Gastric Marginal Zone Lymphoma Is Associated With Polymorphisms In Genes Involved In Inflammatory Response And Anti-Oxidative Capacity.


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Abbreviations used in this paper: GMZL, gastric marginal zone lymphoma; 95% CI, 95% confidence intervals; GST, Glutathione S-transferase; IL-1, Interleukin 1; IL-1ra, Interleukin 1 receptor antagonist; OR, odds ratio; PCR, polymerase chain reaction; VNTR, variable number tandem repeat; ROS, reactive oxygen species.

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Abstract

Gastric marginal zone lymphoma (GMZL) is strongly associated with Helicobacter pylori (H. pylori) infection, which induces an inflammatory response, subsequently resulting in the generation of DNA-damaging reactive oxygen species (ROS). The extent of damage will depend upon the severity of inflammation, the cellular antioxidant capacity, and the integrity of cellular DNA repair mechanisms. Interleukin-1 (IL-1) gene cluster polymorphisms have been shown to be important mediators of inflammation, while polymorphisms in the glutathione S-transferase GST T1 and GST M1 genes are believed to affect cellular antioxidant capacity. We aimed to determine whether polymorphisms at the IL-1 and GST T1 and GST M1 loci modulate the risk of developing GMZL. Archived peripheral blood and biopsy samples were collected for a historical series of 66 GMZL cases; while blood samples from 163 healthy controls were collected for use as a comparison series. Genotypes were determined for GST T1, GST M1, IL-1 RN, and IL-1B-31 using PCR based techniques. For the cases where H. pylori status could be determined, infection was found in 86.0%, while the prevalence of H. pylori infection in the control population was found to be 37.4%. The IL-1 RN genotype was significantly associated with risk of GMZL, (OR 5.51, 95% CI 2.16-14.07) for the IL-1 RN 2/2 genotype compared to the IL-1 RN 1/1. The IL-1B-31 genotype was not associated with GMZL risk. The GST T1 null genotype was strongly associated with risk of GMZL (OR 9.51, 95% CI 4.57-19.81), whereas the GST M1 null genotype was not associated with risk of GMZL. Evidence was found of effect modification between the IL-1 RN, and GST T1 genotypes (p=0.02). The combination of IL-1 RN 2/2 and GST T1 null genotype was most strongly associated with risk of GMZL (OR 32.29, 95% CI 6.92-150.63). These results support the hypothesis that the risk of developing GMZL is influenced by inter-individual variation in inflammatory response, modulating the immune response to H. pylori infection, and anti-oxidative capacity determining the body’s ability to detoxify ROS generated in the immune response.
INTRODUCTION

The association of gastric marginal zone lymphoma (GMZL) with prior infection by Helicobacter pylori (H. pylori) has been reported in both epidemiological and pathological studies. The onset of GMZL is preceded by the development of mucosa-associated lymphoid tissue (MALT), acquired as a result of H. pylori infection, which may undergo multi-step progression through monoclonal proliferation to malignant lymphoma. Transition to GMZL is associated with an increasing level of DNA damage within the infiltrating lymphoid tissue, a putative cause of which is oxidative stress generated as a consequence of H. pylori induced inflammation. Reactive oxygen species (ROS) are important mediators of this effect, and a direct correlation between the level of ROS and the level of DNA damage to the gastric mucosa has been reported. The severity of DNA damage occurring in an infected individual will depend on a number of factors, including the strain and virulence of H. pylori, the severity of the inflammatory response, and the individual’s ability to detoxify ROS. Therefore, H. pylori associated GMZL provides an ideal system in which to study the affects of genetic variation on important modulators of the immune response and on mediators of oxidative stress.

The immune response resulting from H. pylori infection is primarily via Th1, a pro-inflammatory response, mediated by a cascade of cytokines including Interleukin 18, Interleukin 12, Interleukin 1, tumour necrosis factor-α and interferon-γ. These cytokines regulate their own levels of expression by autocrine effects, but also influence downstream cytokine expression, thereby amplifying the inflammatory response. IL-1 is one of the principal pro-inflammatory cytokines that mediates the Th1 immune response following H. pylori infection, with IL-1β production being up-regulated in the presence of H. pylori. IL-1β is also one of the most powerful inhibitors of gastric acid secretion, the hypochlorhydria associated with high producer variants of IL-1 governing the
extent of *H. pylori* infection and distribution of gastritis. As a consequence, polymorphic variants in IL-1 may not only affect the primary inflammatory response, but also the level of response following amplification.

