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Association between a pro-inflammatory genetic profile and the risk of chronic atrophic gastritis among older adults from Germany

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ABSTRACT

Background: Pro-inflammatory polymorphisms have been suggested to explain part of the individual diversity in susceptibility to gastric carcinogenesis. We aimed to assess their impact on the risk of chronic atrophic gastritis (CAG) in a population-based study.
Methods: Among 9953 older adults from Saarland/Germany, eight single nucleotide polymorphisms (SNPs) were assessed for 534 cases with serologically defined CAG and 534 age- and sex-matched controls at baseline examination.
Results: Of the 8 SNPs, only *IL10* T-819C showed a borderline significant association with CAG risk (odds ratio for CC versus TT: 1.67 (95% confidence interval: 1.01–2.76)). No significant differences were observed for the distribution of inferred haplotypes between cases and controls. However, joint evaluation of several cytokine variants suggested an increased risk of CAG among individuals carrying several pro-inflammatory genotypes.
Conclusions: Our findings suggest that a pro-inflammatory genetic profile may contribute to inter-individual variation in gastric cancer risk by increasing the susceptibility to the development of CAG.

1. Introduction

Chronic atrophic gastritis (CAG) is an established precursor of intestinal type gastric cancer, which is the second most common cause of cancer-related death worldwide.[1,2] *Helicobacter pylori*, which is prevalent in 50% of the world's population, is the major cause to trigger gastric inflammation and carcinogenesis.[3] However, only a small fraction of the infected people develops gastric cancer or its precursors. This clinical diversity suggests that factors other than bacterial infection alone determine carcinogenesis. Apart from virulence factors of the pathogen and other environmental risk factors, host genetic risk factors, such as polymorphisms in cytokine genes involved in the local gastric immune response, are likely to contribute.[4,5]

Genetic polymorphisms of inflammatory cytokines, determining the extent and severity of gastric mucosal inflammation, have been widely studied as potential predictors for the chronic inflammatory pathway leading to gastric cancer[6]: variants of genes encoding interleukin-1α (*IL1A*), interleukin-1β (*IL1B*) and tumour necrosis factor-α (*TNFA*) were shown to be associated with *H. pylori* infection[7–9]; polymorphisms of *IL1B*, IL1 receptor antagonist gene (*IL1RN*), *IL8* and *IL10* have been identified as predictors for gastric cancer precursors.[10] However, some other studies failed to confirm any association of cytokine gene polymorphisms with gastric cancer development.[11,12] Reasons for these discrepant results are subject to ongoing discussion. Population differences in sample size, ethnicities and prevalence of various aetiologic factors have been suggested as possible explanations.[13]

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The objective of this study was to assess the association of selected inflammatory polymorphisms with the risk of CAG in cases and controls drawn from a population-based study from Germany.

2. Materials and methods

2.1. Study population

The study population selection and data analyses are based on the baseline examination of the ESTHER-study, a large population-based study conducted among older adults in Germany to investigate new avenues of prevention and early detection of chronic diseases in the elderly. Details of the study design have been described elsewhere.[14] Briefly, 9953 participants (45% males), aged 50–74 years (mean age: 62 years), were recruited between July 2000 and December 2002 by their general practitioners during a general health check-up in Saarland, a state in the south-west of Germany. The study was approved by the ethics committees of the medical faculty of the University of Heidelberg and of the medical board of the state of Saarland. Written informed consent was obtained from each participant. In total, 534 participants without gastric cancer history were serologically defined as CAG cases (see below) at baseline examination. All of them together with a stratified random sample of 534 non-CAG controls (frequency matched on sex and 5-year age group) were included in the present analyses.

2.2. Data collection

2.2.1. Questionnaires

A standardised questionnaire was completed by every participant, providing information on socio-demographic characteristics, medical history, health status, family history and lifestyle factors.

2.2.2. Serological examinations

Serum samples were obtained from all participants and stored at –80 °C. Serum concentrations of pepsinogen (PG) I and II were measured by ELISA (Biohit, Helsinki, Finland) to define CAG. A coefficient of variation (CV) (between-assay precision, within-assay precision) of 6.6% and 3.1% for the PG I ELISA and of 6.8% and 4.5% for the PG II ELISA has been reported. Applying the most frequently used serological definition, CAG was assumed to be present when PG I < 70 ng/mL and PG I/II < 3.[15] Descriptive statistics of the PG I/II levels among study subjects are presented in Supplementary Table. Infection with *H. pylori* was assessed serologically by a commercial ELISA based on antibodies to IgG (ravo Diagnostika, Freiburg, Germany). Classification of infection status followed the manufacturers' instructions and borderline results were treated as negative. All analyses were carried out in a blinded fashion in the same laboratory.

