

Clinicopathological Features and Gene Mutation Analysis of Gastrointestinal Stromal Tumors: A Series of 58 Patients

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Abstract

Background In gastrointestinal stromal tumors (GISTs), mutually exclusive gain-of-function mutations of KIT and PDGFRA are associated with different mutation-dependent clinical behavior. The study aims to analyze the characteristics of the clinicopathology and genotypes in GISTs in China.

Methods All adult patients with GIST located in the stomach or small intestine who underwent surgical resections in the Cancer Hospital, Chinese Academy of Medical Sciences from January 2009 to January 2019 without prior Imatinib(Glivec) treatment were included. Specimens were collected for histopathological examination, and mutations in c-kit and PDGFRA genes were analyzed by PCR and the next generation sequencing(NGS). The clinicopathological characteristics of each gene were also analyzed.

Results A total of 58 GIST patients was included in the study. Among the genotypes, there were 51(87.9%) c-kit mutations, five(8.6%) PDGFRA mutations, and two(3.4%) wild-type mutations. Among the cell types, there were 40 cases(69.0%) of spindle cell type, three cases(5.2%) of epithelioid cell type, and three cases(5.2%) of mixed cell type. Among the four mutant forms of c-kit exon-11, the most common were point mutation in 16 cases(38.1%), deletion mutation in 13 cases(31.0%), insertion mutation in four cases(9.5%), and mixed mutation in nine cases(21.4%). According to the National Institutes of Health(NIH) risk grade, there were three cases(5.2%) with very-low risk, nine cases(15.5%) with low risk, 19 cases(32.8%) with medium risk, and 23 cases(39.7%) with high risk. There were significant differences in cell types among different gene types($P = 0.022$) and significant differences in tumor risk among different mutant forms of c-kit gene exon-11($P = 0.039$).

Conclusion In c-kit mutations, spindle cell type was significantly more than epithelioid cell type and mixed cell type. In PDGFRA mutations, spindle cell type and mixed cell type were prevalent. In wild type, spindle cell type and epithelioid cell type were significantly common. A high risk of deletion mutation and mixed mutation is expected in the c-kit exon-11 mutation form, while the intermediate risk of point and insertion mutations are common.

Introduction

Gastrointestinal stromal tumors(GISTs) are the most common mesenchymal tumors of the gastrointestinal system. More than 85% of GISTs occur due to mutations in genes receptor tyrosine kinases(KIT) and platelet-derived growth factor receptor(PDGFRα)^[1]. Also, about 15% of adult GISTs and 85% of children lack mutations in c-kit and PDGFRA, known as Wild-Type(WT) GISTs^[2]. The typical hot spots for c-kit gene mutations are exon 9, 11, 13, and 17, most of which are active mutations for c-kit exon-11^[3].

Mutations in the PDGFRA gene can be detected in about 10% of GIST patients, and the most common form of mutation is the exon-18 D842V point mutation, accounting for more than 90% of all PDGFRA

mutation types^[4]. Presently, several researchers are trying to reveal the prognostic significance of gene mutations, and some scholars have found out that c-kit mutations are related to liver metastasis and poor prognosis of tumors^[5]. Simultaneously, the PDGFR α mutation is characterized by low nuclei mitosis and low potential for malignant potential, suggesting a good prognosis^[6, 7].

Due to the incomplete and inconsistent nature of the numerous results, we retrieved clinical records of adult patients with GIST located in the stomach or small intestine who underwent surgical resections in the Cancer Hospital, Chinese Academy of Medical Sciences from January 2009 to January 2019 without prior Imatinib(Glivec) treatment. The retrieved clinical records were used to explore the c-kit/PDGFR α gene mutation and the relationship between its clinical-pathological and biological features.

Materials And Methods

1.1 Patients and samples

Primary GISTs patients(n = 58) who underwent complete resection of the lesion in the Cancer Hospital, Chinese Academy of Medical Sciences from January 2009 to January 2019 were included. Multiple focal GISTs, pediatric GISTs, familial GISTs, neurofibromatosis type-I, and Carney triad were excluded. None of the patients had received Imatinib treatment before surgery.

