The translocations t(6;18;11)(q24;q21;q21) and t(11;14;18)(q21;q32;q21) lead to a fusion of the *API2* and *MALT1* genes and occur in MALT lymphomas

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ABSTRACT

So far, only one variant translocation of the t(11;18)(q21;q21), the t(11;12;18)(q21;q13;q21), has been reported. We herein describe two new variant translocations, the t(6;18;11)(q24;q21;q21) and the t(11;14;18)(q21;q32;q21), occurring in mucosa-associated lymphoid tissue (MALT) lymphomas. In both cases, fluorescence *in situ* hybridization (FISH) and reverse transcriptase polymerase chain reaction (RT-PCR) revealed the presence of an 5'*API2-3'MALT1* fusion product, encoded on the derivative chromosome 11. Exon 7 of *API2* was fused with exon 5 of *MALT1* in the t(11;14;18) and with exon 8 of *MALT1* in the t(6;18;11). FISH revealed the involvement of the immunoglobulin locus in the t(11;14;18). Rapid amplification of cDNA ends (RACE)-PCR to detect the involved partner gene on 6q showed exclusively wild-type *API2* and *MALT1* sequences.

Key words: t(11;18), *MALT1*, variant translocation, MALT lymphoma.

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So far, only one variant translocation of the t(11;18)(q21;q21) has been described, the three-way translocation t(11;12;18)(q21;q13;q21), occurring in a mucosa-associated lymphoid tissue (MALT) lymphoma of the lung.[1,2] Cloning of the t(11;12;18) showed that the pathologically relevant event is the fusion of *API2* and *MALT1*, similar to the standard t(11;18). Both translocations lead to a fusion of the three baculovirus *IAP* repeat (BIR) domains present in the N-terminus of API2 and a variable part of *MALT1*, which always contains the caspase p20-like domain.[3-9] The chimeric protein resulting from the t(11;18) effectively activates the NF-κB transcription factor and confers a potential pro-survival signal in B cells.[8,9] The t(11;18) represents the most common structural chromosomal abnormality in MALT lymphomas and occurs in 20 to 50% of the cases.[7,10-13] The recognition of the t(11;18) and its variants is of particular importance, since the t(11;18) characterizes the clinically distinct low grade MALT lymphomas and identifies gastric MALT lymphomas, which respond poorly to *Helicobacter pylori* eradication therapy, even those at an early stage.[14]

In this report, we describe the cytogenetic and molecular genetic features of two new variant translocations, the t(6;18;11)(q24;q21;q21) and the t(11;14;18)(q21;q32;q21), both occurring in MALT lymphomas.

Design and Methods

Case reports

Case 1. In October 1997, this 45-year-old male patient was diagnosed as having a gastric extranodal marginal zone B-cell lymphoma of the MALT-type, stage IE. Standard cytogenetic analysis revealed a variant translocation of the classical t(11;18) defined as: I.46,XY,t(6;18;11)(q24;q21;q21)[7], II.46, idem,del(1)(q43)[10], III.46,XY[3] (Figure 1A). The patient was treated with antibiotics and omeprazol to eradicate *H. pylori*. Because of persistence of the lymphoma and abdominal pain, the patient was treated from April 1998 to January 1999 with chlorambucil. This therapy produced a complete remission. A relapse of the lymphoma was diagnosed 19 months later and a gastrectomy was performed. At the time of the last follow-up in September 2005, the patient was in complete remission.

