REVIEW ARTICLE

Catalog of 5′ fusion partners in *RET*+ NSCLC Circa 2020

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ABSTRACT

Since the discovery of *RET* fusion–positive (*RET*+) NSCLC around late 2011 to early 2012, clinical trials of multikinase inhibitors and highly potent and selective RET tyrosine kinase inhibitors have indicated that *RET* fusion is an actionable oncogenic driver in NSCLC. There seems to be a differential response to multikinase inhibitors depending on the fusion partner (*KIF5B-RET* versus non–*KIF5B-RET*); thus, knowledge of the fusion partners in *RET*+ NSCLC is important. To date, we identified 48 unique fusion partners in *RET* from published literature and congress proceedings. Two of the novel fusion partners (*CCNYL2* and *TRIM24*) were identified in *RET* fusions that emerged as resistant to EGFR tyrosine kinase inhibitors. In addition, multiple intergenic rearrangements were identified.

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Keywords: 5′ fusion partners; RET; NSCLC; Selpercatinib; Pralsetinib; Whole-transcriptome sequencing

Introduction

RET fusion–positive (*RET*+) NSCLC was discovered in early 2012,[1-4] 5 years after the discovery of *ALK* and *ROS1* fusion–positive NSCLC. There have been prospective studies investigating multikinase inhibitors (MKIs) such as vandetanib, cabozantinib, lenvatinib, sorafenib, and RXDX-105, which revealed modest clinical activity.[5-9] More importantly, differential responses were observed on the basis of the specific fusion partner *KIF5B* verus non-*KIF5B* in *RET*+ NSCLC. The *KIF5B-RET* variant in NSCLC seems to be more resistant to MKIs than the other dominant *CCDC6-RET* fusion variant.[6,9] Two highly potent and selective *RET* tyrosine kinase inhibitors (TKIs), selpercatinib (LIBRETTO-001, NCT03157128) and pralsetinib (ARROW, NCT03037385),[10,11] are undergoing clinical trials for *RET*+ and *RET*-mutated tumors. In addition, *RET* fusion is one of the major receptor tyrosine kinase fusions identified as a resistance mechanism to EGFR TKIs.[12] We undertook this review to catalog the fusion partners identified in literature up to April 2020 for easy reference.

Methods and Results

We searched PubMed publications and conference or congress abstracts and presentations extensively to identify novel *RET* fusion partners (including noncoding RNAs). We also communicated with authors who had presented posters to obtain lists of novel fusion partners. We included only fusion partners that retained the 3′ *RET* kinase domain. Overall, a total of 48 distinct *RET* fusion partners have been identified in literature as of

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Table 1. Catalog of Fusion Partners in *RET*+ NSCLC

