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Authors

Ou, Sai-Hong

Zhu, Viola

Nagasaka, Misako

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REVIEW ARTICLE

Catalog of 5' Fusion Partners in *ALK*-positive NSCLC Circa 2020

Sai-Hong Ignatius Ou, MD, PhD,[a,*] Viola W. Zhu, MD, PhD,[a] Misako Nagasaka, MD[b,c]

[a]*Department of Medicine, Division of Hematology-Oncology, Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, Orange, California*
[b]*Department of Oncology, Karmanos Cancer Institute/Wayne State University School of Medicine, Detroit, Michigan*
[c]*Department of Advanced Medical Innovations, St. Marianna University Graduate School of Medicine, Kawasaki, Kanagawa, Japan*

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ABSTRACT

Since the discovery of anaplastic lymphoma kinase fusion-positive (*ALK*+) NSCLC in 2007, the methods to detect *ALK*+ NSCLC have evolved and expanded from fluorescence in situ hybridization and immunohistochemistry to next-generation DNA sequencing, targeted RNA sequencing, and whole transcriptome sequencing. As such, the deep sequencing methods have resulted in the expansion of distinct fusion partners identified in *ALK*+ NSCLC to 90 (one variant *PLEKHM2-ALK* is found in small cell lung cancer but included in this catalog) by the end of January 2020; about 65 of them (since 2018) and most of the recent novel fusion partners were reported from China. Thirty-four of the distinct fusion partners are located on the short arm of chromosome 2; 28 of these 34 fusion partners are located on 2p21-25, in which *ALK* is located on 2p23.2-p23.1. Many of these new *ALK*+ NSCLC fusion variants have responded to ALK tyrosine kinase inhibitors (TKIs). Several of these novel *ALK* fusion variants were identified as being resistant to EGFR TKIs or as dual 3'ALK fusions. In addition, at least 28 intergenic *ALK* rearrangements have also been reported, with three of them reported as responding to crizotinib. This review aims to serve as a central source of reference of fusion partners in *ALK*+ NSCLC for clinicians and scientists. We aim to update and improve the list going forward.

Keywords: *ALK* fusion partners; Next-generation sequencing; *ALK*+ NSCLC; Whole transcriptome sequencing

Introduction

Since the discovery of anaplastic lymphoma kinase fusion-positive (*ALK*+) NSCLC (*EML4-ALK, TPF-ALK*) in 2007,[1,2] there has been a rapid development of ALK tyrosine kinase inhibitors (TKIs) to treat *ALK*+ NSCLC with five ALK TKIs approved in the United States (crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib) by 2018. At the same time, the detection of *ALK*+ NSCLC has expanded and shifted from the original methods of fluorescence in situ hybridization and immunochemistry (IHC) to next-generation sequencing (NGS), targeted RNA seqencing, and even whole transcriptome sequencing being offered by commercial sequencing companies. Targeted RNA sequencing and whole transcriptome sequencing have been used to supplement

*Corresponding author.

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Address for correspondence: Sai-Hong Ignatius Ou, MD, PhD, Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, 200 South Manchester Avenue, Suite 407, Orange, CA 92868-3298. E-mail: siou@uci.edu