The *IL-1* gene cluster is situated on chromosome 2q, and is comprised of three related genes within a 430-kilobase region: *IL-1A, IL-1B* and *IL-1 RN*, which encode the pro-inflammatory cytokines IL-1α, IL-1β, and their endogenous receptor antagonist IL-1ra, respectively. Three biallelic polymorphisms in *IL-1B* have been described, all C>T base transitions found at positions -511, -31, and +3954 base pairs (bp) from the transcriptional start site. Strong linkage-disequilibrium between the *IL-1B*-31 C and *IL-1B*-511 T variants has been reported, with the *IL-1B*-31, *IL-1B*-511 T C haplotype occurring at a frequency of 0.38 in the Caucasian population. The *IL-1B*-31 polymorphism is situated within a TATA sequence of the *IL-1B* promoter, and has been shown to markedly affect DNA-protein interaction in vitro. The homozygous genotype *IL-1B*-31 TT has been associated with increased IL-1β production, but this finding remains unconfirmed.

For *IL-1 RN* a penta-allelic 86-bp variable number tandem repeat (VNTR) in intron 2 has been described, with the most common allele *IL-1 RN*#1 corresponding to 4 repeats. The *IL-1 RN*#2 allele corresponding to 2 repeats, has been reported at a frequency of 0.12 in the Caucasian population, and has been associated with chronic inflammatory conditions such as ulcerative colitis, and autoimmune conditions such as Sjögrens syndrome. The *IL-1 RN*#2 allele has been associated with enhanced IL-1β production in vitro; however, data regarding its effects on IL-1ra production are contradictory. It has been reported that *IL-1B* and *IL-1 RN* alleles are inherited as an extended haplotype, associated with inflammatory diseases.
Major cellular defence mechanisms against DNA damage are the glutathione S-transferase (GST) enzymes. In addition to their role in the detoxification of potential carcinogens by catalysing conjugation to glutathione, these enzymes also have a strong antioxidant function, neutralizing free radicals. There are four cytosolic GST families, including GST T1 and GST M1. Independent gene deletions exist at both the GST T1 and M1 loci resulting in a lack of active protein \(^{22}\), and the null genotypes of both loci have been associated with several malignancies \(^{23-27}\). We hypothesise that lack of GST T1 or M1 activity may be associated with an increased risk of developing GMZL in \(H. pylori\) infected individuals, and that this may be enhanced by interaction with the pro-inflammatory genotypes of \(IL-1\).

**METHODS**

**Subjects**

66 cases of GMZL (aged 38-86) were identified from multiple sources throughout the Yorkshire region, in the North of England. Archived samples, comprising paraffin blocks of biopsies, surgical specimens, and peripheral blood smears were obtained, as were available. Pure populations of normal cells were extracted where possible from biopsy and surgical blocks, the presence of tumor cell contamination monitored by comparison with sections stained with haematoxylin and eosin. Normal cells were present in all samples extracted, although the presence of a small amount of tumor material in some samples cannot be excluded. All cases were histologically validated according to the criteria of the Revised European-American Classification of Lymphoid Neoplasms (REAL) classification \(^{28}\), using the standard panel of markers utilized by the Hematological Malignancy Diagnostic Service at Leeds General Infirmary (CD20, 79, 10, 5, 23, 3, Ki67 and BCL-2). A reference series of 163 healthy population controls (aged 28-65) were
collected as part of an ongoing Lymphoma study being carried out by the LRF Epidemiology and Genetics Unit (main study paper in preparation), each control provided a blood sample. Ethical approval to establish a DNA repository for cases of hematological malignancy and to carry out a case-control comparison of genotypes was obtained from North and Yorkshire MREC.

