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Risk of advanced gastric precancerous lesions in *Helicobacter pylori* infected subjects is influenced by ABO blood group and *cagA* status

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Abstract

A higher incidence of stomach cancer in ABO blood type A individuals than in those with blood type O has been known for a long time. We studied this association in relation to *Helicobacter pylori* (Hp) of different *cagA* status.

For this study we used baseline gastric histopathology data and DNAs from frozen gastric biopsies of 2077 subjects enrolled in a chemoprevention trial for gastric precancerous lesions in Venezuela. We analyzed 6 single nucleotide polymorphisms in the *ABO* gene and we assessed the presence of the Hp *cagA* gene. Odds ratios for risk of advanced precancerous gastric lesions were calculated using individuals with normal gastric epithelium or non-atrophic gastritis as a reference.

Among individuals carrying a *cagA* negative Hp infection or no Hp infection, those with blood type A had a lower risk of intestinal metaplasia and dysplasia than those with blood type O (OR=0.60; 95% CI 0.38-0.94). In carriers of *cagA* positive Hp strains, individuals with blood type A had a higher risk of intestinal metaplasia or dysplasia than those with blood type O (OR=1.42, 95% CI 1.09-1.86) and a higher risk if compared with subjects carrying cagA$^-$ strain and non-A blood group (OR=3.82, 95%CI=2.80-5.20). The interaction between Hp *cagA* status and blood type was statistically significant (P=0.0006).

We showed that SNPs in the *ABO* gene, predictive of ABO blood groups, are associated with risk of advanced precancerous gastric lesions in individuals infected with Hp, but the assessment of the risk is strictly dependent on *cagA* status.

Keywords

Helicobacter pylori; ABO blood groups; risk of preneoplastic gastric lesions

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Introduction

Helicobacter pylori (Hp) is one of the most common chronic bacterial infections in humans and it has been acknowledged to be a causative factor for gastric adenocarcinoma. To colonize mucosal surfaces and invade the epithelium, microbes, including Hp, commonly interact with glycan structures of the host glycocalyx. In particular, the adherence of Hp to the human gastric epithelial lining can be mediated by the blood-group antigen-binding adhesin (BabA) that targets human fucosylated blood group antigens H type I (type O substance) and Lewis b (Leb) [1, 2]. Secure attachment is crucial for bacteria to transfer their virulence molecules, such as the CagA protein, to host cells. The *cagA* gene resides within the cytotoxin-associated gene pathogenicity island (cagPAI) of the Hp genome, and is responsible for most of the Hp-associated malignant phenotypes: it triggers IL-8 secretion priming an inflammatory response, promotes cell proliferation, scattering and migration through phosphorylation-dependent and independent mechanisms [3, 4].

A higher proportion of ABO blood type A in gastric cancer patients than in control individuals was noticed as early as in the 1950s [5].

The *ABO* gene encodes enzymes known as glycosyltransferases which transfer specific sugar residues to a precursor substance (the H antigen) to produce the A and B antigens. Glycosylation is one of the most prevalent modifications mediated by complex enzymatic machinery, whereby glycans (sugars) are covalently attached to specific amino acid sites of proteins. Glycans have important biological functions in protein maturation and turnover, cell adhesion and trafficking, and receptor binding and activation [6].

There are three major alleles at the *ABO* locus on chromosome 9q34: A, B and O, defined by single base deletions and substitutions (SNP) occurring in exons 6 and 7. The A allele encodes α1→3 N-acetylgalactosaminyltransferase, which adds N-acetylgalactosamine (GalNAc) to the H antigen to form the A antigen. The B allele encodes α1→3 galactosyltransferase which transfers galactose to the H antigen to construct the B antigen [7]. The O allele does not produce an active enzyme [7]. Four SNPs at nucleotides (nt) 526, 703, 796 and 803 resulting in amino acid substitutions (Arg176Gly, Gly235Ser, Leu266Met and Gly268Ala) explain all the differences in the activity and the nucleotide-sugar donor specificity of the A and B transferases. In addition, a base substitution (rs1053878) at nt 467, resulting in an amino acid substitution (Pro156Leu), distinguishes the A1 from A2 subtypes. A2 is present in approximately 20% of subjects with A blood group among Caucasians and shows an intermediate phenotype, between the “full” enzymatic activity defined by the A1 allele and the nonfunctioning enzyme defined by the O allele [8].

