Diagnostic Pathology

CASE REPORT

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A case of quadruple wild-type gastrointestinal stromal tumor with *CDC42BPB::NTRK3* fusion and abundant lymphoid infiltration

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Abstract

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. The most common mutations in GISTs are those in receptor tyrosine kinase (*KIT*) and platelet-derived growth factor receptor alpha (*PDGFRA*). GISTs without *KIT* or *PDGFRA* mutations are defined as wild-type (WT) GISTs. The molecular changes, prognosis, and treatments of WT GISTs remain uncertain. Among WT GISTs, neurotrophic tyrosine receptor kinase (*NTRK*) fusions have rarely been reported. We report a case of quadruple wild-type GIST harboring a novel *CDC42BPB::NTRK3* fusion. In this study, we described a 66-year-old male patient with intrajejunal lesion. This case showed massive lymphocytic and plasma cell infiltration, which caused diagnostic difficulties in morphology. *CDC42BPB::NTRK3* fusion was detected via next-generation sequencing (NGS), and this finding was confirmed by fluorescence in situ hybridization (FISH), which revealed *NTRK3* breakage. However, the expression of the Trk protein in tumor tissue was not detected by immunohistochemistry (IHC). This finding expands the genetic spectrum of *NTRK* rearrangements in GISTs.

Keywords Gastrointestinal stromal tumor, *NTRK*, Lymphoid infiltration

Background

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. The incidence rate of GISTs is approximately 1.1–1.8/100,000/year [1–3]. GISTs exhibit a broad spectrum of biological behaviors ranging from benign to malignant. Most GISTs harbor *KIT* (80%) or *PDGFRA* (10%) mutations [4, 5]. A small group of GISTs lack *KIT* or *PDGFRA* mutations, and this group is defined as wild type (WT) GISTs [6]. The most common type of WT GIST is *SDHA/SDHB* expression-deficient. Mutations in the *RAS* pathway genes are as follows. GISTs that lack *KIT/PDGFRA/SDH/RAS-P (RAS* pathways*)* mutations are known as quadruple WT GISTs, and this subgroup accounts for 5% of all GISTs [7]. Reported genetic alterations in quadruple WT GISTs include *NTRK*, *FGFR*, and *ALK* [8, 9].

Tyrosine receptor kinase (Trk) is expressed in the human nervous system and plays an important role in the growth and functional regulation of the nervous system by activating nerve growth factor (NGF) [10]. The neurotrophic receptor tyrosine kinase (*NTRK*) family consists of three members, *NTRK1*, *NTRK2*, and *NTRK3*, which encode three homologous kinases, TrkA, TrkB and TrkC. The locations of *NTRK* family members on chromosomes are 1q22, 9q21, and 15q25 [11].

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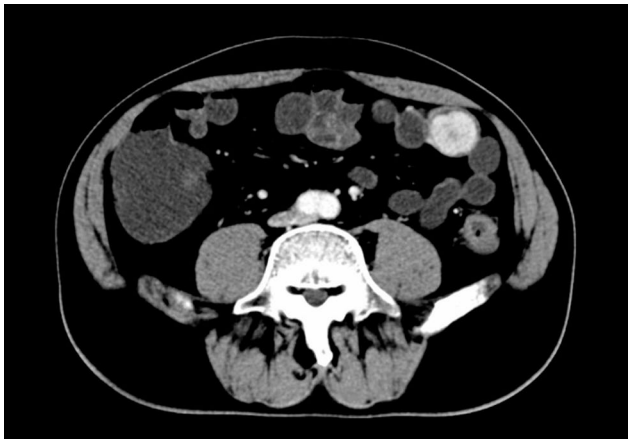

Fig. 1 Lesion in the jejunum (CT scan)

