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Original Article

Presence of *PDGFRA* and *DOG1* mutations in gastrointestinal stromal tumors among Chinese population

Jiehua Li, Haitian Zhang, Yunfei Lu, Zhibai Chen, Ka Su

Department of Gastrointestinal and Gland Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning 530021, Guangxi Province, China

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Abstract: Approximately 15% of gastrointestinal stromal tumors (GIST) do not express *KIT* mutations and of these about 5 to 7% harbor mutations in *PDGFRA*. DOG1 was specifically expressed in GISTs. These cases require special attention for *PDGFRA* and *DOG1* mutational status. Hundred cases of GIST were diagnosed between August 2007 and October 2012 at the First Affiliated Hospital of Guangxi Medical University. DNA from tumor tissues and normal adjacent tissues was isolated and amplified for the 22 exons of *PDGFRA* and 26 exons of *DOG1*. Each PCR product was sequenced. Amino acid sequences were inferred from DNA and aligned to GenBank reference sequences to determine the position and type of mutations. Overall, 16.0% of the samples had a mutation in *PDGFRA*, and GISTs with mutations in the *DOG1* gene were not found. Of the mutations detected, they were in *PDGFRA* exon 18 (8 cases, 8%), *PDGFRA* exon 12 (5 cases, 5%), *PDGFRA* exon 14 (1 cases, 1.0%), *PDGFRA* exon 11 (1 cases, 1.0%), and *PDGFRA* exon 8 (1 cases, 1.0%). Of these, Y392S, L521P and T632K mutant occurred in *PDGFRA* exon 8, exon 11 and exon 14, respectively. The mutation of *PDGFRA* has been considered as another causative genetic event as *PDGFRA* mutations were found in most GISTs lacking a *KIT* mutation. *PDGFRA* mutations occurred preferentially in exon 18 and exon 12. Mutations occurring in *PDGFRA* exon 8 (Y392S), exon 11 (L521P) and exon 14 (T632K) also were first identified. The over-expression of DOG1 was not related to *DOG1* gene mutation.

Keywords: Gastrointestinal stromal tumor, mutation, platelet-derived growth factor alpha, *DOG1*

Introduction

GISTs are the most frequent sarcoma [1] that arises from the interstitial cells of Cajal (ICC) [2, 3]. GIST has an estimated annual incidence worldwide of approximately 10-20 per million individuals [4]. ICC can be immunohistochemically identified by antihuman *KIT* (CD117) antibody since *KIT* is strongly expressed in most GISTs [5, 6]. *KIT* is a transmembrane tyrosine kinase which serves as a receptor for stem cell factor [7]. The pathogenesis of GISTs is by activation of the *KIT* receptor tyrosine kinase resulting from the mutations occurring in two oncogenes, *KIT* and *PDGFRA* [3, 8]. These mutations can cause the receptors to get constitutively activated, leading to the dysfunction of cellular signalling pathways and uncontrolled cell growth and proliferation [9]. Approximately, 85% of GIST tumors were found to have an active mutation in the *KIT* proto-oncogene [10], this affects the diagnosis of GIST in patients who may benefit from treatment with receptor tyrosine kinase inhibitors. Another close homologous tyrosine kinase *PDGFRA* was seen in 5% to 7% of GISTs [11]. *KIT* and *PDGFRA* are mutually exclusive, and they are involved in similar cellular signaling pathways which results in GIST oncogenesis, but act at different receptor site [12]. Also, 5% of GISTs have no detectable kinase mutations [13]. *Discovered on GIST-1* (*DOG-1*) was reported to have a high sensitivity and specificity in GISTs [14]. *DOG1* is identified as a gene in the CCND1-EMS1 locus on human chromosome 11q13, which is a sensitive immunohistochemical marker for GIST. The pathogenesis of DOG-1 in GISTs is still unknown.