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

No.	Fusion Partner	Year Published in Print/Presented	Chromosomal Location	Fusion Breakpoint	Response to ALK TKI at the Time of Publication	Tumor Source	Method of Detection	Variant Frequency in Tumor	FISH/ IHC	References[a]
1	*EML4*	2007	2p21	(E13, A21) (E20, A21)	Not treated with ALK TKI	Tumor	PCR/Sanger sequencing	NR	ND/ND	Soda, 2007[1]
		2007	2p21	(E13, A20)	Not treated with ALK TKI	Cell line/ Tumor	5'RACE PCR DNA sequencing	NR	ND/ND	Rikova, ,2007[2]
2	*TFG*	2007	3q12.2	(T3, A20)	Not treated with ALK TKI	Tumor	5'RACE PCR DNA sequencing	NR	ND/ND	Rikova, 2007[2]
		2007	3q12.2	NR	Not treated with ALK TKI	Tumor	PCR/Sanger sequencing	NR	ND/ND	Soda, 2007[1]
3	*KIF5B*	2009	10p11.22	(K24, A20)	Not treated with ALK TKI	Tumor	RT-PCR	NR	+/+	Takeuchi, 2009[6]
		2011	10p11.22	(K15, A20)	Not treated with ALK TKI	Tumor	RT-PCR	NR	+/+	Won, 2011[7]
		2012	10p11.22	(K17, A20)	Not treated with ALK TKI	Tumor	RT-PCR	NR	+/+	Takeuchi, 2012[8]
4	*KLC1*	2012	14q32.33	(K9, A 20)	Not treated with ALK TKI	Tumor	RT-PCR	NR	+/ND	Togashi, 2012[9]
5	*STRN*	2013	2p22.2	(S3, A20)	NR	Tumor	RT-PCR	NR	+/+	Majewski, 2013[10]
		2017	2p22.2	(S3, A20)	PR to crizotinib	Plasma	DNA NGS	1%	ND/ND	Yang, 2017[11]
		2017	2p22.2	(S3, A20)	PR to alectinib	Tumor	RNA sequencing	NR	+/+	Nakanishi, 2017[12]
	STRN[b]	2019	2p22.2	(S3, A20)	Not treated with ALK TKI	Tumor	DNA NGS	NR	NR/NR	Xu, 2019[13]
6	*HIP1*	2014	7q11.23	(H2, A20)	Not treated with ALK TKI	Tumor	RNA sequencing	NR	ND/ND	Fang, 2014[14]
		2014	7q11.23	(H21, A 20)	PR to crizotinib	Tumor	RT-PCR	NR	+/+	Hong, 2014[15]
		2014	7q11.23	(H30, A20)	PR to crizotinib and alectinib	Tumor	DNA NGS	NR	+/ND	Ou, 2014[16]
7	*TPR*	2014	1q31.1	(T15, A20)	Not treated with ALK TKI	Tumor	PCR	NR	+/+	Choi, 2014[17]
8	*BIRC6*	2015	2p22.3	NR	PR to crizotinib	Tumor	DNA NGS	NR	-/+	Shan 2015[18]
9	*DCTN1*	2015	2p13.1	(D26, A20)	NR	Tumor	DNA NGS	NR	+/ND	Iyevleva, 2015[19]
10	*SQSTM1*	2015	5q35.3	(S5, A20)	NR	Tumor	DNA NGS	NR	+/ND	Iyevleva, 2015[19]
11	*SOCS5*	2015	2p21	NR	NR	Tumor	NGS	NR	-/ND	Drilon, 2015[20]
12	*SEC31A*	2016	4q21.22	(S21, A20)	Adjuvant setting, not treated with ALK TKI	Tumor	NGS	NR	+/+	Kim, 2016[21]
13	*CLTC*	2016	17q23.1	(C31, A20)	Unknown	Tumor	NGS	NR	NR/NR	Ali, 2016[22]
14	*PRKAR1A*	2016	17q24.2	(P5, A20)	PR to crizotinib	Tumor	NGS	NR	+/+	Ali, 2016[22]
15	*PPM1B*	2016	2p21	(P1, A20)	PR to crizotinib	Tumor	NGS	NR	NR/NR	Ali, 2016[22]
16	*EIF2AK3*	2016	2p11.2	(E2, A20)	PR to crizotinib	Tumor	NGS	NR	-/-	Ali, 2016[22]
17	*CRIM1*	2016	2p22.2	NR	NR	Tumor	NGS	NR	NR/NR	Tan, 2016[23]
18	*CEBPZ*	2017	2p22.2	(C2, A20)	Not treated with ALK TKI	Tumor	NGS	25.3%	+/+	Li, 2017[24]
	CEBPZ[b]	2019	2p22.2	NR	Crizotinib, unknown results	Tumor	NGS	NR	NR/NR	Xu, 2019[13]
19	*PICALM*	2017	11q14.2	(P19, A20)	Not treated with ALK TKI	Tumor	NGS	10.2%	-/+	Li, 2017[24]
20	*CLIP1*	2017	12q24.31	(C22, A20)	PR to crizotinib	Tumor	Targeted RNA sequencing	NR	+/+	Vendrelll, 2017[25]

(continued)

