**Interleukin-8 Promoter Polymorphism Increases the Risk of Atrophic Gastritis and Gastric Cancer in Japan**

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**Abstract**

Host genetic susceptibility may influence gastric carcinogenesis caused by *Helicobacter pylori* infection. We aimed to clarify the relationship of interleukin (IL)-8 polymorphism with the risk of atrophic gastritis and gastric cancer. We examined IL-8 –251 T > A, IL-1B –511 C > T, and IL-1RN intron 2 polymorphisms in 252 healthy controls, 215 individuals with atrophic gastritis, and 396 patients with gastric cancer. We also investigated the effect of the IL-8 polymorphism on IL-8 production and histologic degree of gastritis in noncancerous gastric mucosa. Although no correlation was found in the analysis of the IL-1B and IL-1RN polymorphisms, IL-8 –251 A/A genotype held a higher risk of atrophic gastritis [odds ratio (OR), 2.35; 95% confidence interval (CI), 1.12-4.94] and gastric cancer (OR, 2.22; 95% CI, 1.08-4.56) compared with the T/T genotype. We also found that the A/A genotype increased the risk of upper-third location (OR, 3.66; 95% CI, 1.46-9.17), diffuse (OR, 2.79; 95% CI, 1.21-6.39), poorly differentiated (OR, 2.70; 95% CI, 1.14-6.38), lymph node (OR, 2.50; 95% CI, 1.01-6.20), and liver metastasis (OR, 5.63; 95% CI, 1.06-30.04), and p53-mutated (OR, 1.91; 95% CI, 1.13-3.26) subtypes of gastric cancer. The A/A and A/T genotypes were significantly associated with higher levels of IL-8 protein compared with the T/T genotype. Neutrophil infiltration score was significantly higher in the A/A genotype than in the T/T genotype. In conclusion, we showed that the IL-8 –251 T > A polymorphism is associated with higher expression of IL-8 protein, more severe neutrophil infiltration, and increased risk of atrophic gastritis and gastric cancer. (Cancer Epidemiol Biomarkers Prev 2005;14(11):2487–93)

**Introduction**

Despite the decreasing incidence and mortality rates observed worldwide, gastric cancer still ranks second as the cause of cancer-related deaths (1). Many epidemiologic studies have revealed a strong association between *Helicobacter pylori* infection and gastric cancer (2, 3), and in 1994, the IARC classified the bacterium as a definite biological carcinogen. *H. pylori* colonizes persistently in the gastric mucosa and leads to chronic mucosal inflammation, atrophic gastritis, and finally, gastric cancer (4). However, there are distinct differences in the extent of gastric inflammation among *H. pylori*-infected patients, and only a small group of them develop gastric cancer, indicating that gastric carcinogenesis may be under the combined influence of bacterial pathogenicity, host genetics, and environmental factors.

As one candidate for the host genetic factors, recent reports have revealed that pro- and anti-inflammatory cytokine [interleukin (IL)-1B, IL-1RN, tumor necrosis factor (TNF) A, and IL-10] polymorphisms are associated with a risk for atrophic gastritis and gastric cancer (5-8). Proinflammatory cytokines such as IL-1β, TNF-α, and IL-8 are up-regulated during chronic *H. pylori* infection (9, 10), and play a crucial role in inflammation of gastric mucosa. In addition, T helper cell 1 phenotype–predominant immune response, generally observed in *H. pylori*-positive gastritis (11), is possibly associated with the development of cancer (12).

IL-8, a member of the CXC chemokine family, was originally identified as a potent chemotactic agent for neutrophils and lymphocytes (13, 14). Subsequent studies confirmed that IL-8 could also induce cell proliferation (15) and migration (16), as well as angiogenesis (17). Some studies have reported that IL-8 –251 T > A polymorphism in the promoter region is associated with respiratory syncytial virus bronchiolitis (18), prostate cancer (19), enteraggregative *Escherichia coli* diarrhea (20), and colorectal cancer (21). Furthermore, the IL-8 –251 A allele tended to be associated with increased IL-8 production by lipopolysaccharide-stimulated whole blood (18). Concerning the role of IL-8 polymorphisms in gastric carcinogenesis, one recent study has reported that the IL-8 –251 A allele increases the risk of non-cardia and intestinal-type gastric cancer (22). From these findings, we hypothesized that the IL-8 –251 A allele increases the risk of non-cardia and intestinal-type gastric cancer (23-25), and the risk of development and the different growth of gastric cancer.

