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Germline variations of the *MALT1* gene as risk factors in the development of primary gastric B-cell lymphoma

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ABSTRACT

Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is a histologically distinct tumour derived from MALT acquired as a result of *Helicobacter pylori* infection. The genetic susceptibility to develop primary gastric B-cell lymphoma in patients with chronic *H. pylori* infection is unknown. *MALT1* plays a key role in malignant B-cell transformation and lymphoma progression. Thus, we investigated germline variations of *MALT1* as risk factors for gastric lymphoma in a large cohort from a European multicentre study and in total 214 lymphoma patients, 593 *H. pylori* infected controls and 348 healthy blood donors were genotyped for four single nucleotide polymorphisms (SNPs) covering the *MALT1* locus by Taqman technology. Haplotype and single marker analyses were conducted for association testing in a case-control setting. A distinct haplotype was identified that showed a trend towards protection from high-grade and low-grade lymphomas. In single marker analysis individuals homozygous for the rare allele G of SNP3 (rs12969413) were significantly protected only from gastric high-grade lymphoma compared with controls ($p = 0.002$, odds ratio (OR): 0.2, Wald 95% confidence interval (CI): $0.1 < OR < 0.6$). This association could not be confirmed in a second independent cohort of high-grade lymphoma patients from the Lymph node registry in Kiel ($p = 0.531$, OR: 0.8, Wald 95% CI: $0.4 < OR < 1.5$). Due to the fact that SNPs 2, 3 and 4 are arranged in one LD block exhibiting nearly complete linkage disequilibrium it is rather unlikely that germline variations of *MALT1* might be involved in the pathogenesis of gastric lymphoma. This is the first genetic association study that investigated polymorphisms of *MALT1* as genetic risk factors in the development of primary gastric lymphoma.

1. Introduction

Mucosa-associated lymphoid tissue (MALT) lymphoma was first described by Isaacson and Wright in 1984 and accounts for 8% of all non-Hodgkin lymphoma.[1] Gastric MALT lymphoma arises from a background of lymphoid follicles, which are acquired in response to *Helicobacter pylori* infection, a gram-negative spiral microaerophilic organism that colonises the stomach of over 50% of the world's population.

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However, only 1–2% of infected individuals will develop gastric MALT lymphoma but about 90% of gastric MALT lymphoma patients are infected with *H. pylori*.[2] Thus, gastric MALT lymphoma depicts a paradigm of an infection-associated malignant disease.[3]

The pathogenesis of gastric lymphoma is a multi-step process that is characterised by reactive immune response, lymphocyte development and somatic mutations.[4]

The translocation t(11;18)(q21;q21) is common in gastric MALT lymphomas involving the genes *MALT1* on chromosome 18 and *API2* on chromosome 11.[4,5] The resulting *API2–MALT1* fusion protein bypasses the normal cellular signalling pathway and seems to be the driving force in the progression of MALT lymphoma.[6,7] Moreover, lymphomas harbouring t(11;18)(q21;q21) do often not respond to eradication of *H. pylori*.[8]

To date it is unknown why some *H. pylori* infected individuals develop MALT lymphoma and others do not. Besides the virulence of different strains, that do not seem to play a role in the etiopathogenesis of gastric lymphoma,[9,10] the host genetic background influences the clinical course of *H. pylori* infection. A familial clustering of *H. pylori* infection and gastric carcinoma is well-known.[11,12] El-Omar and colleagues identified genetic variants of the *IL-1* gene cluster as risk factors for the development of gastric cancer in *H. pylori* infected individuals.[13]

In preceding studies we identified genes involved in the innate immune response as part of a genetic risk profile for lymphoma development.[14,15]

The *MALT1* gene plays a key role in the etiopathogenesis of gastric MALT lymphoma and thus qualifies as an ideal candidate for a genetic association study. We investigated germline variations of *MALT1* as risk factors for gastric lymphoma.