Determination of *H. pylori* status

*H. pylori* status of the reference population was determined using a commercial ELISA system (Sigma) on frozen plasma. The *H. pylori* status of the cases was determined using the above ELISA test where plasma samples were available, in conjunction with microscopic inspection of gastric biopsy sections stained with modified giemsa by an expert pathologist to determine the presence or absence of the *H. pylori* bacterium. For the cases where it was possible to determine *H. pylori* status, 91% were determined by inspection of stained sections, and 9% using ELISA. An overlap for 1 case occurred, with identical results for *H. pylori* status being determined for both techniques.

Genotyping

Genomic DNA was extracted using the method of Jackson *et al*, 1990. In order to check the integrity of the DNA all samples extracted from paraffin blocks were amplified using a primer set expected to amplify a product of 600bp, ensuring that genotypic status was not miss-classified due to the absence of a PCR product resulting from poor quality DNA. *IL-1B-31* genotypes were determined using TaqMan™ allelic discrimination PCR. *IL-1 RN* alleles were determined using PCR product sizing, whereby products were sized relative to a 100bp DNA ladder and were coded as follows: allele 1 = 4 repeats (442bp), allele 2 = 2 repeats (270bp), allele 3 = 5 repeats (528bp), allele 4 = 3 repeats (356bp), allele 5 = 6 repeats (614bp); due to their rarity the 3, 4 and 5
alleles were grouped for statistical analysis. \textit{GST T1} and \textit{GST M1} genotypes were determined using PCR as previously described\textsuperscript{27, 30}, with the modification that an annealing temperature of 56°C was used. These assays do not allow for discrimination between carriers of one or two intact alleles. As such, heterozygous and homozygous wild type individuals were grouped for analysis.

Statistical Analysis

Within the case series, and within the population based control series, associations between age and \textit{H. pylori} status were tested using a non-parametric test for trend\textsuperscript{31}. Associations between sex, genotype and \textit{H. pylori} status were tested using Pearson’s chi-squared test, as were associations between age, sex, \textit{H. pylori} status and polymorphism distribution. Hardy Weinberg equilibrium was assessed for \textit{IL-1 RN}, and \textit{IL-IB-31} within the case and control series. Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI), associated with risk of GMZL, adjusted for age and sex. Statistical interactions were tested using the likelihood ratio test, by comparing the model with two genotype effects included as independent factors, against the model where both independent effects plus an interaction term were included\textsuperscript{32}. All analyses were conducted using STATA version 7.

RESULTS

The median age at diagnosis of the GMZL case-series was 65 years (range 38-86), with 27 (43.6%) being male. The median age of the reference population was 60 years (range 28-65) with 99 (60.7%) being male. \textit{H. pylori} status was determined for 50/66 (75.8%) of the GMZL cases, with 43 (86.0%) of the 50 cases confirmed as being positive for the presence of \textit{H. pylori}. \textit{H. pylori} status was determined for all individuals in the reference population with 61 (37.4%) individuals being \textit{H. pylori} positive. Among controls, positive \textit{H. pylori} status was significantly associated with
increasing age (P<0.01) but there was no significant difference in *H. pylori* distribution between the sexes.

**Distribution of IL-1 genotypes**

The distribution of *IL-1B-31* was not significantly associated with age or sex in either the case series or in the reference population (data not shown). Allele distributions at *IL-1B-31* were in Hardy-Weinberg equilibrium for both the cases and reference samples (P=0.17 cases, P=0.06 controls). The frequency of the *IL-1B-31* homozygous genotype (CC) in the reference population was 14.2%, in accordance with previously published data\textsuperscript{10, 11}. Although there was an increased incidence of the *IL-1B-31* CC genotype in the *H. pylori* negative controls (16.8%) compared to the *H. pylori* positive controls (9.8%), there was no statistically significant difference in *IL-1B-31* genotype distribution between these two groups (p=0.24). The *IL-1B-31* CC genotype was observed in 19.0% of the GMZL cases compared with 14.2% of the controls, with no associated risk of GMZL being suggested (OR 1.13, 95% CI 0.47-2.73) (table 1). The *IL-1B-31* CT genotype was observed in 34.9% of the GMZL cases compared with 40.1% of the controls, also with no associated risk of GMZL being suggested (OR 0.76, 95% CI 0.38-1.54).

