA2	NM_020318	exon2	c.G806T	p.R269L	14.47
chr1	196658711	C	A	nonsynonymous	CFH	NM_000186	exon8	c.C1126A	p.Q376K	11.83
chr1	206145464	G	A	nonsynonymous	FAM72C	NM_001287385	exon3	c.G241A	p.V81I	10
chr1	217787512	C	T	nonsynonymous	GPATCH2	NM_018040	exon3	c.G806A	p.G269E	18.84
chr1	227152744	G	T	nonsynonymous	ADCK3	NM_020247	exon3	c.G221T	p.G74V	25.46
chr1	234614023	G	A	nonsynonymous	TARBP1	NM_005646	exon1	c.C827T	p.A276V	6.98
chr1	238053767	C	A	nonsynonymous	ZP4	NM_021186	exon1	c.G169T	p.A57S	13.64
chr1	243328887	G	T	stopgain	CEP170	NM_014812	exon13	c.C2375A	p.S792X	11.67
chr1	248616823	G	T	nonsynonymous	OR2T2	NM_001004136	exon1	c.G725T	p.C242F	21.11
chr1	248652293	G	T	nonsynonymous	OR2T5	NM_001004697	exon1	c.G404T	p.R135L	6.83
chr1	248722389	C	A	nonsynonymous	OR2T29	NM_001004694	exon1	c.G404T	p.R135L	7.3
chr1	248801838	C	A	nonsynonymous	OR2T35	NM_001001827	exon1	c.G722T	p.C241F	5.91
chr2	1426888	G	T	nonsynonymous	TPO	NM_000547	exon3	c.G166T	p.A56S	19.38
chr2	32641207	G	C	nonsynonymous	BIRC6	NM_016252	exon10	c.G2848C	p.D950H	28.82
chr2	43934613	C	A	nonsynonymous	PLEKHH2	NM_172069	exon11	c.C1895A	p.S632Y	30.46
chr2	55126878	C	G	nonsynonymous	EML6	NM_001039753	exon21	c.C3083G	p.S1028C	12.23
chr2	69043463	G	T	nonsynonymous	ARHGAP25	NM_014882	exon6	c.G826T	p.D276Y	26.15
chr2	70524576	C	G	nonsynonymous	FAM136A	NM_032822	exon3	c.G262C	p.D88H	47.1
chr2	70524606	G	A	nonsynonymous	FAM136A	NM_032822	exon3	c.C232T	p.R78C	41.71
chr2	74701720	A	T	nonsynonymous	CCDC142	NM_032779	exon9	c.T2185A	p.W729R	13.32
chr2	75105876	C	A	nonsynonymous	HK2	NM_000189	exon9	c.C1093A	p.Q365K	13.27
chr2	79254957	T	G	nonsynonymous	REG3G	NM_198448	exon5	c.T358G	p.W120G	11.75
chr2	99438982	G	A	nonsynonymous	KIAA1211L	NM_207362	exon7	c.C1754T	p.P585L	10.53
chr2	105883916	C	A	nonsynonymous	TGFBRAP1	NM_004257	exon12	c.G2507T	p.G836V	16.23
chr2	105883917	C	T	nonsynonymous	TGFBRAP1	NM_004257	exon12	c.G2506A	p.G836S	15.89
chr2	141143512	C	A	nonsynonymous	LRP1B	NM_018557	exon67	c.G10481T	p.R3494L	21.88
chr2	155711605	G	T	nonsynonymous	KCNJ3	NM_002239	exon3	c.G1286T	p.S429I	28.73
chr2	158178192	T	C	nonsynonymous	ERMN	NM_001009959	exon4	c.A485G	p.N162S	35.14
chr2	163208875	C	A	nonsynonymous	GCA	NM_012198	exon3	c.C220A	p.Q74K	12.2
chr2	173349924	C	T	stopgain	ITGA6	NM_000210	exon13	c.C1786T	p.R596X	14.62
chr2	179306433	T	A	other	PRKRA	NM_003690	intron5	c.515-2A>T	nil	5.14
chr2	179309165	G	A	nonsynonymous	PRKRA	NM_003690	exon4	c.C380T	p.P127L	51.12
chr2	179309229	T	A	other	PRKRA	NM_003690	intron3	c.318-2A>T	nil	8.38
chr2	179312231	C	G	other	PRKRA	NM_003690	intron3	c.317+1G>C	nil	7.11
chr2	179437465	T	G	nonsynonymous	TTN	NM_003319	exon154	c.A46199C	p.D15400A	29.97
chr2	179485014	A	T	nonsynonymous	TTN	NM_003319	exon76	c.T19039A	p.C6347S	34.17
chr2	179496928	G	T	nonsynonymous	TTN	NM_003319	exon64	c.C16498A	p.Q5500K	8.36