In this case-control study, we determined IL-8 –251 T/A genotype, as well as IL-1B –511 C/T genotype and IL-1RN variable number of tandem repeat region in intron 2, and elucidated the relationship of these genetic variants to the risk of atrophic gastritis and to the risk of gastric cancer, including its subtypes and clinicopathologic features. We also evaluated the effects of IL-8 polymorphism on IL-8 production in the *H. pylori*-infected gastric mucosa and on histologic degree of gastritis in the noncancerous gastric mucosa adjacent to cancer of surgical specimens.

**Materials and Methods**

**Study Population.** A total of 863 subjects were enrolled in this study, including healthy controls (*n* = 252), individuals with atrophic gastritis (*n* = 215), and patients with gastric cancer (*n* = 396). The healthy controls (mean age, 51 years; range, 26-86 years; male/female, 188/64) and individuals with...
atrophic gastritis (mean age, 56 years; range, 26-81 years; male/female, 162/53) were recruited consecutively from health checkup examinees who had undergone gastroscopy and/or double contrast radiography as part of a screening program for gastric cancer from January to March 2000 at Aichi Prefecture Health Care Center, Japan. These two groups were discriminated by the presence of gastric atrophy, defined as the spread of atrophic mucosa to the cardia in the lesser curvature of the stomach by gastroscopy, and/or double contrast radiography.

Patients with gastric cancer (mean age, 62 years; range, 30-91 years; male/female, 291/105) had been diagnosed histologically and treated at Nagoya University Hospital (Nagoya, Japan) between January 1989 and January 2002. Gastric cancers were histologically classified according to Lauren’s classification (26) and the Japanese Classification of Gastric Carcinoma (27); detailed information about TNM staging, anatomic location, venous and lymphatic invasion, lymph node and distant metastasis, and peritoneal dissemination was available. Furthermore, in noncancerous gastric mucosa adjacent to cancer from 194 surgical specimens, the degree of neutrophil infiltration, mononuclear cell infiltration, atrophy, and intestinal metaplasia were assessed according to the updated Sydney system (28), and were scored as follows: normal, 0; mild, 1; moderate, 2; marked, 3.

All subjects were Japanese and were surveyed about their history of any illness, and smoking habits. Individuals with past history of gastrectomy were excluded from this study. The Ethics Committee of the Nagoya University Graduate School of Medicine approved the protocol, and prior, written informed consent was obtained from all participating subjects.

Detection of Helicobacter pylori Infection. H. pylori status was assessed by serologic analysis. Peripheral blood was collected from each subject and serum samples separated by centrifugation were stored at −20°C until analysis. The anti- H. pylori IgG antibody titer was determined by HM-CAP IgG EIA assay (Kyowa Medex, Tokyo, Japan), and ELISA values >2.2 were regarded as H. pylori-seropositive.

Genotyping of Cytokine Gene Polymorphisms. Genomic DNA was isolated from peripheral blood using a standard phenol/chloroform extraction method. The IL-8 polymorphism was genotyped by PCR-RFLP. Primer sequences for PCR were as follows: forward primer, 5'-TCTTAAACCTGCGCACTTAG-3'; reverse primer, 5'-CTGAGGCTCACAATTGGTG-3'. PCR was carried out in a volume of 10 μL containing 40 ng of genomic DNA, 1× reaction buffer, 0.125 mmol/L deoxynucleotide triphosphates, 1.5 mmol/L MgCl₂, 0.75 μmol/L of each primer and 0.5 units of Platinum Taq DNA polymerase (Gibco BRL, Gaithersburg, MD). The DNA was denatured at 94°C for 4 minutes, followed by 35 cycles at 94°C for 30 seconds, 60°C for 30 seconds, and 72°C for 30 seconds with a final extension at 72°C for 7 minutes. The enzyme digestion using 5 units of MfeI (New England Biolabs, Inc., Beverly, MA) was done to analyze the IL-8 −251 T > A polymorphism and yielded a product of 108 bp (−251 T) and 76 + 32 bp (−251 A). The digestion was incubated overnight at 37°C and then its products were visualized on a 5% agarose gel stained with ethidium bromide.