1.2 Genomic DNA isolation

QIAamp DNA Mini Kit(Qiagen, Germany) was obtained to extract DNA from the selected tumor blocks, according to the manufacturer's instructions. NanoDrop(Thermo, USA) was used to detect the quality of DNA samples, while the Quantus™ Fluorometer was used to determine the concentration of the DNA samples with the Qubit® dsDNA HS Assay Kit.

1.3 DNA library construction and sequencing

Significantly, 10ng of DNA was used to construct an amplicon DNA library. PCR amplified the genomic DNA and then was ligated to different barcodes. The library of each sample was mixed. Next, the mixed library was clonally amplified onto the IonSpheres(ISP) and then enriched on the IonOneTouch system to prepare the DNA template, using the Ion PGM(TM)Hi-Q(TM) OT2 Kit (Thermo Fisher). Finally, the enriched ISPs were added onto a 318 Chip, and sequencing was carried out on the Ion Torrent PGM platform using Ion PGM HI-Q SEQ Kit (Thermo Fisher), following the manufacturer's instructions.

1.4 Sequence data analysis

Sequence data from PGM runs were generated using Torrent Suite Software. Initial variant calling was filtered via comparing the 1000 Genomes data to GRCh 37, and mutations were designated and annotated through Torrent Variant Caller. Mutations were identified when the coverage depth ≥ 1000 reads and mutant allele frequency $\geq 5\%$. All mutations were further visually examined using the Integrative Genomics Viewer.

1.5 Statistical analysis

SPSS 21.0 software was used for statistical analysis of all data. Categorical variables were expressed by frequency. Chi-square test or Fisher's exact probability was used for comparison between groups, and correlation analysis was performed by association analysis of unordered categorical variables. First, the chi-square test of independence of two attributes was performed according to the linked list of cross-classification counts; then, the correlation coefficient was calculated. Probability values (P) were considered to be statistically significant at a level < 0.05 .

Result

2.1 Clinicopathologic features

Of the 58 GIST patients, 29 were males(50%), and 29 were females(50%). The age ranged from 20 to 87-years, with a median age of 57.5 years. Thirty cases(51.7%) had primary tumors in the stomach, 16 cases(27.6%) in the small intestine, three cases(5.2%) in the colorectal area, and nine cases(15.5%) in the extragastrointestinal area(including the abdominal, pelvic, and peritoneal cavity). There were 40 cases(69.0%) of spindle cell type, three cases(5.2%) of epithelioid cell type, three cases(5.2%) of mixed cell type, and 12 cases(20.7%) of data deletion. There were 35 cases(60.3%) with mitotic count $\leq 5/50$ HPF and 17 cases(29.3%) with $> 5/50$ HPF, and six cases(10.3%) with data missing.

The tumor size was 0.7 ~ 15.0cm, with a median diameter of 5.5cm. Five cases(8.6%) were ≤ 2 cm, 19 cases(32.8%) were > 2 to ≤ 5 cm. There were 23 cases(39.7%) with > 5 to ≤ 10 cm. There were nine cases(15.5%) with > 10 cm and two cases(3.4%) with missing data. Classification risk for GISTs, according to the United States national institutes of health(NIH)^[8], is divided into very-low risk, low risk, intermediate, and high risk. Three cases were very-low risk(5.2%), while nine were low-risk(15.5%). On the other hand, 19 were intermediate cases(32.8%), while 23 were high-risk cases(39.7%). Significantly, four cases lacked data(6.9%). The positive rates of CD117, DOG-1, and CD34 were 96.6%, 96.6%, and 93.1%, respectively. Concerning the Ki-67 index of $\leq 5\%$, 5–10%, and $\geq 10\%$, there were 24 cases(47.1%), eight cases(15.7%), and 19 cases(37.3%), respectively with four cases(6.9%) of concurrent metastasis.

