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ORIGINAL RESEARCH

Molecular Characterisations and the Association with Clinical Factors in *RET* Fusion-Positive NSCLC: A Retrospective Study of the Single Center Cohort

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Background: *RET* fusion is a pathogenic driver factor in lung cancer patients. Currently, the conclusions on the clinical factors of *RET* fusion in NSCLC are inconsistent.

Methods: From 2018 to 2024, 6,204 lung cancer patients received next-generation sequencing (NGS) testing, among whom 102 were confirmed to be positive for *RET* fusion. The clinical and molecular characteristics of these patients were analyzed and compared.

Results: In this cohort, the prevalence of *RET* fusions was 1.6% (102/6204). Most patients were female (54.90%), <60 years (53.92%), non-smokers (72.55%), with advanced-stage (68.63%), metastatic (69.61%, mostly lymph nodes), adenocarcinoma (98.04%), and PS 0–1 (90.20%). The most common fusion partners of *RET* were *KIF5B* (50.00%, 51/102) and *CCDC6* (22.55%, 23/102).; noval partners including *C16orf95, CARNMT1-AS1, CXCL12, MTUS1* and *MYRFL* were identified. Common fusion partners were associated with age (P=0.023) and PS score (P=0.040), with higher rates of *RET* fusion in patients <60 years of age and those with a PS score of 0–1 (81.80% and 76.10%, respectively. *TP53* represented the most frequent concomitant alteration in *RET* fusions, occurring at a rate of 14.71% (15/102).

Conclusion: The new discoveries of *RET* fusion partners were founded in NSCLC. In addition, the broad-panel NGS is essential for NSCLC patients to catch these rare/novel fusions that PCR or small panels might miss.

Keywords: NSCLC, *RET* fusion, molecular characteristics, NGS

Introduction

Gene fusion is a key molecular variation in non-small cell lung cancer (NSCLC), affecting 8%–12% of NSCLC patients. Approved tyrosine kinase inhibitors (TKIs) targeting distinct gene fusions have brought substantial benefits to affected patients.

Rearranged during transfection (*RET*) fusion, identified post *EGFR/ALK*, is an emerging driver in NSCLC, with an incidence of 1%–2%.[1–3] *RET* fusion-positive patients often have distinct clinical features: younger age, non-smoking status, adenocarcinoma histology, better performance status, and similar male/female prevalence.[4,5] Brain metastasis is common, and *RET* fusions are generally considered mutually exclusive with other oncogenic drivers such as *EGFR* mutations and *ALK* rearrangements, although rare co-occurrences have been reported. However, Tsuta K et al[6] and Michels S et al[7] found no significant gender/smoking differences in *RET* fusion cases. Cheng Ying et al's Phase II study[8] identified *KIF5B, CCDC6*, and *NCOA4* as *RET* fusion partners in brain metastasis cases, but other partners remain unclear current conclusions on *RET* fusion-related clinical factors are inconsistent. According to the ESMO recommendations,[9] for patients with *RET* fusion-positive NSCLC, it is recommended to use next-generation sequencing technology (NGS) to sequence samples from different tissue types. Although significant progress has been made in the study of *RET* fusions in NSCLC, most current studies have focused primarily on common fusion partners such as *KIF5B*

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and *CCDC6*, and systematic investigations into the molecular characteristics and clinical significance of rare fusion partners remain limited. Recent studies have suggested that different *RET* fusion partners may influence the clinical characteristics and therapeutic responses of patients. A study by Sun et al[10] found that patients with non-*KIF5B* fusion partners had a significantly longer median progression-free survival (mPFS) when treated with pralsetinib than those with *KIF5B* fusions (17.0 months vs. 5.5 months, P = 0.0473), indicating that the type of fusion partner may affect sensitivity to targeted therapy. In addition, Wang et al[11] reported a rare case of *RET:FOXJ3* fusion in which the patient showed no response to pralsetinib, further demonstrating that rare fusion partners may exhibit distinct biological behaviors and clinical implications.

At present, descriptive data based on NGS testing regarding the spectrum of rare *RET* fusion partners and their associations with clinical factors in *RET* fusion-positive NSCLC remain scarce, particularly reports involving systematic identification using large multigene panels.

