A genetic basis for atrophy: dominant non-responsiveness and helicobacter induced gastritis in F₁ hybrid mice

P Sutton, J Wilson, R Genta, D Torrey, A Savinainen, J Pappo, A Lee

Abstract

Background—The importance of host factors in helicobacter induced gastritis has been shown in animal models. Infection of most mouse strains with Helicobacter felis results in a functional atrophic gastritis, while other strains remain gastritis free.

Aims—To investigate these host factors further by using genetic crosses of responder and non-responder mice.

Methods—F₁ hybrids of the non-responder CBA/Ca strain and three strains of mice known to develop H felis induced gastritis were infected for three months with H felis. Gastritis was assessed by histopathology and serum antibody responses by ELISA.

Results—Infection of CBA/Ca mice and F₁ hybrids induced little or no gastritis. Analyses of the antibody responses in these mice revealed virtually undetectable anti-helicobacter antibody levels despite colonisation with high numbers of H felis. In contrast, infection of H felis responsive strains induced gastritis and a significant humoral immune response.

Conclusions—The non-responsiveness of CBA/Ca mice to H felis infection is dominantly inherited. The lack of gastritis in CBA mice and their offspring is probably due to active suppression of the immune response normally mounted against H felis. Investigation of these mechanisms will provide important insights relevant to induction of gastric atrophy and cancer in humans.

Keywords: helicobacter; non-responsiveness; gastritis; F, hybrid; CBA

Helicobacter pylori is a Gram negative bacterium responsible for a large degree of morbidity and mortality in humans. Following infection of the stomach, H pylori colonises the gastric mucosa for the life of the host and by a variety of mechanisms, stimulates a chronic inflammatory reaction which is characterised by the infiltration of lymphocytes and neutrophils into the gastric mucosa.¹ In a small proportion of those infected, the chronic stimulation can lead to the development of gastric and duodenal ulceration and may also result in the development of malignant disease such as mucosa associated lymphoid tissue lymphoma² and adenocarcinoma.³

There are many factors believed to contribute to the progression to helicobacter induced diseases, including strain variation, dietary and environmental differences, and host factors. For example, some strains of H pylori express virulence factors which are associated with the development of more severe disease. Expression of the cag pathogenicity island, a collection of over 30 genes, by some strains of bacteria is associated with an increased chance of developing the more serious complications of helicobacter infection.¹ Environmental factors are also clearly important, with smoking being associated with an increased incidence of ulcers⁴ and high levels of salt in the diet associated with an increased risk of cancer (reviewed in Cohen and Roe⁵). In addition, treatment of infected patients with acid suppressive drugs leads to loss of bacterial colonisation in the antrum and a reduction in antral gastritis, while the H pylori remains in the body of the stomach and the body gastritis increases.⁶

Thus, acid levels can control both the location of the infection and the extent of gastritis, which has led to the proposal of a unifying hypothesis linking H pylori infection, local acid production, and gastroduodenal disease.⁷ Recently, evidence has arisen which indicates that host genetic factors are also heavily involved in the development of helicobacter associated pathologies. In previous work, we have shown that the development of helicobacter induced gastritis in a mouse model of H felis infection is host dependent, as infection of different strains of mice with the same culture of bacteria produced varying degrees of inflammation in the gastric mucosa.⁸ Infection of C3H/He, DBA/2, SJL, and C57BL/6 mice induced a destructive gastritis in the body, whereas the stomachs of infected BALB/c and CBA/Ca mice had relatively normal histology.

Abbreviations used in this paper: LPS, lipopolysaccharide; MHC, major histocompatibility complex; BHI, brain heart infusion.
despite the presence of large numbers of colonising bacteria. Later, we showed that this gastritis may be linked to the production of helicobacter lipopolysaccharide (LPS) as the LPS non-responder C3H/HeJ strain failed to mount a significant inflammatory response to infection, in contrast to the closely related C3H/He strain which has normal LPS responsiveness.\(^\text{13}\) The host dependent nature of these responses did not seem to be related to the major histocompatibility complex (MHC) haplotype of the mouse strains as C3H/He mice which gave an inflammatory phenotype and the non-responder CBA/Ca mice are MHC identical. However, a similar study by Mohammadi et al using congenic mice suggested that both host MHC and non-MHC genes contributed to helicobacter induced inflammation\(^\text{11}\) and a recent study in humans has also implied an association of MHC expression and the development of atrophic gastritis and adenocarcinoma.\(^\text{12}\)