chr2	183066249	C	A	nonsynonymous	PDE1A	NM_001003683	exon11	c.G1090T	p.A364S	33.52
chr2	186671593	C	A	nonsynonymous	FSIP2	NM_173651	exon17	c.C17827A	p.Q5943K	22.22
chr2	215797412	G	T	nonsynonymous	ABCA12	NM_173076	exon53	c.C7734A	p.S2578R	16.56
chr2	225688340	C	T	nonsynonymous	DOCK10	NM_001290263	exon28	c.G3043A	p.E1015K	24.81
chr2	242147069	C	A	nonsynonymous	ANO7	NM_001001891	exon11	c.C1223A	p.A408D	30.69
chr3	386317	C	A	nonsynonymous	CHL1	NM_006614	exon9	c.C773A	p.T258N	48.02
chr3	33686384	C	T	nonsynonymous	CLASP2	NM_001207044	exon2	c.G28A	p.D10N	5.71
chr3	38592144	C	T	nonsynonymous	SCN5A	NM_000335	exon28	c.G5716A	p.V1906I	46.11
chr3	96706411	C	A	nonsynonymous	EPHA6	NM_001080448	exon3	c.C688A	p.H230N	59.89
chr3	97596090	G	A	nonsynonymous	CRYBG3	NM_153605	exon4	c.G6052A	p.A2018T	5.31
chr3	108822733	C	G	nonsynonymous	MORC1	NM_014429	exon4	c.G186C	p.M62I	45.03
chr3	108822736	G	T	nonsynonymous	MORC1	NM_014429	exon4	c.C183A	p.F61L	45.7
chr3	112997077	C	A	nonsynonymous	BOC	NM_033254	exon10	c.C1675A	p.Q559K	24.25
chr3	121421397	C	T	nonsynonymous	GOLGB1	NM_004487	exon11	c.G1435A	p.E479K	32.41
chr3	164905759	G	T	nonsynonymous	SLITRK3	NM_014926	exon2	c.C2860A	p.L954I	59.44
chr3	185316217	G	T	nonsynonymous	SENP2	NM_021627	exon3	c.G175T	p.V59L	20.27
chr4	13383186	C	T	nonsynonymous	RAB28	NM_001017979	exon5	c.G424A	p.E142K	5.94
chr4	15964110	C	G	nonsynonymous	FGFBP2	NM_031950	exon1	c.G643C	p.A215P	48.9
chr4	38126751	A	T	nonsynonymous	TBC1D1	NM_015173	exon18	c.A3131T	p.Q1044L	46.46
chr4	39466679	C	T	nonsynonymous	LIAS	NM_194451	exon5	c.C407T	p.T136I	5.22
chr4	70361045	C	T	nonsynonymous	UGT2B4	NM_021139	exon1	c.G535A	p.A179T	53.59
chr4	91230123	T	C	nonsynonymous	CCSER1	NM_001145065	exon2	c.T688C	p.C230R	6.59
chr4	114274207	A	T	nonsynonymous	ANK2	NM_001148	exon38	c.A4433T	p.E1478V	5.11
chr4	138450809	G	A	nonsynonymous	PCDH18	NM_019035	exon1	c.C2434T	p.H812Y	24.66
chr4	151829486	C	A	nonsynonymous	LRBA	NM_001199282	exon11	c.G1493T	p.C498F	51.6
chr4	156864349	C	T	nonsynonymous	CTSO	NM_001334	exon2	c.G203A	p.G68E	5.41
chr4	174216955	A	T	nonsynonymous	GALNT7	NM_017423	exon5	c.A926T	p.N309I	52.68
chr4	186065930	A	T	nonsynonymous	SLC25A4	NM_001151	exon2	c.A124T	p.S42C	44.22
chr5	41181623	G	C	stopgain	C6	NM_000065	exon7	c.C765G	p.Y255X	37.71
chr5	76330334	G	A	stopgain	AGGF1	NM_018046	exon2	c.G302A	p.W101X	7.02
chr5	79950727	G	A	nonsynonymous	MSH3	NM_002439	exon1	c.G181A	p.A61T	6.19
chr5	82948574	A	T	nonsynonymous	HAPLN1	NM_001884	exon3	c.T170A	p.V57D	56.02
chr5	89971213	C	T	nonsynonymous	ADGRV1	NM_032119	exon24	c.C5264T	p.A1755V	48.81
chr5	90085588	T	C	nonsynonymous	ADGRV1	NM_032119	exon69	c.T13963C	p.S4655P	5.7
chr5	127647633	G	T	nonsynonymous	FBN2	NM_001999	exon38	c.C4892A	p.T1631N	55.56
chr5	140559284	G	T	nonsynonymous	PCDHB8	NM_019120	exon1	c.G1669T	p.D557Y	17.07