The present study aimed to systematically analyze the molecular features and clinicopathological factors of *RET* fusion-positive NSCLC patients in a single-center cohort from Jilin Province using multigene NGS, with a focus on the identification of rare fusion partners and their potential clinical significance. This study was designed to supplement the existing data on rare fusion partners and provide new evidence for the precise classification of *RET* fusion-positive NSCLC.

Materials and Methods

We performed a retrospective study involving 6,204 consecutive lung cancer patients who underwent next-generation sequencing for treatment plan formulation in the Translational Oncology Research Lab of Jilin Cancer Hospital between June 2018 and September 2024. We collected tissue samples via surgery or puncture for patients from whom tissue could be obtained, and used blood, malignant effusion, or cerebrospinal fluid specimens for those unable to provide tissue samples for NGS detection. Patients with *RET* fusion identified by NGS sequencing were included in the positive rate statistics of this study. We extracted basic clinical and pathological characteristics of the patients from the electronic medical record system. These characteristics included age, gender, smoking status, clinical stage at diagnosis, pathological type, metastatic status, as well as other variables. All included cases are consecutive NGS-tested cases without any purposeful artificial screening. In the statistics of clinical characteristics, if there is missing data for patients, the missing data are handled by listwise deletion, and only cases with complete data for all variables are retained.

The NGS panels used for *RET* fusion detection in DNA level included 8-gene, 59-gene, 68-gene, 168-gene, 520-gene, and 1021-gene. The 8-gene panel does not cover *FAM107B-RET* (F1:R8), but covers 10 out of the 11 rare fusion variants listed in Table 1, accounting for 90.9% (10/11). Sequencing was performed on the Illumina NovaSeq 6000 and Gene+ Seq-2000 platforms. Gene fusions were identified using FusionCaller v1.2, STAR-Fusion v1.10, an in-house pipeline markSV v4.2.4, and NCSV2 v1.2.0 software. A threshold of ≥4 supporting split reads was applied for samples sequenced on the Illumina platform, and ≥10 supporting split reads for those on the Gene+ Seq-2000 platform. All final fusions were manually reviewed for breakpoint accuracy and sequencing background noise. Limit of detection in our panels was 2% and the sensitivity was >98%.

Sequence data were mapped to the reference human genome (hg19) using Burrows-Wheeler Aligner version 0.7.10. Local alignment optimization, duplication marking and variant calling were performed using Genome Analysis Tool Kit version 3.2, and VarScan version 2.4.3. Tissue and plasma samples were compared against their own white blood cell control to identify somatic variants. Variants were filtered using the VarScan fpfilter pipeline, loci with depth less than 100 were filtered out. Analysis of gene fusion was performed using Factera version 1.4.3.

Statistical Analysis

Patient clinical characteristics were described using percentages. Clinical characteristics between different groups, including sex, age, smoking history, histology, and metastatic status, were compared using the χ^2-test or Fisher's exact test. The strength of association was quantified using odds ratios (OR) and 95% confidence intervals (CI). Statistical significance was defined as a two-sided P value < 0.05, and Benjamini–Hochberg false discovery rate (FDR) correction was applied for multiple comparisons.

Table 1 The *RET* Fusion Partners Discovered in Lung Cancer Patients in This Study

Fusion Partner	Fusion Site	Breakpoint	Sample	Supporting Read Counts	RET Kinase Domain Retention	Presumed Promoter (P)/ Dimerization Domain (D) from Partner	Partner Reported
RET-ARHGAP12	R11:A12	10:32114092_10:43610272	S014	136	No	P: yes. D: no.	[12]
			S025	145			
C16orf95-RET	C5'UTR:R12	16:87200765_10:43611539	S006	144	Yes	P: yes. D: no.	No
CARNMT1-AS1-RET	C5'UTR:R12	9:77587812_10:43611145	S018	69	Yes	P: yes. D: no.	No
CNTNAP2-RET	C1:R11	7:146008168_10:43609096	S016	170	Yes	P: yes. D: no.	[13]
CXCL12-RET	Cintergenic:R12	10:44966425_10:43611954	S004	22	Yes	P: uncertain. D: yes (CXC).	[14]
FAM107B-RET	F1:R8	10:14812710_10:43606824	S055	77	Yes	P: yes. D: no.	No
FRMD4A-RET	F3:R12	10:13844773_10:43610210	S065	116	Yes	P: yes. D: no.	[15]
MTUS1-RET	M13:R12	8:17506166_10:43610668	S101	107	Yes	P: yes. D: yes (coiled coil).	No
MYRFL-RET	M22:R12	12:70350003_10:43610214	S046	210	Yes	P: yes. D: yes (coiled coil).	No
NPAS3-RET	N6:R12	14:34141927_10:43611964	S082	40	Yes	P: yes. D: yes (bHLH).	[16]
ZNF487-RET	Zintergenic:R12	10:43923008_10:43611853	*S002*	96	Yes	P: uncertain. D: no.	[16]