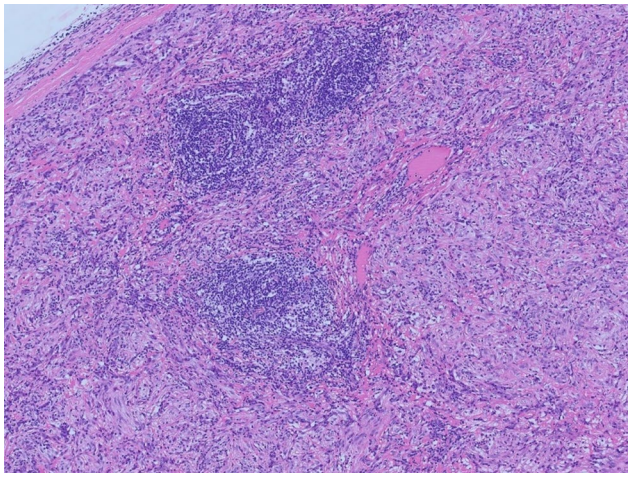

Fig. 2 Tumor cells with lymphocytic infiltration and tertiary lymphoid follicular structures (HE 100X)

NTRK was initially discovered as an oncogene. In 1982, the *TPM3::NTRK1* fusion protein was found to have a strong ability to promote the reproduction of tumor cells in colorectal cancer [12]. Studies have revealed many *NTRK* fusion partners, such as *ETV6::NTRK3* [13], the most explored partner. *NTRK* fusion mutations are frequently observed in infantile fibrosarcoma (IFS), secretory breast carcinoma (SBC), mammary analogue secretary carcinoma (MASC), acute myeloid leukemia (AML), papillary thyroid carcinoma (PTC), and non-small cell lung cancer (NSCLC) [14].

NTRK-rearranged GIST was first reported by Eileen Shi et al. This patient had an *ETV6::NTRK3* fusion [8]. *ETV6::NTRK3* is also the most common form of *NTRK* fusion in GISTs. Other rare fusions include *LMNA::NTRK1* and *RBPMS::NTRK3* [15, 16]. In this study, we report a 66-year-old man with quadruple WT GIST detected by next-generation sequencing (NGS). The *CDC42BPB::NTRK3* fusion, which has not been reported in GISTs, was identified in this case.

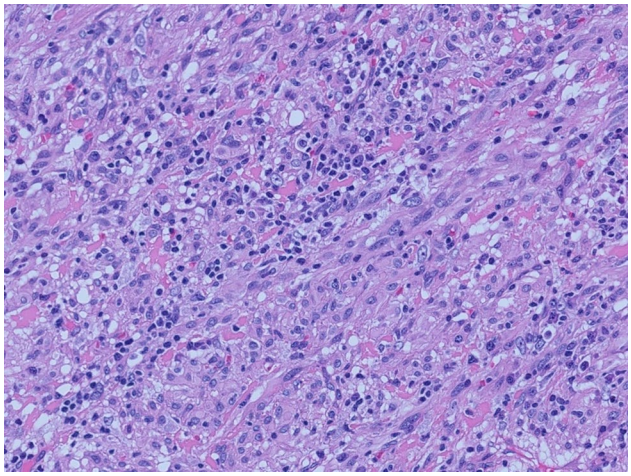

Fig. 3 Spindle-shaped tumor cells (HE 200X)

Case presentation

A 66-year-old male was admitted to the hospital because of melena. The patient underwent a computed tomography (CT) scan of the abdomen. CT showed intrajejunal lesion in the left lower abdomen measuring approximately 38 × 26 × 24 mm with clear borders (Fig. 1). Accumulation of fluid and gas was observed in the small intestine and colon. The patient then underwent resection of the tumor and part of the small intestine in September 2023. Postoperative pathology revealed that the tumor cells were spindle-shaped, with massive lymphocytic and plasmacytic infiltration, and locally lymphocytic cells formed tertiary lymphoid follicles. The tumor infiltrated the intrinsic muscular layer, resembling the morphology of the inflammatory myofibroblastic tumor (IMT) (Figs. 2 and 3). Immunohistochemically, the tumor cells were negative for ALK and focally positive for α-SMA, which may exclude the diagnosis of IMT. In contrast, the tumor cells were diffusely positive for CD117, DOG-1 and CD34 (Figs. 4 and 5). Pathological mitoses were difficult to find. According to the National Institute of Health (NIH) criteria, the diagnosis of low-risk GIST was rendered [17, 18].