chr6	31952180	C	A	nonsynonymous	C4A	NM_007293	exon9	c.C1040A	p.S347Y	53.51
chr6	31984918	C	A	nonsynonymous	C4B_2	NM_001242823	exon9	c.C1040A	p.S347Y	51.98
chr6	32009651	C	T	nonsynonymous	TNXB	NM_019105	exon43	c.G12524A	p.S4175N	43.28
chr6	32009661	C	T	nonsynonymous	TNXB	NM_019105	exon43	c.G12514A	p.D4172N	44.99
chr6	32010126	C	T	nonsynonymous	TNXB	NM_019105	exon41	c.G12218A	p.R4073H	27.58
chr6	38913317	C	G	nonsynonymous	DNAH8	NM_001206927	exon80	c.C12082G	p.L4028V	35.41
chr6	44271964	C	A	nonsynonymous	AARS2	NM_020745	exon14	c.G1961T	p.G654V	31.26
chr6	56031711	G	T	nonsynonymous	COL21A1	NM_030820	exon7	c.C1271A	p.P424H	37.28
chr6	56482114	T	C	nonsynonymous	DST	NM_001723	exon24	c.A6151G	p.R2051G	38.77
chr6	63990035	T	C	nonsynonymous	LGSN	NM_016571	exon4	c.A1421G	p.Q474R	32.81
chr6	94128975	C	A	nonsynonymous	EPHA7	NM_001288629	exon1	c.G85T	p.A29S	58.72
chr6	132211577	C	T	stopgain	ENPP1	NM_006208	exon25	c.C2704T	p.Q902X	10.95
chr6	155123238	C	T	nonsynonymous	SCAF8	NM_014892	exon7	c.C740T	p.A247V	7.78
chr7	11022682	G	T	nonsynonymous	PHF14	NM_014660	exon3	c.G796T	p.G266W	16.99
chr7	11500304	C	A	nonsynonymous	THSD7A	NM_015204	exon11	c.G2590T	p.G864W	57.29
chr7	19748495	C	A	nonsynonymous	TWISTNB	NM_001002926	exon1	c.G145T	p.V49L	16
chr7	20782633	G	A	nonsynonymous	ABCB5	NM_178559	exon16	c.G1823A	p.G608D	21.53
chr7	44185152	C	G	nonsynonymous	GCK	NM_000162	exon9	c.G1197C	p.E399D	43.55
chr7	44185187	C	T	nonsynonymous	GCK	NM_000162	exon9	c.G1162A	p.G388S	44.81
chr7	44874131	A	G	nonsynonymous	H2AFV	NM_012412	exon5	c.T356C	p.I119T	5.14
chr7	55227884	C	T	nonsynonymous	EGFR	NM_005228	exon12	c.C1351T	p.R451C	4.21
chr7	65579819	C	T	stopgain	CRCP	NM_001142414	exon1	c.C4T	p.Q2X	5.17
chr7	92838136	C	A	nonsynonymous	HEPACAM2	NM_198151	exon3	c.G733T	p.V245L	18.02
chr7	94057732	G	T	nonsynonymous	COL1A2	NM_000089	exon50	c.G3654T	p.R1218S	18.9
chr7	96115607	G	C	nonsynonymous	C7orf76	NM_001201450	exon3	c.C135G	p.I45M	53.76
chr7	97363087	C	A	nonsynonymous	TAC1	NM_003182	exon3	c.C176A	p.P59H	16.18
chr7	100183717	C	T	nonsynonymous	LRCH4	NM_002319	exon1	c.G7A	p.A3T	6.82
chr7	120911406	A	C	nonsynonymous	CPED1	NM_024913	exon22	c.A2790C	p.E930D	6.23
chr7	122081583	G	A	nonsynonymous	CADPS2	NM_017954	exon16	c.C2335T	p.L779F	5.17
chr7	124510972	C	A	nonsynonymous	POT1	NM_015450	exon7	c.G248T	p.R83M	59.35
chr7	126173822	A	C	nonsynonymous	GRM8	NM_000845	exon8	c.T1614G	p.C538W	16.87
chr7	135329642	G	C	other	NUP205	NM_015135	intron39	c.5560-1G>C	nil	8.21
chr7	149499247	C	T	nonsynonymous	SSPO	NM_198455	exon51	c.C7615T	p.R2539C	6.67
chr7	151664524	A	G	nonsynonymous	GALNTL5	NM_145292	exon2	c.A193G	p.K65E	38.58
chr8	2855613	G	T	nonsynonymous	CSMD1	NM_033225	exon54	c.C8297A	p.T2766K	34.31
chr8	52366226	C	A	stopgain	PXDNL	NM_144651	exon10	c.G1102T	p.G368X	48.61
chr8	87591337	G	T	nonsynonymous	CNGB3	NM_019098	exon16	c.C1925A	p.A642D	42.86