Notes: This table details the molecular features of 11 rare and novel RET fusion events identified in this cohort, including fusions with *ARHGAP12, C16orf95, CARNMT1-AS1, CNTNAP2, CXCL12, FAM107B, FRMD4A, MTUS1, MYRFL, NPAS3*, and *ZNF487*. For each fusion, the table lists the fusion junction site, exact genomic breakpoint coordinates, number of supporting sequencing reads, retention of the RET kinase domain, and the functional domain contributed by the 5′ partner (promoter [P] or dimerization domain [D]). The partner reported column specifies whether the fusion has been previously documented.

Results

Patients' Characteristics

This study included a total of 102 lung cancer patients with *RET* fusion. There were more female patients, accounting for 54.90% (56/102); 53.92% (55/102) of the patients were under the age of 60, with a median age of 60.5 years (ranging from 19 to 79 years); 27.45% (28/102) of the patients had a smoking history; the majority were in the advanced stage, accounting for 68.63% (70/102); surgical patients accounted for 24.51% (25/102); and distant metastasis was observed in 69.61% (71/102) of patients. The patients with the lowest physical condition score (Performance Status, PS score) were the most, accounting for 90.20% (92/102); the most common histological type was adenocarcinoma, accounting for 98.04% (100/102), and other histological types included 2 patients with sarcomatoid carcinoma.(Table 2).

Table 2 Clinical Characteristics of *RET* Fusion-Positive NSCLC Patients

Clinical Characteristic (N=102)	Proportion (%)
Sex	
Male	46(45.10%)
Female	56(54.90%)
Age	
≥60	47(46.08%)
<60	55(53.92%)
Smoking History	
Never	74(72.55%)
Current or Former	28(27.45%)
Clinical Stages	
I-IIIA	32 (31.37%)
IIIB-IV	70 (68.63%)
PS score	
0 or 1	92(90.20%)
>1	10(9.80%)

(*Continued*)

Table 2 (Continued).

Clinical Characteristic (N=102)	Proportion (%)
Pathological Type	
Adenocarcinoma	100(98.04%)
Non Adenocarcinoma	2(1.96%)
Metastasis	
Yes	71(69.61%)
No	31(30.39%)
Surgery	
Yes	25(24.51%)
No	77(75.49%)

Notes: This table summarizes the frequency and classification of all *RET* fusion partners detected in the cohort. *KIF5B* (38.06%) and *CCDC6* (17.16%) were the most common partners. Intergenic fusions accounted for 20.15% of events. Five previously unreported novel partners (*MTUS1*, *C16orf95*, *CARNMT1-AS1*, *MYRFL*, *FAM107B*) were identified, each at 0.75% prevalence. All other partners were classified as rare.

Metastatic sites were defined based on radiologic and pathological data documented in the patient records from the case system. Among the *RET* fusion-positive patients, 71 developed metastasis. As shown in Figure 1, lymph nodes were the most frequent metastatic site (n=53, 74.65%), followed by the pleura (n=33, 46.48%), bone (n=30, 42.25%), lung (n=28, 39.44%), brain (n=15, 21.13%), liver (n=9, 12.68%), and kidney (n=5, 7.04%).

Molecular Characteristic

To investigate *RET* fusion patterns, we performed ultra-deep targeted sequencing with six panels covering exons/introns of different genes. Among 102 *RET* fusion-positive patients (1.6% fusion rate, 102/6204), a total of 134 *RET* fusion events were detected (Supplementary Table 1), 31 patients with multiple fusion events detected in a single sample (Supplementary Table 2). The predominant fusion partners were *KIF5B* (50.00%, 51/102) and *CCDC6* (22.55%, 23/102). Other partners included *NCOA4* and additional genes (Figure 2). Most *RET* breakpoints were in exon 12; others were