In this study, paraffin-embedded tumor tissues from 100 cases of GIST were subjected to DNA

Table 1. Primers used for PCR

PDGFRA EXON	PRIMER	DOG1 EXON	PRIMER
EXON 1 FORWARD	gccccattgattctttcatc	EXON 1 FORWARD	cggaaaatctgaccggcg
EXON 1 REVERSE	aactgccactggagagcatt	EXON 1 REVERSE	tgagctcttggttgggctc
EXON 2 FORWARD	gggtgaatctagtggggctt	EXON 2 FORWARD	agtgagtggatgaagggagc
EXON 2 REVERSE	acaggagagacaggaagagaag	EXON 2 REVERSE	ggatggcctcgatctcttga
EXON 3 FORWARD	agtggggcaattcttctgga	EXON 3 FORWARD	ttgtggtggcctctgaagat
EXON 3 REVERSE	acgcaccttatgattttgcct	EXON 3 REVERSE	acatggtctttgcaggggta
EXON 4 FORWARD	ctgaggaatgcggtgttctg	EXON 4 FORWARD	gtgggatggttctctgacca
EXON 4 REVERSE	atgtgcccatcagtgacaga	EXON 4 REVERSE	gaacacgctcttctttgggg
EXON 5 FORWARD	tagcctcccaccttgtcaac	EXON 5 FORWARD	gtctgttccaaatgcccagg
EXON 5 REVERSE	ggttgacagcttccaactgg	EXON 5 REVERSE	cacagacaattagagccggc
EXON 6 FORWARD	atgtcagttgtccatgctgc	EXON 6 FORWARD	acacgtcactagtcaagggg
EXON 6 REVERSE	agtgacctgtctttccccag	EXON 6 REVERSE	caatgctgatctcaagcccc
EXON 7 FORWARD	tcattcagaagtcaggccgt	EXON 7 FORWARD	ttctgccaatcgagcatgtg
EXON 7 REVERSE	ttttcttccatgaccgggga	EXON 7 REVERSE	ttcagaggaagtcgaggcag
EXON 8 FORWARD	ccggagtgttttgaatgcca	EXON 8 FORWARD	tgttgccccaggatgatctt
EXON 8 REVERSE	acatgcagtccgactaccaa	EXON 8 REVERSE	tgctccgctccatcaactta
EXON 9 FORWARD	tcccaactccttgccatctt	EXON 9 FORWARD	tctttgcatcccgtgagagt
EXON 9 REVERSE	tctgccttgggaccttcatt	EXON 9 REVERSE	gcttcatctaatgctggccc
EXON 10 FORWARD	cagacacagccacactacct	EXON 10 FORWARD	ctgcttctgggatgagggaa
EXON 10 REVERSE	gtgtgcaagggaaaagggag	EXON 10 REVERSE	atgtcctttcctcctgacgg
EXON 11 FORWARD	tggtgctgttggtgattgtg	EXON 11 FORWARD	cccgtcccattgtgtgtttt
EXON 11 REVERSE	gtgtgcaagggaaaagggag	EXON 11 REVERSE	aagacagacagaagcagcct
EXON 12 FORWARD	ctcctttctcccgtctgtgt	EXON 12 FORWARD	agaatcgcttgaacccagga
EXON 12 REVERSE	ccaacatacaggcagcaaga	EXON 12 REVERSE	tgtccatttcctctccaccc
EXON 13 FORWARD	gcactgaggccaagtagcta	EXON 13 FORWARD	tcaccctcaagcagcagtaa
EXON 13 REVERSE	atgtgtggggatggagagtg	EXON 13 REVERSE	agggtgctggaaggaaagaa
EXON 14 FORWARD	actctccatccccacacatg	EXON 14 FORWARD	tgttctcagggccagttcat
EXON 14 REVERSE	aagactggacagggtggttt	EXON 14 REVERSE	taccatggcagagttgagca
EXON 15 FORWARD	ccagttagctcccatgccta	EXON 15 FORWARD	tttaaaacgcccagaacccg
EXON 15 REVERSE	gaactggttgtgcagacctg	EXON 15 REVERSE	tggcatgcatgttaacgagg
EXON 16 FORWARD	cctcctccctgattcaagca	EXON 16 FORWARD	gcttcttggaaccctatgcg
EXON 16 REVERSE	gtccacactccactcactga	EXON 16 REVERSE	aagccaatcacttccttgcg
EXON 17 FORWARD	ctctccttcatcccctacgc	EXON 17 FORWARD	ccatctgtctctggtgggtt
EXON 17 REVERSE	caatcagggagacagagggg	EXON 17 REVERSE	acccattgagaaccagggag
EXON 18 FORWARD	tgtggccgtgatagctgtaa	EXON 18 FORWARD	ctccctggttctcaatgggt
EXON 18 REVERSE	cctggggcttgaaagaacac	EXON 18 REVERSE	tggggaaaggctgaagatgt
EXON 19,20 FORWARD	aaaaccagtgcttcaaggct	EXON 19 FORWARD	ttgccttaatcccctcctgg
EXON19,20 REVERSE	gctcctctagaactgcggaa	EXON 19 REVERSE	tgcacccgtccctcattaat
EXON 21 FORWARD	tggccccttcttcatgttct	EXON 20 FORWARD	acaccccagcatgaaaacac
EXON 21 REVERSE	tctgcaacttgtccctgagt	EXON 20 REVERSE	cctccttctctccctgcttc
EXON 22 FORWARD	gctttcgtttgtctctgggg	EXON 21 FORWARD	gcaacactgtgaaaccccat
EXON 22 REVERSE	gacatcaggtttcaagaggga	EXON 21 REVERSE	tgcatctctcttctccctgc
		EXON 22 FORWARD	ggtccatcccaagagctcat
		EXON 22 REVERSE	caaacccagcacgcactc
		EXON 23 FORWARD	cctcaacagcaaagccatgt
		EXON 23 REVERSE	ccaaggtccctgatgtcact
		EXON 24 FORWARD	accctgcatccattcactca
		EXON 24 REVERSE	cacaacgcccggctatttaa
		EXON 25 FORWARD	agtaggctctgcactcttgg
		EXON 25 REVERSE	agcaagttctccaagcctct
		EXON 26 FORWARD	aaagtcggccaacatttccc
		EXON 26 REVERSE	tgccgtattaccagccatca