The distribution of *IL-1 RN* was not significantly associated with age or sex in either the case series or in the reference population (data not shown). Allele distributions for *IL-1 RN* were in Hardy-Weinberg equilibrium for the controls (P=0.08), while the cases were strongly out of equilibrium (P=0.0001). The frequency of the *IL-1 RN* 2/2 genotype was 8.0% (table 1), in accordance with previously published data\textsuperscript{10, 11}. The *IL-1 RN* 2/2 genotype was present at a similar frequency in *H. pylori* negative controls 7.9%, and *H. pylori* positive controls 8.2%. The *IL-1 RN* 2/2 genotype was observed in 33.9% of cases compared to 8.0% in the control reference population, showing an association with an increased risk of GMZL (OR 5.51, 95% CI 2.16-14.07) (table 1). No
associations were seen with GMZL risk for either the 1/2 genotype (OR 0.66, 95% CI 0.29-1.53) or the 1/3,4,5 genotype (OR 1.87, 95% CI 0.48-7.31). No evidence was found for statistical interaction between the IL-IB-31 and IL-1 RN genotypes (p=0.25).

Distribution of GST genotypes

The frequency of the GST T1 null genotype in the reference population was 13.5% (table 1), which was comparable with previously published data. The distribution of GST T1 was not significantly associated with age or sex in either the case series or in the reference population (data not shown). The GST T1 null genotype was present in 16.7% of the H. pylori negative, and 8.2% of the H. pylori positive controls, there was no statistically significant difference in GST T1 genotype distribution (p=0.13) between these two groups. The GST T1 genotype was significantly associated with risk of GMZL, 57.6% of GMZL cases had the GST T1 null genotype compared with 13.5% of the reference population (OR 9.51, 95% CI 4.57-19.81).

The frequency of the GST M1 null genotype in the reference population was 54.6% (table 1), comparable with previously published data. The distribution of GST M1 was not significantly associated with age or sex in either the case series or in the reference population (data not shown). The GST M1 null genotype was present in 57.8% of the H. pylori negative controls and 49.2% of the H. pylori positive controls (p=0.28). The distribution of the GST M1 null genotype between the cases (62.1%) and reference population (54.6%) was similar (OR 1.10, 95% CI 0.59-2.07), suggesting no association with GMZL risk (table 1). No evidence was found for statistical interaction between the GST T1 and GST M1 genotypes (p=0.75).

Combination of GST T1 and IL-1 RN genotype
IL-1 RN and GST T1 were both found to have significant associations with risk when they were analysed together using a multiple variable logistic regression model. Evidence was found for a statistical interaction between IL-1 RN and GST T1 genotypes (p=0.02), suggesting that the effect of IL-1 RN may be modified depending on the GST T1 genotype and vice versa. Odds ratios, adjusted for age and sex, were calculated for each combination of the two genotypes (table 1), using GST T1 H/H and IL-1 RN 1/1 as the baseline genotype in the comparison. In combination with the GST T1 H/H genotype the estimated effect of IL-1 RN 1/2 was non-significant (OR 0.50, 95% CI 0.18-1.36), whereas in combination with the GST T1 null genotype a significant association was estimated (OR 4.82, 95% CI 1.08-21.41) (table 1). In combination with the GST T1 H/H genotype no significant effect was found for the IL-1 RN 2/2 genotype (OR 0.90, 95% CI 0.17-4.78), whereas in combination with the GST T1 null the IL-1 RN 2/2 genotype was associated with a significant risk (OR 32.29, 95% CI 6.92-150.63). These results suggest that the risk associated with the IL-1 RN 2 allele may be dependent on the additional presence of the GST T1 null genotype.

DISCUSSION

Our results suggest that the development of GMZL is modulated by genetic variants at both the IL-1 and GST loci. It is proposed that the genetic variants analyzed modulate the severity of the immune response to H. pylori, and determine the body’s anti-oxidative capacity, (figure 1).