chr8	91090603	C	T	nonsynonymous	CALB1	NM_004929	exon3	c.G229A	p.E77K	6.32
chr8	135614997	G	A	nonsynonymous	ZFAT	NM_001029939	exon7	c.C929T	p.T310I	18.18
chr8	135615082	T	A	nonsynonymous	ZFAT	NM_001029939	exon7	c.A844T	p.T282S	19.63
chr8	143310845	T	G	stoploss	TSNARE1	NM_145003	exon13	c.A1542C	p.X514C	5.44
chr8	143399951	G	T	nonsynonymous	TSNARE1	NM_145003	exon7	c.C938A	p.A313D	9.3
chr9	17747083	G	T	nonsynonymous	SH3GL2	NM_003026	exon2	c.G65T	p.G22V	36.03
chr9	26999648	C	T	nonsynonymous	LRRC19	NM_022901	exon2	c.G45A	p.M15I	6
chr9	67968012	T	A	nonsynonymous	ANKRD20A1	NM_032250	exon15	c.T1571A	p.L524H	5.03
chr9	84547596	G	T	nonsynonymous	SPATA31D4	NM_001145197	exon4	c.G2520T	p.E840D	15.15
chr9	84562688	G	T	nonsynonymous	SPATA31D3	NM_207416	exon4	c.G2520T	p.E840D	21.93
chr9	91150515	G	A	nonsynonymous	NXNL2	NM_145283	exon1	c.G166A	p.V56M	5.04
chr9	99285654	T	A	nonsynonymous	CDC14B	NM_033331	exon11	c.A1134T	p.L378F	50.58
chr9	108483817	G	T	other	TMEM38B	NM_018112	intron2	c.270-1G>T	nil	30.16
chr9	112542775	G	C	nonsynonymous	PALM2	NM_001037293	exon2	c.G13C	p.E5Q	9.8
chr9	137646168	G	A	nonsynonymous	COL5A1	NM_000093	exon16	c.G1823A	p.R608K	54.57
chr10	26457783	G	T	nonsynonymous	MYO3A	NM_017433	exon28	c.G3254T	p.S1085I	21.78
chr10	37508731	A	C	nonsynonymous	ANKRD30A	NM_052997	exon34	c.A3923C	p.H1308P	21.31
chr10	46250489	G	T	nonsynonymous	FAM21C	NM_015262	exon15	c.G1346T	p.G449V	11.56
chr10	71020967	G	T	nonsynonymous	HKDC1	NM_025130	exon16	c.G2289T	p.Q763H	38.95
chr10	81317231	G	T	nonsynonymous	SFTPA2	NM_001098668	exon6	c.C481A	p.R161S	6.39
chr10	81373603	C	A	nonsynonymous	SFTPA1	NM_005411	exon6	c.C481A	p.R161S	7.57
chr10	87614258	G	T	nonsynonymous	GRID1	NM_017551	exon8	c.C1228A	p.R410S	10.21
chr10	118030574	C	G	nonsynonymous	GFRA1	NM_145793	exon2	c.G94C	p.A32P	23.12
chr10	124742926	A	C	nonsynonymous	PSTK	NM_153336	exon3	c.A647C	p.K216T	31.64
chr10	126086636	C	T	nonsynonymous	OAT	NM_000274	exon10	c.G1195A	p.D399N	10.46
chr10	134647616	G	T	nonsynonymous	CFAP46	NM_001200049	exon49	c.C6878A	p.P2293H	13.08
chr10	135087278	C	A	nonsynonymous	ADAM8	NM_001109	exon5	c.G371T	p.C124F	43.03
chr11	5373389	T	G	nonsynonymous	OR51B6	NM_001004750	exon1	c.T652G	p.L218V	45.83
chr11	7324590	C	A	nonsynonymous	SYT9	NM_175733	exon2	c.C466A	p.R156S	41.94
chr11	45926036	A	T	nonsynonymous	MAPK8IP1	NM_005456	exon8	c.A1697T	p.Q566L	42.38
chr11	46329496	C	T	nonsynonymous	CREB3L1	NM_052854	exon3	c.C461T	p.A154V	5.94
chr11	55111576	G	T	nonsynonymous	OR4A16	NM_001005274	exon1	c.G900T	p.W300C	16.23
chr11	56468459	A	T	nonsynonymous	OR9G9	NM_001013358	exon1	c.A596T	p.Y199F	15.45
chr11	63276389	C	T	nonsynonymous	LGALS12	NM_033101	exon3	c.C364T	p.R122W	30.03
chr11	63276390	G	T	nonsynonymous	LGALS12	NM_033101	exon3	c.G365T	p.R122L	29.43
chr11	65632085	G	A	other	MUS81	NM_025128	intron11	c.1176+1G>A	nil	8.61