The IL-1β −311 C > T polymorphism was distinguished by 5' nuclease PCR assay (TaqMan) using Taq for −511. For the TaqMan assay, sequences of primers and probes were courtesy of Dr. Emad M. El-Omar. Thermal cycling of optical plates was done in GeneAmp PCR System 9700 and end point analysis was done in the ABI PRISM 7700 Sequence Detection System (Applied Biosystems, Foster City, CA). For IL-1RN, genomic DNA was amplified using PCR encompassing an 86-bp variable number of tandem repeats in intron 2. The PCR products were separated by electrophoresis on 2% agarose gels and stained with ethidium bromide. The alleles were coded conventionally as follows: allele 1, four repeats; allele 2, two repeats; allele 3, five repeats; allele 4, three repeats; and allele 5, six repeats. Because alleles 3, 4, and 5 were very rare, these alleles were classified into the short (allele 2: *2) and long alleles (alleles 1, 3, 4, and 5: L) for the purpose of statistical analysis in accordance with the recent study (7).

Detection of p53 Mutational Analysis. In 226 of 396 patients with gastric cancer, DNA was extracted from frozen tumor tissue by the standard phenol/chloroform method. Complete coding sequences and splice junctions for exons 5 to 8 of p53 gene were screened for mutations by PCR-based single-strand conformational polymorphism analysis as previously described by us (29). The sequences of the used primers were: forward, 5'-TCTGTCTCTCCCTCTTCTCTG-3'; reverse, 5'-TCTTCTCACGCCCCAGCTG-3'; forward, 5'-CTGATTCTCCTCAGTGGTC-3'; reverse, 5'-GAGACCCCCAGTTGCAAAC-3'; forward, 5'-CTTGCGCTTGTTGCTC-3'; reverse, 5'-AGGTTGGAAGTGGTCCTC-3'; and forward, 5'-GCTTCTTCTTTCTATCTCCTGA-3'; reverse, 5'-GCTTCTTGTTCCTCCTGTC-3' for exons 5 to 8, respectively. PCR was carried out with Platinum Taq DNA polymerase (Gibco BRL) for 1 cycle at 94°C for 4 minutes followed by 35 cycles at 94°C for 30 seconds, 46°C to 61°C for 30 seconds, and 72°C for 30 seconds with a final 7-minute extension at 72°C in the presence of 0.2 mCi of [32P]dCTP. PCR-single-strand conformational polymorphism was done using MFE (FMC BioProducts, Rockland, ME) gels. The DNA fragments that showed mobility shifts were excised from the gels and reamplified using the same primers. The PCR fragments were purified using the Microcon-100 microconcentrator (Amicon, Stonehouse, United Kingdom) and sequenced using the ABI Prism Big-Dye Terminator Cycle Sequencing Reaction Kit (Applied Biosystems).

No significant differences were found between cases without analysis of p53 mutations and cases with analysis with respect to sex, age, distribution of IL-8 polymorphism, histologic type, tumor location, staging, and other clinical features.

IL-8 Protein Measurement. In 50 patients with gastric cancer, two biopsy specimens were obtained from the greater curvature of the upper gastric body mucosa during gastroscopy and were immediately placed in 3 mL of RPMI 1640 (Gibco BRL) at 4°C. After 6 hours, samples were mechanically homogenized and aliquots of homogenate supernatants, obtained by centrifugation (1,000 × g for 10 minutes), were stored at −80°C until use. Total protein in the biopsy method was assayed using the Bradford method. IL-8 protein was measured by chemiluminescent immunoassay using commercially available assay kits (Research and Diagnostic Systems, Minneapolis, MN) according to the manufacturer’s instructions. The mucosal IL-8 levels were expressed as picograms of cytokine per milligram of biopsy protein (pg/mg protein). A Mann-Whitney U test or Kruskal-Wallis rank test. P < 0.05 were considered statistically significant.