Table 1. Continued

No.	Fusion Partner	Year Published in Print/Presented	Chromosomal Location	Fusion Breakpoint	Response to ALK TKI at the Time of Publication	Tumor Source	Method of Detection	Variant Frequency in Tumor	FISH/ IHC	References[a]
21	*BCL11A*	2017	2p16.1	(B4, A20)	PR to crizotinib	Tumor	DNA and RNA NGS	NR	ND/ND	Tian, 2017[26]
	BCL11A[c]	2019	2p16.1	(B2, A18)	PR to crizotinib	Tumor and plasma	DNA NGS	54.2% (PPFE) 14.9% (plasma)	ND/ND	Qin 2019[27]
22	*GCC2*	2017	2q12.3	(G12, A20)	NR	Tumor	RT-PCR, NGS	NR	+/+	Noh, 2017[28]
		2017	2q12.3	(G19, A20)	Adjuvant setting, not treated with ALK TKI	Tumor	Targeted RNA sequencing	NR	+/+	Vendrelll, 2017[25]
		2018	2q12.3	(G18, A20)	PR to crizotinib and then ceritinib	Tumor	RT-PCR, sanger sequencing	NR	NR/NR	Jiang, 2018[29]
23	*LMO7*	2017	13q22.2	(L15, A20)	NR	Tumor	RT-PCR, NGS	NR	+/+	Noh, 2017[28]
24	*PHACTR1*	2017	6p24.1	(P7, A20)	NR	Tumor	RT-PCR, NGS	NR	+/+	Noh, 2017[28]
25	*CMTR1*	2018	6p21.2	(C2, A20)	No with crizotinib, SD with pemetrexed	Tumor	NGS	~7.5%	-/-	Du, 2018[30]
26	*VIT*	2018	2p22.2	(V7, A20)	PR to alectinib	Tumor	NGS	NR	+/+	Hu, 2018[31]
27	*DYSF*	2018	2p13.2	NR	Extracranial PR but intracranial progression to crizotinib	Pleural effusion	DNA NGS	23.7%	ND/+	Yin 2018[32]
28	*ITGAV*	2018	2q32.1	NR	Extracranial PR but intracranial progression to crizotinib	Pleural effusion	DNA NGS	15.2%	ND/+	Yin, 2018[32]
29	*PLEKHA7*[b]	2018	11p15.2-p15.1	(P26, A19)	PR to alectinib + osimertinib	Plasma	DNA NGS	NR	ND/ND	Schrock, 2018[33]
30	*CUX1*	2018	7q22.1	(C8, A20)	PR to crizotinib	Tumor	NGS	11%	NR/NR	Zhang 2018[34]
31	*VKORC1L1*	2018	7q11.21	(V1, A20)	PR with crizotinib and alectinib	Plasma	NGS	NR	+/ND	Zhu, 2018[35]
32	*FBXO36*	2018	2q36.3	NR	PR to crizotinib	Tumor	NGS	NR	ND/+	Xu, 2018[36]
33	*SPTBN1*[c]	2018	2p16.2	NR	NR	Plasma	NGS	NR	NR/NR	Ramalingam, 2018[37]
34	*EML6*[d]	2018	2p16.1	(E1, A20)	PR to crizotinib	Tumor	NGS	NR	ND/+	Lin, 2018[38]
35	*FBXO11*[d]	2018	2p16.3	(F1, A20)	PR to crizotinib	Tumor	NGS	NR	ND/+	Lin, 2018[38]
36	*CLIP4*	2018	2p23.2	(C7, A20)	NR	Tumor	NGS	NR	ND/+	Zhao, 2018[39]
37	*CAMKMT*	2019	2p21	(C3, A 20)	Not treated with ALK TKI	Tumor	NGS	NR	+/+	Hu, 2019[40]
38	*NCOA1*	2019	2p23.3	(N12, A20)	PR to crizotinib, PFS > 18 months	Tumor	NGS	NR	ND/+	Cao, 2019[41]
39	*MYT1L*	2019	2p25.3	(M14, A20)	PR on crizotinib, PD on ceritinib and alectinib	Tumor	NGS	NR	-/ND	Tsou, 2019[42]
40	*SRBD1*	2019	2p21	(S20, A20)	Not treated with ALK TKI	Tumor	NGS	2.6%	ND/+	Hou, 2019[43]
41	*SRD5A2*	2019	2p23.1	(S1, A20)	NR	Tumor	NGS	NR	ND/+	Zhao, 2019[44]

(continued)