chr11	75298598	C	G	nonsynonymous	MAP6	NM_033063	exon4	c.G1948C	p.E650Q	17.89
chr11	89607255	A	T	nonsynonymous	TRIM64B	NM_001164397	exon3	c.T697A	p.W233R	11.92
chr11	89703604	T	A	nonsynonymous	TRIM64	NM_001136486	exon3	c.T697A	p.W233R	6.37
chr11	92615950	G	C	nonsynonymous	FAT3	NM_001008781	exon23	c.G12328C	p.G4110R	19.95
chr11	94170342	C	T	other	MRE11A	NM_005590	intron16	c.1842+1G>A	nil	5.88
chr11	100211195	G	T	nonsynonymous	CNTN5	NM_014361	exon22	c.G2731T	p.V911F	23.61
chr11	103907663	C	T	nonsynonymous	DDI1	NM_001001711	exon1	c.C113T	p.S38F	36.02
chr11	113935196	G	T	nonsynonymous	ZBTB16	NM_006006	exon2	c.G1174T	p.A392S	33.64
chr11	133779134	G	A	stopgain	IGSF9B	NM_001277285	exon20	c.C4144T	p.Q1382X	25.34
chr12	6128787	G	T	nonsynonymous	VWF	NM_000552	exon28	c.C3797A	p.P1266Q	5.8
chr12	14578003	C	T	nonsynonymous	ATF7IP	NM_018179	exon2	c.C1154T	p.A385V	6.52
chr12	25398282	C	A	nonsynonymous	KRAS	NM_004985	exon2	c.G37T	p.G13C	66.26
chr12	25699307	C	T	other	LMNTD1	NM_152590	intron3	c.428+1G>A	nil	5.04
chr12	30873836	G	A	nonsynonymous	CAPRIN2	NM_023925	exon12	c.C2057T	p.P686L	5.31
chr12	50492496	G	A	other	SMARCD1	NM_003076	intron11	c.1393-1G>A	nil	16.19
chr12	56862919	C	T	nonsynonymous	SPRYD4	NM_207344	exon2	c.C182T	p.P61L	18.75
chr12	57003990	G	A	nonsynonymous	BAZ2A	NM_013449	exon9	c.C1795T	p.R599C	10.37
chr12	57437666	G	T	nonsynonymous	MYO1A	NM_005379	exon10	c.C866A	p.P289Q	41.05
chr12	64609577	C	A	nonsynonymous	C12orf66	NM_152440	exon2	c.G402T	p.Q134H	46.67
chr12	71155288	C	T	nonsynonymous	PTPRR	NM_002849	exon4	c.G590A	p.S197N	48.25
chr12	72028073	T	C	nonsynonymous	ZFC3H1	NM_144982	exon12	c.A2372G	p.Q791R	47.69
chr12	78225411	C	T	nonsynonymous	NAV3	NM_001024383	exon1	c.C170T	p.A57V	45.74
chr12	78362350	C	T	nonsynonymous	NAV3	NM_001024383	exon5	c.C539T	p.S180F	15.88
chr12	80933690	A	T	nonsynonymous	PTPRQ	NM_001145026	exon17	c.A2605T	p.S869C	33.8
chr12	96707112	C	T	nonsynonymous	CDK17	NM_002595	exon4	c.G404A	p.R135Q	6.74
chr12	103762754	G	A	nonsynonymous	C12orf42	NM_198521	exon4	c.C170T	p.T57I	9.23
chr13	25473571	G	A	nonsynonymous	CENPJ	NM_018451	exon9	c.C2977T	p.R993C	5.56
chr13	36748909	C	T	nonsynonymous	SOHLH2	NM_017826	exon7	c.G739A	p.D247N	37.98
chr13	94482568	C	G	nonsynonymous	GPC6	NM_005708	exon3	c.C481G	p.L161V	62.42
chr13	98116646	G	T	nonsynonymous	RAP2A	NM_021033	exon2	c.G502T	p.A168S	7.02
chr14	24606768	G	T	nonsynonymous	PSME1	NM_006263	exon5	c.G286T	p.D96Y	51.99
chr14	38678658	G	A	nonsynonymous	SSTR1	NM_001049	exon3	c.G64A	p.G22S	15.48
chr14	44973784	C	A	stopgain	FSCB	NM_032135	exon1	c.G2407T	p.G803X	55.51
chr14	92076859	C	T	nonsynonymous	CATSPERB	NM_024764	exon21	c.G2563A	p.D855N	6.52
chr14	94394752	C	A	nonsynonymous	FAM181A	NM_138344	exon3	c.C307A	p.L103M	50.83
chr14	102452063	G	A	nonsynonymous	DYNC1H1	NM_001376	exon8	c.G1501A	p.E501K	27.62