Statistical Analysis. Statistical analyses were done with Fisher’s exact probability test or χ² test for the comparison of IL-8, IL-1β, and IL-1RN genotype frequencies between cases and controls. The odds ratios (OR) with 95% confidence intervals (CI) were computed using unconditional logistic models, adjusting for sex, age, and H. pylori seropositivity. Differences among groups in the gastric mucosa levels of IL-8 protein and in the histologic score of gastritis were determined using the Mann-Whitney U test or Kruskal-Wallis rank test. P < 0.05 were considered statistically significant.
NOTE: Smokers, current and ex-smokers.

### Results

**Subjects.** A total of 252 healthy controls, 215 individuals with atrophic gastritis, and 396 patients with gastric cancer participated in this study. Demographic comparison of healthy controls, individuals with atrophic gastritis, and patients with gastric cancer are summarized in Table 1. There was no significant difference among these groups in the distribution of sex and smoking habits. The average age increased successively among healthy controls, individuals with atrophic gastritis, and patients with gastric cancer. We could not find any significant correlation between the risk of gastric cancer and IL-1B –511 or IL-1RN polymorphisms.

We further investigated whether the IL-8 –251 polymorphism might affect the clinicopathologic features of gastric cancer. Tumor location, staging, histologic classification, lymphatic and venous invasion, lymph node metastasis, peritoneal dissemination, liver metastasis, other distant metastasis, and p53 mutations were included in this stratification analysis. Among these clinicopathologic features, we found that IL-8 –251 A/A genotype increased the risk of upper-third location (OR, 3.66; 95% CI, 1.46-9.17), diffuse type (OR, 2.79; 95% CI, 1.21-6.39), poorly differentiated type (OR, 2.70; 95% CI, 1.14-6.38), lymph node metastasis (OR, 2.50; 95% CI, 1.01-6.20), liver metastasis (OR, 5.63; 95% CI, 1.06-30.04), and p53-mutated type (OR, 2.95; 95% CI, 1.18-7.39). IL-8 –251 A carriers also had an association with diffuse type (OR, 1.88; 95% CI, 1.16-3.04), poorly differentiated type (OR, 1.84; 95% CI, 1.11-3.05), and p53-mutated type (OR, 1.91; 95% CI, 1.13-3.26; Table 3).