Table 1
GIST genotype and clinicopathological features

	<i>c-kit</i> (51)	<i>PDGFRa</i> (5)	Wild type (2)	<i>P</i>
Sex, n(%)				0.117
Male	23(45.10)	4(80.00)	2(100.00)	
Female	28(54.90)	1(20.00)	0(0.00)	
Age, n(%)				0.765
≤ 50	12(23.53)	1(20.00)	1(50.00)	
> 50	39(76.47)	4(80.00)	1(50.00)	
Location, n(%)				0.619
Stomach	24(47.06)	4(80.00)	2(100.00)	
Small intestine	16(31.37)	0(0.00)	0(0.00)	
colorectum	3(5.88)	0(0.00)	0(0.00)	
parenteral	8(15.69)	1(20.00)	0(0.00)	
Cell type, n(%)				0.022
spindle	37(72.55)	2(40.00)	1(50.00)	
epithelioid	2(3.92)	0(0.00)	1(50.00)	
mixed	1(1.96)	2(40.00)	0(0.00)	
NA	11(21.57)	1(20.00)	0(0.00)	
Mitotic count(/50HPF), n(%)				1.000
≤ 5	30(58.82)	4(80.00)	1(50.00)	
> 5	15(29.41)	1(20.00)	1(50.00)	
NA	6(11.76)	0(0.00)	0(0.00)	
Tumor diameter(cm), n(%)				0.805
≤ 2	5(9.80)	0(0.00)	0(0.00)	
> 2to ≤ 5	16(31.37)	2(40.00)	1(50.00)	
> 5to ≤ 10	21(41.18)	2(40.00)	0(0.00)	
> 10	7(13.73)	1(20.00)	1(50.00)	
NA	2(3.92)	0(0.00)	0(0.00)	

	<i>c-kit</i> (51)	<i>PDGFRa</i> (5)	Wild type (2)	<i>P</i>
Risk, n(%)				0.580
Very low	3(5.88)	0(0.00)	0(0.00)	
Low	6(11.76)	2(40.00)	1(50.00)	
Intermediate	18(35.29)	1(20.00)	0(0.00)	
High	20(39.22)	2(40.00)	1(50.00)	
NA	4(7.84)	0(0.00)	0(0.00)	
CD117, n(%)				1.000
+	49(96.08)	5(100.00)	2(100.00)	
-	1(1.96)	0(0.00)	0(0.00)	
NA	1(1.96)	0(0.00)	0(0.00)	
DOG1, n(%)				1.000
+	49(96.08)	5(100.00)	2(100.00)	
NA	2(3.92)	0(0.00)	0(0.00)	
CD34, n(%)				0.288
+	48(94.12)	4(80.00)	2(100.00)	
-	1(1.96)	1(20.00)	0(0.00)	
NA	2(3.92)	0(0.00)	0(0.00)	
Ki-67(%), n(%)				1.000
≤ 5	24(47.06)	3(60.00)	1(50.00)	
5–10	8(15.69)	0(0.00)	0(0.00)	
≥ 10	19(37.25)	2(40.00)	1(50.00)	
Metastasis, n(%)				1.000
+	4(7.84)	0(0.00)	0(0.00)	
-	47(92.16)	5(100.00)	2(100.00)	

2.2 Genetic mutation

2.2.1 A total of 51 cases (87.9%) of c-kit gene mutations and 42 cases (82.4%) of exon-11 mutations were the most common, involving 23 mutation types, for which W557_K558del (6 cases, 14.3%) and W557R (6 cases, 14.3%) were prevalent. Among the 13 c-kit deletion mutation cases in exons-11, two cases (4.8%) had one codon deletion, while 11 cases (26.2%) had ≥ 2 codon deletion, for which two cases (4.8%) had large fragment deletion containing codon 557–558. There were 16 cases of point mutation involving codon 557, 559, and 560, where seven cases (16.7%) had the most prevalent codon 559.

The exon-9 mutation was found in seven cases (13.7%), with only one type of insertion mutation (all Y503_F504insAY), with five cases occurring in the small intestine, and two cases in the stomach and esophagus, respectively. Among the seven cases, four cases were at high risk, three were in the small intestine, and one case in the stomach. The exon-13 mutation occurred in one case (2%), and the mutation type was a point mutation (K642E) occurring in codon 642 with a high risk located in the rectum.