Table 2. Characteristics of patients with *PDGFRA* gene mutations

Case no.	Tumor site	Exon	Nucleotide change	Amino acid change
9	Stomach	18	GAC→GTC	Asp→Val (D842V)
11	Stomach	18	TGT→CGT	Cys→Arg (C814R)
15	Stomach	18	GAC→GTC	Asp→Val (D842V)
19	Stomach	18	CCGTG→CG	Arg817del
25	Stomach	18	GAC→GTC	Asp→Val (D842V)
29	Stomach	18	AGACATCATGCATG→AG	AspIleMetHis842_845del
49	Stomach	18	GAC→GTC	Asp→Val (D842V)
77	Peritoneum	18	CGTGAT→CGTCGAT	ArgAsp→ArgArg817ins
23	Stomach	12	CCG→CAG	Pro→Gln (P553Q)
44	Stomach	12	ATT→CTT	Ile→Leu (I562L)
52	Stomach	12	CTT→GTT	Leu→Val (L595V)
81	Small bowel	12	AGC→ATC	Ser→Ile (S566I)
91	Small bowel	12	GAAATT→GACAAT	GluIle→AspAsn556ins
43	Stomach	14	ACG→AAG	Thr→Lys (T632K)
61	Peritoneum	11	CTG→CCG	Leu→Pro (L521P)
46	Small bowel	8	TAT→TCT	Tyr→Ser (Y392S)

extraction, PCR amplification, DNA sequencing and prediction of mutation. The results of this study contributes to gain a better understand the mutations of *PDGFRA* and screen the mutation in *DOG1* gene to explain the over-expression mechanism in GIST. This may provide a better target for more effective therapy in patients with GIST based on molecular analysis. It is often considered that molecular analyses are necessary to confirm the diagnosis of GIST and to determine further therapeutic strategy for the patients [15].

Materials and methods

This study was approved by the Ethics Committee of The First Affiliated Hospital of Guangxi Medical University and written informed consent was obtained from every participant.

Patient information

100 GIST patients were diagnosed between August 2007 and October 2012 at the First Affiliated Hospital of Guangxi Medical University. The samples were anonymous and without identifying any personal information. All patients underwent surgical resection through laparotomy and the final diagnosis was obtained from the analysis of clinicopathological findings. The morphological diagnosis was confirmed by standard H&E staining and immunoreactivity to KIT (CD117) on routinely formalin-fixed paraffin-embedded specimens. Our study was approved by the Ethics Committee of the First Affi-liated Hospital of Guangxi Medical University (NO. 2011 KY022).

DNA extraction from tumor tissues and normal adjacent tissues

After manual microdissection of tumor tissues and normal adjacent tissues, DNA was extracted from formalin-fixed paraffin-embedded tissues using the QIAamp DNA FFPE Tissue Kit (Qiagen, Mainz, Germany). Paraffin was removed by dissolving in xylene. Samples were lysed under denaturing conditions with proteinase K. Incubation at 90°C reversed formalin cross-linking. Residual contaminants were washed away. Pure DNA was eluted from the membrane. The purity of DNA is determined by UV spectrophotometry.