Two previous studies investigating the role of IL-1 RN and IL-1B genotypes on gastric cancer susceptibility have been carried out 10, 11, 34. Both reported an increased associated risk of gastric carcinoma with inheritance of the IL-1B-31 (CC) /IL-1 RN 2/2 genotype. The authors suggest
that the IL-1B-31 C allele in the context of H. pylori infection is associated with a pro-inflammatory phenotype, and therefore an increased risk of DNA damage and ultimately gastric carcinoma. However, reports on the functional effects of the IL-1B-31 polymorphism are conflicting, and functional effects at cytokine loci are often governed by extensive haplotypes.

Our data suggests a significant association between GMZL and inheritance of the IL-1 RN 2/2 genotype, consistent with that previously observed in gastric carcinoma. In contrast, we found no associated risk with IL-1B-31 genotype. An explanation for this may be that changes in IL-1 pro-inflammatory responses associated with IL-1B-31 may be mediated via an interaction with IL-1 RN, however we found no evidence for this in our data.

IL-1 RN encodes the IL-1 receptor antagonist IL-1ra, the IL-1 RN*2 allele has been associated with decreased IL-1ra levels, and consequently increased IL-1β levels. We postulate that the association between the IL-1 RN *2 allele with GMZL functions via a similar mechanism to that seen in gastric carcinoma. The high IL-1β levels associated with the IL-1 RN *2 allele favor the pro-inflammatory response, at the same time the concomitant inhibition of gastric acid facilitates widespread H. pylori colonization of the gastric mucosa, promoting the development of MALT in response to infection. This decreased gastric acid secretion may also heighten DNA damage by permitting superinfection by enteric bacteria that enhance the production of carcinogenic N-nitroso compounds. H. pylori induced hypochlorhydria also significantly decreases levels of vitamin C in gastric juice, further facilitating the formation of N-nitroso compounds.

We describe a significant association between the null genotype of GST T1 and increased risk of GMZL. No effect was observed for the GST M1 null genotype. Associations between the
GST T1 null genotype and increased risks of astrocytoma, meningioma, myelodysplasia, and acute myeloid leukaemia, have been reported. GST T1 has a strong antioxidant function in neutralising free radicals. We propose that in GMZL, the associated risk seen with the GST T1 null genotype is due to compromised antioxidant capacity and not due to the metabolism of a specific xenobiotic substrate. Combinations of genetic variants, which increase IL-1β levels, promoting the immune response to H. pylori infection and the production of ROS, plus variants that decrease the levels of antioxidants would likely increase the risk of GMZL further (figure 1). We found evidence of modulation of effect between the IL-1 RN and GST T1 genotypes and GMZL risk illustrating that both play an important role in the pathway of disease development.

H. pylori has been shown to be an infection strongly linked to the development of GMZL, thus in our hypothesis the effects of IL-1 variants would be through their modulation of the immune response to H. Pylori, and the effects of GST variants would be through the anti-oxidative capacity they provide, enabling the body to detoxify ROS produced in this response. For cases where H.pylori status could be determined, 86.0% were positive for the presence of the bacterium, however the frequency of both the GST T1 null and IL 1 RN 2/2 genotypes was similar in cases determined as H. pylori positive and those with unknown or negative status. However the absence of H. pylori in the biopsy blocks examined does not preclude the presence of H. pylori elsewhere in the gastric mucosa. The demonstrated presence of H. pylori in the majority of cases strongly supports the link between the presence of H. pylori and development of GMZL in our case series. Within the reference population no associations were found between the IL-1-31, IL-1 RN, GST T1 or GST M1 genotypes and H. pylori status, providing no evidence that these genes are associated with the development of H. pylori infection. The whole reference population serves well as a group
with which to make comparisons of genotype frequencies in the cases, to determine which genotypes may modulate the development of GMZL subsequent to *H. pylori* infection.