2.2.2 There were five cases (8.6%) of PDGFR mutations (all exon-18 mutations), including four cases of D842V mutation and one case of I843_846delIMHD mutation originating from the stomach. No exon-12 and 14 mutations were detected.

Table 2
The form of c-kit exon-11 mutation and clinicopathological characteristics

	Deletion (13)	Point mutation (16)	Insertion (4)	Mixed (9)	<i>P</i>
Sex, n(%)					0.233
Male	8(61.54)	4(25.00)	2(50.00)	3(33.33)	
Female	5(38.46)	12(75.00)	2(50.00)	6(66.67)	
Age, n(%)					0.075
≤ 50	2(15.38)	2(12.50)	0(0)	5(55.56)	
> 50	11(84.62)	14(87.50)	4(100.00)	4(44.44)	
Location, n(%)					0.250
Stomach	5(38.46)	12(75.00)	3(75.00)	3(33.33)	
Small intestine	4(30.77)	2(12.50)	0(0.00)	4(44.44)	
colorectum	2(15.38)	0(0.00)	0(0.00)	0(0.00)	
parenteral	2(15.38)	2(12.50)	1(25.00)	2(22.22)	
Cell type, n(%)					0.395
spindle	7(53.85)	12(75.00)	2(50.00)	8(88.89)	
epithelioid	2(15.38)	0(0.00)	0(0.00)	0(0.00)	
mixed	1(7.69)	0(0.00)	0(0.00)	0(0.00)	
NA	3(23.08)	4(25.00)	2(50.00)	1(11.11)	
Mitotic count(/50HPF), n(%)					0.408
≤ 5	6(46.15)	12(75.00)	3(75.00)	4(44.44)	
> 5	6(46.15)	2(12.50)	1(25.00)	3(33.33)	
NA	1(7.69)	2(12.50)	0(0.00)	2(22.22)	
Tumor diameter (cm), n(%)					0.120
≤ 2	1(7.69)	1(6.25)	1(25.00)	1(11.11)	
> 2to ≤ 5	5(38.46)	3(18.75)	0(0.00)	5(55.56)	
> 5to ≤ 10	4(30.77)	10(62.50)	3(75.00)	2(22.22)	
> 10	3(23.08)	0(0.00)	0(0.00)	1(11.11)	
NA	0(0.00)	2(12.50)	0(0.00)	0(0.00)	

	Deletion (13)	Point mutation (16)	Insertion (4)	Mixed (9)	<i>P</i>
Risk, n(%)					0.039
Very low	1(7.69)	1(6.25)	0(0.00)	1(11.11)	
Low	1(7.69)	2(12.50)	0(0.00)	2(22.22)	
Intermediate	2(15.38)	10(62.50)	3(75.00)	1(11.11)	
High	8(61.54)	1(6.25)	1(25.00)	4(44.44)	
NA	1(7.69)	2(12.50)	0(0.00)	1(11.11)	
CD117, n(%)					0.528
+	13(100.00)	15(93.75)	4(100.00)	8(88.89)	
-	0(0.00)	0(0.00)	0(0.00)	1(11.11)	
NA	0(0.00)	1(6.25)	0(0.00)	0(0.00)	
DOG1, n(%)					1.000
+	12(92.31)	15(93.75)	4(100.00)	9(100.00)	
NA	1(7.69)	1(6.25)	0(0.00)	0(0.00)	
CD34, n(%)					1.000
+	13(100.00)	15(93.75)	4(100.00)	9(100.00)	
NA	0(0.00)	1(6.25)	0(0.00)	0(0.00)	
Ki-67, n(%)					0.212
≤ 5	5(38.46)	10(62.50)	3(75.00)	3(33.33)	
5–10	1(7.69)	3(18.75)	1(25.00)	1(11.11)	
≥ 10	7(53.85)	3(18.75)	0(0.00)	5(55.56)	
Metastasis, n(%)					0.174
+	1(7.69)	0(0.00)	0(0.00)	2(22.22)	
-	12(92.31)	16(100.00)	4(100.00)	7(77.78)	

2.3 The relationship between the type of gene mutation and clinicopathological characteristics

2.3.1 As shown in Table 1, there were significant differences in cell types among different gene types. The spindle cell type is the most common in c-kit genes, accounting for 72.55%. In the PDGFR α gene, the spindle cell type and the mixed type are prevalent, each accounting for 40%. Among the wild type, the spindle cell type and the epithelioid cell type were the most common. Each accounted for 50%.

