TABLE 1. Structure of Breakpoint Junctions of *RET* Fusions in Lung Adenocarcinoma

No.	Sample Name	Fusion Partner	Reciprocal/ Nonreciprocal	Deletion in the Joining		DNA Segment Duplication by Inversion		Nucleotide Overlap at Junction		Nucleotide Insertion at Junction		Mode of DNA End Joining	LOH Proximal to *RET*	Smoking
				RET	Partner	*RET*	Partner	Partner -*RET*	*RET*-Partner	Partner -*RET*	*RET*-Partner			
1	BR0020	*KIF5B*	Reciprocal	—	—	—	—	—	—	—	—	NHEJ	NT	No
2	L07K201T	*KIF5B*	Reciprocal	14 bp	19 bp	—	—	C	—	—	ATA	NHEJ	NT	Yes
3	349T	*KIF5B*	Reciprocal	1 bp	7 bp	—	—	—	—	A	A	NHEJ	NT	Yes
4	AD08-341T	*KIF5B*	Reciprocal	16 bp	26 bp	—	—	—	—	—	—	NHEJ	NT	No
5	RET-030	*CCDC6*	Reciprocal	52 bp	1021 bp		—	— —		—	—	NHEJ	NT	No
6	RET-024	*CCDC6*	Reciprocal	14 bp	2 bp	—	—	—	—	—	—	NHEJ	NT	Yes
7	AD12-106T	*KIF5B*	Reciprocal	—	573 bp	490 bp	—	—	—	—	—	BIR	NT	Yes
8	BR0030	*KIF5B*	Reciprocal	—	—	—	211 bp	—	—	—	—	BIR	NT	No
9	442T	*KIF5B*	Reciprocal	269 bp	—	—	232 bp	—	—	—	—	BIR	NT	No
10	AD08-144T	*KIF5B*	Reciprocal	5 bp	—	—	33 bp	—	—	—	—	BIR	NT	No
11	BR1001	*KIF5B*	Nonreciprocal					—		AGT		NHEJ	+	No
12	AD09-369T	*KIF5B*	Nonreciprocal					CTC		—		NHEJ (alternative end joining)	NT	No
13	BR1002	*KIF5B*	Nonreciprocal					A		—		NHEJ	NT	No
14	AD12-001T	*KIF5B*	Nonreciprocal					—		—		NHEJ	NT	Yes
15	BR1003	*KIF5B*	Nonreciprocal					—		CTTT		NHEJ	+	No
16	BR1004	*KIF5B*	Nonreciprocal					—		RET exon 7 to intron 7 (359 bp)		Complex rearrange	+	No
17	AK55[a]	*KIF5B*	Nonreciprocal					—		GT		NHEJ	NT	No
18	LC-2/ad[b]	*CCDC6*	Nonreciprocal					—		—		NHEJ	NT	Unknown

[a]Ju et al.[4]
[b]Suzuki et al.[21]
LOH, loss of heterozygosity; NHEJ, nonhomologous end joining; NT, not tested; BIR, break-induced replication; blank, not applicable.