2. Patients and methods

2.1. Gastric lymphoma patients

2.1.1. European multicentre study (German–Austrian-Lymphoma Study Group)

Patients participated in an intention-to-treat prospective multicentre study of the German–Austrian-Lymphoma Study Group.[16] Caucasian patients with newly diagnosed primary gastric B-cell lymphoma, median age 61 (range 29–75, 54% males), were recruited from March 1993 to March 1996 at 166 centres in Germany and 13 in Austria. The exclusion criteria were age above 75 years, primary nodal or HIV-associated lymphoma of any type, and prior or concomitant malignancies including gastric collision tumours. The primary character was defined histopathologically for low-grade MALT lymphoma and high-grade lymphoma with evidence of a low-grade component (secondary high-grade lymphoma). Patients with high-grade lymphoma without low-grade features were regarded as having primary gastric lymphoma if they met the criteria described by Lewin et al.[17] Patients with secondary high-grade lymphoma ($n = 9$) were excluded from analysis due to the ambiguous phenotype. In all the remaining 144 cases diagnosis was based on morphological and immunophenotypic analysis. Immunostaining was carried out using standard peroxidase–antiperoxidase techniques with diaminobenzidine (DAB) as chromogen. The antibodies used were L26 (specificity CD29), CD3, CD5, CD23 CAM5.2 (cytokeratins 8, 18, 19), Mib-1 (Ki-67-antigen), anti-IgM, anti-IgG, anti-IgA, anti-kappa and anti-lambda. *H. pylori* was detected in 80% of the patients by urease test from the antrum and corpus and histological examination of biopsy specimen. Staging work-up included patienťs history and physical examination, blood cell count and serum chemistry, inspection of Waldeyer's tonsillar ring, chest and small bowel radiography, cervical and abdominal ultrasound, computed tomography of the chest and abdomen, bone-marrow aspirate and biopsy, ileocolonoscopy and upper gastrointestinal endoscopy with biopsies of visible lesions and macroscopically normal mucosa. The stage was defined according to the Ann Arbor staging system[18] with modification by Musshoff[19] and Radaszkiewicz et al.[20]

2.1.2. Lymph Node Registry Kiel

The Lymph Node Registry Kiel was founded in 1965 by Prof. Dr. H.C. Karl Lennert as an institution for the diagnosis, documentation and research in the field of haemato-lymphatic diseases. The registry serves as a nationwide reference centre. Using the registries data base 68 patients with the diagnosis of primary gastric high-grade lymphoma according to the WHO-Classification were identified retrospectively from June 2007 to January 2006. The referring pathologists were contacted to acquire biopsy samples from normal gastric mucosa. DNA was extracted from paraffin-embedded non-neoplastic tissue using the QIAamp DNA mini kit (Qiagen) according to the manufacturer's recommendations.

2.2. H. pylori positive patients

Five hundred and ninety three consecutive Caucasian patients, median age 68 (range 22–96, 53% males), attending the University Hospital in Kiel and five other General Hospitals in North Germany for an upper GI endoscopy from 1998 until 2000, were recruited. Patients were included in the study only if *H. pylori* infection was confirmed either by rapid urease test or by histology of two biopsies taken from the antrum and the corpus of the stomach, and gastric lymphoma was excluded by histology. Informed consent was obtained prior to enrolment and the local ethics committee approved the study. Findings in upper GI endoscopy and the results of histopathological examination of biopsies, classified according to the Sydney classification were recorded.

2.3. Healthy controls

Three hundred and forty eight Caucasian blood donors from Kiel, median age 37 (range 18–65, 48% males) were genotyped as healthy controls. Participants were allowed to donate blood if HIV-, Hepatitis- and CMV-serology was negative. Serious diseases were excluded by physical examination and history. Blood donors resemble the genotype distribution of the general population.