The aim of this study was to augment these observations, using the \(H\). \(f\)elis mouse model to dissect the role of host factors in the production of helicobacter induced gastritis. To address this, we bred \(F_1\) hybrid crosses of a strain of mouse known to be non-responsive to infection with helicobacter, with three strains which were known to produce strong inflammatory responses to infection. Comparison of the phenotypes of these \(F_1\) progeny with that of their parental strains following chronic infection with \(H\). \(f\)elis provides us with important information regarding the mechanisms controlling the development of helicobacter induced gastritis.

### Materials and methods

#### ANIMALS

Parental CBA/Ca and SJL mice were obtained from the Animal Resource Centre, Perth, Australia; C57BL/6 from CULAS, Sydney, Australia; and C3H/He mice from the Walter Elisa Hall Institute, Melbourne, Australia. For this study, seven week old specific pathogen free mice were examined and scored in a blinded fashion. The grade of colonisation in the gastric mucosa of mice are considerably from those observed in the human stomach, the guidelines of the updated Sydney System for the grading of gastritis\(^\text{12}\) were modified to take the differences into account. To determine the degree and the topographical distribution of gastritis, H&E stained sections which included a portion of the squamous epithelium of the cardia and the full length of the

#### BACTERIA

\(H\). \(f\)elis, strain CS1 (ATCC 49179), was grown on campylobacter selective agar consisting of 5% (vol/vol) sterile horse blood in blood agar base no 2 (Oxoid Ltd, Basingstoke, UK) containing 10 \(\mu\)g/ml vancomycin (Sigma, St Louis, Missouri, USA), 5 \(\mu\)g/ml trimethoprim (Sigma), 2500 IU/l polymyxin B (Sigma), and 5 \(\mu\)g/ml amphotericin B (ER Squibb and Sons, Princeton, New Jersey, USA). The plates were incubated in an anaerobic jar with a microaerophilic gas generating kit (code no BR 56, Oxoid) for two days at 37°C. \(H\). \(f\)elis was harvested from plates and suspended in brain heart infusion broth (BHI; Oxoid); the final concentration was adjusted to approximately 10\(^8\) bacteria/ml with BHI broth.

#### EXPERIMENTAL PROCEDURE

For infection, mice were inoculated intragastrically twice in a three day period with 0.1 ml of bacterial suspension (10\(^8\) bacteria) using a polyethylene stomach catheter (0.58 mm internal diameter \(\times\) 0.97 mm outer diameter; Critchley Electrical Products, Auburn, Australia). Ten infected animals (five males and five females) and four non-infected controls (two males and two females) of each strain of mouse were infected. Mice were anaesthetised by intraperitoneal injection with 50 mg/kg of both ketamine and xylazine (Parnell Laboratories, NSW, Australia). Blood was collected from the aortic arch and the sera stored at \(-20°C\). Mice were sacrificed by cervical dislocation and their stomachs collected. Gastric tissue was collected for the assessment of colonisation and the development of pathological responses and sera were collected for determination of anti-\(H\). \(f\)elis\(\) IgA and IgG antibody levels. Half of the stomach was fixed in neutral buffered formalin, embedded in paraffin wax, and 4 \(\mu\)m thick sections cut. These sections were stained with haematoxylin-eosin stain (H&E) for histopathology and May Grünwald-Giemsa stain for assessment of \(H\). \(f\)elis\(\) colonisation. All 115 slides were examined and scored in a blinded fashion.

### ASSESSMENT OF COLONISATION

The degree of colonisation in \(H\). \(f\)elis\(\) infected mice was assessed by semiquantitative analysis of bacteria in the antrum, the antral/body transitional zone, the body, the body/cardia transitional zone, and the cardia. Bacterial colonisation was graded from 0 to 4 where 0 = no bacteria, 1 = 1–2 bacteria/crypt, 2 = 3–10 bacteria/crypt, 3 = 11–20 bacteria/crypt, 4 = >20 bacteria/crypt.

