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Molecular Characterization of the Genomic Breakpoint Junction in the t(11;18) (q21;q21) Translocation of a Gastric MALT Lymphoma

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The t(11;18) translocation, fusing the *API2* and *MALT1* genes, is one of the most frequent chromosomal translocations associated with mucosa-associated lymphoid tissue (MALT) lymphomas. The translocation breakpoints have been cloned and characterized at the mRNA sequence level. Although the genomic organization of the *API2* gene has been described, hitherto the genomic sequence of *MALT1* remains unknown. To gain some insight into the mechanism that generates this translocation, we cloned and sequenced an *API2–MALT1* fused transcript as well as genomic DNA of the t(11;18) translocation from a MALT lymphoma. We localized the *API2* breakpoint within intron 7. Nucleotide sequence analysis revealed that the genomic breakpoint junction possesses the consensus heptamers of immunoglobulin V(D)J recombination signal sequences, all the matches being completely present on the *API2* allele and five of seven matches on the *MALT1* allele. These data suggest that the translocation in the MALT lymphoma might have been mediated in part by an aberrant V(D)J recombination event.

Key Words: **MALT lymphoma; translocation; API2; MALT1; V(D)J recombination; heptamer.**

Marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) type are the most common subtype of lymphomas arising at extranodal sites such as the stomach, thyroid, salivary gland, and lung (1–4). In MALT lymphomas, the recurrent abnormalities are trisomies of chromosomes 3, 7, 12, and 18, and t(11;18) (q21;q21) and t(1;14) (p22;q32) translocations (5–8). The t(11;18) (q21;q21) translocation, fusing the *API2* and *MALT1* genes, is a characteristic cytogenetic abnormality in MALT lymphomas (9–14).

The *API2* gene is a member of the human IAP (inhibitor of apoptosis) family, and the protein coded by *API2* has been shown to be highly expressed in lymphoid cells (15). Common features of the gene family members include one to three copies of a motif termed the baculovirus IAP repeat (BIR) domain in the N-terminal region, a caspase recruitment domain (CARD), and a single RING finger domain close to the C-terminus (15). API2 and API1, which are members of the IAP family exhibiting a 70% homology in their amino acid sequences, directly interact with and inhibit caspases-3 and -7, and thus inhibit apoptosis (16). Breakpoints in the *API2* gene in MALT lymphomas have been frequently found between the third BIR and CARD domains, and much less frequently between the CARD and RING domains (10–14).

The *MALT1* gene encodes a 813-amino acid protein, and contains two immunoglobulin (Ig)-like C2 domains and a domain similar to the murine Ig γ chain VDJ4 sequence (10, 11). The function of the MALT1 protein is unknown. The genomic organization of the *MALT1* gene has not been reported. Breakpoints in the *MALT1* gene in MALT lymphomas have been found to be variable compared with those in *API2* (10–14).

The BLAST search with the predicted MALT1 protein revealed homologies with some cell surface glycoproteins. The *MALT1* cDNA sequence shows a homology with that of *CD22β,* which is expressed in B cells. CD22 appears to be a heterodimer consisting of 130-kDa (α) and 140-kDa (β) glycoproteins with protein cores of 80 and 100 kDa, respectively. The *CD22* gene covers 22 kb of DNA and comprises 15 exons, and its

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TABLE 1

Primer Sets and RT-PCR Conditions

Primer sets		Sense primer		Antisense primer	Annealing temperature (°C)
API2–MALT1					
Set 1[a]	API2-U	5′-TTAATGCTGCCGTGGAAATGGGC-3′	MALT1-D1	5′-CAGGATGACCAAGATTATTTAATTC-3′	63
Set 2[a]	API2-U		MALT1-D2	5′-TGAGGTGGCTGCAGAACTCTGG-3′	65
API2–CD22 β					
Set 3	API2-U		CD22 β-D[b]	5′-TGAGTGGAGGATCTGAACCGTGG-3′	65
API2–laminin5α3b					
Set 4	API2-U		laminin5α3b-D[b]	5′-CTCGGAGAGTTGTGAGATTGGTG-3′	65
API1–MALT1					
Set 5	API1-U[b]	5′-GTTAAATCTGCCTTGGAAATGGGC-3′	MALT1-D1		63
MALT1–API2					
Set 6	MALT1-U	5′-GATCGAGACAGTCAAGATAGCAAG-3′	API2-D	5′-AGAGTTTCTGAATACAGTGGCTGC-3′	65

[a] We used primer set 1 for detection of *API2–MALT1* fusion transcripts. To detect translocations with a breakpoint in the C-terminal region of *MALT1*, we also designed MALT1-D2 as an antisense primer for set 2.