Afterwards, the gene mutation status of the patient was tested. The first NGS test was performed using a 40-gene panel including *KIT*, *PDGFRA*, *KRAS*, *BRAF*, *NRAS*, and *PIK3CA*, and no clear mutations were detected. This test was performed on the extracted DNA using the AmoyDx® HANDLE Classic Panel (Amoy DiagnosticsDx, Xiamen, China). This assay utilized an amplicon-based approach to capture the targeted regions, with sequencing performed on the Illumina platform. And the concentration of extracted DNA was measured using the QuantiFluor® dsDNA System (Promega, Madison, Wisconsin, USA). For further verification, the second NGS test was performed using a 2000-gene panel, containing *KIT*, *PDGFRA*, *KRAS*, *BRAF*, *NRAS*, *PIK3CA*, *NF1*, *ALK*,

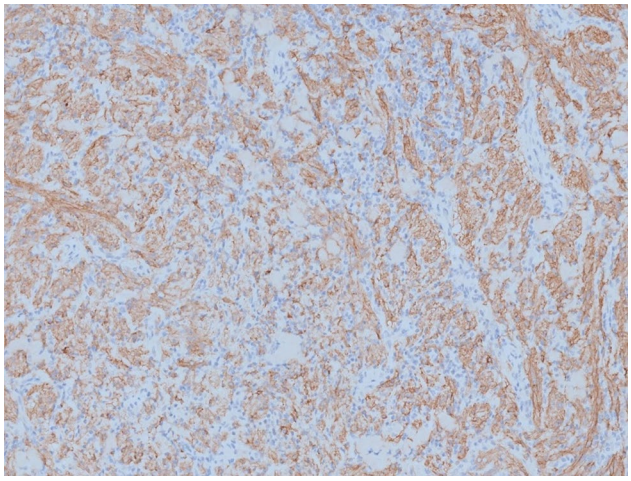

Fig. 4 Immunohistochemical staining for CD117 (200X)

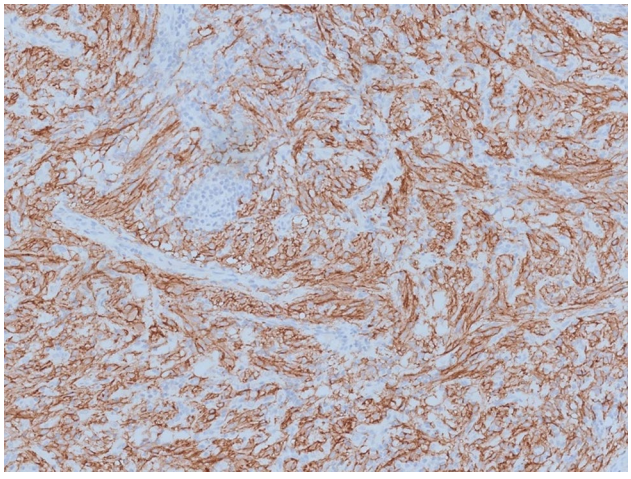

Fig. 5 Immunohistochemical staining for DOG-1 (200X)

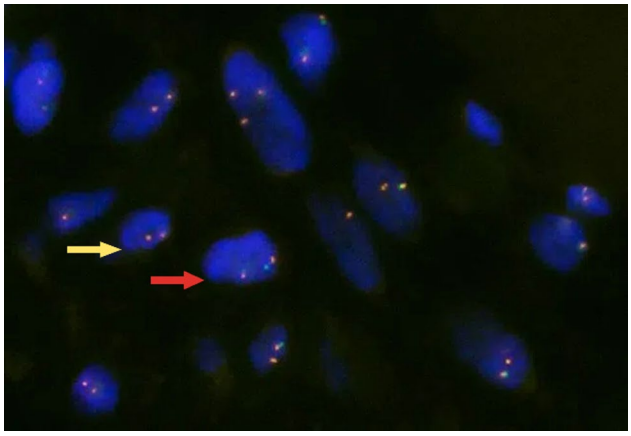

Fig. 7 FISH analysis using break-apart probes shows split signals for *NTRK3*. The yellow arrow points to negative cells and the red arrow points to fusion-positive cells

and *NTRK*. The sequencing library was prepared using the AmoyDx® Master Panel (AmoyDx), which includes 571 genes for DNA mutation and genomic signatures detection and 2,660 genes for RNA expression and fusion detection. Sequencing was performed on the Illumina NovaSeq 6000 platform (Illumina, San Diego, USA), utilizing a probe-based approach. DNA and RNA concentrations were measured using the Quantus fluorometer (Promega, Madison, USA), and the quality of the samples was assessed using the Agilent 2100 Bioanalyzer (Agilent, Santa Clara, USA). The results revealed a *CDC42BPB:exon24-NTRK3:exon15* gene fusion, a novel *NTRK* gene fusion (Fig. 6). The *NTRK3* break-apart probe was used in the subsequent FISH analysis, and the positive result confirmed this rearrangement (Fig. 7). However, the