2.2.3. Genotyping analysis

Eight single nucleotide polymorphisms (SNPs) in seven cytokine genes were assessed, including *IL1A* C-889T (rs1800587), *IL1B* C-511T (rs16944), *IL1RN* A9589T (rs454078), *IL8* T-251A (rs4073), *IL10* T-819C (rs1800871), *IL10* A-1082G (rs1800896), *LTA* C+80A (rs2239704) and *TNFA* G-308A (rs1800629). Genotyping of the polymorphisms was performed by Pyrosequencing™ technology (Biotage, Uppsala, Sweden). Primer sequences can be obtained from the authors upon request. Repeated measurements of a random 6% subset of samples yielded >99.5% identical results. Based on the previous publications, the following genotypes were considered to be the pro-inflammatory variants: *IL1A* -889TT, *IL1B* -511TT, *IL1RN* 9589TT, *IL8* -251AA, *IL10* -819CC, *IL10* -1082AA, *LTA* +80AA and *TNFA* -308AA.[16–18]

2.3. Statistical analysis

Hardy–Weinberg equilibrium was examined in controls using asymptotic Pearson's chi-square test for each SNP. Unconditional logistic regression analysis was used to estimate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) comparing cases to controls in association with genotypes using dominant, recessive and co-dominant models, respectively, adjusted for age and sex. Linkage disequilibrium (LD) was assessed by Linkage Disequilibrium Analyser software (http://www.chgb.org.cn/lda/lda.htm). Haplotypes were reconstructed from genotype data using Unphased software (version 3.0.12) (http://www.stat.washington.edu/stephens/software.html). The associations between inferred haplotypes and CAG risk were estimated by unconditional logistic regression adjusting for age and sex. To estimate the combined impact of a pro-inflammatory profile, risk of CAG was assessed according to the number of pro-inflammatory genotypes.

All statistical analyses were carried out using SAS statistical software, release 9.1.

3. Results

The distribution of the study population by sex, age and *H. pylori* infection is provided in Table 1. Fifty eight percent of cases and controls were women. Median age was 65 years, and more than 80% of participants were between 60 and 74 years of age. Seroprevalence of *H. pylori* was more common among cases than among controls (75.1% versus 52.8%, $p < 0.01$).

Table 1 – Distribution of the study population by sex, age and *H. pylori* infection

	Cases		Controls	
	N	%	N	%
Total	534	100	534	100
Sex				
Female	310	58.1	310	58.1
Male	224	41.9	224	41.9
Age				
50–54 years	44	8.2	44	8.2
55–59 years	59	11.1	59	11.1
60–64 years	132	24.7	132	24.7
65–69 years	165	30.9	165	30.9
70–74 years	134	25.1	134	25.1
H. pylori infection				
No	133	24.9	252	47.2
Yes	401	75.1	282	52.8

Genotyping data for each SNP were successfully obtained for >95% of the subjects. Among controls, the genotype distribution for each of the eight assessed SNPs was in Hardy–Weinberg equilibrium (data not shown). Associations between each of the SNPs and the presence of CAG in co-dominant, dominant and recessive models are shown in Table 2. A significant association was only observed for *IL10* T-819C, with an OR of 1.67 (95% CI: 1.01–2.76) for CC genotype carriers when compared with the more frequent TT genotype carriers. None of the other 7 SNPs was significantly associated with the presence of CAG.

Linkage disequilibrium analysis suggested that all the three loci in IL1 cluster genes (*IL1A* C-889T, *IL1B* C-511T and *IL1RN* A9589T) were in LD with each other. Compared with the most common *IL1A/1L1B/1LIRN* haplotype CCA (consisting of the common allele from each polymorphic site), no significant association was observed for haplotypes containing at least one variant allele (Table 3). The genotype distributions of (i) *IL10* T-819C and A-1082G and (ii) lymphotoxin-α gene (*LTA*) C+80A and *TNFA* G-308A were also in LD, respectively. *IL10* and *LTA/TNFA* haplotype distributions in cases and controls were likewise not significantly different (Tables 4 and 5).