2.3.2 As shown in Table 2, there were significant differences in tumor risk among different c-kit gene exon-11 mutation types. Among deletion mutation types, high risk was the most common, accounting for 61.54%. Concerning point mutation types, the intermediate-risk was the most common, accounting for 62.50%, while the intermediate-risk was prevalent for insertion mutation types, accounting for 75.00%. Significantly, high risk was the most common for mixed mutations, accounting for 44.44%.

2.3.3 As shown in Table 3, 58 GIST patients were cross-classified according to the two attributes of gene type and cell type, and Fisher's exact probability test was performed. The chi-square value was 13.366. A *P*-value of <0.05 indicated a moderate correlation between gene type and cell type.

Table 3
A cross - classification table of 58 GIST patients by gene type and cell type

Cell types	Genetic types			Total
	c-kit	PDGFR α	Wild-type	
Spindle	37	2	1	40
epithelioid	2	0	1	3
mixed	1	2	0	3
NA	11	1	0	12
Total	51	5	2	58

2.3.4 As shown in Table 4, 42 GIST patients were cross-classified according to two attributes of c-kit exon-11 mutation form and tumor risk, and Fisher's exact probability test was performed. The chi-square value was 20.270. A *P*-value of <0.05 indicated a moderate correlation between c-kit exon-11 mutation type and tumor risk.

Table 4
A cross-classification table of 42 GIST patients by c-kit exon-11 mutation form and tumor risk

Risk	c-kit exon-11 mutant form				Total
	Deletion	Point mutation	Insertion	Mixed	
Very low	1	1	0	1	3
Low	1	2	0	2	5
Intermediate	2	10	3	1	16
High	8	1	1	4	14
NA	1	2	0	1	4
Total	13	16	4	9	42

Discussion

The c-kit proto-oncogene is located on chromosome 4q12-13, and its expression product c-kit receptor is the transmembrane glycoprotein type-III tyrosine kinase receptor(CD117). Under normal circumstances, the c-kit protein must be combined with a ligand called stem cell factor(SCF) to form a dimer and activate transcription factors in the cytoplasm, thereby regulating gene expression and controlling cell proliferation and differentiation^[9]. The PDGFR α gene is very similar to the c-kit. It belongs to the type-III tyrosine-protein kinase family and encodes platelet-derived growth factor receptor- α . When PDGFR α binds to the ligand PDGF, it can stimulate phosphorylation of tyrosine residues, thereby regulating cell growth, proliferation, differentiation, and apoptosis^[10]. Mutations in the proximal region of the c-kit and PDGFR α genes can cause related proteins to be continuously activated without ligand binding, induce the activation of downstream signaling pathways, and participate in the occurrence of GISTs. Therefore, the mutant c-kit/PDGFR α is an essential indicator for the diagnosis and treatment of GIST.

GIST is generally seen in older adults with an average age of 60-years and an incidence ratio of 1:1 for men and women^[11]. In the 58 cases of GIST patients in the study, 29 were males and 29 females(1:1), with a median age of 57.5-years. Notably, the most common anatomical location for GIST is the stomach(55.6%), followed by the small intestine(31.8%), colon(6.0%), esophagus(0.7%), and other parts of the body(5.5%)^[11]. In the present study, 30 cases(51.7%) of tumors originated in the stomach, 16 cases(27.6%) in the small intestine, three cases(5.2%) in the colorectum, and nine cases(15.5%) outside the gastrointestinal tract(including the abdomen, pelvic, and peritoneal cavity).

Notably, in the study, the spindle cell type was the most common in the c-kit gene, accounting for 72.55%. On the other hand, the spindle cell type and the mixed type were prevalent in the PDGFR α gene, accounting for 40%. Significantly, the spindle cell type and epithelioid cell type were the most common in the wild type, accounting for 50%. The difference between cell types in different gene types was

statistically significant ($P = 0.022$), with a moderate correlation. It has been reported in the literature that, histologically, PDGFR α mutant GIST usually has an epithelioid or mixed epithelioid-spindle appearance^[12], which is inconsistent with the report of the present study.