Table 1. Continued

No.	Fusion Partner	Year Published in Print/Presented	Chromosomal Location	Fusion Breakpoint	Response to ALK TKI at the Time of Publication	Tumor Source	Method of Detection	Variant Frequency in Tumor	FISH/ IHC	References[a]
42	*NYAP2 (KIAA 1486)*	2019	2q36.3	(N3, A20)	NR	Tumor	NGS	NR	ND/-	Zhao, 2019[44]
43	*MPRIP*	2019	17p11.2	(M21, A20)	PR to crizotinib	Tumor	RNA sequencing	NR	+/+	Fan, 2019[45]
44	*ADAM17*	2019	2p25.1	(A4, A20)	PR to alectinib	Plasma	DNA NGS	3.68%	NR/NR	Supplee, 2019[46]
45	*ALK*	2019	2p23.2-p23.1	(A6, A20)	NR	Plasma	DNA NGS	26.63%	NR/NR	Supplee, 2019[46]
46	*LPIN1*[b]	2019	2p25.1	NR	Response to crizotinib + erlotinib	Tumor	NR	NR	NR/NR	Supplee 2019[46]
47	*WDPCP*	2019	2p15	(W17, A20)	PR to crizotinib	Tumor	DNA NGS	52.6%	+/+	He, 2019[47]
48	*CEP55*	2019	10q23.33	(C3, A20)	NR	Tumor	DNA NGS	NR	NR/NR	Couëtoux du Tertr, 2019[48]
49	*ERC1*[e]	2019	12p13.33	(E15, A20)	NR	Tumor	DNA NGS	NR	NR/NR	Couëtoux du Tertr, 2019[48]
		2019	12p13.33	NR	NR	Tumor/ plasma	DNA NGS	NR	NR/NR	Zhou, 2019[49]
50	*SLC16A7*[e]	2019	12q14.1	(S1, A 20)	PR to crizotinib prolonged PFS	Tumor	DNA NGS	NR	NR/NR	Couëtoux du Tertr, 2019[48]
51	*TNIP2*	2019	4p16.3	(T5, A20)	PR to crizotinib	Tumor/ plasma	DNA NGS	0.1% (plasma) 3.3% (tumor)	ND/+	Feng, 2019[50]
52	*ATAD2B*	2019	2p24.1-p23.3	(A1, A20)	Treated with crizotinib	Tumor	DNA NGS	NR	ND/+	Bai, 2019[51]
53	*SLMAP*	2019	3p14.3	(S12, A20) (S13, A20)	Unknown, adjuvant treatment with crizotinib	Tumor	Anchored Multiplex RNA sequencing	NR	+/+	Paga, 2019[52]
54	*FBN1*	2019	15q21.1	NR	NR	Tumor/ plasma	DNA NGS	NR	NR/NR	Zhou, 2019[49]
55	*SWAP70*	2019	11p15.4	NR	NR	Tumor/ plasma	DNA NGS	NR	NR/NR	Zhou, 2019[49]
56	*TCF12*	2019	15q21.3	NR	NR	Tumor/ plasma	DNA NGS	NR	NR/NR	Zhou, 2019[49]
57	*TRIM66*	2019	11p15.4	NR	NR	Tumor/ plasma	DNA NGS	NR	NR/NR	Zhou, 2019[49]
58	*WNK3*	2019	Xp11.22	NR	NR	Tumor/ plasma	DNA NGS	NR	NR/NR	Zhou, 2019[49]
59	*AKAP8L*	2019	19p13.12	NR	ensartinib	plasma	DNA NGS	NR	NR/NR	Horn,2019[53]
60	*SPECC1L*	2019	22q11.23	(S9, A20)	Not treated with ALK TKI	Tumor	DNA NGS	NR	NR/NR	Pan, 2019[54]
61	*PRKCB*[f]	2019	16p12.2-p12.1	(P2, A19)	PR to crizotinib, disappearance of PRKCB-ALK fusion variant	Tumor and plasma	NGS	2.6% (tumor) 0.8% (plasma)	NR/NR	Luo, 2019[55]

(continued)