**Table 2. Association between cytokine gene genotypes and risk of atrophic gastritis and gastric cancer**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Healthy controls, n (%)</th>
<th>Atrophic gastritis n (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>Gastric cancer n (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IL-8 –251</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/A</td>
<td>22 (8.7)</td>
<td>26 (12.1)</td>
<td>2.35 (1.12-4.94)</td>
<td>0.02</td>
<td>44 (11.1)</td>
<td>2.22 (1.08-4.56)</td>
<td>0.03</td>
</tr>
<tr>
<td>A/T</td>
<td>105 (41.7)</td>
<td>99 (46.0)</td>
<td>1.35 (0.87-2.11)</td>
<td>0.18</td>
<td>191 (48.2)</td>
<td>1.38 (0.91-2.11)</td>
<td>0.13</td>
</tr>
<tr>
<td>A carrier</td>
<td>127 (50.4)</td>
<td>125 (58.1)</td>
<td>1.50 (0.98-2.23)</td>
<td>0.06</td>
<td>235 (59.3)</td>
<td>1.50 (1.00-2.25)</td>
<td>0.05</td>
</tr>
<tr>
<td>T/T</td>
<td>125 (49.6)</td>
<td>90 (41.9)</td>
<td>1.0 (Reference)</td>
<td></td>
<td>161 (40.7)</td>
<td>1.0 (Reference)</td>
<td></td>
</tr>
<tr>
<td><strong>IL-1B –511</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T/T</td>
<td>49 (19.6)</td>
<td>46 (21.4)</td>
<td>1.40 (0.76-2.61)</td>
<td>0.28</td>
<td>81 (21.7)</td>
<td>1.69 (0.92-3.08)</td>
<td>0.09</td>
</tr>
<tr>
<td>T/C</td>
<td>133 (53.2)</td>
<td>104 (48.4)</td>
<td>0.93 (0.57-1.52)</td>
<td>0.77</td>
<td>188 (50.4)</td>
<td>1.08 (0.67-1.73)</td>
<td>0.77</td>
</tr>
<tr>
<td>T carrier</td>
<td>182 (72.8)</td>
<td>150 (69.8)</td>
<td>1.04 (0.65-1.66)</td>
<td>0.86</td>
<td>269 (72.1)</td>
<td>1.22 (0.77-1.92)</td>
<td>0.40</td>
</tr>
<tr>
<td>C/C</td>
<td>68 (27.2)</td>
<td>65 (30.2)</td>
<td>1.0 (Reference)</td>
<td></td>
<td>104 (27.9)</td>
<td>1.0 (Reference)</td>
<td></td>
</tr>
<tr>
<td><strong>IL-1RN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*2/2</td>
<td>2 (0.8)</td>
<td>0 (0)</td>
<td>0</td>
<td>1.00</td>
<td>3 (0.8)</td>
<td>1.09 (0.09-13.70)</td>
<td>0.95</td>
</tr>
<tr>
<td>*2/L</td>
<td>21 (8.8)</td>
<td>17 (8.2)</td>
<td>1.08 (0.49-2.41)</td>
<td>0.84</td>
<td>25 (6.8)</td>
<td>0.71 (0.32-1.57)</td>
<td>0.39</td>
</tr>
<tr>
<td>*2 carrier</td>
<td>23 (9.7)</td>
<td>17 (8.2)</td>
<td>0.83 (0.43-1.60)</td>
<td>0.58</td>
<td>28 (7.7)</td>
<td>0.78 (0.44-1.38)</td>
<td>0.39</td>
</tr>
<tr>
<td>L/L</td>
<td>215 (80.5)</td>
<td>191 (85.8)</td>
<td>1.0 (Reference)</td>
<td></td>
<td>337 (92.3)</td>
<td>1.0 (Reference)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: A carrier, A/A + A/T; T carrier, T/T + T/C; L, alleles 1, 3, 4, and 5. *2 carrier, *2/*2 + *2/L. ORs are adjusted for sex, age, and H. pylori seropositivity.

*Fourteen healthy-control, 7 atrophic-gastritis, and 31 gastric cancer samples could not be genotyped.
NOTE: A carrier, A/A + A/T. All data are adjusted for sex, age, and
seropositivity.

Effects of the IL-8 –251 T > A Polymorphism on Histologic Degree of Gastritis in Noncancerous Gastric Mucosa Adjacent to Cancer. Using samples of noncancerous gastric mucosa adjacent to cancer from 194 surgical specimens, we assessed the histologic degree of gastritis according to the updated Sydney system (28) and scored them as follows: normal, 0; mild, 1; moderate, 2; marked, 3. A significant difference of neutrophil infiltration score was found among IL-8 –251 A/A, A/T, and T/T genotypes; the IL-8 –251 A allele was associated with significantly higher levels of IL-8 protein compared with the –251 T/T genotype.

Discussion

It has been reported that IL-8 production in H. pylori-infected gastric mucosa is influenced by the presence of the cag pathogenicity island of H. pylori (32), in which major virulence factors are included. However, as most clinical isolates of H. pylori are similar within Japan (33), it is suggested that host genetic factors may play an important role in the differences in IL-8 expression in H. pylori-infected subjects. In the present study, we showed that the IL-8 –251 T > A polymorphism was associated with increased risk of atrophic gastritis and gastric cancer. The –251 A/A genotype showed a 2-fold risk of atrophic gastritis and gastric cancer, and a similar tendency was observed in the analysis of the –251 A carrier. These epidemiologic findings were confirmed by the differences in IL-8 expression in gastric mucosa among genotypes; the –251 A allele was associated with significantly higher levels of IL-8 protein compared with the –251 T/T genotype.