No.	Fusion Partner	Year Presented/ Published in Print With Page Numbers	Chromosomal Location	Fusion Breakpoint	Response to RET TKI at the Time of Publication	Tumor Source	Method of Detection	Variant Frequency in Tumor	FISH/IHC	References
1	KIF5B	2012	10p11.22	(K15, R12) (K16, R12) (K23, R12)	Not treated with RET TKI	FFPE	RNA sequencing	NR	NR/NR	Ju et al.[1]
		2012	10p11.22	(K15, R12) (K16, R12) (K23, R12) (K24, R8)	Not treated with RET TKI	FFPE	RT-PCR, Sanger sequencing	NR	NR/+	Kohno et al.[2]
		2012	10p11.22	(K15, R12) (K16, R12) (K23, R12) (K23, R12) (K24, R11)	Not treated with RET TKI	FFPE	RT-PCR, Sanger sequencing	NR	NR/NR	Takeuchi et al.[3]
		2012	10p11.22	(K15, R12)	Not treated with RET TKI	FFPE	NGS	NR	NR/NR	Lipson et al.[4]
		2012	10p11.22	(K15, R12) (K22, R12)	Not treated with RET TKI	FFPE	RT-PCR, Sanger sequencing	NR	NR/NR	Yokota et al.[13]
2	CCDC6	2012	10q21.2	(C1, R12)	Not treated with RET TKI	FFPE	RT-PCR, Sanger sequencing	NR	NR/NR	Takeuchi et al.[3]
			10q21.2	(C1, R12)	Not treated with RET TKI	Cell line	RT-PCR	NR	NR/NR	Matsubara et al.[14]
3	NCOA4	2012	10q11.22	(N6, R12)	Not treated with RET TKI	FFPE	RT-PCR	NR	+/+	Wang et al.[15]
4	TRIM33	2013	1p13.2	(T14, R12)	PR to cabozantinib	FFPE	NGS	NR	+/NR	Drilon et al.[16]
5	RUFY2	2014	10q21.3	(R9, R12)	Not treated with RET TKI	FFPE	Targeted RNA sequencing	NR	+/NR	Zheng et al.[17]
6	CUX1	2014	7q22.1	C10, R12)	Not treated with RET TKI	FFPE	Anchored multiple PCR, NGS	NR	+/NR	Lira et al.[18]
7	KIAA1468/ (RELCH)[a]	2014	18q21.33	(K10, R12)	Not treated with RET TKI	FFPE	RT-PCT	NR	NR/NR	Nakaoku et al.[19]
	KIAA1468/ (RELCH)[a]	2019	18q21.33	NR	Treated with selpercatinib	FFPE or plasma	NGS	NR	NR/NR	Drilon et al.[20]
	RELCH[a]	2020	18q21.33	(R10, R12)	Not treated with RET TKI	FFPE	NGS	NR	+/NR	Jiang et al.[21]
8	MPRIP	2016	17p11.2	(M19, R12)	Not treated with RET TKI	FFPE	Targeted RNA sequencing	NR	NR/NR	Fang et al.[22]
9	CLIP1	2016	12q24.31	NR	PR to cabozantinib	FFPE	NGS	NR	NR/NR	Drilon et al.[5]
10	ERC1	2016	12p13.33	NR	SD to cabozantinib	FFPE	NGS	NR	NR/NR	Drilon et al.[5]
11	KIAA1217	2016	10p12.2-p12.1	(K11, R10)	Not treated with RET TKI	FFPE	NGS	NR	+/NR	Lee et al.[23]
12	MYO5C	2016	15q21.2	(M25, R12)	SD to vandetanib	FFPE	NGS	NR	+/NR	Lee et al.[7]

(continued)

Table 1. Continued

No.	Fusion Partner	Year Presented/ Published in Print With Page Numbers	Chromosomal Location	Fusion Breakpoint	Response to RET TKI at the Time of Publication	Tumor Source	Method of Detection	Variant Frequency in Tumor	FISH/IHC	References
13	EPHA5	2017	4q13.1-q13.2	NR	Response to RET TKI	FFPE	NGS	NR	NR/NR	Gautschi et al.[24]
14	PICALM	2017	11q14.2	NR	NR	FFPE	NGS	NR	NR/NR	Gautschi et al.[24]
15	FRMDA4 (KIAA1294)	2017	10p13	(F12, R12)	Not treated with RET TKI	FFPE	NGS	NR	+/NR	Velcheti et al.[25]
16	RASSF4	2017	10q11.21	(R3, R12)	Not treated with RET TKI	FFPE	NGS	NR	NR/NR	Zehir et al.[26]
17	KIF13A	2018	6p22.3	(K18, R12)	Not treated with RET TKI	FFPE	NGS	NR	NR/NR	Zhang et al.[27]
18	WAC	2018	10p12.1-p11.2	(W3, R12)	Not treated with RET TKI	FFPE	NGS	NR	NR/NR	Velcheti et al.[28]
19	TBC1D32 (C6orf170)	2019	6q22.31	(T9, R12)	Not treated with RET TKI	FFPE	NGS	NR	NR/NR	Peng et al.[29]
20	EML4	2019	2p21	NR	PR to RXDX-105	FFPE	NGS	NR	NR/NR	Drilon et al.[9]
21	PARD3	2019	10p11.22-p11.21	NR	PR to RXDX-105	FFPE	NGS	NR	NR/NR	Drilon et al.[9]
22	ARHGAP12	2019	10p11.22	NR	Treated with selpercatinib	FFPE or plasma	NGS	NR	NR/NR	Drilon et al.[20]
		2019	10p11.22	NR	NR	FFPE	NGS	NR	NR/NR	Liu et al.[30]
23	CCDC88C	2019	14q32.11-q32.12	NR	Treated with selpercatinib	FFPE or plasma	NGS	NR	NR/NR	Drilon et al.[20]
24	DOCK1[b]	2019	10q26.2	NR	Treated with selpercatinib	FFPE or plasma	NGS	NR	NR/NR	Drilon et al.[20]
25	RBPMS[b]	2019	8p12	NR	Treated with selpercatinib	FFPE or plasma	NGS	NR	NR/NR	Drilon et al.[20]
26	PRKAR1A	2019	17q24.2	NR	Treated with selpercatinib	FFPE or plasma	NGS	NR	NR/NR	Drilon et al.[20]
27	ADD3	2019	10q25.1-q25.2	(A1, R12)	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
28	ANKS1B	2019	12q23.1	(A1, R12)	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
29	CCDC186	2019	10q25.3	(C10, R12)	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
30	CCNYL2[c]	2019	10q11.21	(C6, R16)	SD to combination of cabozantinib and osimertinib	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
31	PCM1	2019	8p22	(P29, R12)	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
32	PRKG1	2019	10q11.23-21.1	(P7, R12)	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]