Although the association between ABO blood groups and risk of gastric cancer is well established, very little is known about the possible relation between ABO blood groups and preneoplastic gastric lesions, in particular advanced ones such as intestinal metaplasia and dysplasia. Here, we conducted a study to assess the impact of *ABO* genotype on the risk of advanced precancerous lesions in a Venezuelan population in relation with the infection with different strains of Hp. In particular we tested the relevance of the presence of the *cagA* gene which is known to increase the risk of more severe gastric lesions [9].

Materials and Method

Study population

The randomized trial that provided the infrastructure for this study has been described previously [10]. Briefly, eligible subjects were participants in the gastric cancer control program of Tachira State, Venezuela, between 35 and 69 years of age. After they gave

written informed consent, all subjects underwent gastroscopic examination with collection of gastric biopsies, blood, and urine specimens, and they were administered a questionnaire on sociodemographic and lifestyle variables by a trained interviewer. During the study recruitment period from July 1991 to February 1995, there were 4349 eligible subjects, of whom 2272 were invited to participate in the trial. Of these, 72 refused to participate. All participants signed an informed written consent. The study was approved by the ethical review boards of the institutions responsible for subject recruitment in each of the recruitment centres.

Ethical clearance for the study was obtained from the International Agency for Research on Cancer (IARC) Ethical Committee in Lyon, France, and the Cancer Control Center in San Cristobal, Venezuela.

The presence of the *cagA* gene in gastric biopsies from the study subjects was previously assessed by reverse hybridization using a line probe assay or a DNA enzyme immunoassay at Delft Diagnostic Laboratory as described [11]. Basic characteristics of this study population are presented in Table 1.

Genotyping

Total DNA was extracted from gastric biopsy specimens after digestion with Proteinase K. Briefly, biopsies were incubated in 250 μL of a solution of 10 mM Tris – HCl (pH 8.0), 5 mM EDTA, 0.1% sodium dodecyl sulfate, and 0.1 mg/mL Proteinase K for at least 2 hours at 55°C. Proteinase K was inactivated by incubation at 95°C for 10 minutes.

In this study we examined 6 single nucleotide polymorphisms (SNPs) on the *ABO* gene: rs505922 (tagging rs8176719 [12]), rs1053878, rs8176720, rs8176741, rs8176746 (tagging rs7853989, rs8176743 and rs8176749), and rs8176747. They account for all the variability in the functional polymorphisms and predict the ABO blood groups, as shown in Table 2.

Genotyping was performed at the German Cancer Research Center (Heidelberg, Germany) using an allele-specific PCR-based KASPar SNP genotyping system (KBiosciences, Hoddesdon, UK). Thermocycling was performed according to the manufacturer's instructions. Detection was performed using an ABI PRISM 7900 HT sequence detection system with SDS 2.4 software (Applied Biosystems, Foster City, CA, USA).

Haplotype blocks were constructed from genotyping data using Phase software [13] and SNP tool (http://www.dkfz.de/de/molgen_epidemiology/tools/SNPtool.html)[14].

In addition, we typed two SNPs in the *cagA* gene in position 154 (cagA154_GA) and 858 (cagA858_CT), by allele-specific PCR-based KASPar SNP genotyping system. The presence of the two polymorphic sites has been assessed by sequencing in a small subset of the same population [15]. The results obtained with the KASPar assays were compared with the sequencing results with 100% concordance. A sample was defined as *cagA* positive when it showed a signal in at least two out of three PCRs (i.e. the reverse hybridization/ DNA enzyme immunoassay and the two SNP assays).

Statistical analysis

After excluding 138 subjects whose DNA samples were unavailable or failed in *ABO* genotyping assays, 2062 subjects were left for statistical analysis.