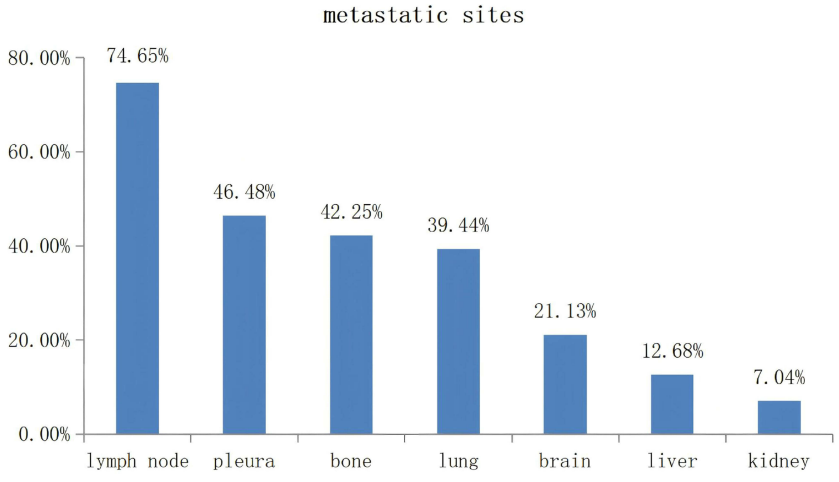

Figure 1 Distribution of metastatic sites in RET fusion-positive NSCLC patients. This bar chart depicts the prevalence of distant metastatic sites in the cohort of *RET* fusion-positive NSCLC patients. Among 71 patients with confirmed distant metastasis, lymph node involvement was the most common (n=53, 74.6%), followed by pleural (n=33, 46.5%), bone (n=30, 42.3%), lung (n=28, 40.5%), brain (n=15, 21.2%), liver (n=9, 12.7%), and kidney (n=5, 7.0%) metastases.

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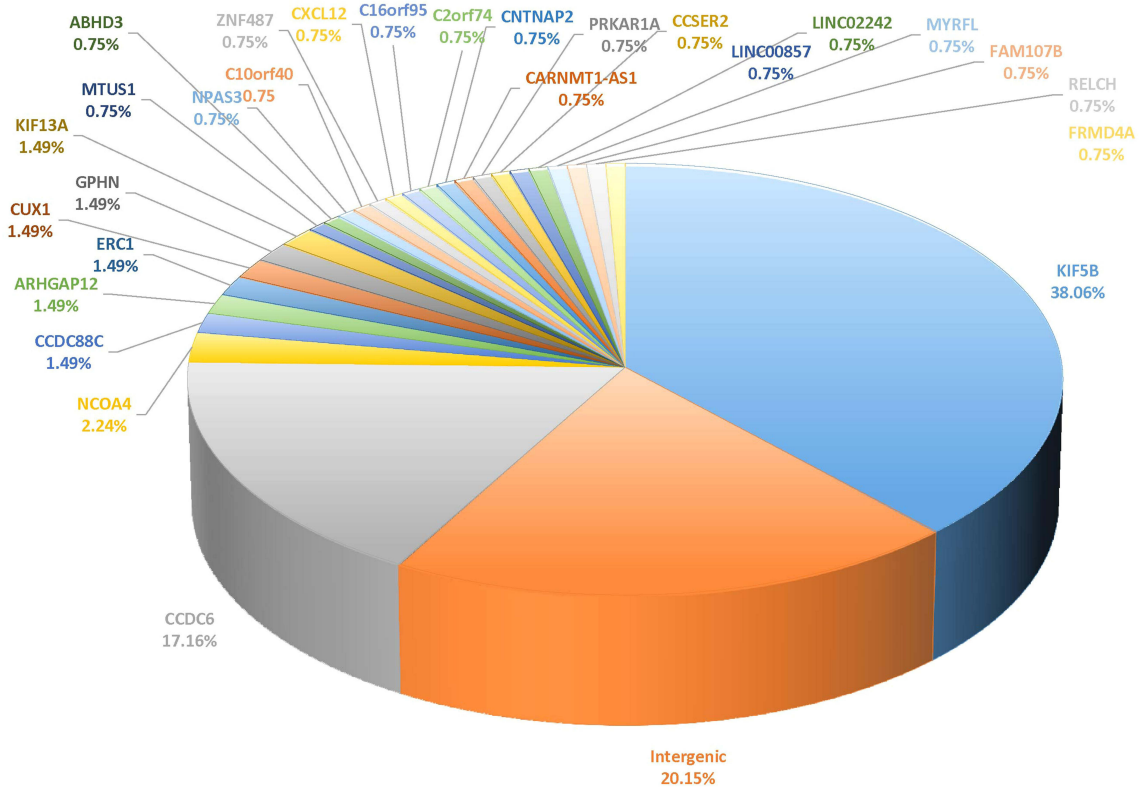