[b] Primers for the *CD22β* (Accession No. X59350) and *laminin 5α3b* (Accession No. X84900) genes were designed to cover all the regions where there are homologies with *MALT1*. A primer for *API1* (Accession No. NM001167) was designed in the correspondent region where the *API2* primer was located. CD22β-D, codons 790–798; laminin5α3b-D, codons 736–744; API1-U, codons 396–403.

locus is located within band 19q13.1 (17). Moreover, amino acids 308–476 of the MALT1 protein exhibited a homology with the laminin 5α3b subunit (18). Laminin 5 is an isoform within the laminin family of proteins consisting of three distinct polypeptides, i.e., the α-3, β-3 and γ-2 chains (19). *Laminin 5α3b* is located on 18q11.2.

Recurrent chromosomal translocations acquired in a multistep process of transformation leading to the evolution of autonomous cell clones are well recognized in nodal B-cell lymphomas (20). These translocations characterize distinct disease subtypes, and involve genes controlling cell proliferation and apoptosis. The biological relevance of these translocations is underscored by the fact that a number of known and putative protooncogenes have been identified through the study of genes located at these translocation breakpoints (21). The precise molecular mechanisms underlying chromosomal translocations remain largely unknown. In some cases there is compelling evidence that the translocation is caused by aberrant V(D)J recombinase activity, as evidenced by the presence of cryptic heptamer/nonamer sequences (22, 23). However, since the sequences of the genomic breakpoint junction in the t(11;18) (q21;q21) translocation have not been reported, the molecular mechanisms underlying translocation in MALT lymphomas were unknown.

The t(11;18) translocation has not been frequently detected in gastric MALT lymphomas (12). Therefore, homologs of the *MALT1* and/or *API2* genes might be associated with translocation in some gastric MALT lymphomas.

Here we searched for *API2–MALT1* fusion transcripts in 10 gastric lymphomas, including the MALT type, using the reverse transcription (RT)-PCR method. Then we also examined the presence or absence of fused transcripts of *API2–CD22β*, *API2–laminin 5α3b*, and *API1–MALT1*. Since we found a *API2–MALT1* fusion transcript in one MALT lymphoma, we further analyzed it at the genomic sequence level.

MATERIALS AND METHODS

Patient samples. A total of 10 frozen tissue samples (6 MALT lymphomas and 4 diffuse large B-cell lymphomas) obtained from patients with gastric B-cell non-Hodgkin lymphomas were analyzed in this study. The pathologic diagnosis in each case was established according to the REAL classification (24).

RNA and DNA extraction and cDNA synthesis. RNA was extracted from frozen tissue sections using an RNeasy Mini kit (QIAGEN, Dusseldorf, Germany) following the manufacturer's recommendation. One microgram of total RNA was used for RT. RT was performed using Superscript II reverse transcriptase (Life Technologies, Inc., Grand Island, NY) according to the manufacturer's instruction.

For the preparation of high-molecular-weight DNA, tissue sections were processed with the standard phenol/chloroform extraction protocol that includes digestion with proteinase K (100 μg/ml, Boehringer Mannheim, Indianapolis, IN).

PCR. Each RT-PCR comprised 35 cycles of denaturation for 1 min 94°C, annealing for 2 min at 63 or 65°C, and extension for 1 min (sets 1, 5, and 6) or 3 min (sets 2, 3, and 4) at 72°C, followed by final extension for 10 min at 72°C (Table 1).

For long and accurate (LA)-PCR (Takara, Kyoto, Japan) for examination of genomic translocation sequences, PCR comprised 30 cycles of 94°C for 30 s and 65°C for 20 min, followed by final extension for 10 min at 72°C. Amplification of the *GAPDH* gene was examined for quality control with a primer pair (sense primer, 5′-GACCACAGTCCATGCCATCAC-3′; antisense primer, 5′-GTCCACCACCCTGTTGCTGTA-3′).