PCR amplification of the PDGFRA and DOG1 gene

The primers for the exons of *PDGFRA* and *DOG1* gene were designed from the earlier submitted sequences from the Genbank. All exons of *PDGFRA* and *DOG1* gene were amplified by polymerase chain reaction (PCR) using the primers detailed in **Table 1**. PCR was performed in a total volume of 50 μL containing 1000 ng of template DNA, 25 μL 2×Taq Plantinum PCR MasterMix (Tiangen, Beijing, China), 2 μL of 10 μM primer1, and 2 μL of 10 μM primer2 (**Table 1**).

DNA sequencing

Amplified products were separated in 2% agarose gel electrophoresis to confirm correct amplification. Each PCR product was sequenced by using an ABI DNA Analyzer (Applied Biosystems, Foster City, CA). Mutated amino acids within the sequences were determined based on a comparison to Genbank reference sequences.

Results

100 GIST cases had been examined, 16 cases (16%) had *PDGFRA* mutations tumor tissues

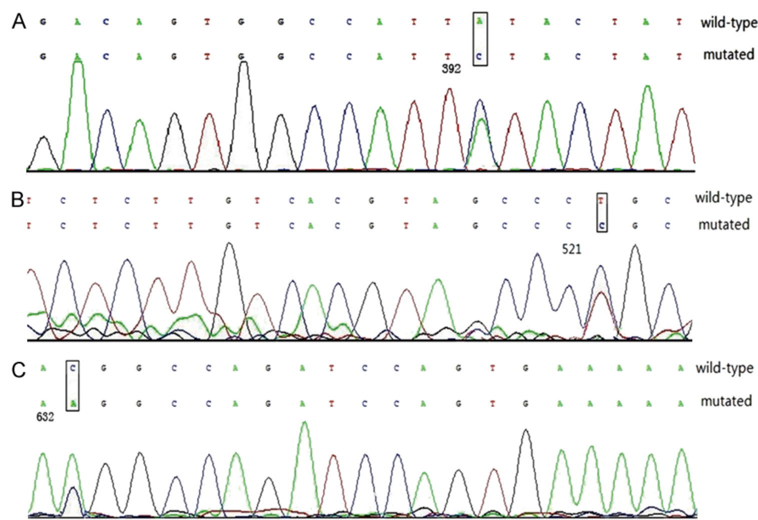

Figure 1. Demonstration of *PDGFRA* mutations A: Showing *PDGFRA* exon 8 Y392S; B: Showing *PDGFRA* exon 11 L521P; C: Showing *PDGFRA* exon 14 T632K.

(**Table 2**; **Figure 1**). No mutations were detectable in normal adjacent tissues of the 100 cases .The majority of *PDGFRA* mutations were observed in exon 18 (8 cases, 8%) and in exon 12 (5 cases, 5%). Exon 8, 11 and 14 mutations were seen in 3 cases, respectively. The missense mutation occurring in *PDGFRA* exon 8 led to the substitution of Tyr to Ser in codon 392. The missense mutation occurring in *PDGFRA* exon 11 led to the substitution of Leu to Pro in codon 521. The missense mutation in *PDGFRA* exon 14 led to the substitution of Thr to Lys in codon 632. Of the 8 *PDGFRA* exon 18 mutations, 5 (50%) were in codon 842, and 4 were in D842V substitutions. Across exon 18, 5 substitutions, 2 deletions, and 1insertion were observed. The patients with single amino acid substitutions encoded by the *PDGFRA* exon 18 were in codons 814 and 842 and the substitutions were D842V (n=4), and C814R (n=1), respectively. The amino acid deletions in exon 18 was R817del (n=1), D842-845Hdel (n=1). Of the 5 *PDGFRA* exon 12 mutations, 4 substitutions and 1 insertion was seen. These substitutions were P553Q (n=1), I562L (n=1), L595V (n=1), and S566I (n=1), respectively. Ex-on 8, 11 and 14 mutations identified in 3 cases respectively, all of which were substitutions. Of the 16 *PDGFRA* mutations, 11 tumors originated from the stomach (7 with *PDGFRA* exon 18, 3 *PDGFRA* exon 12 and 1 *PDGFRA* exon 14), 3 from the small bowel (2 with *PDGFRA* exon 12 and 1 *PDGFRA* exon 8) and 2 from the peritoneum (1 with *PDGFRA* exon 18 and 1 *PDGFRA* exon 11). *DOG1* gene has 26 exons. No *DOG1* mutations were found in 100 patients.