Case 2. In this 72-year-old male, an extranodal marginal zone B-cell lymphoma of the MALT-type of the lung, stage IE, was diagnosed on a pulmonary biopsy in July 2004. A lobectomy was performed, but the lymphoma could not be completely removed. Therapy with chlorambucil was started in September 2004 and a partial remission with persistence of a 5 mm lesion in the lung was achieved in May 2005. Conventional cytoge-

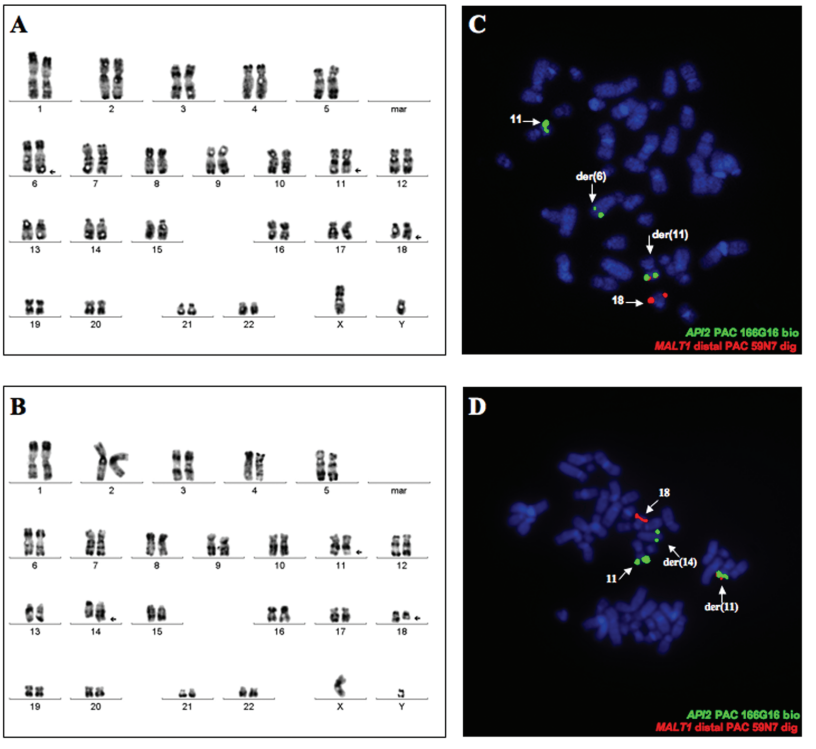

Figure 1. A, B. R-banded karyotypes of the two patients with the three-way variant translocations t(6;18;11)(q24;q21;q21) and t(11;14;18)(q21;q32;q21). Arrows point to the abnormal chromosomes. **C, D.** Dual color FISH analysis of the t(6;18;11) and t(11;14;18) using PAC 116G16 spanning the *API2* gene (green) and PAC 59N7 hybridizing distal to *MALT1* (red). Hybridization signals of the PAC 116G16 are located on the derivative chromosome 11 and on the derivative chromosomes 6 and 14, respectively. Hybridization signals of the PAC 59N7 are seen on the derivative chromosomes 11 in both cases. Fusion signals of PAC 116G16 and PAC 59N7 are detected on the derivative chromosomes 11 in both cases.

netic analysis showed a variant translocation of the classical t(11;18): 46,XY,t(11;14;18)(q21;q32;q21)[23] (Figure 1B).

Fluorescence in situ hybridization (FISH)

Interphase FISH was performed according to standard methods using methanol-acetic acid fixed tumor cells. For the detection of the *5'API2-3'MALT1* fusion P1 artificial chromosome (PAC) clones 59N7 and 116G16 were used as previously described.[10] PAC 59N7 contains genomic sequences derived immediately downstream of the *MALT1* gene. The PAC clone 166G16 spans approximately 100 kb and contains the complete *API2* gene.[10] For the t(6;18;11), painting probes for chromosomes 6, 11, and 18 (Clinisciences, Montrouge, France) were applied to confirm the three-way translocation. To demonstrate the exchange of genetic material between chromosomes 18 and 14 in the t(11;14;18), PAC clone 117B5 containing genomic sequences derived immediately upstream of *MALT1*[10,12] and a yeast artificial chromosome (YAC) clone hybridizing to sequences of the variable region of the

Table 1. Oligonucleotide primer sequences.