Sequencing. The PCR products were sequenced directly with a cycle sequencing kit (Takara, Kyoto, Japan) using end-labeled primers. Approximately 100 ng of *API2–MALT1* cDNA products were sequenced using 2 pmol of a forward (API2-U) or reverse (MALT1-

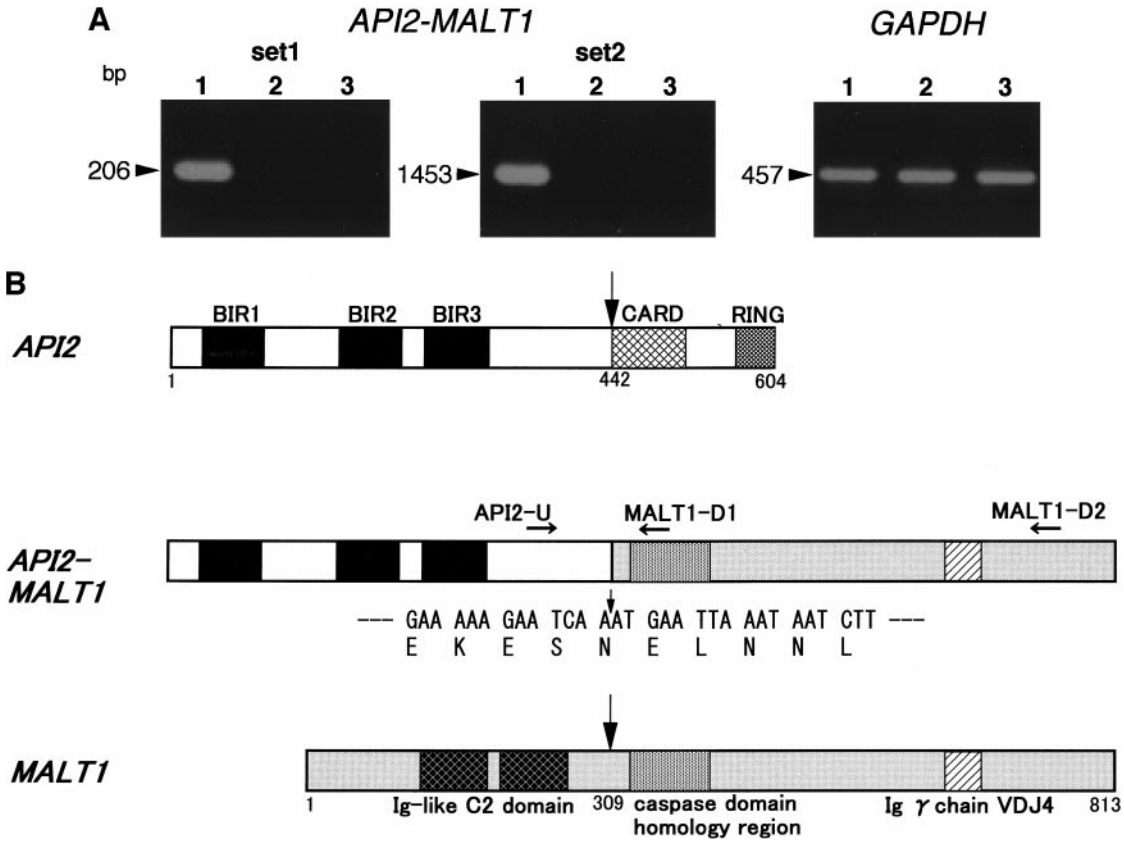

FIG. 1. RT-PCR detection and molecular structure of the *API2–MALT1* fusion transcripts. (A) Gel electrophoresis of the *API2–MALT1* fusion transcripts. RT-PCR with primer set 1 revealed a specific product in case 1. The remaining cases did not show any amplified fragments (cases 2 and 3 are shown). The size of the amplified fragment is 206 bp (left). The same case also showed an amplified fragment (1453 bp) when analyzed with primer set 2 (center). RT-PCR products with a *GAPDH* primer pair that amplifies 457 bp are also shown (right). Sample identities are indicated at the top. (B) The structure of the *API2–MALT1* fusion cDNA. The cDNA structure of *API2* (Accession No. NM001165) is shown at the top with three BIR domains separated from the C-terminal RING domain by a CARD domain. The cDNA structure of *MALT1* (Accession No. AB026118) is shown at the bottom with two Ig-like C2 domains and a domain similar to the mouse Ig γ chain VDJ4 sequence at the C-terminal. The arrows with names indicate the locations of the RT-PCR primers used to detect the *API2–MALT1* transcript (Table 1). The breakpoints in *API2* and *MALT1* are indicated by large arrows (↓). The *API2* cDNA is truncated after the third BIR domain and fused in-frame to *MALT1*. The nucleotide and amino acid sequences of the breakpoint junction are shown underneath the fusion cDNA (*API2–MALT1*).