(continued)

Table 1. Continued

No.	Fusion Partner	Year Presented/ Published in Print With Page Numbers	Chromosomal Location	Fusion Breakpoint	Response to RET TKI at the Time of Publication	Tumor Source	Method of Detection	Variant Frequency in Tumor	FISH/IHC	References
33	PTPRK	2019	6q22.33	(P3, R12)	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
34	SIRT1	2019	10q21.3	(S8, R12)	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
35	SORBS1	2019	10q24.1	(S8, R12)	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
36	TSSK4	2019	14q1	(T1, R12)	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
37	TRIM24	2019	7q33-q34	NR	Treated with selpercatinib	FFPE or plasma	NGS	NR	NR/NR	Drilon et al.[20]
	TRIM24[d]	2019	7q33-q34	NR	NR	Plasma	NGS	NR	NR/NR	Rich et al.[32]
38	CCDC3	2019	10p13	NR	NR	FFPE	NGS	NR	NR/NR	Liu et al.[30]
39	CTNNA3	2019	10q21.3	NR	NR	FFPE	NGS	NR	NR/NR	Liu et al.[30]
40	DYDC1	2019	10q23.1	NR	NR	FFPE	NGS	NR	NR/NR	Liu et al.[30]
41	EML6	2019	2p16.1	NR	NR	FFPE	NGS	NR	NR/NR	Liu et al.[30]
42	PRKCQ	2019	10p15.1	NR	NR	FFPE	NGS	NR	NR/NR	Liu et al.[30]
43	PRPF18	2019	10p13	NR	NR	FFPE	NGS	NR	NR/NR	Liu et al.[30]
44	LSM14A	2020	19q13.11	(L9, R20)	NR	FFPE	NGS	NR	+/NR	Lv et al.[33]
45	GPRC5B[e]	2020	16p12.3	NR	NR	FFPE or plasma	NGS	NR	NR/NR	Lu et al.[34]
46	GPR139[e]	2020	16p12.3	NR	NR	FFPE or plasma	NGS	NR	NR/NR	Lu et al.[34]
47	ANK3	2020	10q21.2	NR	NR	FFPE or plasma	NGS	NR	NR/NR	Lu et al.[34]
48	EPC1[f]	2020	10p11.22	NR	NR	FFPE or plasma	NGS	NR	NR/NR	Lu et al.[34]

[a]KIAA1468 is the same as RELCH.
[b]DOCK1-RET and RBPMS-RET occurred in the same tumor.
[c]CCNYL2-RET as resistance to osimertinib (EGFR L858R).
[d]TRIM24-RET as resistance to EGFR del 19.
[e]GPRC5B and GPR139 were detected as dual fusions in one case.
[f]EPC1 was detected as dual fusions in one case with the other fusion partner being KIF5B.
FFPE: formalin-fixed paraffin-embedded; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; NR: not reported; PR: partial response; RT-PCR, reverse transcriptase polymerase chain reaction; SD: stable disease; TKI, tyrosine kinase inhibitor.

Table 2. List of Chromosomal Locations of Intergenic Translocations With Potential Fusion Partners

No.	Year Presented/ Published in Print	Chromosomal Location	Potential Fusion Partner Gene	RET Exon Fusion	Response to RET TKI at the Time of Publication	Tumor Source	Method of Detection	Variant Frequency in Tumor	FISH/IHC	References
1	2019	10p14-p13	CDC123[a]	R12	Treated with capmatinib, unknown response	FFPE	NGS	NR	NR/NR	Xu et al.[35]
2	2019	10q11.21	ALOX5	R11	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
3	2019	10q21.2	ANK3	R11	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
4	2019	10q25.2	DUSP5	R12	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
5	2019	10p13	FAM188A (MINDY3)	R12	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
6	2019	10p15.1	IL2RA	R12	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
7	2019	10q23.31	LOC101926942 (LINC02653)	R12	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
8	2019	10p12.1	LOC105376468	R12	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
9	2019	10q11.21	LOC105378269	R12	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
10	2019	5p12	MRPS30	R12	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
11	2019	10p11.22	NRP1	R12	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
12	2019	16q23.2	PRCAT47 (ARLNC1)	R11	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
13	2019	10p13	PTER	R12	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
14	2019	10q21.1	UBE2D1	R12	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
15	2019	19p12	ZNF43	R12	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]
16	2019	10p11.23	ZNF438	R11	NR	FFPE or plasma	NGS	NR	NR/NR	Zhang et al.[31]