Primer	*Oligonucleotide sequence (5'-3')*	*Gene*	*Nucleotides*	*Application*
API2-7f1	ATTAATGCTGCCGTGGAAAT	*API2*	3926-3945	RT-PCR
API2-8r	GAGAGTTTCTGAATACAGTGGCTGCAA	*API2*	4322-4296	RT-PCR
API2-9r	CTGAAACATCTTCTGTGGGA	*API2*	4303-4384	5' RACE-PCR
API2-8r1	AACACAGCTTCAGCTTCTTGC	*API2*	4344-4324	5' RACE-PCR
API2-8r2	TTAATAATTCCGGCAGTTAGTAGAC	*API2*	4206-4182	5' RACE-PCR
MALT1-11r	ATGGATTTGGAGCATCAACG	*MALT1*	1558-1539	RT-PCR
MALT1-3f	CAGTCTTGGCTGGACAGTTTGTGA	*MALT1*	668-691	RT-PCR
MALT1-6f1	GGTGCCTTATGTGGATTTGGAAC	*MALT1*	1086-1108	3' RACE-PCR
MALT1-6f2	TCGAGACAGTCAAGATAGCAAG	*MALT1*	1143-1164	3' RACE-PCR
API2-for(3)	CAACTTGGAAGCTACCTCTCA	*API2*	3091-3111	Real-time RT-PCR
API2-rev(1)	TCCTGTAAACTCCAGAGCAAATCA	*API2*	3214-3237	Real-time RT-PCR
PBGD-for	TGAGAGTGATTCGCGTGGGTAC	*PBGD*	210-231	Real-time RT-PCR
PBGD-rev	CATTGCTATGTCCACCACAGGG	*PBGD*	316-337	Real-time RT-PCR
Hs_BIRC2_1_SG QuantiTect Primer Assay (Qiagen, Hilden, Germany)		*API1*		Real-time RT-PCR
Hs_MMP7_1_SG QuantiTect Primer Assay (Qiagen, Hilden, Germany)		*MMP7*		Real-time RT-PCR

Nucleotides according to Genebank Accession No. NM_006785 (MALT1), NM_001165 (API2), NM_000190 (PBGD), NM_001166 (API1), and NM_002423 (MMP7).

immunoglobulin heavy chain locus (*IGH*) on 14q32 (YAC Y6)[15] were applied. Cosmid clones Cα1 (hybridizing to the alpha constant region of *IGH*)[15] and C3/64 (hybridizing to the delta constant and joining region of *IGH*)[15] were used to narrow the breakpoint within *IGH*. PAC 59N7 and cosmid Cα1 were used to exclude the presence of a *IGH-MALT1* fusion product resulting from the standard t(14;18) (q32;q21) observed in MALT lymphomas.[12,16]

MALT1 immunohistochemistry

MALT1 was immunostained in both cases with mouse monoclonal antibodies to the MALT1 amino terminus and the MALT1 carboxyl terminus as previously described.[17] The antibody against the MALT1 amino terminus recognizes full-length MALT1, but not the API2-MALT1 fusion product, whereas the antibody against the MALT1 carboxyl terminus reacts with both full-length MALT1 and the API2-MALT1 fusion product. In addition, in the case with t(11;14;18), immunohistochemistry using a mouse monoclonal antibody for BCL10 (clone 151) was performed as previously described.[17] The case with t(6;18;11) could not be stained for BCL10 because of lack of suitable material.

Reverse transcriptase polymerase chain reaction (RT-PCR)

Total RNA was isolated using the RNeasy Mini Kit (Qiagen, Hilden, Germany). First-strand cDNA was reverse transcribed from 1μg of total RNA with the SuperScript Preamplification System and oligo(dT) primer (Invitrogen, Karlsruhe, Germany). For the detection of the 5'*API2-3'MALT1* fusion transcript a forward primer specific for exon 7 of *API2* (API2-7f1) and a reverse primer specific for exon 11 of *MALT1* (MALT1-11r) were used.[1] The reciprocal *MALT1-API2* fusion was analyzed with primers specific for exon 3 of *MALT1* (MALT1-3f) and exon 8 of *API2* (API2-8r).[1] All primer sequences are summarized in Table 1. Amplification products were cloned in pGEM T-easy (Promega, Madison, WI, USA) sequenced and analyzed using the BLAST algorithm at NCBI (*http://www.ncbi.nlm.nih.gov/blast*).