chr14	102466375	G	T	nonsynonymous	DYNC1H1	NM_001376	exon17	c.G3854T	p.G1285V	9.73
chr14	104497444	G	C	other	TDRD9	NM_153046	intron28	c.3283-1G>C	nil	16.2
chr15	34014966	C	T	nonsynonymous	RYR3	NM_001036	exon44	c.C6670T	p.R2224C	16.72
chr15	44959368	G	A	nonsynonymous	PATL2	NM_001145112	exon14	c.C1399T	p.H467Y	7.14
chr15	50784950	C	T	nonsynonymous	USP8	NM_005154	exon15	c.C2287T	p.R763W	14.19
chr15	50784955	C	A	nonsynonymous	USP8	NM_005154	exon15	c.C2292A	p.N764K	15.44
chr15	75500778	G	C	nonsynonymous	C15orf39	NM_015492	exon2	c.G2389C	p.A797P	44.44
chr15	80843573	G	A	nonsynonymous	ARNT2	NM_014862	exon9	c.G911A	p.G304E	40.15
chr15	83718872	C	T	nonsynonymous	BTBD1	NM_001011885	exon3	c.G617A	p.S206N	8
chr15	92988160	G	T	other	ST8SIA2	NM_006011	intron5	c.842+1G>T	nil	47.34
chr16	9892133	C	T	other	GRIN2A	NM_000833	intron12	c.2356+1G>A	nil	29.08
chr16	46655235	C	T	nonsynonymous	SHCBP1	NM_024745	exon1	c.G37A	p.A13T	5.04
chr16	83251042	G	C	nonsynonymous	CDH13	NM_001257	exon5	c.G576C	p.E192D	30.48
chr17	7577067	T	A	stopgain	TP53	NM_000546	exon8	c.A871T	p.K291X	47.72
chr17	21318890	G	T	nonsynonymous	KCNJ12	NM_021012	exon3	c.G236T	p.R79L	11.37
chr17	27010334	A	T	stopgain	SUPT6H	NM_003170	exon16	c.A1927T	p.K643X	32.49
chr17	33491143	C	T	nonsynonymous	UNC45B	NM_173167	exon9	c.C1109T	p.P370L	25.18
chr17	39742891	C	A	nonsynonymous	KRT14	NM_000526	exon1	c.G196T	p.G66W	32.55
chr17	40666354	G	T	nonsynonymous	ATP6V0A1	NM_001130020	exon20	c.G2299T	p.V767L	38.19
chr17	45247328	C	T	nonsynonymous	CDC27	NM_001114091	exon4	c.G332A	p.G111D	5
chr17	79899056	A	T	nonsynonymous	MYADML2	NM_001145113	exon3	c.T562A	p.Y188N	22.65
chr18	5419861	T	A	nonsynonymous	EPB41L3	NM_012307	exon12	c.A1355T	p.Q452L	12.89
chr18	9122540	G	A	nonsynonymous	NDUFV2	NM_021074	exon5	c.G330A	p.M110I	5.81
chr18	29340449	T	A	nonsynonymous	SLC25A52	NM_001034172	exon1	c.A206T	p.Q69L	21.35
chr18	58039110	T	C	nonsynonymous	MC4R	NM_005912	exon1	c.A473G	p.H158R	31.23
chr19	1418364	C	T	stopgain	DAZAP1	NM_170711	exon3	c.C232T	p.R78X	41.99
chr19	7990362	C	T	nonsynonymous	CTXN1	NM_206833	exon2	c.G62A	p.G21D	5.36
chr19	17397503	G	T	nonsynonymous	ANKLE1	NM_001278444	exon8	c.G1935T	p.L645F	6.25
chr19	18497006	G	T	nonsynonymous	GDF15	NM_004864	exon1	c.G7T	p.G3W	59.47
chr19	36674536	T	C	nonsynonymous	ZNF565	NM_152477	exon5	c.A332G	p.E111G	9.89
chr19	47969105	C	T	nonsynonymous	SLC8A2	NM_015063	exon2	c.G556A	p.A186T	44
chr19	52249205	T	C	nonsynonymous	FPR1	NM_002029	exon2	c.A1043G	p.Q348R	51.44
chr19	55325535	C	T	nonsynonymous	KIR2DL4	NM_001080770	exon7	c.C998T	p.A333V	9.09
chr20	238439	T	C	nonsynonymous	DEFB132	NM_207469	exon1	c.T20C	p.V7A	9.13
chr20	2638627	C	A	nonsynonymous	NOP56	NM_006392	exon12	c.C1472A	p.P491H	10.44
chr20	3673760	C	T	nonsynonymous	SIGLEC1	NM_023068	exon14	c.G3527A	p.R1176H	44.38
chr20	19664945	C	T	nonsynonymous	SLC24A3	NM_020689	exon11	c.C1027T	p.R343W	39.72