As shown in Table 6, an increased risk was observed for subjects carrying several pro-inflammatory genotypes. Individuals carrying three or more pro-inflammatory genotypes were at a significantly increased risk with an OR of 1.72 (95% CI: 1.03–2.89) compared to those carrying no such variants.

Table 2 – Associations between genotypes and CAG risk

Genotype	Model	Cases	Controls	OR (95% CI)[a]
IL1A C-889T (rs1800587)	CC	276	282	Ref.
	CT	213	203	1.07 (0.83–1.38)
	TT	37	43	0.88 (0.55–1.41)
	Dominant	TT + CT versus CC		1.04 (0.82–1.32)
	Recessive	TT versus CT + CC		0.85 (0.54–1.35)
IL1B C-511T (rs16944)	CC	263	248	Ref.
	CT	205	230	0.84 (0.65–1.09)
	TT	59	52	1.07 (0.71–1.62)
	Dominant	TT + CT versus CC		0.88 (0.69–1.12)
	Recessive	TT versus CT + CC		1.16 (0.78–1.72)
IL1RN A9589T (rs454078)	AA	273	277	Ref.
	AT	212	219	0.98 (0.76–1.26)
	TT	39	35	1.13 (0.70–1.84)
	Dominant	TT + AT versus AA		1.00 (0.79–1.28)
	Recessive	TT versus AT + AA		1.14 (0.71–1.83)
IL8 T-251A (rs4073)	TT	152	161	Ref.
	TA	273	254	1.14 (0.86–1.51)
	AA	100	114	0.93 (0.65–1.32)
	Dominant	AA + TA versus TT		1.07 (0.82–1.40)
	Recessive	AA versus TA + TT		0.98 (0.82–1.16)
IL10 T-819C (rs1800871)	TT	283	300	Ref.
	TC	200	199	1.07 (0.83–1.38)
	CC	44	28	**1.67 (1.01–2.76)**
	Dominant	CC + TC versus TT		1.14 (0.89–1.46)
	Recessive	CC versus TC + TT		**1.63 (1.00–2.66)**
IL10 A-1082G (rs1800896)	AA	169	148	Ref.
	AG	246	262	0.82 (0.62–1.09)
	GG	109	116	0.82 (0.58–1.16)
	Dominant	GG + AG versus AA		0.82 (0.63–1.07)
	Recessive	GG versus AG + AA		0.93 (0.69–1.25)
LTA C+80A (rs2239704)	CC	156	158	Ref.
	CA	253	259	0.99 (0.75–1.31)
	AA	112	108	1.05 (0.75–1.48)
	Dominant	AA + CA versus CC		1.00 (0.77–1.31)
	Recessive	AA versus CA + CC		1.06 (0.79–1.42)
TNFA G-308A (rs1800629)	GG	389	393	Ref.
	GA	125	129	0.98 (0.74–1.30)
	AA	13	8	1.64 (0.67–4.02)
	Dominant	AA + GA versus GG		1.02 (0.77–1.34)
	Recessive	AA versus GA + GG		1.65 (0.68–4.03)

Abbreviations: CAG, chronic atrophic gastritis; CI, confidence interval; and OR, odds ratio.
a Adjusted for age and sex.

Table 3 – Frequencies of inferred IL1A/IL1B/IL1RN haplotypes

Haplotypes[a]			Frequencies[b]				OR (95% CI)[c]
			Cases		Controls		
IL1A C-889T	*IL1B* C-511T	*IL1RN* A9589T	*N*	%	*N*	%	
C	C	A	357	37.0	378	39.2	Ref.
T	C	A	232	24.0	221	22.9	1.11 (0.88–1.41)
C	T	T	133	13.9	153	15.9	0.93 (0.70–1.22)
C	T	A	127	13.2	124	12.9	1.09 (0.80–1.48)
C	C	T	114	11.9	88	9.1	1.38 (0.98–1.93)

Abbreviations: CI, confidence interval and OR, odds ratio.
a All of the three loci were in LD with each other ($\chi^2 = 39.18$, $p < 0.001$ and $D' = 0.33$ for *IL1A/IL1B*; $\chi^2 = 50.50$, $p < 0.001$ and $D' = 0.41$ for *IL1A/IL1RN*; $\chi^2 = 295.82$, $p < 0.001$ and $D' = 0.41$ for *IL1B/IL1RN*).
b Haplotypes with frequencies <5% are not reported.
c Adjusted for age and sex.