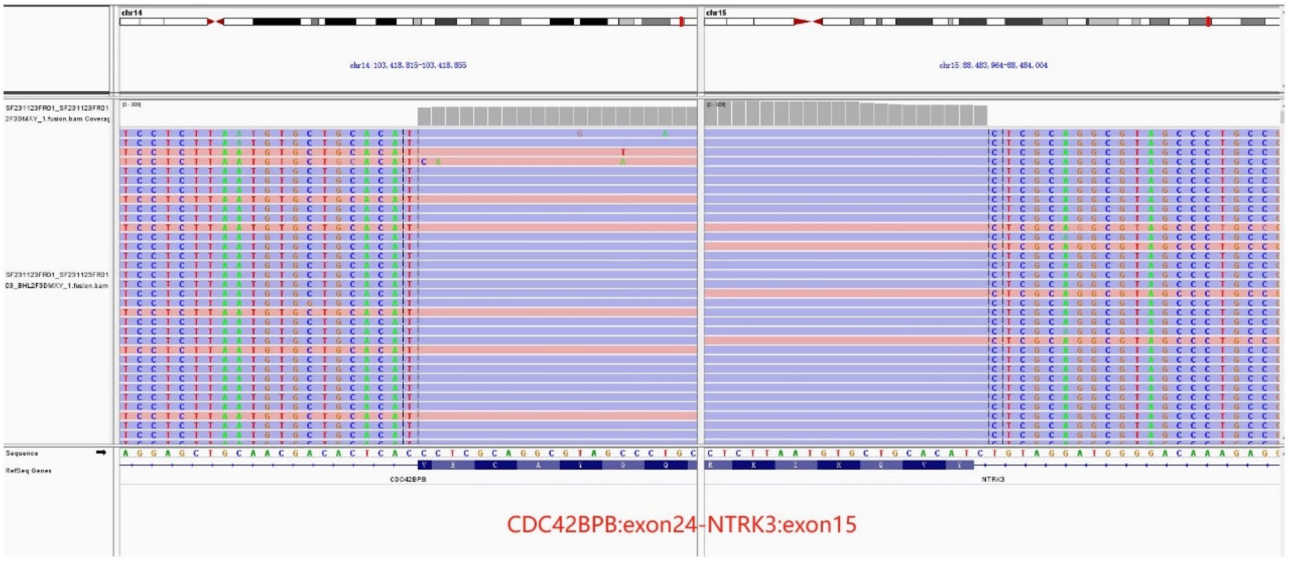

Fig. 6 NGS reveals *CDC42BPB::NTRK3* gene fusion

expression of the Trk protein in tumor tissue was not detected by IHC using the EPR17341 antibody (Fig. 8).

Previous studies have reported that GISTs with *NTRK* rearrangement do not significantly benefit from Imatinib therapy [19]. Given that the patient's NIH risk classification was low, close clinical follow-up was recommended for this patient instead of using any targeted therapy. Until December 2024, the patient showed no signs of recurrence according to a CT scan.

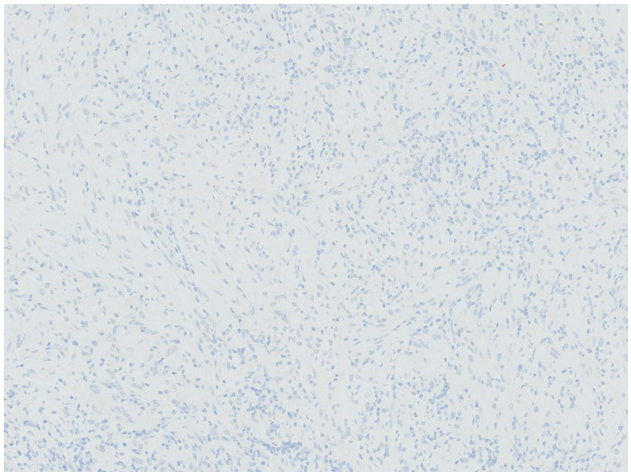

Fig. 8 Immunohistochemical staining for Trk (200X)

Discussion

In this study, we report a case of quadruple WT GIST. Morphologically, in this tumor a large number of inflammatory cells infiltrated the interstitium, potentially leading to misdiagnosis as an inflammatory myofibroblastic tumor. A *CDC42BPB::NTRK3* gene fusion was identified in the tumor by NGS testing.