Figure 2 Distribution of RET fusion partners in RET fusion-positive NSCLC patients. The pie chart shows the proportional distribution of *RET* fusion partners identified in this study. *KIF5B* (38.06%) and *CCDC6* (17.16%) were the most prevalent common fusion partners. Intergenic fusions constituted 20.15% of all detected events. A total of 24 rare and novel fusion partners were identified, with each rare/novel partner accounting for 0.75% to 1.49% of the cohort, including 5 previously unreported novel partners: *C16orf95, CARNMT1-AS1, FAM107B, MTUS1*, and *MYRFL*. Percentages were calculated based on the total number of *RET* fusion events (n=134) as multiple fusion events were detected in a single sample.

exons 8, 9, 11, 13, 19. *KIF5B*'s main breakpoint was exon 15 (84.31%, 43/51), *CCDC6*'s exon 1 (91.30%, 21/23). Novel partners including *C16orf95, CARNMT1-AS1, FAM107B,MYRFL* and *MTUS1* were identified (Table 1).

The RET Fusion Positivity in NSCLC is Often Associated with Age and PS Score

According to the description in the RETING study regarding the common fusion partners of *RET* fusion in NSCLC, they are *KIF5B* and *CCDC6*. We define *KIF5B* and *CCDC6* as the common fusion partners. The other fusion breakpoints are considered as rare partners. We compared the occurrence of common fusion partners with that of rare fusion partners and investigated their association with those clinical factors. Through statistical analysis, it was found that the occurrence of *KIF5B* and *CCDC6* was related to age (P = 0.023) and PS score (P = 0.040), but not related to gender, smoking history, clinical stage, metastasis history, and tissue subtype in Table 3. We compared the association between the two common fusion partners *KIF5B* and *CCDC6* and those clinical factors, and found that their occurrence was related to smoking history (P = 0.037), but not related to gender, age, PS score, clinical stage, metastasis history, and tissue subtype (Table 4).

Accompanied by Genetic Mutation Characteristics

Among the 102 patients with *RET* fusion detected, 54 patients had other mutation forms coexisting with *RET* mutations (54/102, 52.94%). Among them, *TP53* was the most common change (15/102, 14.71%), followed by *EGFR* (11/102, 10.78%), *CDKN2A* (7/102, 6.86%), *KRAS* (5/102, 4.90%), and *SETD2* (3/102, 2.94%). Other genomic alterations were also present, including *MYC, CDK4, MET, FGFR3, and PIK3CA*, etc. Among the 93 patients with *RET* fusion, 19 (18.63%, 19/102) harbored concurrent driver gene alterations, including *EGFR L858R* (n=3), *EGFR* exon 19 deletion (n=2), *KRAS G12X* (n=2), and *EML4-ALK* (n=1), among others (Figure 3).

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Table 3 The Common and Rare Fusion Partners Characteristics of RET Fusion-Positive NSCLC Patients

Clinical Characteristic	Common Fusion Partners (%)	Rare Fusion Partners (%)	χ^2	OR	95% CI	p Value	q Value
Sex							
Male	32(69.60)	14(30.40)	0.38	0.76	0.32–1.82	0.54	0.63
Female	42(75.00)	14(25.00)					
Age							
≥60	29(61.70)	18(38.30)	5.15	0.36	0.15–0.88	0.02	0.14
<60	45(81.80)	10(18.20)					
Smoking History							
Never	51(68.90)	23(31.10)	1.78	0.48	0.16–1.43	0.18	0.26
Current or Former	23(82.10)	5(17.90)					
Clinical Stages							
I-IIIA	27(84.40)	5(15.60)	3.27	2.64	0.90–7.76	0.07	0.16
IIIB-IV	47(67.10)	23(32.90)					
PS score							
0 or 1	70(76.10)	22(23.90)	4.23	4.77	1.23–18.46	0.04	0.14
>1	4(40.00)	6(60.00)					
Metastasis							
Yes	48(67.60)	23(32.40)	2.87	0.40	0.14–1.18	0.09	0.16
No	26(83.90)	5(16.10)					
Pathological Type							
Adenocarcinoma	72(72.00)	28(28.00)	0.77	0.51	0.02–10.95	1.00	1.00
Non Adenocarcinoma	2(100.00)	0(0)					