2.4. Selection of SNPs

In total four SNPs with a frequency of the rare allele higher than 30% were selected to cover the *MALT1* locus for calcula-

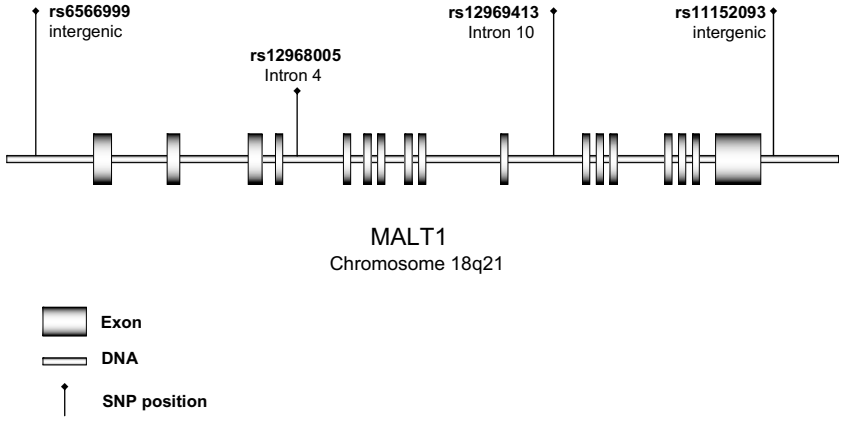

Fig. 1 – Relative exon–intron structure of the *MALT1* gene on chromosome 18q21 and position of SNPs genotyped.

tion of linkage disequilibrium and haplotype analysis (Fig. 1). Assays were provided by Applied Biosystems, Foster City, CA, USA as Assay on Demand or Assay by Design products.

2.5. *Genotyping*

We prepared genomic DNA from 10 mL fresh or frozen blood samples with the blood Gigakit (Invitec, Berlin, Germany). SNPs were genotyped by Taqman technology using assays provided by Applied Biosystems, Foster City, CA (Table 1). In brief, genomic DNA was arrayed and dried on 96-well and 384-well plates. Taqman PCR was set up with Genesis pipetting robots (Tecan, Männedorf, Switzerland). We amplified samples with ABI9700 PCR machines (Applied Biosystems), and measured fluorescence with ABI7700 and ABI7900 fluorometers (Applied Biosystems). PCR cycling conditions were 50 °C for 2 min, 95 °C for 10 min, 45 cycles at 95 °C for 10 s and 60 °C for 1 min. All data were managed and analysed with an integrated laboratory information system.[21]

2.6. *Statistical analysis*

In the first step haplotype analysis was performed including all markers covering each locus to assess association with development of ulcer disease. Haplotype case-control analysis was performed using the GENEHUNTER program[22] with an implementation of an expectation maximisation algorithm (HAPMAX).[23] We also used HAPMAX for significance testing of haplotype frequency differences, making use of the fact that twice the log-likelihood ratio between two nested data models approximately follows a χ^2 distribution with k degrees of freedom, where k is the difference in parameter number between the two models. After identification of markers determining the association of distinct haplotypes single marker analysis was conducted to prove the association. Hardy-Weinberg equilibrium was confirmed for all single markers tested. Statistical analysis of single markers was performed using 'SISA Binominal' program (Uitenbroek, Daan G, Binomial SISA, 1997. http://home.clara.net/sisa/binomial.htm (1 January 2002)). Fischer's 2by3 test was used to compare genotype distribution in cases and controls in general. Pearson's χ^2 test, odds ratio and Wald 95% confidence interval were applied to compare carrier status. Linkage disequilibrium (LD) coefficients $D' = D/D_{max}$ between pairs of SNPs were obtained in controls according to Devlin and Risch.[24]

Three types of analysis were performed:

1. *H. pylori* infected patients were compared against healthy blood donors.
2. Patients with low-grade gastric B-cell lymphoma (MALT) were compared against *H. pylori* infected patients without lymphoma since *H. pylori* is known to be the causative agent in MALT lymphoma development.[25]
3. Patients with high-grade gastric B-cell lymphoma were compared against healthy blood donors as high-grade lymphoma is considered to arise independently of *H. pylori* infection.[25]

3. Results

3.1. *Haplotype analysis*

Haplotype analysis identified five different haplotypes indicating a high degree of linkage disequilibrium. None of the haplotypes was significantly associated with high-grade or low-

Table 1 – Context sequences of all SNPs genotyped by Taqman technology.