Table 4 – Frequencies of inferred IL10 haplotypes

Haplotypes[a]		Frequencies				OR (95% CI)[b]
		Cases		Controls		
T-819C	A-1082G	*N*	%	*N*	%	
T	G	464	44.3	492	47.1	Ref.
T	A	300	28.6	302	28.9	1.05 (0.86–1.29)
C	A	284	27.1	250	24.0	1.21 (0.97–1.49)

Abbreviations: CI, confidence interval and OR, odds ratio.
a These two loci were in LD with $\chi^2 = 14.92$, $p < 0.001$; and $D' = 0.23$.
b Adjusted for age and sex.

Table 5 – Frequencies of inferred LTA/TNFA haplotypes

Haplotypes[a]		Frequencies				OR (95% CI)[b]
		Cases		Controls		
LTA C+80A	*TNFA* G-308A	*N*	%	*N*	%	
C	G	473	45.4	481	45.8	Ref.
A	G	425	40.7	428	40.7	1.01 (0.83–1.23)
C	A	92	8.9	94	8.9	1.00 (0.70–1.43)
A	A	53	5.0	47	4.5	1.14 (0.71–1.84)

Abbreviations: CI, confidence interval and OR, odds ratio.
a These two loci were in LD with $\chi^2 = 604.28$, $p < 0.001$; and $D' = 1.00$.
b Adjusted for age and sex.

Table 6 – Association between number of pro-inflammatory genotypes and CAG risk

No. of pro-inflammatory genotypes[a]	Cases		Controls		OR (95% CI)[b]
	N	%	*N*	%	
0	166	32.2	164	31.5	Ref.
1	197	38.2	214	41.2	0.89 (0.67–1.18)
2	105	20.3	115	22.1	0.88 (0.63–1.24)
⩾3	48	9.3	27	5.2	**1.72 (1.03–2.89)**
P for linear trend					0.30

Abbreviations: CAG, chronic atrophic gastritis; CI, confidence interval; and OR, odds ratio.
a Pro-inflammatory genotypes: *IL1A* -889TT, *IL1B* -511TT, *IL1RN* 9589TT, *IL8* -251AA, *IL10* -819CC, *IL10* -1082AA, *LTA* +80AA and *TNFA* -308AA.
b Adjusted for age and sex.

4. Discussion

To our knowledge, this is the largest epidemiological study that addressed the role of pro-inflammatory polymorphisms for the susceptibility to CAG. A pro-inflammatory genetic profile was weakly associated with the risk of CAG among the older adults from Germany. A significant association was observed for *IL10* T-819C. None of the other 7 SNPs (*IL1A* C-889T, *IL1B* C-511T, *IL1RN* A9589T, *IL8* T-251A, *IL10* T-819C, *LTA* C+80A and *TNFA* G-308A) was individually related to CAG. No significant differences were observed between cases and controls for the prevalence of inferred haplotypes in *IL1A/IL1B/IL1RN*, *LTA/TNFA* and *IL10* genes, respectively.

In the past few years, cytokine gene polymorphisms have been linked to individual susceptibility to *H. pylori* infection and the development of gastric cancer. IL-10 is a multifunctional anti-inflammatory cytokine that inhibits the production of pro-inflammatory cytokines such as IL-1β and TNF-α to down-regulate the inflammatory response. Polymorphisms in the 5′-flanking region of *IL10* at positions A-1082G, T-819C and A-592C were shown to be related with high transcriptional promoter activity.[19] All of them and the combined haplotypes have been suggested to be associated with gastric cancer risk in different populations.[20,21] A-1082G and T-819C have also been related to intestinal metaplasia in Venezuelan and Italian populations.[22,23] In our study *IL10* T-819C, but not A-1082G, was significantly associated with an increased risk for CAG. This finding is consistent with the results of Sugimoto et al.,[24] who reported carriage of the *IL10* -819C allele to be associated with an increased risk for gastric cancer, while no such association was seen for *IL10* A-1082G. However, the effects of *IL10* T-819C on the development of gastric cancer seem controversial. *IL10* 819T allele was observed to be related with an increased risk of *H. pylori* infection and gastric cancer.[6,23,25] In addition, a case-control study performed in Finland did not find a significant association between this polymorphism and gastric cancer.[12] While such inconsistency may be partly explained by the different genetic background of the study populations, further studies are required to clarify the role of *IL10* polymorphisms in the process of gastric carcinogenesis.