Table 1. Continued

No.	Fusion Partner	Year Published in Print/Presented	Chromosomal Location	Fusion Breakpoint	Response to ALK TKI at the Time of Publication	Tumor Source	Method of Detection	Variant Frequency in Tumor	FISH/ IHC	References[a]
62	*CDK15*[f]	2019	2q33.1	(C10, A19)	NR	Tumor	DNA NGS	NR	NR/NR	Wen, 2019[56]
63	*LCLAT1*	2019	2p23.1	NR	NR	Tumor	DNA NGS	NR	NR/NR	Wen, 2019[56]
64	*YAP1*	2019	11q22.1	NR	NR	Tumor	DNANGS	NR	NR/NR	Wen, 2019[56]
65	*PLEKHM2 (SCLC)*	2020	1p36.21	(P7, A20)	SD to crizotinib and brigatinib	Tumor	NGS	NR	ND/+	Li, 2020[57]
66	*DCHS1*	2020	11p15.4	NR	PR or SD to ensartinib	Tumor	NGS	NR	NR/NR	Yang, 2020[58]
67	*PPFIBP1*	2020	12p11.23-p11.22	NR	PR or SD to ensartinib	Tumor	NGS	NR	NR/NR	Yang, 2020[58]
68	*ATP13A4*	2020	3q29	(A9, A19)	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
69	*C12orf75*	2020	12q23.3	(C1, A20)	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
70	*EPAS1*	2020	2p21	(E1, A20)	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
71	*FAM179A (TOGARAM2)*	2020	2p23.2	(F1, A20)	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
		2020	2p23.2	(F13, A20)	NR	Plasma	NGS	NR	ND/NR	Zhang, 2020[60]
72	*FUT8*	2020	14q23.3	(F3, A20)	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
73	*LIMD1*	2020	3p21.31	(L2, A20)	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
74	*LINC00327*	2020	13q12.12	(L2, A20)	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
75	*LOC349160*	2020	7q33	(L1, A20)	SD to crizotinib	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
76	*LYPD1*	2020	2q21.2	(L3, A20)	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
77	*RBM20*	2020	10q25.2	(R1, A20)	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
78	*TACR1*	2020	2p12	(T1, A20)	PR to crizotinib	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
79	*TANC1*	2020	2q24.2	(T3, A20)	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
80	*TTC27*	2020	2p22.3	(T12, A20)	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
81	*TUBBB*	2020	6p21.33	(T3, A20)	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
82	*SMPD4*	2020	2q21.1	(S1, A20)	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
83	*SORCS1*	2020	10q25.1	(S10, A20)	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
84	*LINC00211*	2020	2p22.2	(L?, A20)	PR with crizotinib and alectinib, SD with lorlatinib	CSF	NGS	33.2%	NR/+	Li, 2020[61]
85	*SOS1*	2020	2p22.1	(S2, A20)	PR to crizotinib	FFPE	NGS	NR	ND/ND	Chen, 2020[62]
86	*C9orf3*	2020	9q22.32	(C12, A20)	NR	FFPE	NGS	22.6%	ND/+	Zhang, 2020[60]
87	*CYBRD1*	2020	2q31.1	(C21, A20)	NR	FFPE	NGS	12.5%	ND/NR	Zhang, 2020[60]
88	*MTA3*[g]	2020	2p21	(M6, A 20)	SD with crizotinib, no response to alectinib	FFPE	NGS	15.3%	ND/NR	Zhang, 2020[60]
89	*THADA*	2020	2p21	(T25, A20)	SD to crizotinib, PR to ceritinib	Plasma	NGS	0.3%	ND/NR	Zhang, 2020[60]

(continued)

Table 1. Continued

No.	Fusion Partner	Year Published in Print/Presented	Chromosomal Location	Fusion Breakpoint	Response to ALK TKI at the Time of Publication	Tumor Source	Method of Detection	Variant Frequency in Tumor	FISH/ IHC	References[a]
90	*TSPYL6*[f]	2020	2p16.2	(T6, A20)	PR to crizotinib, SD to alectinib	FFPE	NGS	8.5%	ND/NR	Zhang, 2020[60]
91	*WDR37*	2020	10p15.3	(W6, A20)	PR to crizotinib	FFPE	NGS	30.2%	ND/NR	Zhang, 2020[60]
92	*PLEKHH2*	2020	2p21	(P6, A20)	PR to alectinib	FFPE	Targeted RNA seqencing	NR	+/+	M. Nagasaka, written communication, 2020