SNP		Context sequence
1	rs6566999	TATCACAATGCCATTTTTGTAATAA[C/T]GCCTGGTGTTATTCCTATTGTAATA
2	rs12968005	GCATATTCACACTCCACATCTTTGC[A/G]TCACTTCTTCCTTCCATCTTGAATA
3	rs12969413	GTTGTTAGGCATGCAATGATAAACA[A/G]AAAGTACCGGTTTGGCTCCTGTATC
4	rs11152093	CAGGTGCTCAGCTGTGGTTACCACC[A/G]AGCAGCACTGTCCAGTGAACTTGCT

Table 2 – Estimated haplotype frequencies of the MALT1 locus in patients with chronic gastritis and gastric low-grade lymphoma (European multicentre study). Only haplotypes with a frequency higher than 1% are shown. (p(χ^2) = single point p-value based on χ^2 test, OR = odds ratio). The presence of the G allele in SNPs 2, 3 and 4 in combination with allele C in SNP 1 showed a trend towards protection from low-grade lymphoma.

Haplotype	Chronic gastritis (n = 559) (%)	Low-grade lymphoma (n = 83) (%)	p-Value (χ^2)	OR
C-A-A-A	32.2	35.6	0.405	1.2
C-G-G-G	**27.8**	**21.6**	**0.098**	**0.7**
T-A-G-G	13.8	15.1	0.665	1.1
T-A-A-A	20.3	22.9	0.440	1.2
T-G-G-G	4.5	4.9	0.849	1.1

Table 3 – Estimated haplotype frequencies of the MALT1 locus in healthy controls and patients with primary gastric high-grade lymphoma (European multicentre study). Only haplotypes with a frequency higher than 1% are shown. (p(χ^2) = single point p-value based on χ^2 test, OR = odds ratio). The presence of the G allele in SNPs 2, 3 and 4 in combination with allele C in SNP 1 showed a trend towards protection from high-grade lymphoma.

Haplotype	Healthy controls (n = 330) (%)	High-grade lymphoma (n = 53) (%)	p-Value (χ^2)	OR
C-A-A-A	28.9	37.0	0.095	1.4
C-G-G-G	**29.7**	**21.5**	**0.085**	**0.7**
T-A-G-G	13.9	16.0	0.564	1.2
T-A-A-A	20.5	18.7	0.666	0.9
T-G-G-G	5.7	5.8	0.954	1.0

Table 4 – Genotype distribution in patients with low grade and high grade primary gastric B-cell lymphoma (European multicentre study), H. pylori infected patients without gastric lymphoma and healthy controls (blood donors). Genotype distribution in healthy controls was in Hardy-Weinberg equilibrium (p > 0.05). Fischer's 2by3 was used to test for overall differences in genotype distribution (p(χ^2) = p-value based on Fischer's 2by3 χ^2 test, n.s. = not significant).

SNP	Genotype	Low grade lymphoma (n/%)	*H. pylori*+ (n/%)	p-Value (χ^2)	High grade lymphoma (n/%)	Healthy controls (n/%)	p-Value (χ^2)
1	C/C	25/28.7	229/39.0	n.s.	17/30.4	125/36.8	n.s.
	C/T	47/54.0	262/44.6		33/58.9	158/46.5	
	T/T	15/17.2	96/16.4		6/10.7	57/16.8	
2	A/A	49/57.7	267/45.5	n.s.	29/51.8	145/41.7	n.s.
	G/A	27/31.8	259/44.1		23/41.1	155/44.5	
	G/G	9/10.6	61/10.4		4/7.1	48/13.8	
3	G/G	13/15.1	128/22.1	n.s.	4/7.4	91/26.5	0.001
	G/A	45/52.3	297/51.3		39/72.2	163/47.4	
	A/A	28/32.6	154/26.6		11/20.4	90/26.2	
4	A/A	27/31.4	160/27.0	n.s.	12/21.8	89/26.4	0.013
	G/A	46/53.5	299/50.4		37/67.3	160/47.5	
	G/G	13/15.1	134/22.6		6/10.9	88/26.1	

Table 5 – Homozygosity for the rare allele was tested in cases and controls assuming a recessive model of inheritance (p(χ^2) = Pearson's χ^2 test, OR = odds ratio, Wald 95% CI = 95% confidence interval).