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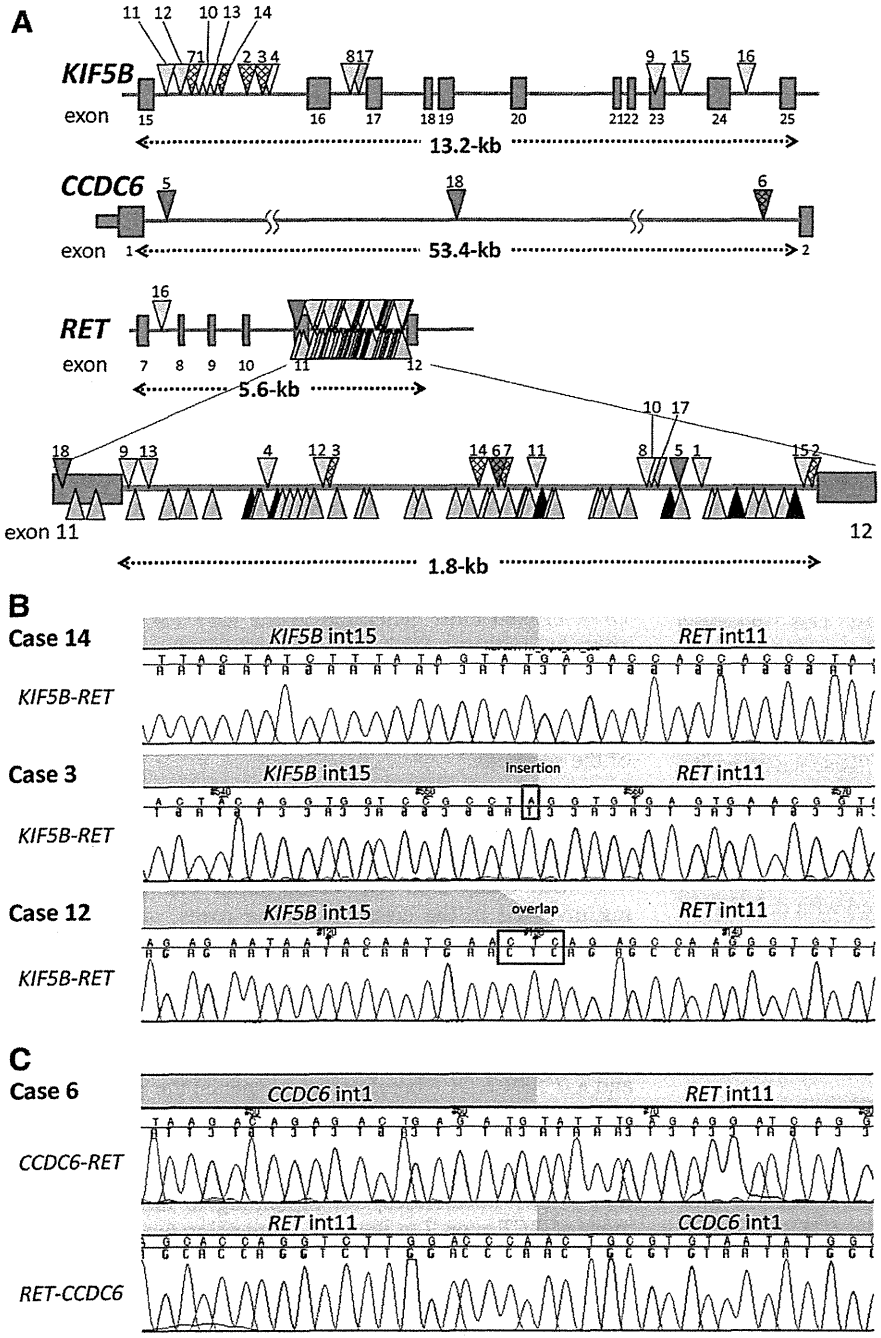

FIGURE 2. Breakpoint analysis. *A*, Distribution of breakpoints in the *CCDC6*, *KIF5B*, and *RET* genes. Yellow arrowheads indicate the locations of breakpoints for *KIF5B-RET* fusions in Japanese cases (cases 1–4 and 7–16 in Table 1), whereas the orange arrowhead indicates the breakpoints in a single Korean case (case 17). Green arrowheads indicate the locations of breakpoints of *CCDC6-RET* fusions in three Japanese cases (cases 5, 6, and 18). Arrowheads for ever-smoker LADC cases are hatched. Gray and black arrowheads indicate breakpoints of *RET-ELE1* fusion in 38 radiation-induced post-Chernobyl PTCs and six sporadic PTCs, respectively.[14–17] *B*, Electropherograms for Sanger sequencing of genomic fragments encompassing *KIF5B-RET* breakpoint junctions. PCR products were directly sequenced. Examples of three fusion patterns (joined without any nucleotide insertions or overlaps, joined with a nucleotide insertion, and joined with three nucleotide overlap) are shown. Inserted and overlapping nucleotides at breakpoint junctions are indicated, respectively, by the blue and red boxes. *C*, Electropherogram for Sanger sequencing of genomic fragments encompassing *CCDC6-RET* and *RET-CCDC6* breakpoint junctions. LDAC, lung adenocarcinoma; PCR, polymerase chain reaction; PTC, papillary thyroid carcinoma.