Notes: This table compares the baseline clinical and demographic features of patients with common *RET* fusion partners (defined as *KIF5B* and *CCDC6*) versus rare fusion partners (all other non-canonical partners). For each variable, the table presents the proportion of patients in each fusion subgroup, along with χ^2 values, odds ratios (OR) with 95% confidence intervals (CI), unadjusted P values, and q values adjusted for multiple comparisons using the Benjamini–Hochberg false discovery rate method. Significant associations were observed between fusion partner type and patient age (P=0.023) as well as PS score (P=0.040), with common fusions more prevalent in patients younger than 60 years and those with a PS score of 0–1.

Table 4 *KIF5B-RET* (N=51) and *CCDC6-RET* (N=23) of Clinical Characteristic

Clinical Characteristic	*KIF5B-RET*(%)	*CCDC6-RET*(%)	χ^2	OR	95% CI	p Value	q Value
Sex							
Male	21(65.63)	11(34.37)	0.29	0.76	0.28–2.06	0.59	0.83
Female	30(71.43)	12(28.57)					
Age							
≥60	23(79.31)	6(20.70)	2.40	2.33	0.79–6.87	0.12	0.21
<60	28(62.20)	17(37.80)					
Smoking History							
Current or Former	12(52.20)	11(47.80)	4.37	0.34	0.12–0.95	0.04	0.21
Never	39(76.50)	12(23.50)					
Clinical Stages							
I-IIIA	22(81.50)	5(18.50)	3.13	2.73	0.88–8.50	0.08	0.21
IIIB-IV	29(61.70)	18(38.30)					
PS score							
0 or 1	49(70.00)	21(30.00)	0.08	2.33	0.31–17.69	0.78	0.90
>1	2(50.00)	2(50.00)					
Metastasis							
Yes	30(62.50)	18(37.50)	2.63	0.40	0.13–1.24	0.11	0.21
No	21(80.80)	5(19.20)					
Pathological Type							
Adenocarcinoma	50(69.40)	22(30.60)	0.00	2.27	0.14–38.01	1.00	1.00
Non Adenocarcinoma	1(50.00)	1(50.00)					

Notes: This table compares the baseline clinicopathological features of patients harboring the two most common *RET* fusion partners, *KIF5B-RET* (n=51) and *CCDC6-RET* (n=23). For each variable, the table presents the proportion of patients in each fusion subgroup, along with χ^2 values, odds ratios (OR) with 95% confidence intervals (CI), unadjusted P values, and q values adjusted for multiple comparisons using the Benjamini–Hochberg false discovery rate method. A significant association was observed between fusion partner type and smoking history (P=0.037), with *KIF5B-RET* more prevalent in never-smokers and *CCDC6-RET* more common in current or former smokers.

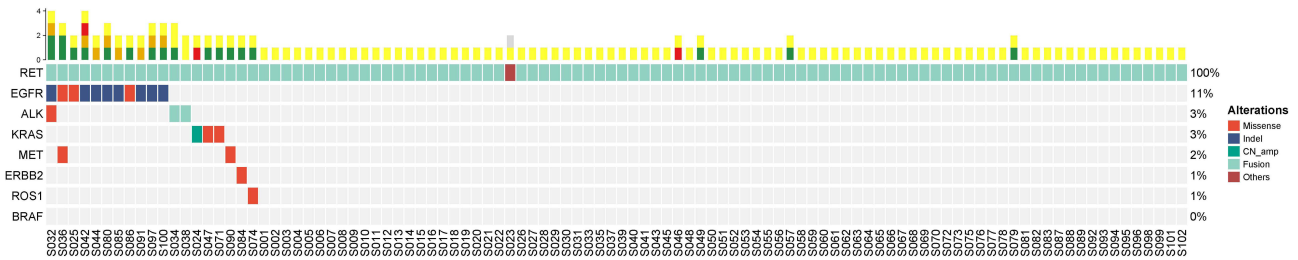

Figure 3 Genomic alteration landscape in *RET* fusion-positive NSCLC patients. The percentages on the right side indicate the overall alteration prevalence in the cohort: *RET* (100%), *EGFR* (11%), *ALK* (3%), *KRAS* (3%), *MET* (2%), *ERBB2* (1%), *ROS1* (1%), and *BRAF* (1%). Different alteration types are color-coded according to the legend, including missense mutations, small insertions/deletions (indel), copy number amplification (CN_amp), gene fusions (Fusion), and other variants (Others). This visualization comprehensively illustrates the co-occurrence patterns of driver genes, such as concurrent *EGFR* mutations, *ALK* rearrangements, and *KRAS* mutations, alongside *RET* fusions in this cohort.