A small proportion of GMZL may not necessarily be associated with *H. pylori*, such as those in patients with autoimmune disease [38]. Ideally we would have been able to classify cases as to whether or not they were *H. pylori* associated, and evaluate the genotype effects within the two subgroups. From the archive samples it could not be definitively demonstrated that *H. pylori* had not been involved, *H. pylori* serology and or presence in tissue may change with increasing pathologic progression and thus *H. pylori* may not always be evident in samples of more advanced disease. Analysis restricted to cases and controls where *H. pylori* status had been demonstrated estimated effects for *GST T1* and *IL-1 RN* consistent with the full analysis. The *IL-1 RN 2/2* genotype was seen in 30.0% of the cases, compared with 8.2% in the controls (OR 3.93, 95% CI 1.08-14.33). The *GST T1* genotype was seen in 58.1% of the cases compared with 8.2% in the controls (OR 15.01, 95% CI 4.67-48.23). Making this restriction substantially reduced the number of cases and controls, and the precision of the estimates was reduced, particularly for the more rare variants. Differential effects of the *IL-1 RN 2/2* genotype in combination with *GST T1* were not observed in this restricted analysis, as had been observed in the full analysis, however this may have been because of limited statistical power due to small numbers. No evidence was found for a differential frequency of the *GST T1 null* and *IL-1 RN 2/2* genotypes between cases determined as *H. pylori* positive and those with unknown or negative status.

Within the study we were unable to obtain samples from population controls of a comparable age for all the cases. Population controls aged between 28 and 65 were used as a reference population for cases aged 38-86. In a study of metabolic gene polymorphism frequencies
in control populations\textsuperscript{33}, it has been shown that the allele frequencies of metabolic genes including \textit{GST M1} and \textit{GST T1} do not differ significantly by age. Within our control series age was not significantly associated with the allele frequencies of any of the genotypes used in our analyses. This would indicate that the controls could act as an appropriate reference group for the older cases. Adjusting for age and sex in our analyses of association between genotype and risk of GMZL did not alter the estimates to any substantial degree. Similarly repeating the analyses using data restricted to cases and controls of comparable ages did not produce estimates substantially different to the estimates based on the full data (data not shown). This confirmed that the age differences between the case-series and population controls were not leading to bias in our estimates.

The limited statistical power of small studies to detect associations between polymorphic genotypes and disease predisposition is particularly important with regard to effect modification. To achieve adequate statistical power to estimate individual gene effects with good precision, and further describe interaction between genes, large sample sizes may be required \textsuperscript{39}. This study, although small, suggests associations between genotypes and susceptibility to GMZL, which it would be valuable to investigate further in larger studies.

This study provides support for the hypothesis that the risk of developing GMZL is influenced by inter-individual variation in inflammatory response and anti-oxidative capacity, particularly through combination of the effects of the \textit{IL-1 RN} genotype and \textit{GST T1} genotype. \textit{H. pylori} infection, the anticipated exposure, was confirmed in the majority of the cases and it is proposed that the genetic variants analyzed modulate the effects of this exposure.
The model which we describe is common to the development of gastric carcinoma, and it would be valuable to determine whether there are also parallels, in genetically determined risk, with the development of other MALT lymphomas, such as the marginal zone lymphomas occurring at the site of inflammation in Hashimoto’s thyroiditis and Sjögren’s disease. Excesses in risk of the Non Hodgkin’s Lymphomas have been described for patients with various conditions involving substantial immune dysfunction, particularly conditions where chronic antigenic stimulation is present. The consideration of polymorphisms involved in the immune response, in combination with those involved with the prevention of DNA damage, and further those involved in DNA repair, could allow the mechanisms underlying these associations to be explored further.
Table 1. Comparison of IL-1B-31, IL-1 RN, GST T1 and GST M1 gene frequencies in the GMZL case series and the reference population.

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*H/H; heterozygous/ homozygous wild type
Figure 1. Model to assess genetic modification of risk for *H. pylori* induced GMZL

- Altered gastric pH
- Altered Gastric Flora
- Generation of genotoxins
- *H. pylori* Infection
- Induction of MALT
- IL1 variants
- Gastritis
- DNA damage
- GST variants
- Reactive oxygen species
- Antioxidant Status
- DNA damage
- Diffuse Large B-cell NHL
- Inflammation
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Gastric marginal zone lymphoma is associated with polymorphisms in genes involved in inflammatory response and anti-oxidative capacity

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