#### ASSESSMENT OF PATHOLOGICAL RESPONSES

As the inflammatory and metabolic responses in the gastric mucosa of mice are considerably different from those observed in the human stomach, the guidelines of the updated Sydney System for the grading of gastritis\(^\text{13}\) were modified to take the differences into account. To determine the degree and the topographical distribution of gastritis, H&E stained sections which included a portion of the squamous epithelium of the cardia and the full length of the

### Table 1: Assessment of colonisation with \(H\). \(f\)elis

<table>
<thead>
<tr>
<th>Strain</th>
<th>Antrum</th>
<th>Antrum/body</th>
<th>Body</th>
<th>Body/cardia</th>
<th>Cardia</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBA/Ca</td>
<td>3.2 (0.4)</td>
<td>2.8 (0.6)</td>
<td>0.5 (0.3)</td>
<td>2.1 (1.0)</td>
<td>1.9 (0.9)</td>
</tr>
<tr>
<td>C3H/He</td>
<td>2.7 (0.2)</td>
<td>2.4 (0.2)</td>
<td>1.6 (0.8)</td>
<td>1.9 (0.5)</td>
<td>1.2 (0.6)</td>
</tr>
<tr>
<td>C57BL/6</td>
<td>2.1 (1.0)</td>
<td>2.5 (0.8)</td>
<td>1.3 (0.7)</td>
<td>1.6 (0.8)</td>
<td>1.9 (0.6)</td>
</tr>
<tr>
<td>SJL</td>
<td>1.6 (0.8)</td>
<td>1.7 (1.0)</td>
<td>0.9 (0.2)</td>
<td>1.2 (0.8)</td>
<td>1.1 (0.8)</td>
</tr>
</tbody>
</table>

\(\text{Bacteria colonisation was assessed by light microscopic examination of May Grünwald-Giemsa stained sections. Scores are mean (SEM) grades of colonisation between 0 and 4, where 0 = no bacteria, 1 = 1–2 bacteria/crypt, 2 = 3–10 bacteria/crypt, 3 = 11–20 bacteria/crypt, 4 = >20 bacteria/crypt.} \)

*\(\text{CBA/Ca}\) and \(\text{C3H/He}\) mice and \(\text{CBA}\) and \(\text{C57BL/6}\) mice had a significantly reduced level of colonisation in the body compared with the \(\text{C3H/He}\) and \(\text{C57BL/6}\) parent respectively (p<0.05).*
corpus and antrum were evaluated. The intensity of the polymorphonuclear and mononuclear infiltration was graded from 0 (absent) to 3, where 3 indicated the most severe infiltrate observed. The inflammatory scores for both cells were considered separately for corpus and antrum, and then combined into a gastritis score for each of the two gastric compartments.

Lymphoid aggregates were counted and expressed as the total number seen in the combined sections from each animal. The changes defined here as “functional atrophy” consisted of the apparent substitution of the parietal and chief cells of the corpus with mucous metaplasia consisting of larger, pale, globular cells that did not resemble the goblet cells found in intestinal metaplasia in the human stomach. The functional atrophy was also graded from 0 (absent) to 3. The highest score represented the most severe change seen in this group of mice (large areas of the corpus mucosa substituted by the metaplastic mucous cells). None of the animals showed complete replacement of the mucosa which would normally be defined as atrophy in humans.

MEASUREMENT OF ANTI-HELCOBACTER SERUM ANTIBODIES
An enzyme linked immunosorbent assay (ELISA) was used to measure anti-helicobacter antibody levels. Triplicate wells of microtitre plates (Dynatech, Chantilly, Virginia, USA) were incubated with H. felis lysate preparation (100 µg/ml) in carbonate buffer, pH 9.6. After washing with phosphate buffered saline (PBS)-0.5% Tween 20, the wells were blocked with PBS containing 2.5% non-fat dried milk and then incubated for one hour at 37°C with serial dilutions of sera. The wells were next incubated with biotinylated goat-antimouse IgA, IgG1, or IgG2a (Southern Biotechnology, Birmingham, Alabama, USA) and then with streptavidin-alkaline phosphatase (Calbiochem). Following addition of substrate (Sigma 104 phosphatase substrate tablets in diethanolamine buffer), the plates were read spectrophotometrically in an automated ELISA reader at a wavelength of 405 nm.