[a]RET fusion as potential resistance to osimertinib for EGFR (del 19, T790M, C797G/S)

FFPE: formalin-fixed paraffin-embedded; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; NR, not reported; TKI, tyrosine kinase inhibitor.

April 2020 (Table 1).[1–5,7,9,13-34] The *RET* gene is located on chromosomal 10q11.21. A total of 11 fusion partners are located on the long arm of chromosome 10 (10q), and three of the fusion partners are located around 10q11. Given the discovery of *RET*+ NSCLC occurred about 5 years after that of *ALK*+ and *ROS1*+ NSCLC, many of these novel *RET* fusion variants have not been treated with either MKIs or highly selective RET TKIs. Multiple intergenic rearrangements, mostly to exon 12 of *RET*, have also been identified and listed separately in Table 2.[31,35] To date, none of these intergenic *RET* rearrangements have been reported to respond to RET TKIs; thus, the significance of these intergenic rearrangements remains to be determined, including whether functional fusion RNAs can be transcribed from these intergenic rearrangements.

Discussion

The number of *RET* fusion partners identified in *RET*+ NSCLC as of April 2020 is about 48, which is fewer than the number of *ALK* fusion partners identified.[36] Again, we expect that more fusion partners in *RET*+ NSCLC will be identified with the continual use of next-generation sequencing (NGS), including whole-transcriptome sequencing as the diagnostic platform migrates to exhaustively identify all the actionable driver mutations in NSCLC, particularly *RET* fusions, given the impending approval of selpercatinib and pralsetinib. Furthermore, not all the fusion partners identified in other tumor types such as thyroid cancer have been identified in *RET*+ NSCLC.[26,37] Currently, only the KIF5B fusion partner in *KIF5B-RET* has been reported to confer poor response to MKIs,[6,9] because the kinesin domain of KIF5B interacts with the kinase domain of RET to create a signaling hub rendering resistance to RET inhibition alone.[38] With this catalog of 5′ fusion partners in *RET*+ NSCLC, we hope to increase awareness of the various fusion partners in *RET*+ NSCLC and stimulate further translational research.

Concluding Perspectives

1. *RET*+ NSCLC is a heterogeneous disease with at least 48 distinct fusion partners identified in the literature as of April 2020.
2. With the anticipated approval of selpercatinib and pralsetinib for *RET*+ NSCLC, many more fusion partners and intergenic rearrangements will likely be identified with the ever-increasing adoption of targeted RNA sequencing and whole-transcriptome sequencing because of the need to identify rare actionable fusions such as *NTRK* and *NRG1* fusions in general, and also *RET* fusions in particular.
3. *RET* fusions are also common receptor tyrosine kinase fusions identified as acquired resistance to EGFR TKIs. Two novel fusion partners (*CCNYL2* and *TRIM24*) were identified as resistance mechanisms to EGFR TKI in *EGFR*+ NSCLC.
4. The functional significance of intergenic rearrangements remains to be determined. In one study, intergenic rearrangements accounted for 7.7% of the *RET* fusions identified. However, it is yet to be determined whether these intergenic rearrangements are transcribed into functional *RET* RNA fusions.
5. We recommend that clinicians from all over the world continue to report these novel fusions and intergenic rearrangements with information on the following: (1) exon or fusion breakpoints; (2) response to RET TKIs; (3) allele frequency; and (4) whether the tumor is *RET*-positive on fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC), if possible. Although RET TKIs are being developed after ALK and ROS1 TKIs, RET detection by IHC and FISH has not gone through health agency regulations given that NGS is the primary companion diagnostic platform used to detect *RET* fusions; thus, not much is known about the sensitivity and specificity as well as the positive and negative predictive values of these two testing modalities. We do realize that the uptake and utility of IHC and FISH for RET detection may be limited when NGS is likely the first approved companion diagnostic platform for *RET* fusions and increasing uptake to identify even rarer actionable driver alterations such as *NRG* fusions.

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