5'- and 3'-rapid amplification of cDNA ends (RACE)-PCR

Total RNA was isolated in the case with the t(6;11;18) and rapid amplification of cDNA ends (RACE) was performed as previously described.[1] Briefly, for 3'-RACE, nested PCR was performed with primers MALT1-6f1 and MALT1-6f2. For 5'-RACE, reverse transcription was performed with oligonucleotide API2-9r. 5'-first-step PCR was performed with primer API2-8r1 and the second-step with API2-8r2. Amplification products were cloned as described above and colonies were screened by PCR with universal primers for the vector.

Real-time quantitative-PCR

The *API1*, *API2*, and *MMP7* genes are located on chromosome 11q21 close to each other and their expression could be altered by the juxtaposition to the *IGH* locus in the t(11;14;18). Therefore, quantitative real-time PCR was performed to quantify the *API1*, *API2*, and *MMP7* mRNA expression in this case using LightCycler technology (Roche, Mannheim, Germany). The 'QuantiTect SYBR Green PCR' (Qiagen, Hilden, Germany) kit was used for amplification. RNA levels were calculated relative to porphobilinogen deaminase gene (*PBGD*) expression using the Relative Expression Software Tool (REST).[18] Lymph nodes and lung tissue from healthy donors were used as controls to calculate the relative mRNA expression of *API1* and *MMP7*. The *API2* gene expression in the case with the t(11;14;18) was compared with that in six t(11;18)-positive MALT lymphomas. Primer sequences are shown in Table 1.

Results and Discussion

We here describe two novel variant translocations of the t(11;18)(q21;q21): a three-way translocation t(6;18;11)(q24;q21;q21), occurring in a low grade MALT lymphoma of the stomach, and another three-way translocation t(11;14;18)(q21;q32;q21) occurring in a MALT lymphoma of the lung. To the best of our knowledge, only one variant translocation of the t(11;18) has been reported so far, namely the t(11;12;18)(q21;q13;q21).[1,2,19] The t(6;18;11) and t(11;14;18) were identified by routine cytogenetic analysis (Figure 1A, B). Their presence was confirmed by FISH experiments with the *API2* and *MALT1* specific probes, PAC 166G16 and PAC 59N7.[10] Fusion signals of both PAC clones were detected on the derivative chromosomes 11 in 48% (case 1) (Figure 1C) and 73% (case 2) (Figure 1D) of analyzed interphase cells, indicating the presence of the *5'API2-3' MALT1* fusion product. Split hybridization signals of the *API2* specific probe were located on the derivative chromosome 11 in both cases and on the der(6) in case 1 (Figure 1C) and the der(14) in case 2 (Figure 1D), confirming the presence of three-way translocations. For the t(6;18;11), painting probes for chromosomes 6, 11, and 18 showed exchange of genetic material between chromosomes 6, 11, and 18.

In the case with the t(11;14;18), FISH experiments with PAC 117B5[12] and YAC Y6[15] demonstrated a co-localization of genomic sequences derived immediately upstream of *MALT1* and sequences of the variable region of the *IGH* locus on the derivative chromosome 18. Moreover, FISH with cosmid clones hybridizing to the alpha constant (Cα1) and the delta constant and joining region (C3/64) of *IGH*, respectively, showed hybridization signals on the derivative chromosome 14 narrowing the breakpoint on chromosome 14 to a region between the joining region and the variable region gene segments of *IGH*. Further analyses