[h]The earlier detected ALK fusion partners were not treated with crizotinib at the time of publication; but all of them have been shown to respond to ALK TKIs. The column entry is for the later discovery of ALK fusion partners.
[a]The first report(s) are cited except when response information from ALK TKIs are from later reports on some of the rare fusion partners, or if the fusion is identified as a resistance mechanism to EGFR TKI.
[b]*ALK* fusions identified as resistance to EGFR TKIs.
[c]Dual fusion with *EML4-ALK* (E18, A20).
[d]Dual fusions (*EML6* and *FBXO11*) together.
[e]Dual fusion (*ERC1* and *SLC16A7*) together.
[f]Dual fusion with *EML4-ALK* (E6, A20)
[g]Dual fusion with *EML4-ALK* (E7; A18)
+, positive; -, negative; ALK, anaplastic lymphoma kinase; CSF, cerebrospinal fluid; FISH, fluorescence in situ hybridization; FFPE, formalin-fixed paraffin embedded; FNA, fine-needle aspiration; IHC, immunohistochemistry; ND, not done; NGS, next-generation sequencing; NR, not reported; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; *ADAM17*, ADAM metallopeptidase domain 17; *AKAP8L*, A-kinase anchoring protein 8 like; *ATAD2B*, ATPase family AAA domain containing 2B; *ATP13A4*, ATPase 13A4; *BCL11A*, BAF chromatin remodeling complex subunit; *BIRC6*, baculoviral IAP repeat containing 6; *C12orf75*, chromosome 12 open reading frame 75; *CAMKMT*, calmodulin-lysine N-methyltransferase; *CDK15*; cyclin dependent kinase 15; *CEBPZ*, CCAAT enhancer binding protein zeta; *CLIP1*, CAP-Gly domain containing linker protein family member 1; *CLIP4*, CAP-Gly domain containing linker protein family member 4; *CMTR1*, cap methyltransferase 1; *CRIM1*, cysteine rich transmembrane BMP regulator 1; *CUX1*, cut like homeobox 1; *CYBRD1*, cytochrome b reductase 1; *DCHS1*, dachsous cadherin-related 1; *DCTN1*, dynactin subunit 1; *DYSF*, dysferlin; *EIF2AK3*, eukaryotic translation initiation factor 2 alpha kinase 3; *EML4*, echinoderm microtubule-associated protein-like 4; *EML6*, EMAP like 6; *EPAS1*, endothelial PAS domain protein 1; *ERC1*, ELKS/RAB6-interacting/CAST family member 1; *FAM179A*, family with sequence similarity 179 member A; *FBN1*, fibrillin 1; *FBXO11*, F-box protein 11; *FBXO36*, F-box protein 36; *FUT8*, fucosyltransferase 8; *GCC2*, GRIP and coiled-coil domain containing 2; *HIP1*, huntingtin interacting protein 1; *ITGAV*, integrin subunit alpha V; *KLC1*, kinesin light chain 1; *KIF5B*, kinesin family member 5B; *LCLAT1*, lysocardiolipin acyltransferase 1; *LIMD1*, LIM domains containing 1; *LINC00211*, long intergenic non-protein coding RNA 211; *LINC00327*, long intergenic non-protein coding RNA 327; *LMO7*, LIM domain 7; *LOC349160*, uncharacterized LOC349160; *LPIN1*, lipin 1; *LYPD1*, LY6/PLAUR domain containing 1; *MPRIP*, myosin phosphatase Rho interacting protein; *MTA3*, metastasis associated 1 family member 3; *MYT1L*, myelin transcription factor 1 like; *NCOA1*, nuclear receptor coactivator 1; *NYAP2*, neuronal tyrosine-phosphorylated phosphoinositide-3-kinase adaptor 2; *PHACTR1*, phosphatase and actin regulator 1; *PICALM*, phosphatidylinositol binding clathrin assembly protein; *PLEKHA7*, pleckstrin homology domain containing A7; *PLEKHH2*, pleckstrin homology, MyTH4 and FERM domain containing H2; *PLEKHM2*, pleckstrin homology and RUN domain containing M2; *PPFIBP1*, Liprin-beta-1/PPF1A. binding protein 1; *PPM1B*, protein phosphatase, Mg2+/Mn2+ dependent 1B; *PRKAR1A*, protein kinase cAMP-dependent type I regulatory subunit alpha; *PRKCB*, protein kinase C beta; *RBM20*, RNA binding motif protein 20; *SEC31A*, SEC31 homolog A, COPII coat complex component; *SLC16A7*, solute carrier family 16 member 7; *SLMAP*, sarcolemma associated protein; *SMPD4*, sphingomyelin phosphodiesterase 4; *SOCS5*, suppressor of cytokine signaling 5; *SORCS1*, sortilin related VPS10 domain containing receptor 1; *SOS1*, Son of sevenless Ras/Rac guanine nucleotide exchange factor 1; *SPECC1L*, sperm antigen with calponin homology and coiled-coil domains 1 like; *SRBD1*, S1 RNA binding domain 1; *SRD5A2*, steroid 5 alpha-reductase 2; *SPTBN1*, spectrin beta, non-erythrocytic 1; *SQSTM1*, sequestosome 1; *STRN*, Striatin; *SWAP70*, switching B cell complex subunit SWAP70; *TACR1*, tachykinin receptor 1; *TANC1*, tetratricopeptide repeat, ankyrin repeat and coiled-coil containing 1; *TCF12*, transcription factor 12; *TFG*, trafficking from ER to golgi regulator; *THADA*, THADA (thyroid adenoma associated) armadillo repeat containing; *TNIP2*, TNFAIP3 interacting protein 2; *TOGARAM2*, TOG array regulator of axonemal microtubules 2; *TPR*, translocated promoter region, nuclear basket protein; *TRIM66*, tripartite motif containing 66; *TSPYL6*, TSPY like 6; *TTC27*, tetratricopeptide repeat domain 27; *TUBB*, tubulin beta class I; *VIT*, vitrin; *VKORC1L1*, vitamin K epoxide reductase complex subunit 1 like 1; *WDR37*, WD repeat domain 37; *WDPCP*, WD repeat containing planar cell polarity effector; *WNK3*, WNK lysine deficient protein kinase 3; *YAP1*, Yes1 associated transcriptional regulator.