None of the *RET* and *KIF5B* breakpoints mapped at the same position, and no breakpoint was within 6 bp of another. To further investigate the breakpoint clustering, we mapped breakpoints in three cases of *CCDC6-RET* fusion, a minor fusion variant (cases 5, 6, and 18 in Table 1 and Supplementary Table 3, Supplementary Digital Content 1, http://links.lww.com/JTO/A541). Two of these cases were primary tumors, diagnosed by break apart and fusion *FISH*, and their breakpoints were determined by genome-capture deep sequencing of genomic DNAs using a second-generation sequencer. The remaining case was a LADC cell line from a Japanese patient, for which the breakpoints had previously been determined by the same method.[21] Two breakpoints and one breakpoint in the *RET* gene were mapped to intron 11 and exon 11, respectively (green arrowheads in Fig. 2), and no breakpoint was located within 5 bp of another. In total, a 2.0-kb region spanning exon 11 to intron 11 of *RET* and a 5.6-kb region spanning intron 15 of *KIF5B* (10 of 15, 75%) contained the majority of breakpoints (17 of 18 [94%] and 10 of 15 [75%], respectively), and these breakpoints

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were at least 5 bp from each other. Breakpoints within exon 11 to intron 11 of *RET* and intron 15 of *KIF5B* were not distributed in an evidently biased manner, nor did they exhibit any particular nucleotide sequence or composition (Supplementary Table 5, Supplementary Digital Content 1, http://links.lww.com/JTO/A541). Therefore, DNA strand breaks triggering oncogenic *RET* fusions in LADC occur preferentially in a few defined regions, but at nonspecific sites within those regions.

Reciprocal and Nonreciprocal Inversions Causing *RET* Fusions

To explore the modes of DNA end joining that give rise to *RET* fusion, we investigated the structures of *RET* fusion breakpoint junctions. To address whether chromosome inversion events were reciprocal, we cloned genomic segments containing reciprocal breakpoint junctions (i.e., *RET-KIF5B* and *RET-CCDC6*) from 17 Japanese cases (Table 1). Ten of the 17 cases, consisting of eight *KIF5B-RET* and two *CCDC6-RET* cases, allowed amplification of reciprocal genomic segments using PCR primers set 1 kb away from the identified *KIF5B-RET* or *CCDC6-RET* breakpoints. This indicated that these fusions were the results of simple reciprocal inversions (cases 1–10 in Table 1, Fig. 2*C*). On the other hand, the remaining seven cases did not allow amplification of genomic segments encompassing the reciprocal breakpoint junctions (cases 11–16 and 18 in Table 1). Three of these seven cases, for which corresponding noncancerous DNA was available, were subjected to LOH analysis at the *RET* locus. LOH was detected at a region proximal (N-terminal) to the breakpoints in all three cases (cases 11, 15, and 16 in Table 1, Fig. 1*A*), indicating nonreciprocal inversion associated with deletion of a copy of the region proximal to the breakpoints. In addition, the inversion in the aforementioned Korean case (case 17) is also nonreciprocal.[4] These data suggested that only a fraction of *RET* fusions (10 of 18, 56%) are caused by simple reciprocal inversions.

Modes of DNA End Joining That Give Rise to Reciprocal Inversions

Two major types of DNA repair pathways cause structural variations.[11,12] The first type is nonhomologous end joining (NHEJ) of DNA double strand breaks (DSBs). which requires very short (a few base pairs) or no homology, and often inserts a few nucleotides at breakpoint junctions.[8,22,23] NHEJ has canonical and noncanonical forms; in the latter, called alternative end joining, DNA ends are joined using microhomology of a few nucleotides at breakpoints.[24] The second type includes repair pathways that use long (>10 bp) homology at DNA ends, such as break-induced replication (BIR) and nonallelic homologous recombination.[12,25]

Sequence analysis of breakpoint-containing genomic segments in 10 reciprocal cases revealed that deletions frequently (8 of 10, 80%) occur in *RET* and/or its partner locus (i.e., *KIF5B* or *CCDC6*) upon DNA end joining (Table 1). This analysis also enabled us to deduce that both types of repair pathways described above are involved in these joining events. In six of the cases (cases 1–6 in Table 1), four DNA ends were joined, and in two cases, insertions were observed (representative cases in Supplementary Fig. 1, Supplementary Digital Content 3, http://links.lww.com/JTO/A543). The lack of significant homology between the sequences of the *RET* and *KIF5B/CCDC6* breakpoints led us to deduce that DNA end joining was mediated by NHEJ in these six cases: two DSBs formed, one each in *RET* and its partner locus, and the four resultant DNA ends were illegitimately joined by canonical or noncanonical NHEJ (Fig. 3*A*).