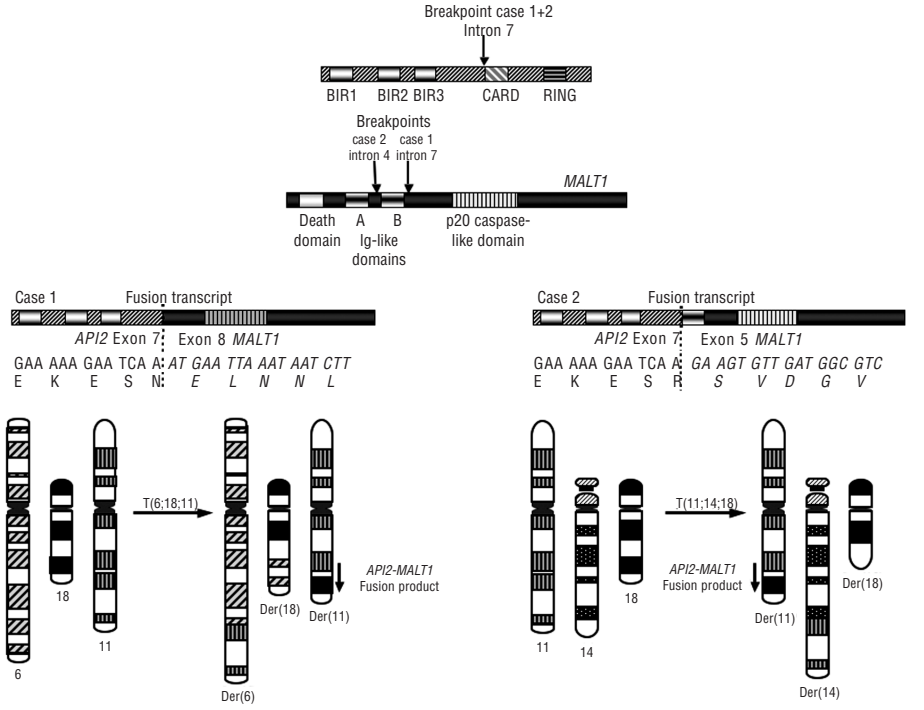

Figure 2. Schematic representation showing the localization of the breakpoints within *API2* and *MALT1* and the corresponding fusion products in the t(6;18;11) (case 1) and the t(11;14;18) (case 2). The corresponding chromosomal ideograms illustrating the three-way translocations t(6;18;11) and t(11;14;18) are shown.

were performed to investigate the possibility of an *IGH-MALT1* rearrangement, resulting from a t(14;18), in addition to the *API2-MALT1* fusion. FISH with probes 59N7 and $C_{\alpha 1}$ did not reveal fusion signals of these probes. The analysis of metaphases showed the localization of PAC 59N7 on chromosome 18 and the der(11) but not on the der(14). Cosmid $C_{\alpha 1}$ was seen on chromosome 14 and the der(14). These results support the assumption that the translocations t(11;18) and t(14;18) are mutually exclusive.[12,16]

Immunohistochemistry with both amino terminus and carboxyl terminus MALT1 antibodies showed weak MALT1 cytoplasmic staining in the cases with a t(6;18;11) and t(11;14;18), similar to the MALT1 expression pattern seen in t(11;18)-positive MALT lymphomas.[17] In contrast, *IGH-MALT1*/t(14;18)-positive MALT lymphomas are characterized by strong cytoplasmic expression of MALT1.[17] The case with the t(11;14;18) showed weak nuclear BCL10 expression, similar to the expression observed in t(11;18)-positive MALT lymphomas.[17]