D1) primer and a Thermosequenase kit (Amersham Pharmacia Biotech, Buckinghamshire, England). The cycling parameters were 30 s at 94°C, 30 s at 65°C, and 1 min at 72°C for 15 cycles, and electrophoresis was performed on 6% polyacrylamide gels containing 15% formamide and 7 mol/liter urea.

As for sequencing of the genomic DNA, the LA-PCR product was cloned into the pT7Blue T-vector (Novagen, Madison, WI) and then sequenced with a cycle sequencing kit (Takara).

RESULTS

Detection of API2–MALT1 Fusion Transcripts

Total RNA was isolated from each specimen and analyzed by RT-PCR for *API2–MALT1* fusion transcripts. Each cDNA sample was examined with primer pair sets 1 and 2 (Table 1). While all 10 lymphoma specimens contained detectable *GAPDH* mRNA, an *API2–MALT1* fusion transcript, 206 bp in size, was identified in 1 (case 1, the MALT type) of the 10 (10%) gastric lymphomas (Fig. 1A) with primer set 1. Primer set 2 also produced fusion cDNA, 1453 bp in size, in only the same case (Fig. 1A). This case was a male Caucasian, aged 43 years, and *Helicobacter pylori*-positive.

The nucleotide sequence analysis revealed that the amplified fragment was a fusion product of *API2* and *MALT1* (Fig. 1B). The *API2* breakpoint seems to lie between exons 7 and 8, because the *API2* sequence in the fused cDNA ends at the 3′ end of exon 7. It should be noted that the chimeric protein retains three BIR domains. The *MALT1* sequence starts from codon 309 in the fused transcript. An important finding was that two genes were fused in-frame and were predicted to produce a chimeric protein comprising API2 and MALT1, as shown schematically in Fig. 1B.