The remaining four cases (cases 7–10 in Table 1) had a distinctive feature. DNA segments of 33 to 490 bp from either the *RET* or *KIF5B* locus were retained at both the *KIF5B-RET* and *RET-KIF5B* breakpoints, resulting in duplication of these segments. Notably, two regions encompassing the breakpoint in a locus exhibited sequence homology to the duplicated segment of the other locus (representative cases in Supplementary Fig. 2, Supplementary Digital Content 3, http://links.lww.com/JTO/A543). This feature led us to deduce that these joining events were mediated by BIR, using both DNA ends generated by DNA single-strand breaks at the *RET* or fusion-partner locus (Fig. 3*B*). Specifically, two DNA broken ends generated at the *RET* (or partner locus) annealed with the DSB sites of the fusion-partner (or *RET*) locus through sequence homology and were then subjected to ectopic DNA replication. This process left the same DNA segment at both breakpoint junctions, resulting in duplication of the segment.

Speculated Mode of DNA End Joining Giving Rise to Nonreciprocal Inversion

Our study also speculated about the modes of joining involved in the eight remaining cases, which were not likely to have been subjected to simple reciprocal inversion and are therefore defined here as nonreciprocal (cases 11–18 in Table 1). Due to the lack of sequence information from breakpoints in reciprocal counterparts, deletions could not be assessed. The lack of significant homology between the *RET* and *KIF5B/CCDC6* breakpoints suggested the involvement of NHEJ. Consistent with this idea, insertion of a few nucleotides, a common trace of NHEJ, was observed in three cases (cases 11, 15, and 17). A single case (case 16) had an insertion of 349 nucleotides, corresponding to the inverted segment of *RET* exon 7 to intron 7, suggesting the occurrence of an unspecified complex rearrangement mediated by a process other than NHEJ, such as fork stalling and template switching (Lee et al., 2007). These results suggest that the predominant molecular process is illegitimate NHEJ repair, in which two DSBs are formed both in the *RET* and partner loci, and one end of the partner locus (the N-terminal part of *KIF5B* or *CCDC6*) and one end of the *RET* locus (the C-terminal part) are joined by NHEJ. Nevertheless, the remaining two DNA ends were not joined in a simple manner. DNA segments within the DNA ends were either lost or joined with DNA ends other than those at the *RET*, *KIF5B*, and *CCDC6* loci, consistent with the observations of LOH at regions proximal to breakpoints in *RET* (Table 1). In fact, in case 17, the 3′ part of the *KIF5B* gene was fused to the *KIAA1462* gene, 2.0 Mb away from *KIF5B*.[4]

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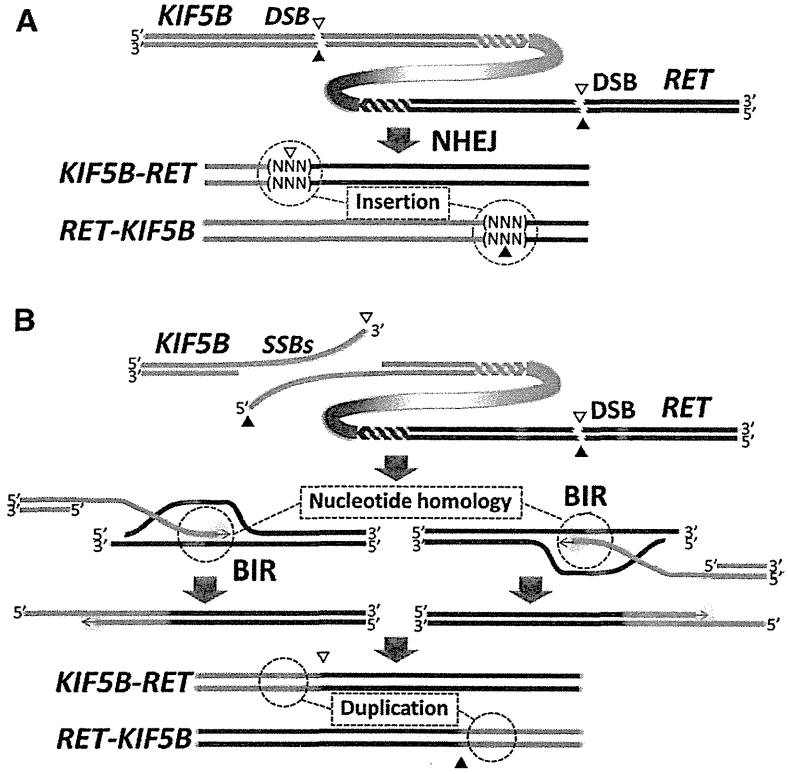