STATISTICS
The differences in H. felis colonisation and histopathology scores between different strains of mice were tested by non-parametric Kruskal Wallis (K-W) analysis. Only one stomach section from each animal was analysed. This raises the possibility of sampling error arising from only evaluating a small part of each stomach. However, 10 mice were studied per group, and any such effect should be minimal. Differences were considered significant at p<0.05.

Results
EVALUATION OF GASTRITIS
To investigate the role of host factors in the generation of helicobacter induced gastritis, various strains and F1 crosses of mice (n=10) were infected with H. felis. Three months following infection, stomach and serum samples were collected. Analysis of stained stomach sections for bacterial burden revealed that all strains challenged with H. felis were colonised, but that levels of colonisation varied between strains (table 1). The CBA/Ca parental strain and its F1 hybrid

Table 2  Assessment of the inflammatory response induced by H. felis infection

<table>
<thead>
<tr>
<th>Strain</th>
<th>Antrum</th>
<th>Body</th>
<th>Functional atrophy</th>
<th>Lymphoid aggregates</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBA/Ca</td>
<td>0.2 (0.4)</td>
<td>0.3 (0.9)</td>
<td>0.5 (1.0)</td>
<td>0.2 (0.6)</td>
</tr>
<tr>
<td>C3H/He</td>
<td>0.8 (0.4)</td>
<td>1.8 (1.2)</td>
<td>1.1 (1.5)</td>
<td>0.8 (1.0)</td>
</tr>
<tr>
<td>C57BL/6</td>
<td>0.6 (0.5)</td>
<td>1.3 (1.0)</td>
<td>1.0 (1.3)</td>
<td>1.1 (1.0)</td>
</tr>
<tr>
<td>SJL</td>
<td>0.9 (0.7)</td>
<td>1.8 (1.1)</td>
<td>0.9 (0.9)</td>
<td>1.3 (1.0)</td>
</tr>
<tr>
<td>CBAxC3H/He</td>
<td>0.4 (0.5)</td>
<td>0.2 (0.4)*</td>
<td>0*</td>
<td>0*</td>
</tr>
<tr>
<td>CBAxC57BL/6</td>
<td>0.1 (0.3)*</td>
<td>0*</td>
<td>0*</td>
<td>0*</td>
</tr>
<tr>
<td>SJLxCBA</td>
<td>0.2 (0.4)*</td>
<td>0.3 (0.9)*</td>
<td>0*</td>
<td>0.3 (0.6)*</td>
</tr>
</tbody>
</table>

Gastric inflammation was assessed by light microscopic examination of H&E stained sections. The values represent the mean (SEM) scores from n=10 mice per group.

*Values shown for the F1 hybrid strains were significantly reduced compared with their respective responder strain parent (C3H/He, C57BL/6, SJL; p<0.05) but not significantly different from their non-responder CBA/Ca parent.
crosses had comparable colonisation levels in the antrum and the transitional zones, compared with C3H/He and C57BL/6 mice, but had significantly lower bacterial levels in the body (p=0.005). There was no significant difference in colonisation in the body of the SJL, CBA, and the three F1 hybrid strains. However, there were significant differences in the degrees of gastric inflammation observed for the various strains. Infection of C3H/He, C57BL/6, and SJL mice with *H. felis* resulted in cellular infiltration (predominantly in the body but also in the antrum), the formation of lymphoid aggregates, and also what we now term functional atrophy (table 2; fig 1). In contrast, the extent of inflammation in CBA/Ca mice was significantly lower when compared with the three helicobacter responsive strains (p<0.015). The three strains of F1 progeny had levels of gastritis which were not significantly different from the CBA strain, indicating that all the F1 strains had a helicobacter non-responsive phenotype (fig 1). All groups of mice were composed of 50% males and 50% females: no phenotypic variations were observed with respect to the sex of the mice.