IL-8 stimulated by H. pylori infection induces the recruitment of neutrophils, which secrete proinflammatory cytokines such as TNF-α, IFN-γ, and IL-1β. The cytokine response in gastric mucosa is thought to be T helper cell (Th) 1– predominant, characterized by the accumulation of IFN-γ, not of IL-4–expressing T lymphocytes (11, 34). Chronic inflammation with a Th 1–predominant immune response in the gastric mucosa of mice has been reported to cause gastric atrophy, whereas Th2 cytokines are protective against gastric inflammation (35, 36). In addition, proinflammatory cytokines play an important role in cellular proliferation and gastric mucosal damage (37). Our study shows that the –251 A/A genotype is associated with increased risk of both atrophic gastritis and gastric cancer, suggesting that a high producer of IL-8 may induce a Th 1–predominant immune response, lead to more severe gastric atrophy, and be more susceptible to gastric cancer than a low producer of IL-8.

On the other hand, the IL-1B and IL-1RN polymorphisms were not associated with the risk of atrophic gastritis or gastric cancer in the present study. It was reported that the IL-1B –511 T and IL-1RN –2 alleles were associated with increased IL-1β production in H.pylori-infected gastric mucosa (38), and increased the risk of atrophic gastritis (6).
Figure 1. Mucosal IL-8 levels of the gastric body in relation to the genotypes at IL-8 –251. A significant difference was found among A/A, A/T, and T/T genotypes (P = 0.003, assessed by the Kruskal-Wallis rank test). In comparison with the A carrier and T/T genotypes, IL-8 levels in the A carrier were significantly higher than in the T/T genotype (P = 0.021, assessed by the Mann-Whitney U test). Columns, 25th and 75th percentiles; horizontal lines in columns, 50th percentile (median); bars, 10th and 90th percentiles; circles, data outside the 10th and 90th percentiles.

Table 4. Association between IL-8 genotype and histologic scores in noncancerous gastric mucosa adjacent to cancer

<table>
<thead>
<tr>
<th>IL-8 –251 genotype (n)</th>
<th>Neutrophil infiltration</th>
<th>Mononuclear cell infiltration</th>
<th>Atrophy</th>
<th>Intestinal metaplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/A (21)</td>
<td>1.91 ± 0.44*</td>
<td>1.67 ± 0.91</td>
<td>2.00 ± 0.95</td>
<td>1.67 ± 1.07</td>
</tr>
<tr>
<td>A/T (100)</td>
<td>1.58 ± 0.78</td>
<td>1.68 ± 0.72</td>
<td>1.67 ± 1.02</td>
<td>1.44 ± 1.09</td>
</tr>
<tr>
<td>A carrier (121)</td>
<td>1.64 ± 0.74</td>
<td>1.68 ± 0.76</td>
<td>1.73 ± 1.01</td>
<td>1.48 ± 1.08</td>
</tr>
<tr>
<td>T/T (73)</td>
<td>1.47 ± 0.78</td>
<td>1.69 ± 0.74</td>
<td>1.69 ± 0.97</td>
<td>1.41 ± 0.93</td>
</tr>
</tbody>
</table>

NOTE: A carrier, A/A + A/T. Scores shown are mean ± SD.

*P = 0.02, compared among A/A, A/T, and T/T genotype by the Kruskal-Wallis rank test.

P = 0.09, compared with A carrier and T/T genotype by the Mann-Whitney U test.
eradication (57), it is expected that *H. pylori* eradication can suppress p53-mediated gastric carcinogenesis in subjects with the IL-8–251 A/A genotype.

In conclusion, we showed that the IL-8–251 A allele is associated with higher expression of the IL-8 protein, more severe neutrophil infiltration in gastric mucosa, and increased the risk of atrophic gastritis and gastric cancer, especially diffuse type, poorly differentiated adenocarcinoma, lymph node and liver metastasis, and p53 mutations. We investigated the IL-8–251 T > A polymorphism in only a limited area in central Japan. It has been shown that the allelic frequency of the IL-8–251 T > A polymorphism is different between Japanese and Western people (19, 21, 30). Thus, future investigations are needed in a larger and ethnically different population to confirm these genetic influences on gastric carcinogenesis.

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References


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