FIGURE 3. Deduced processes of reciprocal inversion by NHEJ and BIR. *A*, NHEJ. Four DNA ends generated by DSBs at *RET* and a partner locus were directly joined. Often, insertions of nucleotides (NNN) at breakpoint junctions are observed. *B*, BIR. Here, DNA single-strand breaks (SSBs) occur in the *KIF5B* locus and a DSB occurs in the *RET* locus. The two SSBs at the *KIF5B* locus trigger BIR by annealing at two homologous sites in the *RET* locus. BIR results in duplication of a *KIF5B* segment. As a result, the *RET* breakpoints in the *KIF5B-RET* and *RET-KIF5B* fusions are located at the same position (a DSB site), whereas the *KIF5B* breakpoints in these fusions are located at different positions (two SSB sites). ▽, breakpoints for partner-*RET* fusion; ▲, breakpoints for *RET*-partner fusion. NHEJ, nonhomologous end joining; BIR, break-induced replication.

DISCUSSION

In this study, we investigated the molecular mechanisms underlying oncogenic *RET* fusion in LADCs. Distribution of breakpoints made us consider a 2.0-kb segment spanning *RET* exon 11 to intron 11 (and also a 5.6-kb segment spanning *KIF5B* intron 15) as a breakpoint cluster region(s). The breakpoints in these regions were dispersed at intervals larger than 4 bp. The inferred breakpoints do not necessarily indicate the sites of actual DNA breaks because resection of nucleotides from DNA ends sometimes occurs during the DNA repair.[23] In fact, we observed nucleotide deletions in eight of 10 LADC cases with reciprocal *KIF5B/CCDC6-RET* inversions. Nevertheless, when the locations of putative breakpoints before DNA end resection were included, the breakpoint distribution remained scattered. These data strongly suggested that the majority of DNA breaks triggering *RET* fusions occur at nonspecific sites in defined regions of a few kb in size. Furthermore, this seems to hold true irrespective of etiology and tumor type: the distribution of breakpoints was not significantly different between ever- and never-smokers, and *RET* exon 11 to intron 11 was also defined as a breakpoint cluster region for *RET* fusions in PTCs, as previously reported.[14–17] The cases shown in Figure 2 (gray and black arrowheads) include PTCs induced by post-Chernobyl irradiation, in which DNA breaks were presumably caused exclusively by irradiation; the random breakpoint distributions in these PTCs were similar to those of the LADCs we analyzed.

We investigated the DNA end-joining pathways that gave rise to *RET* fusions by analyzing the structures of breakpoint junctions. NHEJ was found to be one of the major pathways of DNA end joining. We and others also showed that NHEJ is also prominently involved in interstitial deletions that inactivate tumor-suppressor genes, such as *CDKN2A/p16* and *STK11/LKB1*, in lung cancer.[13,26,27] Thus, NHEJ contributes to the occurrence of driver mutations in both tumor-suppressor genes and oncogenes during lung carcinogenesis. Our data also reveal a possible contribution of BIR in DNA end joining to generate reciprocal inversions. We deduced that BIR occurred from DNA ends, probably generated by DNA single-strand breaks, in the *RET* or partner locus, beginning with annealing with the other locus through nucleotide homologies of tens to hundreds of base pairs. This process resulted in duplication of breakpoint-flanking DNA segments of tens to hundreds of base pairs. BIR has recently been implicated in oncogenic *RAF* fusions in pediatric brain tumors.[28] In those cases, the sequence homology used for annealing of DNA ends was on the order of a few base pairs. Thus, BIR might generate oncogenic fusions frequently, although the detailed process may differ according to tumor type.