IL-1β and TNF-α have been widely studied, both as pro-inflammatory cytokines and acid inhibitors.[26] Whether the stronger inflammatory response induced by their genetic variants will result in the elimination of *H. pylori* or whether the higher intragastric pH will render people more susceptible to *H. pylori* infection remains unclear. *IL1B* -511T allele and *TNFA* -308A allele have been reported to exhibit higher expression levels of IL-1β and TNF-α and to be associated with increased risk for *H. pylori* infection.[8,9] Recently, they have also been identified as potential risk factors for CAG and gastric cancer.[27] Possibly, these pro-inflammatory genotypes play more important roles during the chronic inflammation process, but do not enhance primary immune protection against *H. pylori*. However, some other studies failed to confirm an association with *H. pylori* infection and gastric cancer development.[11,12] In our study, *IL1B* C-511T and *TNFA* G-308A were likewise not significantly associated with the risk of CAG. *IL1RN* A9589T, which is associated with the expression level of IL-1β,[16] was not related to the presence of CAG as well.

A common SNP, T-251A, in the promoter region of IL-8 gene was identified, and the A allele was associated with increased production of IL-8 *in vitro*.[17] Increased risks for CAG and dysplasia were reported for individuals with the -251A/A genotype.[8] However, such an association was not confirmed in our study population. The other two inflammatory genotypes we assessed, *LTA* C+80A and *IL1A* C-889T, are known to influence the expression level of corresponding cytokines.[7,18] To our knowledge, the current study is the first to explore their role in CAG aetiology; however, no significant associations were observed.

Combined analysis suggested that a pro-inflammatory profile may contribute to CAG risk. Our result is consistent with the results of the previous studies among Portuguese and American populations, where subjects carrying several pro-inflammatory polymorphisms were more susceptible to CAG and gastric cancer.[6,27] These findings provide further support to the hypothesis that host genetic factors which affect the inflammatory response may partly explain inter-individual differences in susceptibility to gastric carcinogenesis. In some other populations, however, such an association was not observed.[11,12] Different genetic background of the studied populations may underlie this inconsistency. Furthermore, due to the multistage character of gastric cancer, genetic factors may play a role at specific stages only and they may interfere with non-genetic risk factors, such as dietary factors, which strongly vary between populations. Therefore, stratification by ethnicity and specific stages appears to be crucial in future studies aiming to clarify the impact of genetic polymorphisms on gastric carcinogenesis. In addition, we cannot exclude the possibility that our positive finding may be due to chance because no dose-response effect was found for the number of pro-inflammatory genotypes on CAG risk in our analyses.

In fact, our study differs from most previous investigations in that CAG rather than gastric cancer was used as end-point. Thus, our results may primarily refer to the early stage of carcinogenesis. However, results were very similar when the analysis was restricted to severe forms of CAG only (defined by PG I < 20 ng/mL and PG I/II < 3), an end-point that is close to gastric cancer.

In the interpretation of our data, some limitations have to be considered. The definition of CAG based on serum pepsinogen concentrations cannot be claimed to be perfect. However, high levels of agreement with classification by gastroscopy with subsequent histological examination of biopsies have been observed, even though the latter has been shown to bear a considerable observer variation[28] and to suffer from sampling error.[29] In addition, we examined only 8 SNPs in 7 genes. The small number of selected SNPs may thus not reflect the whole picture of pro-inflammatory polymorphisms, even though we selected variants with strong indication for their functional relevance in relation to the pro-inflammation phenotypes. Furthermore, the association between *IL10* T-819C and CAG risk possibly originates from the influence of other alleles that are in LD. Although being one of the largest studies on genetic risk factors for CAG reported to date, our study only had limited power to detect weak associations that would be expected for multifactorial diseases such as CAG. Furthermore, no adjustment for multi-

ple comparisons was made, and the possibility that the only significant association for single SNPs was due to chance has to be kept in mind. Further and larger studies, preferably large collaborative studies, are needed to investigate a broader range of polymorphisms in genes possibly related to gastric carcinogenesis.

Ideally, the impact of pro-inflammatory polymorphisms should be addressed separately in *H. pylori* positive and *H. pylori* negative subjects. However, given the frequent secondary clearance of the infection in the course of development of CAG,[30] which makes the interpretation of such analyses very difficult and complicated, we refrained from such analyses in the present study.

Despite its limitations, our study suggests that a pro-inflammatory profile may increase the host susceptibility to the development of CAG. Further functional studies and larger population-based prospective cohort studies are essential to fully understand the role of inflammatory polymorphisms in gastric carcinogenesis.

Conflict of interest statement

None declared.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2008.09.019.

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