A thorough systematic review of the literature was performed through the databases Web of Science and PubMed from dates of inception to February 2025 to identify cases of GISTs with *NTRK* mutations. The search terms "gastrointestinal stromal tumor" AND "*NTRK*" were used as keywords to identify all eligible studies. The literature screening process is illustrated in Fig. 9. We have found 17 *NTRK*-mutant GIST cases with specific information and with the case of our study, a cohort of 18 cases was obtained (Table 1). *NTRK*-rearranged GISTs can arise in various parts of the digestive tract, with tumor sizes ranging from 1.7 to 27 cm. The median age of patients is 54.5 years, with a male predominance (11/18). Among all, *NTRK3* are the most common mutations (14/18), and the most common combination of *NTRK3* rearrangements is *ETV6::NTRK3* (8/18). In second place are *NTRK1* rearrangements (4/18), with *LMNA::NTRK1* being the known partners. Although the overexpression of *NTRK2* in GISTs has been reported, no *NTRK2* rearranged GIST case has been reported [20]. A case of *NTRK3*-mutant GIST with a large number of lymphocytic cells infiltrating the tumor interstitium has been reported, which is similar to our study in morphology [21]. The morphological features of GISTs with *NTRK* rearrangements vary. Consequently, it is important to distinguish GISTs with *NTRK* rearrangements from other types of mesenchymal tumors with *NTRK* rearrangements in the gastrointestinal tract. The most effective method for differential diagnosis is immunohistochemistry. GISTs with *NTRK*