The response variable in this study was histological diagnosis, which was divided into 6 groups: dysplasia, intestinal metaplasia (IM), atrophic gastritis, chronic gastritis, superficial gastritis and normal epithelium. The last three groups were combined to create the control

group in this study because the combined frequency of normal epithelium and superficial gastritis in this population was less than 5%. Multinomial logistic regression analysis was employed, using the SAS CATMOD procedure, to estimate odds ratios (ORs) and 95% confidence intervals (CIs) associated with *ABO* SNPs for atrophic gastritis, IM and dysplasia, in comparison with controls. All ORs were adjusted for basic demographic variables (sex, age and educational levels), and other environmental risk factors reported previously (family history of gastric cancer, cigarette smoking, quintile levels of fruit and starchy vegetable intakes, and duration of refrigerator use) [16]. In addition we calculated the ORs for the association between *cagA*+ HP infection and ABO genotypes in the control group by unconditional logistic regression model including the same covariates.

Results

Basic characteristics of the population included in this study are presented in Table 1. Genotype success was >95%. Blinded duplicate samples (16.7%) included for quality control showed >99% genotype concordance. The genotype frequencies for all SNPs in controls were in accordance with Hardy–Weinberg equilibrium and any deviation from the expected was not statistically significant (data not shown).

We reconstructed the ABO blood groups of the study subjects by using their genotypes at the 6 SNPs we genotyped, as shown in Table 2. The concordance between blood groups assessed by use of genotyping data and serology-obtained blood group data collected at baseline was 96% (data not shown).

We assessed the risk for gastric precancerous lesions, in comparisons with normal epithelium and non-atrophic gastritis, according to blood types and *cagA* status (Table 3).

In individuals carrying *cagA* negative strains or not infected with Hp (748 cases) we found no associations between blood types and risk of atrophic gastritis (105 cases). Individuals with A blood type showed a lower risk of intestinal metaplasia (123 cases) and dysplasia (19 cases) with an OR of 0.60 (95% CI 0.38-0.94) than individuals with blood type O. The association is shown in heterozygous AO subjects with an OR=0.60 (95% CI 0.38-0.95) but not in the homozygotes, due to the small number (3 cases).

In carriers of *cagA* positive Hp strains (1314 subjects) we detected a higher risk of IM (437 cases) and dysplasia (93 cases) in individuals with blood type A compared with blood type O, with an OR of 1.42 (95%CI 1.09-1.86). Due to the larger numbers in the the *cagA* positive stratum, it was possible to estimate separate odds ratios for IM (OR=1.36, 95% CI 1.03-1.79), and dysplasia (OR=1.78, 95% CI 1.11-2.85).

We observed a statistically significant interaction between Hp *cagA* status and blood type, with a P=0.0006 for the combined group of subjects with IM or dysplasia (Table 3).

SNPs in the *ABO* gene were not associated with risk of *cagA* positive Hp infection in the subjects without advanced precancerous lesions (normal epithelium to non-atrophic gastritis; data not shown).

Furthermore, we assessed the risk for advanced gastric precancerous lesions, in comparison with normal epithelium and non-atrophic gastritis, combining blood types and *cagA* status (Figure 1). For this analysis we used subjects with normal epithelium or non-atrophic gastritis carrying *cagA* negative strains as reference group. This analysis confirmed a decreased risk of IM or dysplasia in subjects with blood group A and carriers of *cagA* negative strain (OR=0.60, 95%CI 0.38-0.93). Infection with *cagA* positive strains showed an increased risk of atrophic gastritis and IM or dysplasia in all subjects, but in particular

among subjects with blood group A (OR=2.10; 95%CI 1.41-3.13 for atrophic gastritis and OR=3.84; 95%CI 2.78-5.31 for IM or dysplasia).

We also tested if there was an association between individual SNPs and risk of preneoplastic lesions (Table 4). We found an association with SNP rs505922, which discriminates the O phenotype from A or B: the T allele of the SNP is associated with a increased risk of dysplasia (OR=1.57; 95% CI 1.00-2.48) in carriers of *cagA* positive strains.

None of the other SNPs showed any statistically significant association with the risk of preneoplastic lesions, either in *cagA* positive carriers or in *cagA* negative subjects.

Discussion

ABO genotype has been investigated as a risk factor for a number of different cancer sites. A recent genome-wide association study (GWAS) has revealed associations between variants in the *ABO* locus, predicting blood groups, and susceptibility to pancreatic cancer [17]. The association has been confirmed in other recent studies [8, 12, 18]. Studies of other cancer sites that have tested ABO blood groups by genotyping have shown mixed results: they have not confirmed old epidemiological evidence for an association with breast cancer risk and survival [19, 20], nor with risk for colorectal cancer [21], while the B blood group was positively associated with ovarian cancer incidence [22].