Irrespective of the similarities in breakpoint distribution, several processes involved in *RET* fusions differed between LADC and PTC (Fig. 4). Reciprocal inversion was unlikely to have occurred by BIR in PTC because none of the PTC cases exhibited the duplication of DNA segments that were observed in LADC; therefore, the joining of DNA ends in PTC was likely to have been mediated exclusively by NHEJ.[17] This is plausible because *RET* fusions preferentially occur in PTCs in patients suffering from high-dose radiation exposure, suggesting that DSBs generated at the *RET* or partner loci triggered the chromosome rearrangements that generated *RET* fusions.[29] Repetitive NHEJ repair of abundant

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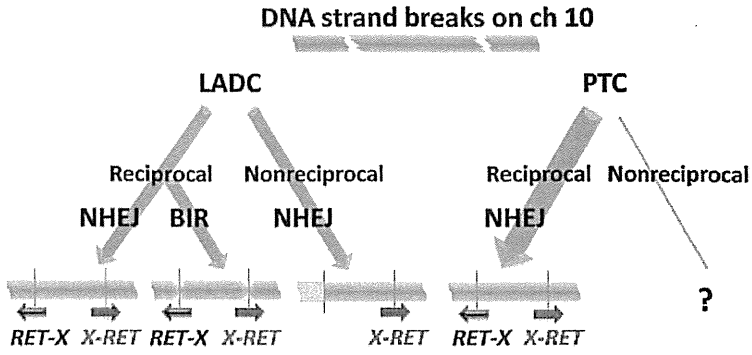

FIGURE 4. Molecular processes underlying *RET* gene fusions in LADC and PTC. Different processes are involved in *RET* fusion in different tumor types. Both reciprocal and nonreciprocal inversions occur in LADC. In LADC, BIR and NHEJ are responsible for DNA end joining in reciprocal inversion, whereas NHEJ is exclusively involved in nonreciprocal inversion. In PTC, reciprocal inversion by NHEJ is dominant. LADC, lung adenocarcinoma; PTC, papillary thyroid carcinoma; NHEJ, nonhomologous end joining; BIR, break-induced replication.

DSBs, which occurs in the context of irradiation, may increase the likelihood of illegitimate repair generating *RET* fusion. On the other hand, in LADC, both DSBs and single-strand breaks formed by multiple causes might trigger rearrangements by multiple DNA repair pathways. The high frequency of nonreciprocal inversion also distinguishes LADC from PTC, for previous study revealed that *RET* fusions result from reciprocal inversion in most cases (43 of 47, 91%).[14,15] Frequent nonreciprocal inversion is consistent with the observation that *KIF5B-RET* fusion-positive tumors contain deletions of the 5′ part of *RET*, as revealed by FISH staining patterns.[1] The present study provides a molecular basis for such a distinct FISH finding and will help to define the criteria used to diagnose *RET*-fusion-positive LADC. Interestingly, FISH analysis also revealed that another driver mutation, *EML4-ALK* fusion, in LADC, caused by a paracentric inversion of chromosome 2, also involves deletion of the 5′ region of the *ALK* oncogene locus.[30,31] Although the structures of breakpoint junctions of *ALK* fusions have not been characterized to the best of our knowledge, these results indicate that a significant fraction of chromosome inversions that cause oncogenic fusions in lung cancer are likely to be nonreciprocal.

Finally, a few issues remain to be elucidated regarding the molecular processes generating oncogenic *RET* fusions. First, although this and previous PTC studies imply that the 2.0-kb region spanning the *RET* exon 11 to intron 11 region is susceptible to DNA strand breaks, the underlying mechanisms remain unknown. For, this region does not exhibit distinctive features known to make DNA susceptible to breaks (Supplementary Fig. 3, Supplementary Digital Content 3, http://links.lww.com/JTO/A543; details in Supplementary Notes, Supplementary Digital Content 2, http://links.lww.com/JTO/A542). Second, the etiological factors that cause DNA strand breaks, and the factors that determine reciprocal or nonreciprocal inversion and selection of DNA repair pathways, also remain unknown. The mode of joining and breakpoint distribution was irrespective of smoking history, and therefore, DNA damage due to smoking is unlikely to be an important factor. The fact that *RET* fusions are more frequent in LADC of never-smokers than in that of ever-smokers indicates that undefined etiological factors play major roles in the occurrence of *RET* fusions.

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