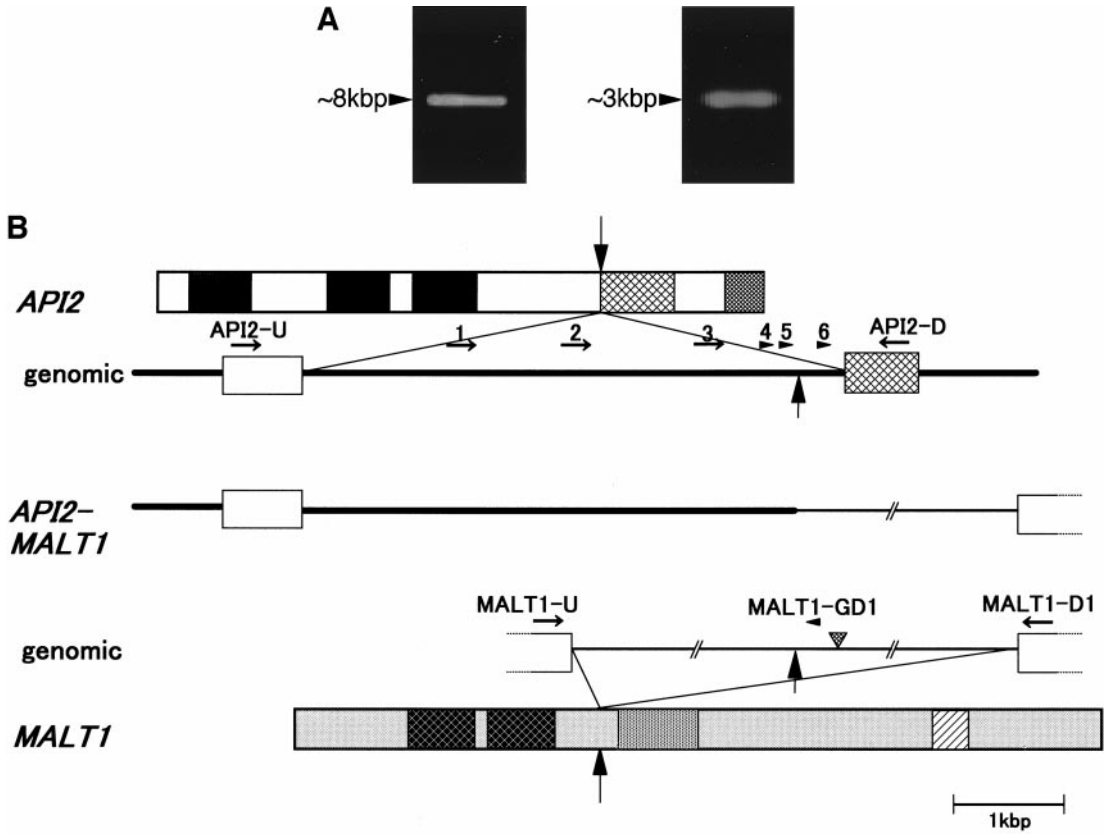

FIG. 2. PCR detection and molecular structure of the genomic *API2–MALT1* DNA. (A) Detection of the genomic *API2–MALT1* DNA by PCR. LA-PCR with primer set 1 (left), and *API2* No. 5 and MALT1-D1(right) revealed specific fragments in case 1. The sizes of the amplified fragments are approximately 8 and 3 kbp, respectively. (B) The structure of the genomic *API2–MALT1* DNA. Exons are boxed, and introns are shown as straight lines. The arrows (→) indicate the locations of the PCR primers used to detect the genomic *API2–MALT1* DNA. To examine the breakpoint of the genomic *API2*, we used six sense primers (Nos. 1–6), indicated by arrows or arrowheads, which we designed in intron 7 according to Accession No. AP001167. The alternative splicing exon of *MALT1* (11 amino acids) is indicated by a triangle (▽).

Detection of Hypothetical Fusion Transcripts

To detect hypothetical fusion transcripts of *API2–CD22β*, *API2–laminin 5α3b*, or *API1-MALT1*, we used three primer pairs (sets 3–5, Table 1). Fusion transcripts were not found in all the 10 cases (data not shown).

Cloning and Analysis of the API2–MALT1 Genomic Breakpoint Junction

The genomic breakpoint junction in case 1 was amplified with primer set 1, the size of product being about 8 kbp (Fig. 2A). To examine the breakpoint, we designed three primers (Nos. 1–3) in *API2* intron 7 as 5′ primers (Fig. 2B), and amplified case 1 DNA with MALT1-D1 as the 3′ primer. All the three primers yielded the PCR products, indicating that the breakpoint is located in the downstream of primer No. 3. To further approach the breakpoint, we designed three more 5′ primers (Nos. 4–6) as shown in Fig. 2B. Since we could detect amplified fragments using up to primer No. 5 as the 5′ primer (Fig. 2A), the breakpoint was shown to be located within a region of 280 bp in size between primer Nos. 5 and 6. The PCR product with primers No. 4 and MALT1-D1 was cloned and sequenced (Fig. 3). The sequence of the 5′ portion of the breakpoint region completely corresponded to that of *API2* intron 7. When the sequence of the 3′ portion of the breakpoint region was applied for the BLAST search, we found a homology with EST AW968625. This sequence contained an alternative splicing small exon (11 amino acids) of the *MALT1* gene (Fig. 2B), suggesting that the 3′ portion of the breakpoint region was derived from the *MALT1* intron (13).

Analyses of the nucleotide sequences determined from the germline *API2* and *MALT1* alleles in the vicinity of the breakpoint revealed characteristic features. The *API2* sequence contains a CACAGTG heptamer identical to the V(D)J recombination signal sequences recognized in Ig or T-cell receptor (TCR) gene rearrangements (23, 25). There are five of seven matches for the heptamer-like sequence in the *MALT1* gene, as indicated in Fig. 3. No nonamer-like sequences were found in either gene.