The results of the present study suggest that the A allele exerts its biological effects in gastric carcinogenesis in the presence of the bacterial *cagA* gene. This may account for inconsistent associations between blood type A and gastric cancer observed in earlier studies that did not take into account the prevalence of Hp infection in the study population.

Glycoconjugates, such as the ABO antigen, are important mediators of intercellular adhesion and membrane signaling, which are both critical to the progression and spread of malignant cells [23]. Altered expression of ABO blood group antigen has been described in colorectal adenocarcinomas, lung carcinoma and urinary bladder cancer [24]. Moreover, as cell surface molecules they are also recognized by the host immune response and may influence immunosurveillance for malignant cells [25].

Studies have found that ABO antigens including H antigen can be present on epidermal growth factor receptor (EGFR), integrins, cadherins, and CD-44 (a cell-surface glycoprotein), which are involved in cell proliferation, cell-cell interaction, cell adhesion and motility, as well as angiogenicity [26, 27].

In addition to gastric cancer, ABO blood types and secretor phenotypes have been associated with various kinds of infection including norovirus, cholera and malaria [28].

Furthermore, recent GWASs suggest that SNPs of the *ABO* gene are associated with several serum markers of inflammation and cell adhesion: TNF-α, soluble intercellular adhesion molecule-1 (ICAM-1), soluble E-selectin, and soluble P-selectin [29-32]. These findings support the possibility that ABO blood group alleles might correlate with systemic inflammatory state and immune cell recruitment, and thereby influence the risk of several cancers [8].

In the gastric epithelium, the ABO blood group antigens and their related carbohydrate structures, such as the Lewis b antigens, are one of the major functional receptors for Hp [8]. The observed association between ABO blood groups and risk of Hp-induced gastric cancer can thus be explained by differential binding of the bacterium to the blood group antigens. In particular, on the bacterial side, the binding is mediated by the outer-membrane protein

BabA, encoded by the gene *baba2* [8]. *baba2*-positive Hp strains are associated with an increased risk of gastric adenocarcinoma [1]. The binding between BabA and Lewis b antigen is important not only for Hp to adhere to the stomach surface but also to anchor the bacterial secretion system (T4SS) to the host cell surface so that bacterial factors, including the CagA protein, can be effectively injected into the host cell cytosol. This interaction plays an important role in potentiating T4SS-mediated secretion, resulting in inflammation and intestinal metaplasia [33], although we cannot address how specifically blood group type A affects HP attachment to gastric epithelial cells. The presence of *babA2* is correlated with the presence of *cagA* and *vacA* s1; strains positive for the three genes carry the highest risk of gastric cancer [1].

Some South American (Amerindian) strains use exclusively blood group O antigen for attachment to gastric epithelial cells [34] and Amerindian strains are known to carry distinct genetic structures from Western and Eastern strains. While attenuated virulence of CagA protein from those strains has been reported[35], sequence variations in the other regions of the genome [36] may account for reduced risk of advanced precursor lesion with type A compared with type O in CagA-negative patients.

The association between ABO blood groups and Hp infection is still unclear because of discordant results. In particular, nine studies have tested the association between ABO blood group and Hp infection in healthy subjects; two of them have found a statistically significant association between the infection and A blood type (in Bangladeshi young children [37] and Estonian blood donors [38]). In other studies no association was detected, either in children [39, 40] or adults [41-44]. Other studies that focused on gastric preneoplastic or gastric cancer cases (two of them in the Japanese population [18, 45]) showed an increased risk for atrophic gastritis in individuals with blood group A. Nevertheless other studies in different populations on gastritis or gastric cancer patients did not confirm the association [46-48].

We realize that our study has some limitations. First, although the overall study is rather large, the sample sizes for some gastric histologies are rather small. Furthermore another possible limitation with the cross-sectional study design is difficulty in inferring causal relationship for the observed associations because temporal relations between exposures and outcomes are not clear. Yet, the cross-sectional analysis has an advantage in accumulating histological changes developing over several decades as Hp is generally acquired in the childhood in high-risk populations [49]. Finally, our study was limited to a Venezuelan population and the results cannot necessarily be extrapolated to other populations.