Discussion

In this study, we retrospectively analyzed genetic data from 6,204 lung cancer patients and identified 102 with *RET* fusions, yielding a detection rate of 1.6%, consistent with the reported prevalence of 1%–2% in NSCLC.[17] In terms of the discovery of *RET* fusion partners, at least 35 partner genes have been reported to fuse with *RET*, included *ACBD5, AFAP1L2,AKAP13,BCR, CCDC6,CLIP1,CUX1,EML4,EPHA5,ERC1,FGFR1OP,FKBP15,FRMD4A,GOLGA5,HOOK3, KIAA1217,KIAA1468,KIF5B,KTN1,MYH13,NCOA4,PARD3,PCM1,PICALM,PPFIBP2,PRKAR1A,PRKG1,RFG9, RUFY2,SNRNP70,SPECC1L,SQSTTM1,TBL1XR1,TNIP1,TRIM24, TRIM27, TRIM33*.[18] Another study reported 11 partners, such as *NCOA4, TSSK4, SORBS1, SIRT1, PTPRK, ADD3-AS1, PRKG1, IL2RA, CCNYL2, CCDC186*, and *ANKS1B*.[19] And in our cohort, we identified 28 distinct fusion partner types, especially reported multiple *RET* fusions that were not reported before, mainly including *C16rf95, CARNMT1-AS1, FAM107B, MTUS1* and *MYRFL*.

The distribution of *RET* fusion partners varies considerably across published studies. The most frequently cited proportions of *KIF5B-RET* and *CCDC6-RET* are 83.6% and 15.1%, respectively, based on early comprehensive profiling studies.[18] However, in our cohort *KIF5B-RET* and *CCDC6-RET* accounted for 50.0% and 22.5%, respectively. More recent large-scale studies have reported a wider range of *KIF5B-RET* frequencies. In a Chinese cohort of 380 *RET* fusion-positive patients, Wang et al reported *KIF5B-RET* in 51.1% of cases and *CCDC6-RET* in 23.4%[20]. In the global LIBRETTO-001 trial, *KIF5B-RET* accounted for 61.9% of pretreated and 69.6% of treatment-naïve patients.[21] Similarly, Sun et al reported a *KIF5B-RET* proportion of 65% in a Chinese cohort of 268 patients.[10]

The observed variation in fusion partner proportions across studies likely reflects a combination of selection effects and biological heterogeneity. Regarding selection effects, differences in detection methodologies may contribute to this variation. Studies employing targeted RNA sequencing or comprehensive DNA/RNA panels may capture a broader spectrum of fusion partners, potentially resulting in a relatively lower proportion of *KIF5B-RET* compared with studies using FISH or RT-PCR that focus on known common partners. Additionally, differences in case mix and referral patterns are important considerations. Single-center studies may reflect regional referral biases, whereas multicenter trials such as LIBRETTO-001 enroll patients from diverse geographic and clinical settings, potentially influencing the distribution of fusion subtypes.

Regarding biological heterogeneity, geographic and ethnic differences may also play a role. Notably, the *KIF5B-RET* proportion reported in Asian cohorts[10,20] and this study ranges from 51% to 65%, which is somewhat lower than the 70%–90% range cited in some Western-focused reviews.[22] This raises the possibility of ethnic differences in the prevalence of specific *RET* fusion partners, although larger multi-ethnic comparative studies are needed to confirm this observation. Importantly, regardless of the variation in reported proportions, *KIF5B-RET* and *CCDC6-RET* consistently emerge as the two most common fusion partners across all studies, underscoring their central role in RET-driven NSCLC. Furthermore, previous studies[14] have reported the fusion partners such as *NCOA4, TSSK4, SORBS1, SIRT1, PTPRK, ADD3-AS1, PRKG1, IL2RA, CCNYL2, CCDC186*, and *ANKS1B*. This study discovered multiple *RET* fusions that were not reported before, mainly including, *C16rf95, CARNMT1-AS1, FAM107B, MTUS1* and *MYRFL*.