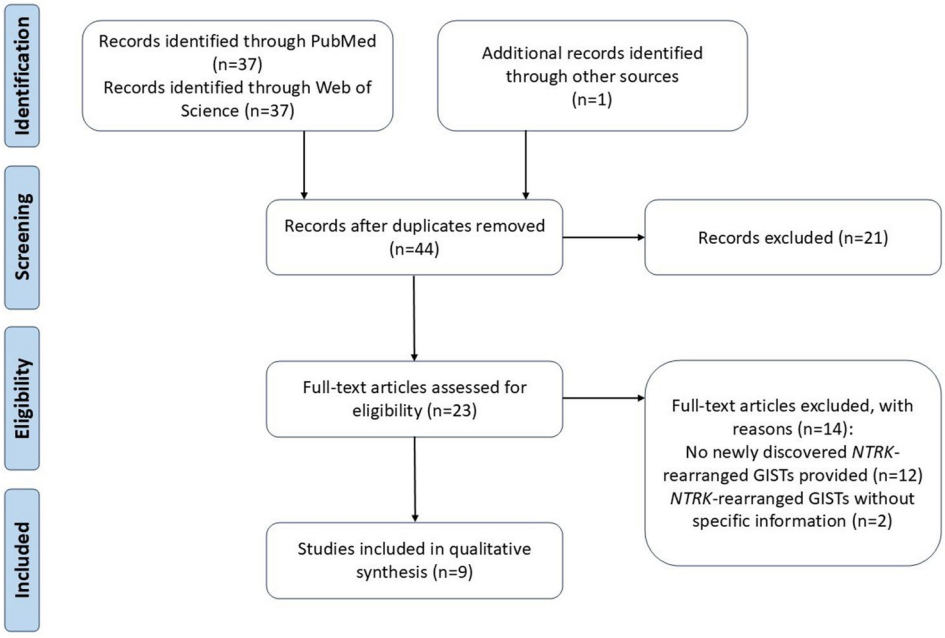

Fig. 9 Flowchart of the literature review process

Table 1 Clinicopathological features of wide-type gists with NTRK fusions

Reference	Sex/Age (year)	Tumors site	Size (cm)	KIT/PDGFRA/ RAS-*P*/SDH mutations	IHC (pan-TRK)	NGS	FISH	Surgery	Drug treatment	Progress or relapse/Time (month)	Death/ Time (month)
Machado I [21]	F/57	Pelvic	27	-/-/-/-	+ focal	*ETV6::NTRK3*	*NTRK3*	Yes	Entrectinib	Yes/1	No/3
Shi E [8]	M/55	Small intestine	NA	-/-/-/-	NA	*ETV6::NTRK3*	NA	No	Sunitinib Sorafenib Nilotinib Regorafenib Larotrectinib	No/4	No/4
	M/54	Colon	NA	-/-/-/-	NA	*ETV6::NTRK3*	NA	No	Imatinib Sunitinib Sorafenib Linsitinib	Yes/NA	No/12
Castillon M [37]	M/59	NA	NA	-/-/NA/NA	-	NA	*ETV6::NTRK3*	No	No	Yes/NA	Yes/NA
Dufresne A [15]	F/74	Duodenal	8	-/-/-/-	NA	*RBPMS::NTRK3*	NA	Yes	Imatinib Sunitinib Cabozantinib	Yes/5	Yes/NA
Lee JH [38]	F/44	Rectum	2.8	-/-/NA/NA	Among 5 *NTRK*-fusion cases, only one was positive	No	*NTRK1*	Yes	No	Yes/108	Yes/132
	M/45	Duodenum	1.7	-/-/NA/NA		No	*NTRK3*	Yes	No	No/72	No/72
	F/65	Stomach	17	-/-/NA/NA		No	*NTRK1*	Yes	Imatinib	Yes/26	Yes/96
	F/61	Jejunum	3.9	-/-/NA/NA		No	*NTRK1*	Yes	Imatinib	No/48	No/48
	M/43	Rectum	11	-/-/NA/NA		*NTRK3*	*NTRK3*	Yes	No	No/36	No/36
Zhang H [39]	M/66	Stomach	12	-/-/NA/NA	+	No	*NTRK3*	Yes	No TRKi	No/112	No/112
	M/47	Duodenum	5	-/-/NA/NA	+	No	*NTRK3*	Yes	No TRKi	No/78	No/78
	F/34	Stomach	NA	-/-/NA/NA	+	No	*NTRK3*	Yes	No TRKi	No/123	No/123
Brenca M [40]	M/44	Rectum	5	-/-/-/-	NA	*ETV6::NTRK3*	*ETV6*	Yes	No	No/44	No/44
D'Alpino Peixoto R [16]	M/20	Rectum	7	-/-/NA/NA	NA	*LMNA::NTRK1*	NA	Yes	No	NA/NA	NA/NA
Cao Z [24]	F/52	Mesentery	10	-/-/-/-	+	*ETV6::NTRK3*	*ETV6::NTRK3*	Yes	No	Yes/11	Yes/11
	M/56	Stomach	16	-/-/-/-	-	*ETV6::NTRK3*	*ETV6::NTRK3*	Yes	Imatinib	No/58	No/58
this study	M/66	Jejunum	3.8	-/-/-/-	-	*CDC42BPB:: NTRK3*	*NTRK3*	Yes	No	No/15	No/15

rearrangements are CD117 and DOG-1 positive, whereas other mesenchymal tumors are CD117 and DOG-1 negative [22].