In summary, our cross sectional study in a Venezuelan population showed that SNPs at the *ABO* gene, predictive of ABO blood groups, were associated with the risk of more severe gastric preneoplastic lesion depending on *cagA* status. In particular, in carriers of *cagA* positive Hp strains, we detected a significantly increased risk of IM and dysplasia associated with blood group A. On the contrary, among individuals carrying *cagA* negative strains or not infected with Hp, presence of the A blood type showed a strong decrease of risk of dysplasia. These findings suggest that ABO blood group can be considered a risk factor for progression towards gastric cancer in individuals infected with Hp, but the association is highly dependent on Hp *cagA* status.

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Novelty and impact

We have studied the impact on the risk of advanced precancerous gastric lesions of ABO blood groups and the presence of cagA in a population characterized by high prevalence of *Helicobacter pylori* (Hp) infection and high rates of gastric cancer.

Our findings suggest that ABO blood groups are associated with risk of advanced precancerous gastric lesions in Hp-infected individuals, but the assessment of the risk is strictly dependent on *cagA* status.

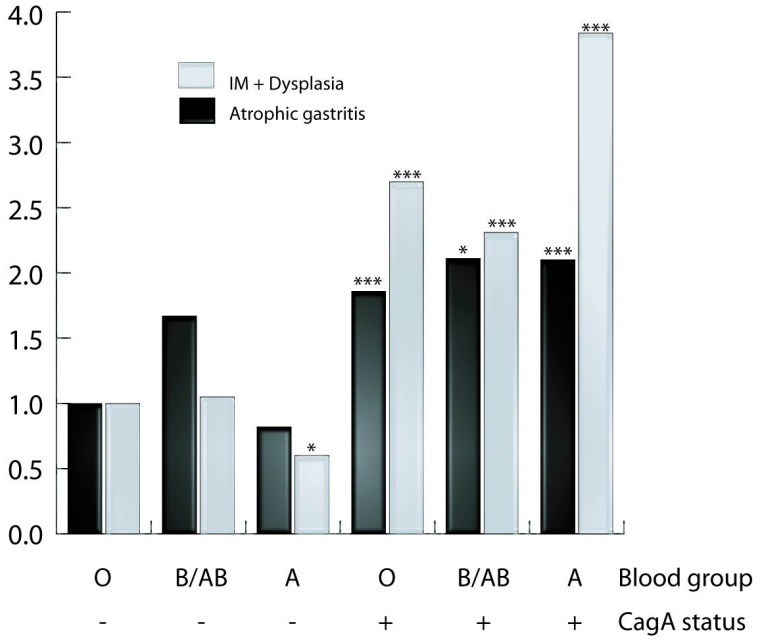

Figure 1.

Risk of gastric lesions in subjects infected with different strains of *Helicobacter pylori* according to *cagA* status and blood group. Subjects with normal epithelium or non-atrophic gastritis carrying *cagA* negative strains were considered the reference group (* $p<0.05$; ***$p<0.001$)

Table 1

Characteristics of study population.

Characteristics		No.[a]	(%)
Gender	Male	971	47.1%
	Female	1091	52.9%
Age	≤39	479	23.2%
	40-49	753	36.5%
	50-59	532	25.8%
	≥60	298	14.5%
Years of schooling	0-5	688	33.4%
	6-8	701	34.0%
	9+	672	32.6%
Years of refrigerator use	0-9	276	13.4%
	10-19	348	16.9%
	20-29	615	29.8%
	30+	823	39.9%
Cigarette smoking	Never	1459	70.8%
	Ever	603	29.2%
Family history of gastric cancer	No	1767	85.7%
	Yes	294	14.3%
Hp status	No Hp	181	8.8%
	cagA− Hp	567	27.5%
	cagA+ Hp	1314	63.7%
Histological diagnosis	Normal	10	0.5%
	Superficial gastritis	78	3.8%
	Chronic gastritis	979	47.5%
	Atrophic gastritis	323	15.7%
	Intestinal metaplasia	560	27.2%
	Dysplasia	112	5.4%
Blood groups	O	1202	58.3%
	A	690	33.5%
	B	141	6.8%
	AB	29	1.4%

[a] 2200 subjects accepted to participate in the study. For 138 subjects the DNA from biopsies was not available anymore or the quality was insufficient for genotyping, leaving thus a total of 2062 subjects who were included in statistical analyses.