chr20	42744591	G	A	nonsynonymous	JPH2	NM_020433	exon4	c.C1724T	p.P575L	8
chr20	51871760	T	C	nonsynonymous	TSHZ2	NM_173485	exon2	c.T1763C	p.V588A	18.81
chr20	56090848	G	T	nonsynonymous	CTCFL	NM_080618	exon7	c.C1102A	p.R368S	56.67
chr20	57429843	C	T	nonsynonymous	GNAS	NM_001077490	exon1	c.C1336T	p.P446S	10.71
chr21	16339472	T	A	nonsynonymous	NRIP1	NM_003489	exon4	c.A1042T	p.N348Y	19.23
chr21	32201970	A	G	other	KRTAP7-1	NM_181606	intron1	c.48-1T>C	nil	77.78
chr21	44589341	C	G	nonsynonymous	CRYAA	NM_000394	exon1	c.C132G	p.I44M	11.99
chr22	17586834	G	T	nonsynonymous	IL17RA	NM_014339	exon11	c.G1035T	p.W345C	43.75
chr22	22989710	C	A	nonsynonymous	GGTLC2	NM_199127	exon4	c.C460A	p.H154N	7.76
chr22	24572217	C	A	nonsynonymous	CABIN1	NM_012295	exon35	c.C6179A	p.T2060K	22.42
chr22	25024305	C	A	nonsynonymous	GGT1	NM_013430	exon15	c.C1513A	p.H505N	8.63
chr22	25750715	C	A	nonsynonymous	LRP5L	NM_182492	exon3	c.G503T	p.R168M	11.85
chr22	26317351	A	T	nonsynonymous	MYO18B	NM_032608	exon34	c.A5492T	p.E1831V	11.84
chr22	26861442	A	C	nonsynonymous	HPS4	NM_022081	exon10	c.T782G	p.F261C	29.1
chr22	29446549	G	T	nonsynonymous	ZNRF3	NM_001206998	exon8	c.G2380T	p.G794C	18.75
chr22	39627815	C	A	stopgain	PDGFB	NM_002608	exon4	c.G268T	p.E90X	48.46
chr22	40814589	G	A	nonsynonymous	MKL1	NM_020831	exon12	c.C1853T	p.P618L	5.04
chrX	1720419	C	G	nonsynonymous	AKAP17A	NM_005088	exon5	c.C2020G	p.H674D	5.26
chrX	15609910	G	C	nonsynonymous	ACE2	NM_021804	exon5	c.C509G	p.S170C	55.32
chrX	26235472	A	T	nonsynonymous	MAGEB5	NM_001271752	exon2	c.A54T	p.R18S	44.78
chrX	27998737	C	G	nonsynonymous	DCAF8L1	NM_001017930	exon1	c.G715C	p.D239H	48.67
chrX	34148862	G	T	nonsynonymous	FAM47A	NM_203408	exon1	c.C1534A	p.R512S	41.19
chrX	41048671	G	A	nonsynonymous	USP9X	NM_001039590	exon26	c.G3920A	p.S1307N	5.36
chrX	53112144	C	T	nonsynonymous	TSPYL2	NM_022117	exon1	c.C464T	p.A155V	5.26
chrX	100912145	C	A	nonsynonymous	ARMCX2	NM_014782	exon5	c.G430T	p.G144W	68.54
chrX	102193072	A	G	nonsynonymous	RAB40AL	NM_001031834	exon1	c.A826G	p.K276E	62.67
chrX	107404875	C	T	nonsynonymous	COL4A6	NM_001847	exon42	c.G4310A	p.G1437E	40.29
chrX	107977593	C	T	nonsynonymous	IRS4	NM_003604	exon1	c.G1982A	p.R661K	60.69
chrX	122336604	C	G	nonsynonymous	GRIA3	NM_001256743	exon3	c.C385G	p.P129A	5.79
chrX	135443655	A	T	stopgain	ADGRG4	NM_153834	exon12	c.A7186T	p.K2396X	65.45
chrX	152822444	G	T	nonsynonymous	ATP2B3	NM_021949	exon14	c.G2396T	p.G799V	66.67

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Table S3 List of indel mutations found in this case

Chr	Position	Ref	Alt	Func.refGene	Gene	Transcript	Region	Nucleotide	Protein	Tumor_AF
chr3	128620156	-	T	frameshift	ACAD9	NM_014049	exon8	c.846_847insT	p.E283*	55.53
chr5	40769535	T	-	frameshift	PRKAA1	NM_006251	exon5	c.579delA	p.E194fs*2	16.92