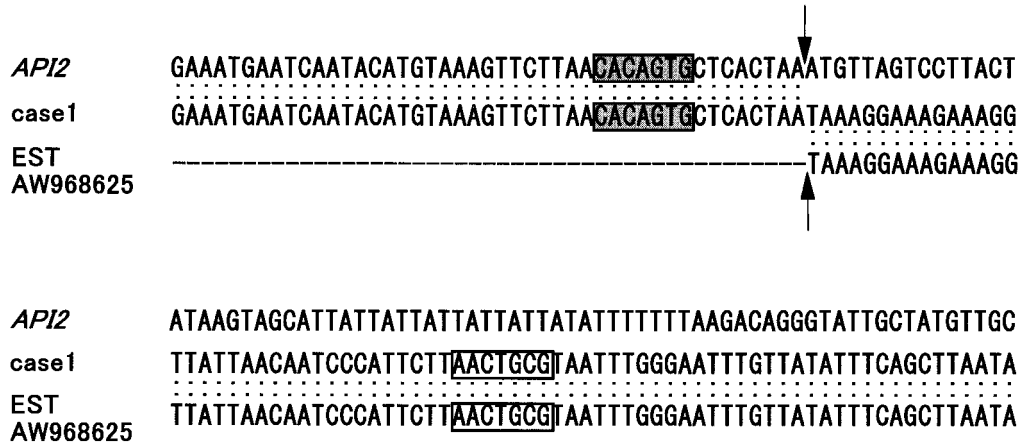

FIG. 3. Sequences flanking the breakpoint junction in case 1. The PCR product with primers *API2* No. 4 and MALT1-D1 was cloned into the pT7Blue T-vector and then sequenced using primers No. 5 and MALT1–GD1 as shown in Fig. 2B. The sequences of *API2,* EST AW968625 and the case 1 genomic DNA are shown. Nucleotide sequences matching the V(D)J heptamer consensus sequence (CACAGTG) are indicated by shadowed boxes. On the other hand, there are 5/7 matches for the heptamer in *MALT1,* as indicated by boxes.

DISCUSSION

In this study, the *API2–MALT1* translocation was detected in one case (10%). Although both *API2–MALT1* and *MALT1–API2* fusion transcripts may potentially be produced by the t(11;18) (q21;q21) translocation, RT-PCR analysis only showed the presence of the *API2–MALT1* transcript (sets 1 and 2), that is, no reciprocal *MALT1–API2* transcript was found (set 6, Table 1) (data not shown). The former protein may therefore play an important role in lymphoma formation.

The cDNA sequence of the case 1 *API2–MALT1* fusion transcript was the same as those reported in several cases earlier, suggesting that this breakpoint may be a hot spot (10, 12). In these cases the 5′ end of the fusion transcript contained all three BIR domains encoded by *API2,* suggesting that if a chimeric protein is produced by the *API2–MALT1* fusion transcript, it would have an antiapoptotic function. On the contrary, the CARD and RING domains of *API2* were not present in the cDNA product. The function of the *MALT1* portion in the context of the *API2–MALT1* fusion transcript is unknown.

As the β subunit of CD22 exhibits an amino acid sequence homology with MALT1, and CD22 is a human B-lymphocyte-restricted antigen that is expressed in B-cells as a membrane protein, we supposed that *CD22*β might be associated with translocation in some MALT lymphomas. Although *CD22*β was expressed in our cases, *API2–CD22*β transcripts were not detected. Likewise, neither *API2–laminin 5*α*3b* nor *API1–MALT1* transcript was detected. These data suggest that *CD22*β*, laminin 5*α*3b,* or *API1* may not be associated with translocation in MALT lymphomas.

To gain some insight into the mechanism underlying *API2–MALT1* translocation, we cloned and sequenced the case 1 breakpoint junction at the genomic DNA level. The 5′ sequence of the breakpoint corresponded to that of *API2* intron 7. On the other hand, the *MALT1* breakpoint was located in the intron that contains the alternative splicing exon.

In many translocations involving Ig or TCR genes, cryptic V(D)J heptamer/nonamer consensus sequences in the immediate vicinity of the breakpoints can be found (26, 27). The significant V(D)J heptamer consensus sequence (CACAGTG) was found on the *API2* side of the breakpoint in our case. However, this heptamer sequence was not present in any other *API2* intron sequences. Therefore, it may be reasonable that this region in intron 7 is a hot spot for recombination events in MALT lymphomas. When we searched for another consensus heptamer sequence, CACTGTG, in the whole *API2* genomic sequence, there was only one site containing this sequence in exon 3. However, there have been no fusion transcript cases involving this area so far. Since this heptamer sequence is located between the first and second BIR domains, these data suggest that more than one BIR sequence may be necessary for lymphomagenesis. On the contrary, the heptamer-like sequence near the *MALT1* breakpoint region showed only five of seven matches. Similar matches have also been reported in *ETV6–AML1* translocations (28).

Although translocations of most, if not all, B-cell lymphomas involve Ig loci, t(11;18) translocations of MALT lymphomas involve *API2* and *MALT1,* but not Ig loci (23). Since the MALT1 protein exhibits a homology with Ig domains, *MALT1* may be a member of the Ig superfamily (11), and might involve the translocational event through an unknown mechanism other than the heptamer.

To clarify the molecular mechanism underlying the t(11;18) translocation, further studies are necessary on more cases of MALT lymphomas with translocations.

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