Table 2

ABO gene SNP selection.

cDNA[a]	aa[b]	SNP	Tag[c]	Blood groups			
				O	A1	A2	B
					aa	aa	aa
261	87	rs8176719	rs505922[1]	del (frame shift)			
293	99	rs8176720			gly	gly	gly
467	156	rs1053878			pro	**leu**	pro
526	176	rs7853989	rs8176746		arg	arg	**gly**
657	219	rs8176741			his	his	his
703	235	rs8176743	rs8176746		gly	gly	**ser**
796	266	rs8176746			leu	leu	**met**
803	268	rs8176747			gly	gly	**ala**
930	268	rs8176749	rs8176746		leu	leu	leu

[a] Position (nucleotide number) within the *ABO* cDNA

[b] Position (aminoacid/codon number) within the ABO protein

[c] SNP that can be used as surrogate because of complete linkage disequilibrium(r^2=1 in HapMap CEU subjects)

Table 3

Associations between ABO blood types determined by 6 *ABO* SNPs and risk of gastric precancerous lesions, in comparison with normal epithelium or non-atrophic gastritis

		Normal/non-atrophic gastritis	Atrophic gastritis			Intestinal metaplasia			Dysplasia			Intestinal metaplasia + Dysplasia		
Hp *cagA* status	**Blood genotypes**	**No.**	**No**	**OR[a]**	**(95% CI)**	**No.**	**OR[a]**	**(95% CI)**	**No.**	**OR[a]**	**(95% CI)**	**No.**	**OR[a]**	**(95% CI)**
Negative	O	285	59	1		76	1		16	1		92	1	
	B/AB	44	16	1.69	(0.88-3.26)	14	1.18	(0.60-2.33)	1	-		15	1.05	(0.54-2.02)
	A	172	30	0.83	(0.51-1.36)	33	0.68	(0.43-1.08)	2	-		35	**0.60**	**(0.38-0.94)**
	AO	155	27	0.83	(0.50-1.38)	31	0.70	(0.43-1.12)	1	-		32	**0.60**	**(0.38-0.95)**
	AA	17	3	0.89	(0.24-3.20)	2	0.48	(0.11-2.17)	1	-		3	0.63	(0.18-2.26)
	A1[b]	132	24	0.84	(0.49-1.42)	25	0.65	(0.39-1.07)	1	-		26	**0.56**	**(0.34-0.91)**
	A2[c]	40	6	0.81	(0.32-2.04)	8	0.80	(0.33-1.82)	1	-		9	0.78	(0.36-1.71)
Positive	O	348	127	1		244	1		47	1		291	1	
	B/AB	46	19	1.12	(0.63-2.00)	26	0.88	(0.52-1.48)	4	0.69	(0.23-2.04)	30	0.85	(0.51-1.41)
	A	172	72	1.14	(0.80-1.61)	167	**1.36**	**(1.03-1.79)**	42	**1.78**	**(1.11-2.85)**	209	**1.42**	**(1.09-1.86)**
	AO	156	63	1.11	(0.77-1.59)	152	**1.38**	**(1.04-1.84)**	38	**1.78**	**(1.09-2.89)**	190	**1.44**	**(1.10-1.90)**
	AA	16	9	1.38	(0.59-3.26)	15	1.16	(0.55-2.45)	4	1.77	(0.55-5.76)	19	1.25	(0.62-2.54)
	A1[b]	122	46	1.02	(0.69-1.53)	118	1.34	(0.98-1.83)	32	**1.88**	**(1.13-3.15)**	150	**1.42**	**(1.06-1.92)**
	A2[c]	50	26	1.40	(0.83-2.36)	49	1.40	(0.90-2.17)	10	1.50	(0.69-3.23)	59	1.42	(0.93-2.17)
	$P_{interaction}$[d]				0.189		**0.006**							**0.0006**

[a]Odd ratios were adjusted for age, gender, family history of gastric cancer, smoking status, length of refrigerator use, educational level, fruit and starchy vegetable intakes. Analyses adjusted only for age and gender showed essentially the same results (data not shown). Values in bold are statistically significant ($p<0.05$). Statistical analysis was not performed for the dysplasia group among *cagA* negative subjects because of the very small numbers.