Cohort	SNP3 genotype	High grade lymphoma (n/%)	Healthy controls (n/%)	p-Value (χ^2)	OR (Wald 95% CI)
European multicentre study	G/G	4/7.4	91/26.5	p = 0.002	0.2
	G/A	39/72.2	163/47.4	(G/G)	(0.1–0.6)
	A/A	11/20.4	90/26.2		
Lymph node registry Kiel	G/G	16/22.9	91/26.5	p = 0.531	0.8
	G/A	33/47.1	163/47.4	(G/G)	(0.4–1.5)
	A/A	21/30.0	90/26.2		

grade lymphoma. Nevertheless, the presence of the G allele in SNPs 2, 3 and 4 in combination with allele C in SNP 1 showed a trend towards protection from low-grade (p = 0.098, OR = 0.7) and high-grade lymphoma (p = 0.085, OR = 0.7) (Tables 2 and 3).

3.2. *Linkage disequilibrium*

Pairwise linkage disequilibrium of all four markers revealed nearly complete LD between SNPs 2, 3 and 4 ($D' = 0.99$), whereas SNP1 is arranged in a different LD block.

3.3. *Single marker analysis*

Single marker analysis could narrow down the association signal to SNP3 in patients with gastric high-grade lymphoma who participated in the European multicentre study (German–Austrian-Lymphoma Study Group) (Table 4). Assuming a recessive model of inheritance patients homozygous for the rare allele G of SNP3 (rs12969413) are significantly protected from gastric high-grade lymphoma ($p = 0.002$, OR = 0.2, 95% CI = 0.1–0.6). To validate this association signal, SNP3 was genotyped in the gastric high-grade lymphoma cohort derived from the Lymph node registry in Kiel. But this finding could not be replicated ($p = 0.531$, OR = 0.8, 95% CI = 0.4–1.5) (Table 5).

4. Discussion

MALT1 interacts with BCL10 and Carma1 as a complex and activates the NF-kappaB pathway, giving rise to malignant B-cell transformation and lymphoma progression.[26,27] Deregulated MALT1 expression occurs in B-cell non-Hodgkin lymphoma of various histologic subtypes either through translocation to the immunoglobulin heavy chain locus or by genomic amplification.[28]

Furthermore MALT1 is shuttling between the nucleus and cytoplasm and regulates the subcellular location of BCL10. High nuclear levels of BCL10 are predictive for high-grade lymphomas.[29,30]

In our study we investigated germline variations of the *MALT1* gene as risk factors for the development of gastric MALT lymphoma. In contrast to 184 intronic SNPs of the *MALT1* gene no validated coding mutations are known according to the NCBI SNP database (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=snp). Nevertheless, intronic SNPs may interfere with splicing sites leading to a modified protein or a complete loss of function. To date no splice variants of *MALT1* transcripts have been described apart from API2–MALT1 fusion proteins.

Investigation of API2–MALT1 fusion proteins identified four breakpoints in introns 4, 6, 7 and 8 of the *MALT1* gene and only one breakpoint in intron 7 of the *API2* gene.[31,32] Comparative sequence analysis showed extensive alterations including deletions, duplications and non-template-based insertions at the fusion junctions. So far any search failed to reveal sequence specific motifs that might be associated with strand breaks and chromosomal recombination.[25] In addition to genetic variants in the promoter region intronic SNPs as well may influence gene transcription. RUNX1, for example, is a transcription factor exclusively involved in haematopoietic differentiation and inflammation. It is inactivated by translocations found in acute myeloid leukaemia and was shown to either repress or activate transcription.[33] A SNP in intron 4 of the *PDCD1* gene disrupts the predicted DNA-binding site for RUNX1 and confers a risk factor for systemic lupus erythematosus.[34]

Our initial association signal in the single marker analysis could not be confirmed in the second cohort of high-grade lymphoma patients. The fact that SNPs 2, 3 and 4 are arranged in one LD block exhibiting nearly complete linkage disequilibrium along with the negative haplotype analysis almost exclude any functional polymorphism at the *MALT1* locus.

Thus, our data does not support the hypothesis that germline variations of MALT1 may play a role as genetic risk factors in the development of primary gastric lymphoma.

Conflict of interest statement

None declared.

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