One of the inconsistencies is related to the small number of samples included in the present study, with another being that the PDGFR α gene mutations in the present study are all exon-18 mutations, whereas the literature reports mentioned above were all exon-14 mutations. Tumor size and mitotic count are indicators for evaluating the degree of malignancy. Generally speaking, the more considerable the tumor, the more the mitotic count. Thus, the faster the cell growth, the higher the degree of malignancy and recurrence risk. Studies have reported that the c-kit exon-11 point mutation is characterized by low mitotic figures, with an average tumor size of ≈ 5 cm, and 5-year recurrence-free survival (RFS) (50.7%), including higher deletion mutations (28.1%) and repeated mutations (40%). The present study results, consistent with previous studies, show that point mutations are common at intermediate risk, while deletion mutations are prevalent at high risk.

The favorable rates of CD117, DOG-1, and CD34 were 96.6%, 96.6%, and 93.1%, respectively, consistent with the total mutation rate of c-kit and PDGFR α (96.6%) in the present study. However, the positive rate of CD117 was independent of the mutation status of c-kit and PDGFR α ^[13]. Notably, Ki-67 was a marker of proliferative cell activity. When Ki-67 is $> 10\%$, it indicates active tumor proliferation; thus indicating a poor prognosis^[14]. The present study did not find a statistical relationship between Ki-67 index and gene status.

In the study herein, the total mutation rate of c-kit and PDGFR α is 96.6%, which is consistent with a study in Panama (94.9%)^[15], but higher than other reports in the literature^[16, 17].

The mutation frequency of c-kit exon-11 was 82.4%, which is quite different from other studies. The reasons for such differences are the different genetic testing methods and the varying sample size and research options. In the study, there were 13 cases of c-kit gene exon-11 deletion mutations, for which there were six cases of W557_K558del (two cases of high risk and two cases of intermediate risk). Some studies have suggested that GIST, which involves the 557–558 codons deletion mutations, is more aggressive and easily metastatic and may be associated with a poor prognosis^[18].

Joensuu et al.^[19] classified them according to the number of missing codons, and believed that the RFS for deletion mutation of the large fragment of c-kit exon-11 was shorter than the mutation with only one codon missing. There were two cases with one codon missing (two high-risk cases) and 11 cases with ≥ 2 codons missing (six high-risk cases). Some studies^[20] believe that mutations in exon-9 of the c-kit gene tend to occur in the small intestine, with a higher malignant potential.

There were seven cases of exon-9 mutations in the study, five cases in the small intestine, and two cases in the stomach and esophagus. Four of the seven cases were at high risk. Three were in the small intestine, and one in the stomach, which is consistent with previous studies.

In summary, the study herein found out that the c-kit gene mutant type had more spindle-shaped cell types than epithelioid cell types and mixed types, whereas with the PDGFR α gene, spindle cell types and mixed types were more prevalent. Significantly, spindle cell types and epithelioid cell types were more common in wild-type. In the c-kit exon-11 mutant form, deletion mutations and mixed mutations were prevalent with high-risk, while point mutations and insertion mutations were dominant with intermediate-risk. Over the past two decades, scholars have understood the molecular events regarding GIST. However, more large-scale clinical and basic research with more complete designs is needed for further exploration in the future.

Abbreviations

GIST: Gastrointestinal Stromal Tumors; c-kit: c-kit proto-oncogene protein; PDGFR α : Platelet-derived Growth Factor Receptor; PCR: Polymerase Chain Reaction; NGS: the Next Generation Sequencing; NIH: the National Institutes of Health; WT: Wild Type; HPF: High Power Field; SCF: Stem Cell Factor; RFS: Recurrence-free Survival.

Declarations

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AUTHOR CONTRIBUTIONS

HC: writing original draft; TQ and SS: writing review and editing. All authors have read and approved the manuscript.

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Availability of data and materials

Data is available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent for publication was obtained from all participants.

Competing interests

The authors declare that they have no conflict of interest.

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