NTRK fusion GISTs are rare, so the detection of *NTRK* rearrangements in WT GISTs is a matter for discussion. IHC is the least expensive and most convenient method. Antibody clone EPR17341 is the most commonly used clone and it reacts with a conserved proprietary peptide sequence at the C-terminus of TrkA, TrkB and TrkC. The antibody showed a sensitivity of 75–96.7% for detecting *NTRK* fusions. However, the sensitivity for *NTRK3* fusions was lower than *NTRK1* and *NTRK2*, as low as 17% [23, 24], which is a possible reason for the negative pan-Trk IHC in this case. FISH usually detects rearrangements of *NTRK* genes via isolation probes that can detect *NTRK* when the fusion partner is not clear. However, there are several limitations in FISH. First, *NTRK* family genes need to be detected separately, which increases medical expenses [25]. Second, most *NTRK1* alterations are internal inversions of chromosome 1, such as *LMNA::NTRK1*. Short inversions and intrachromosomal inversions make it difficult to distinguish abnormal cells from normal cells, which may lead to false-negative results [26]. RT-PCR and NGS based on DNA/RNA are also used in the detection of *NTRK* fusions. The European Society for Medical Oncology (ESMO) recommends FISH or RT-PCR for tumors with a high frequency of *NTRK* gene fusions that have diagnostic value for diseases, and, conversely, NGS for tumors with a low frequency of *NTRK* gene fusions [27]. According to the Chinese Society of Clinical Oncology (CSCO) guidelines, Sanger sequencing of *KIT* and *PDGFRA* is first-line recommendation for GISTs. If the results for both are negative, SDHB IHC and *RAS-P* testing are subsequently performed. If no mutations are detected in either of these tests, a diagnosis of quadruple wild-type GIST can be established. In such cases, NGS is recommended as the next step to detect potential genetic mutations. FISH is then used to validate the results of NGS [28].

NTRK gene fusions can activate Trk protein expression, which causes the development of tumors. Trk inhibitors, such as Larotrectinib and Entrectinib, have shown good anti-tumor effects on a variety of *NTRK*-rearranged tumors [29, 30]. In a clinical trial involving 159 patients with *NTRK*-rearranged tumors, all of four GIST patients achieved a good response [31]. In a pooling of three clinical studies, three patients with GIST all responded with Larotrectinib [32]. Machado et al. reported a case of *ETV6::NTRK3* fusion GIST in which the patient received Entrectinib therapy and achieved a complete response [21]. Therefore, WT GISTs with *NTRK* fusion can be considered for treatment with Trk inhibitors.

CDC42 binding protein kinase beta (*CDC42BPB*) encodes a member of the serine/threonine protein kinase family. *CDC42BPB* has association with Chilton-Okur-Chung neurodevelopmental syndrome and Imerslund-Grasbeck syndrome 2. *CDC42BPB* encodes a serine/threonine protein kinase that is a key mediator of cell growth, proliferation, and apoptosis [33]. CDC42BPB has been identified as a cancer-associated gene for risk stratification in bladder cancer [34]. Recent studies suggest that knocking down *CDC42BPB* increases tumor cell sensitivity to anti-PD-1 therapy [35]. Our team reported a case of a GIST with *CDC42BPB::ALK* fusion [9]. While *CDC42BPB::NTRK* fusions have not been previously reported, a similar fusion involving *NTRK3's exon 15* has been described in salivary gland cancers, with patients benefiting from Larotrectinib treatment [36]. The *CDC42BPB::NTRK3* fusion may therefore lead to altered signaling pathways and could represent a potential therapeutic target.

In this study, we have identified an *CDC42BPB::NTRK3* fusion in GIST through NGS and the breakage of *NTRK3* gene was confirmed via an *NTRK3* break-apart probe. However, due to the constraints of laboratory conditions in clinical practice, we were unable to further validate this rare fusion through PCR or *CDC42BPB::NTRK3* fusion probe. Additionally, we lack data on the kinase activity of this fusion gene. And it remains unknown whether the Trk inhibitors can suppress the kinase activity of this fusion product. These are critical areas that require further investigation.

In conclusion, we identified a case of quadruple wild-type GIST with *CDC42BPB::NTRK3* fusion, which expanded the genetic spectrum of *NTRK* rearrangements in GISTs. The discovery of more *NTRK*-rearranged GISTs suggests the necessity of detecting *NTRK* gene rearrangements in wild-type GISTs. The efficacy of Trk inhibitor therapy for *NTRK*-rearranged GISTs needs to be validated in more cases.

Author contributions

Conceptualization, W.T.X.; Methodology: W.Y.; Data Curation: H.Y.L. and L.R.; Writing– Original Draft Preparation: W.T.X.; Writing– Review & Editing: Y.Y.H.; Visualization: J.H., W.H., and L.J.L.; Supervision: C.X.; Funding acquisition: Y.Y.H. All authors contributed to data interpretation, manuscript editing, and revision.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The participant in our study provided signed informed consent. This study was approved by the ethics committee of the Zhongshan Hospital, Fudan University, and the IRB is B2022-532R2.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

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