The *API2-MALT1* fusion transcript was confirmed by RT-PCR using a primer specific for exon 7 of the *API2* gene in combination with a primer specific for exon 11 of *MALT1*.[1] DNA sequencing revealed an in-frame fusion of exon 7 of *API2* and *MALT1* in both cases. The breakpoints within *MALT1* were found in intron 7 of the transcript variant 1 of *MALT1* in the t(6;18;11) and intron 4 of the transcript variant 2 of *MALT1* in t(11;14;18) (Figure 2). These findings reveal that, analogously to the classical t(11;18), these variant translocations lead to a fusion of the three baculovirus IAP repeat (BIR) domains of *API2* and the caspase-like domain of *MALT1*. The *API2* breakpoints in the t(11;18) occur in the vast majority of reported cases upstream of exon 8, whereas the breakpoints within the *MALT1* gene have been reported to lie upstream of exons 3, 5, 8, and 9.[3-7,20]

In order to identify the potential fusion partner of 3'*API2* on the der(6) and 5'*MALT1* on the der(18) in the case with t(6;18;11), we performed 5'- and 3'-RACE-PCR. Sequencing of 58 clones did not show fusion transcripts of *API2* or *MALT1* in this case. Therefore we suggest that the potential fusion products of *API2* and *MALT1* with sequences derived from chromosome 6 are not expressed. In addition, RT-PCR experiments showed that the expression of a reciprocal *MALT1-API2* is abolished due to the additional translocation events. This phenomenon is also observed in some t(11;18)-positive cases associated with cryptic deletions in *API2* or *MALT1*.[3,6,20] In the case with the t(11;14;18), FISH experiments revealed that the translocation partner on chromosome 14 was the *IGH* locus with a break telomeric to the joining region of *IGH* between cosmid $C_{3/64}$ and YAC Y6. The molecular consequences of the involvement of the *IGH* locus in the t(11;14;18) are not clear. Translocations involving *IGH* typically lead to deregulation of the expression of the partner gene of *IGH*. In the t(11;14;18), a deregulation of *API2* by *IGH* is unlikely since the translocation leads to the juxtaposition of the carboxyl-terminal portion of *API2* and not the complete coding region of *API2*. Moreover, it is important that the *IGH* enhancer cannot deregulate the productive *API2-MALT1* gene fusion product because no sequences of chromosome 14 are translocated to the der(11), where the *API2-MALT1* product lies. This was confirmed by quantitative RT-PCR that did not show differences in the relative expression

ratios of *API2* between the case with the t(11;14;18) and six t(11;18)-positive MALT lymphomas used as controls. However, deregulation of a gene or genes distal to *API2* on chromosome 11 might contribute to the oncogenic potential of the t(11;14;18). Candidate genes are *API1*, an apoptosis inhibitor that lies only 30kb telomeric to *API2*, and *MMP7*, a protease capable of degrading extracellular matrix, associated with invasion and metastasis in solid tumors. Real-time PCR, however, did not show upregulated mRNA-expression levels of either *API1* or *MMP7*.

Summarizing our data, the presence of the *API2-MALT1* fusion transcript, the typical MALT1 and BCL10 protein expression, the exclusive detection of wild type *API2* and *MALT1* sequences by RACE-PCR analysis, and the absence of a reciprocal *MALT1-API2* transcript due to the complex rearrangements, point to *API2-MALT1* as the pathogenetically relevant transcript in the t(6;18;11) and the t(11;14;18) and underline the crucial role of the *API2-MALT1* fusion in the pathogenesis of MALT lymphomas.

Since only three variant translocations of the t(11;18) have been reported so far, more cases need to be analyzed to determine whether clustering to particular chromosomal bands occurs in these variant translocations, and whether MALT lymphomas harboring t(11;18)-variant translocations differ clinically from those with the classical t(11;18).

Authors' Contributions

EMMP: designed and performed the research, analyzed the data, and wrote the paper; EC-B, CC-B, SG, FB and GS: provided patients' samples, cytogenetic data, clinical data and revised the article for intellectual content; KH and NA: performed the research, analyzed the data; CB: revised the article for intellectual content; JD: designed the research, analyzed the data, and made a significant contribution to the discussion. All authors approved the final version of the manuscript.

Conflict of Interest

The authors reported no potential conflicts of interest.

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