Discussion

The present study is the first in China to analyze all exons of *PDGFRA* and *DOG1* mutations associated with GISTs. Recently, the *PDGFRA* mutations have been considered to be causative genetic events. *PDGFRA* mutations were found in most GISTs lacks a *KIT* mutation. *KIT* mutations were observed in 75% to 80% of GISTs [16, 17]. *PDGFRA* mutations are identified in 22.5% of GISTs [17, 18]. In this study, *PDGFRA* mutations were observed in 16 (16%) out of 100 cases. All the 16 GISTs showed a missense mutation. Mutations involved exons 18, 12, 14, 11 and 8. The mutations in *PDGFRA* exons 18 and 12 that have been frequently observed in other studies were also identified in this study. The majority of *PDGFRA* mutations occur in exon 18 [17]. In this study, we found that *PDGFRA* mutations in exons 18 were identified in 8 (50%) of 16 cases. The most common *PDGFRA* mutation is D842V in exon 18. Heinrich et al [8] found that when *PDGFRA* mutation is D842V, it activates phosphorylation cascades independently of the presence of the ligands. *PDGFRA* mutations occurring in exon 12 are very rare [17]. However, we found that *PDGFRA* mutations in exons 12 were identified in 5 (31.2%) of 16 cases in our study. Lasota et al reported that all exon 12 *PDGFRA* mutations in GISTs were clustered between 560 and 577 *PDGFRA* amino-acid residues, and this region is considered as a mutational “hot spot” for GIST [19]. In this study, the *PDGFRA* mutations in exons 12 were clustered between 553 and 595 *PDGFRA* amino-acid residues. No *PDGFRA* exon 8 and 11 mutant, which was identified in this study, was found in the earlier studies. The mutations in *PDGFRA* exon 8 (Y392S; TAT→TCT) and *PDGFRA* exon 11 (L521P; CTG→CCG) are accidental. Mutations have been detected at much lower frequencies in *PDGFRA* exons 14 [16]. In our study, the *PDGFRA* exons 14 mutation was identified in only one sample. The mutation in *PD-*

*GFR*A exons 14 (T632K; ACG→AAG) has not been previously identified. The type and location of *PDGFRA* mutations in GIST can be used to predict the response to imatinib treatment [20]. GISTs with *KIT* exon 11 mutations exhibit better therapeutic outcomes with imatinib therapy in comparision with wild-type tumors and any other mutations [21]. *D842V* in exon 18, the most common *PDGFRA* mutation, is resistant to imatinib [8, 22].

DOG1 (FLJ10261, locus on human chromosome 11q13), encoding a hypothetical protein, has been found to be specifically expressed in GISTs. Although the over-expression of *DOG1* in GIST has been recently identified, the biological function and the mechanism in GIST are still unknown. Two possible over-expression mechanisms were reported by West et al [23]. ICCs were immunoreactive for *DOG1*, as in *KIT*. The protein may be a transmembrane tyrosine kinase which serves as a receptor for stem cell factor. The binding of stem cell receptor to the protein results in activation of tyrosine kinase and downstream intracellular signal transduction pathways. On the other hand, *DOG1* is a possible marker of the GIST, which is irrelevant to the kinase type III signal transduction pathways [24]. Miwa et al [25]. University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan.</auth-address><titles><title>Mutation assay of the novel gene DOG1 in gastrointestinal stromal tumors (GISTs tried to find the mutation of *DOG1* gene to explain the over-expression mechanism in GIST. In their studies, 26 exons of *DOG1* from 4 cases of GIST were selected for the molecular analysis and no *DOG1* mutation was found. In our studies, 26 exons of *DOG1* from 100 cases of GIST were observed and no *DOG1* mutation was found. Sequence analysis did not show any evidence of *DOG1* gene mutation, so we believed that the over-expression mechanism of *DOG1* was not related to *DOG1* gene mutation. *DOG1* was highly expressed in *KIT*-and *PDGFRA*-mutant GISTs [13]. DOG1 identifies the vast majority of both *KIT*- and *PDGFRA*-mutated GISTs. This may be of clinical value in identifying candidates for imatinib therapy. *DOG1* may also be a potential therapeutic target.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Haitian Zhang, Department of Gastrointestinal and Gland Surgery, The First Affiliated Hospital of Guangxi Medical University, 6 Shuang-Yong Road, Nanning 530021, China. Tel: +86-771-5350100; Fax: +86-21-64085875; E-mail: zhanghaitian@msn.com

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