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

No.	Year Published in Print/Presented	Chromosomal Location	Potential Fusion Partner Gene	Response to ALK TKI at the Time of Publication	Tumor Source	Method of Detection	Variant Frequency in Tumor	FISH/ IHC	References
1	2019	12q23.3	*RIC8B*	NR	Tumor	NGS	NR	ND/NR	Zhao, 2019[44]
2	2019	2p21	*LOC388942 (LINC01913)*	NR	Tumor	NGS	NR	ND/NR	Zhao, 2019[44]
	2020	2p21	*LOC388942 (LINC01913)*	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
3	2019	2q22.1-q22.2	*LRP1B*	NR	Tumor	NGS	NR	ND/NR	Zhao, 2019[44]
4	2019	2p16.2	*MIR4431*	NR	Tumor	NGS	NR	ND/NR	Zhao, 2019[44]
5	2019	2p23.3	*CENPA/DPYSL5*	PR to crizotinib	Tumor	NGS	NR	+/+	Fei, 2019[63]
6	2020	18q12.1	*CDH2*	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
7	2020	18q12.2	*CELF4*	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
8	2020	2p23.3	*CENPA*	PR to crizotinib	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
9	2020	15q13.3	*CHRNA7*	PR to crizotinib	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
10	2020	2q14.3	*CNTNAP5*	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
11	2020	2p21	*COX7A2L*	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
12	2020	2p13.2	*DYSF*	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
13	2020	2p16.3	*FSHR*	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
14	2020	13q12.11	*GJB6*	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
15	2020	3q22.3	*LINC01210*	NR	Tumor	NGs	NR	NR/NR	Tian, 2020[59]
16	2020	2p22.3	*MEMO1*	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
17	2020	2p22.3	*MIR548AD*	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
18	2020	4q31.1	*MGST2*	NR	Tumor	NGs	NR	NR/NR	Tian, 2020[59]
19	2020	2q11.2	*PDCL3*	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
20	2020	2p22.2	*QPCT*	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
21	2020	2p23.3	*RAB10*	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
22	2020	2p22.1	*SLC8A1*	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
23	2020	2q32.3	*STK17B*	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
24	2020	6q24.1-q24.2	*VTA1*	NR	Tumor	NGS	NR	NR/NR	Tian, 2020[59]
25	2020	2p22.2	*CDC42EP3*[a]	No response to crizotinib and alectinib	Plasma	NGS	13.0%	ND/+	Zhang, 2020[60]
26	2020	19q13.42	*PR11-433C9.2 (PRPF31)*	NR	Tumor	NGS	18.6%	ND/NR	Zhang, 2020[60]
27	2020	3p22.1	*RPSA*	NR	Tumor	NGS	7.9%	ND/+	Zhang, 2020[60]
28	2020	2p23.3	*UBXN2A*	NR	Tumor	NGS	25.4%	ND/NR	Zhang, 2020[60]

[a]Together with *EML4-ALK* (E6, A20) and breakpoint is 3'UTR of CDC43EP3 to exon 20 of *ALK*. +, positive.