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Multiple studies have explored the correlation between *RET* fusions and clinical demographics of lung cancer. Most studies have shown that *RET* fusions are more likely to occur in lung adenocarcinoma. In our study, we observed similar results, with 98.0% of *RET* fusion patients having a pathological type of lung adenocarcinoma. However, previous studies had differences in other factors such as gender and age. Michels's report[7] study showed that the proportion of *RET* fusion in the European cohort was higher in males (59% vs 41%). Tsuta K.'s study[6] on Japanese patients indicated that *RET* fusion was not related to gender (p = 0.524). In our cohort, we observed that *RET* fusion tended to occur in female patients who were non-smokers (72.6% vs 26.4%) (54.9% vs 45.1%). Rui Wang.'s study[4] showed that *RET* fusion occurred more frequently in younger populations, with a median age of 60 years. This study showed the same result, with a higher proportion occurring in people younger than 60 years (52.9% vs 47.1%), and a median age of 60.5 years. This may be due to differences in population race, lifestyle, environmental factors, or molecular heterogeneity. Therefore, further studies are needed to explore the potential relationships between *RET* fusion patients and these factors.

Brain metastasis is more common in patients with NSCLC with *RET* fusion positive. Multiple studies from different countries have shown that the frequency of brain metastasis ranges from 25% to 47.5%.[23–25] In this study, the metastatic sites more prone to occur in *RET* fusion positive patients are lymph nodes, pleura, bone, lung, brain, liver, and kidney, in descending order. The frequency of brain metastasis is 21.2%, slightly lower than that reported in various literatures. In the II phase clinical study of LIBRETTO-321,[8] it was shown that the fusion partners of *RET* fusion positive patients that cause brain metastasis include *KIF5B, CCDC6* and *NCOA4*. In this study, in addition to these, one novel types of fusion partners, *MYRFL* was also found to cause brain metastasis.

This study also analyzed the accompanying mutations of *RET* fusion patients, and found that *TP53* is the most common accompanying mutation. At the same time, there are also accompanying mutations of *EGFR* and other driver genes. Whether *RET* fusion is mutually exclusive with other carcinogenic driving factors remains controversial. Recently, Qingsong Gao.[26] analyzed the fusion situations of 33 types of cancers and emphasized the exclusivity between fusion and mutations. However, Wang[27] reported that a unique mutation feature in Chinese NSCLC patients is an increase in *EGFR* mutation rate associated with *RET* and *ALK* gene fusion. In our study, concurrent *EGFR* mutations were identified in 11 *RET* fusion-positive patients. However, due to the retrospective nature of the study and the absence of longitudinal treatment history, we cannot determine whether these co-occurrences represent primary driver events, acquired resistance following *EGFR* TKI therapy, or sequencing artifacts. Co-occurrence of *RET* fusions and *EGFR* mutations has been reported in patients with acquired resistance to *EGFR* TKIs,[28] but the functional significance of such co-occurrences in treatment-naïve patients requires further investigation.

Our study has limitations. Firstly, this study is a retrospective study and was completed in a single center., the data can not fully represent all the region. Larger sample sizes andand multi-center *RET* fusion data need to be collected and included to make our study more persuasive. In addition, since this study is a retrospective analysis based solely on DNA-based NGS testing, orthogonal validation at the RNA or FISH level was not performed and could not be conducted retrospectively. Another limitation is that Secondly, the treatment information of *RET* fusion positive NSCLC patients was not statistically analyzed. Lastly, further investigations into the molecular mechanisms that might explain these novel fusions were not performed. The prospective studies, large sample sizes and functional analysis are required in further study.In the next step, we will continue to improve this part.

Our study discovered 5 novel *RET* fusion aberrations using DNA-based NGS assay based upon the clinicopathologic and genomic features of NSCLC patients in a top tier cancer center located in northeast of China. In addition, we observed that *TP53* was predominant co-mutation in both tissue and blood samples. The findings provide valuable insights into the genetic landscape of NSCLC and more evidence for regional differences or the inclusion of rare partners detected by NGS, which might be useful for clinical precise medicine.

Ethics Statement

Our study complies with the Declaration of Helsinki and approved by the ethics committee of the Jilin Cancer Hospital (No. 202507-001-01).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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