[b]A1 includes homozygotes A1/A1 and heterozygotes A1/O

[c]A2 includes heterozygotes A2/A1, heterozygotes A2/O and homozygotes A2/A2

[d]P-value of interaction between Hp *cagA* status and blood type A

Table 4

Associations between individual *ABO* SNPs and risk of gastric precancerous lesions, in comparison with normal epithelium or non-atrophic gastritis.

ABO SNPs	Comparison	Normal/non atrophic gastritis	Atrophic gastritis			Intestinal metaplasia			Dysplasia			Intestinal metaplasia + Dysplasia		
		No*	No*	OR[a]	(95% CI)	No*	OR[a]	(95% CI)	No*	OR[a]	(95% CI)	No*	OR[a]	(95%CI)
CagA negative														
rs505922	(CT+CC)/TT	216/283	46/58	1.02	(0.66-1.58)	46/72	0.80	(0.53-1.22)	3/16	-		49/88	0.70	(0.47-1.05)
rs8176720	(AG+AA)/GG	361/133	75/29	1.01	(0.62-1.64)	88/33	1.01	(0.64-1.60)	12/7	-		100/40	0.95	(0.62-1.46)
rs8176746	(AC+AA)/CC	46/453	16/88	1.72	(0.92-3.24)	14/108	1.28	(0.67-2.46)	1/18	-		15/126	1.17	(0.62-2.21)
rs8176747	(CG+CC)/GG	46/455	16/89	1.71	(0.91-3.21)	14/109	1.28	(0.66-2.46)	1/18	-		15/127	1.16	(0.61-2.21)
rs1053878	(TC+TT)/CC	52/440	9/92	0.95	(0.44-2.03)	9/109	0.71	(0.35-1.58)	2/17	-		11/126	0.82	(0.41-1.65)
rs8176741	(TC+TT)/CC	45/448	16/88	1.72	(0.91-3.23)	14/105	1.32	(0.68-2.54)	1/18	-		15/123	1.19	(0.63-2.27)
Caga positive														
rs505922	(CT+CC)/TT	216/345	89/124	1.14	(0.82-1.57)	189/243	1.25	(0.96-1.62)	46/47	**1.57**	**(1.00-2.48)**	235/290	1.30	(1.01-1.67)
rs8176720	(AG+AA)/GG	430/133	163/54	0.92	(0.63-1.32)	329/104	0.98	(0.72-1.34)	73/20	1.16	(0.67-2.02)	402/124	1.01	(0.75-1.36)
rs8176746	(AC+AA)/CC	48/518	19/198	1.02	(0.58-1.79)	26/411	0.74	(0.44-1.24)	4/89	0.52	(0.18-1.50)	30/500	0.70	(0.43-1.15)
rs8176747	(CG+CC)/GG	48/518	19/199	1.01	(0.58-1.78)	26/411	0.74	(0.44-1.24)	4/89	0.51	(0.18-1.50)	30/500	0.70	(0.43-1.15)
rs1053878	(TC+TT)/CC	69/493	33/183	1.29	(0.82-2.04)	55/381	1.02	(0.69-1.51)	10/83	0.85	(0.41-1.75)	65/464	1.00	(0.68-1.45)
rs8176741	(TC+TT)/CC	48/502	17/186	0.94	(0.52-1.69)	28/391	0.82	(0.50-1.36)	4/84	0.55	(0.18-1.60)	32/475	0.79	(0.48-1.26)

[a]Odd ratios were adjusted for age, gender, family history of gastric cancer, smoking status, length of refrigerator use, educational level, fruit and starchy vegetable intakes. Analyses adjusted only for age and gender showed essentially the same results (data not shown). Values in bold are statistically significant (p<0.05). SNPs were analyzed according to a dominant model. Statistical analysis was not performed for the dysplasia group among cagA negative subjects because of the very small numbers.

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