chr6	139167795	C	-	frameshift	ECT2L	NM_001077706	exon8	c.884delC	p.R296Gfs*8	50.85
chr9	21974689	CCGACCGTAACTATTCGGTGCGTTGGGCAGCGCCC	-	frameshift	CDKN2A	NM_000077	exon1	c.104_138del	p.G35Efs*73	11.11
chr9	39149837	C	-	frameshift	CNTNAP3	NM_033655	exon10	c.1615delG	p.D539Tfs*4	10.04
chr9	43844279	G	-	frameshift	CNTNAP3B	NM_001201380	exon10	c.1613delG	p.D539Tfs*4	10.06
chr11	124095689	T	-	frameshift	OR8G2	NM_001291438	exon1	c.292delT	p.F98Lfs*2	9.84
chr12	10225980	ACTCAGAGTAGCTCTGAG	-	nonframeshift	CLEC1A	NM_016511	exon5	c.557_574del	p.S186_E191del	35.79
chr12	113327841	G	-	frameshift	RPH3A	NM_014954	exon17	c.1564delG	p.T524Pfs*68	49.04
chr15	42041004	-	C	frameshift	MGA	NM_001080541	exon15	c.4756dupC	p.S1587Kfs*10	51.19

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Table S4 List of copy number variations in this case

ID	Gene	Variant type	Copy number
1	AARS2	amplification	3.68
2	ACTB	amplification	3.68
3	ADCY1	amplification	3.95
4	AHCYL2	amplification	3.34
5	AKR1B1	amplification	3.12
6	ARHGAP35	deletion	0.82
7	ASXL1	amplification	3.49
8	BCR	amplification	3.25
9	CARD11	amplification	3.68
10	CCND1	amplification	3.01
11	CCND3	amplification	3.73
12	CDH1	amplification	3.01
13	CREB3L2	amplification	3.12
14	CTTN	amplification	3.09
15	CUX1	amplification	4.25
16	DAXX	amplification	3.17
17	DIDO1	amplification	3.21
18	DIS3L2	amplification	3.15
19	FGF3	amplification	3.01
20	FGF4	amplification	3.01
21	FOXA2	amplification	3.72
22	FRG1B	amplification	3.49
23	GNAS	amplification	3.10
24	HLA-A	amplification	4.19
25	HLA-B	amplification	4.19
26	HLA-C	amplification	4.19
27	HSP90AA1	amplification	3.34
28	HSP90AB1	amplification	3.68
29	IKZF1	deletion	0.92
30	INTS1	amplification	3.68
31	KIAA1549	amplification	3.12
32	KIFC3	amplification	3.12
33	LUC7L2	amplification	3.12
34	MCM7	amplification	3.28
35	MDC1	amplification	4.19
36	MMP2	amplification	3.13
37	MUC16	amplification	3.36
38	MUC4	amplification	3.45
39	NFKBIE	amplification	3.68
40	PIM1	amplification	6.24
41	PLAG1	amplification	3.34
42	PLCG1	amplification	3.44
43	PMS2	amplification	3.68
44	POU5F1	amplification	4.19
45	PRRC2A	amplification	4.19
46	PTPRT	amplification	3.44
47	RAC1	amplification	3.68
48	ROBO2	deletion	0.81
49	SALL4	amplification	4.03
50	SDC4	amplification	3.31
51	SDHA	amplification	3.11
52	SIRPA	amplification	3.32
53	SLC3A2	amplification	3.19
54	SMARCA4	amplification	3.06
55	SMARCB1	amplification	3.25
56	SMO	amplification	3.34
57	SMOX	amplification	3.32
58	SND1	amplification	3.34
59	SS18L1	amplification	3.21
60	SVIL	amplification	3.08
61	TERT	amplification	3.11
62	TFDP1	amplification	3.11
63	TFEB	amplification	3.73
64	TRIM24	amplification	3.12
65	TRIM27	amplification	4.19
66	TRRAP	amplification	3.92
67	TSHZ2	amplification	3.10
68	VEGFA	amplification	3.68
69	ZMYND8	amplification	3.31

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