ALK, anaplastic lymphoma kinase; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; ND, not done; NGS, next-generation sequencing; NR, not reported; PR, partial response; SD, stable disease; *CENPA*, centromere protein A; *CDC42EP3*, CDC42 effector protein 3; *CDH2*, cadherin 2; *CELF4*, CUGBP Elav-like family member 4; *CNTNAP5*, contactin associated protein family member 5; *COX7A2L*; cytochrome c oxidase subunit 7A2 like; *DPYSL5*, dihydropyrimidinase like 5; *DYSF*, dysferlin; *FSHR*, follicle stimulating hormone receptor; *GJB6*, gap junction protein beta 6; *LINC01210*, long intergenic non-protein coding RNA 1210; *LINC01913*, long intergenic non-protein coding RNA 1913; *LRP1B*, LDL receptor related protein 1B; *MEMO1*, mediator of cell motility 1; *MIR4431*, microRNA 4431; *MIR548AD*, microRNA 548ad; *MGST2*, microsomal glutathione S-transferase 2; *PDCL3*, phosducin like 3; *PRPF31*, pre-mRNA processing factor 31; *QPCT*, glutaminyl-peptide cyclotransferase; *RAB10*, RAB10, member RAS oncogene family; *RIC8B*, RIC8 guanine nucleotide exchange factor B; *RPSA*, ribosomal protein SA; *SLC8A1*, solute carrier family 8 member A1; *STK17B*, serine/threonine kinase 17b; *UBXN2A*, UBX domain protein 2A; *VTA1*, vesicle trafficking 1.

DNA NGS to detect even rare actionable driver mutations such as *NTRK* and *NRG1*.[3,4] Although *EML4-ALK* (with multiple fusion breakpoints in *EML4*) remains the major fusion variant in *ALK*+ NSCLC (accounting for approximately 95% of *ALK* fusion variants[5]), multiple case reports have reported novel *ALK* fusion partners in *ALK*+ NSCLC. In this article, we have compiled a list of the *ALK* fusion partners including intergenic rearrangements identified in the literature for easy reference.

Methods and Results

We searched PubMed publications, conference/congress abstracts, and presentations extensively to identify novel *ALK* fusion partners (including noncoding RNAs). We included only those fusion partners that retained the 3'ALK kinase domain. Reciprocal/nonreciprocal *ALK* translocations involving *5-ALK* gene rearrangements (most frequently ALK exons 1-19 fused to a 3'-truncated gene [ALK-XXX]) were not listed although these nonfunctional 5'-ALK fusion variants are usually listed as *ALK* fusion variants in the literature. Overall, a total of 90 distinct ALK fusion partners (including noncoding RNAs) have been identified in the literature (by the end of January 2020) (Table 1). Many of these novel *ALK* fusion variants have been reported to respond to ALK TKIs or shown to be ALK IHC positive. Twenty-five intergenic rearrangements to exon 20 of *ALK* have also been identified and listed separately in Table 2. Three of these intergenic *ALK* rearrangements have been shown to respond to crizotinib, but the significance of these intergenic rearrangements remains to be determined, including whether functional fusion RNAs are translated from these intergenic rearrangements.

Discussion

With the increasing adoption of NGS for molecular profiling of NSCLC, especially in China, the pace at which new fusion partners are being identified and reported has rapidly increased since 2018. In particular, from 2018 onwards, approximately 65 of the 90 fusion partners reported in the literature (calculated at the time page numbers were assigned for this publication) were almost exclusively identified from China, indicating the widespread use of NGS there. Dual in-frame 3'-*ALK* fusion variants with different 5' fusion partners are now being recognized; however, whether the relative contribution of each of the dual *ALK* fusion variant to oncogenesis depends on the allele frequency of each fusion variant remains to be elucidated. We identified at least 28 intergenic 3'-*ALK* rearrangements. Whether these translate to a functional (and truncated)? *ALK* RNA fusion transcript and whether these intergenic rearrangements are related to the isolated 3'-*ALK* fusion signals remain to be determined.

The concluding perspectives are as follows:

1. *ALK*+ NSCLC is a heterogeneous disease with at least 90 distinct fusion partners identified in the literature by January 2020;
2. It is likely that many more fusion partners and intergenic rearrangements will continue to be identified with the ever-increasing adoption of targeted RNA sequencing and whole transcriptome sequencing owing to the need to identify rare actionable fusions such as *NTRK* and *NRG1* fusions;
3. The role of individual 3'-*ALK* fusion variant in a dual 3'-*ALK* fusion variants will need to be elucidated; and
4. The functional significance of intergenic rearrangements remains to be determined.

We recommend that clinicians from around the world to continue to report these novel fusions or intergenic rearrangements with information on the exon or fusion breakpoints, response to ALK TKIs, allele frequency, and if possible, whether the tumor is *ALK* fluorescence in situ hybridization and IHC positive.

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