**SERUM ANTIBODY RESPONSE**

The serum anti-*H felis* antibody response to infection in the various strains of mice was analysed by ELISA. There was a significant difference in the serum levels of anti-*H felis* IgA between the helicobacter responder strains of mice infected with *H felis* and the non-responder CBA mice and their F1 progeny (fig 2A; K-W p<0.001). Similarly, the IgG1 antibody response in CBA and the F1 hybrid strains was low relative to C3H/He and SJL mice, which had high and intermediate levels, respectively (fig 2B; p<0.001). The IgG2a antibody levels in sera from infected CBA and CBA×C3H/He mice were very similar and significantly different from those found in C3H/He mouse sera which produced a high level antibody response (fig 2C; p<0.001). As C57BL/6 and SJL mice have a deletion of the IgG2a gene, anti-*H felis* IgG2a data are not shown. In summary, the sera from *H felis* infected CBA/CaH mice and the three F1 hybrids contained little or no anti-*H felis* IgG or IgA antibodies, in contrast to the responder C57BL/6, SJL, and C3H/He strains.

**Discussion**

Chronic infection with *H pylori* can cause a range of diseases including peptic ulcers and gastric cancer. The first studies which attempted to explain these differences postulated bacterial factors as being important. Certainly there are strains of the bacterium that cause more severe inflammation if they possess what is termed the “pathogenicity island.” However, we have previously challenged the simplistic view of the “ulcerogenic strain” as the sole explanation. Based on animal studies, we suggested that host factors are likely to be equally important in determining the outcome of disease. C57BL/6, C3H/He, DBA/2, and SJL mice all developed severe functional atrophy in the body mucosa with loss of parietal and chief cells after long term infection with *H felis*, while BALB/c and CBA/Ca mice showed no remarkable lesions.

We originally hypothesised that the lack of inflammation during *H felis* infection in BALB/c and CBA mice may have been due to one of two possibilities. Firstly, an inherent immunological defect in these strains of mice could prevent the development of gastritis. In support of this possibility, we have recently reported that C3H/HeJ mice, which have a genetic defect for LPS responsiveness, do not develop gastritis when infected with *H felis*, in contrast to the LPS responsive C3H/He strain from which it arose. An alternative explanation was that the non-responder mice actively suppressed the immune response to the helicobacter antigens. The study reported here was designed to test this possibility. The *H felis*
non-responsive CBA/Ca strain was crossed with three strains of mice known to develop a severe gastritis following *H felis* infection. The non-responder CBA strain was selected instead of non-responder BALB/c mice as this allowed the study of the role of the impact of MHC status; the C3H/He and CBA strains are both H-2<sup>k</sup>, whereas the C57BL/6 and SJL strains are MHC disparate with CBA. We reasoned that if the non-responsiveness was due to an immune defect, the F<sub>1</sub> hybrids would develop gastritis as the deficiency would be overcome by genes of the responsive parent. As we only used a single sex of CBA/Ca mice in producing each F<sub>1</sub> cross, the effect of imprinting was not examined. This raises the possibility that there may be different phenotypic expression of susceptibility or resistance genes inherited from the mother or father. However, as the CBA/Ca mice used to breed the F<sub>1</sub> crosses were both maternal (for father. However, as the CBA/Ca mice used to produce offspring which produced very low levels of both serum IgG2a and IgG1 anti-*H felis* antibodies. These antibodies are considered markers of Th1 and Th2 type immunity, respectively, and thus a reduction in both of these suggests that the lack of gastritis in the F<sub>1</sub> mice is not due to a switch in the Th profile, but is rather a generalised down regulation of the humoral immune response. Also of interest is the observation that the IgA serum antibody levels were reduced in all non-inflammatory strains; IgA is the antibody isotype normally secreted into the intestine and so is the antibody which is most likely to encounter the bacteria.

We found that crossing C3H/He mice with CBA/Ca created F<sub>1</sub> offspring which produced very low levels of both serum IgG2a and IgG1 anti-*H felis* antibodies. These antibodies are considered markers of Th1 and Th2 type immunity, respectively, and thus a reduction in both of these suggests that the lack of gastritis in the F<sub>1</sub> mice is not due to a switch in the Th profile, but is rather a generalised down regulation of the humoral immune response. Also of interest is the observation that the IgA serum antibody levels were reduced in all non-inflammatory strains; IgA is the antibody isotype normally secreted into the intestine and so is the antibody which is most likely to encounter the bacteria.

We found that whereas C57BL/6, C3H/He, and SJL mice developed helicobacter induced lymphofollicular gastritis with associated functional atrophy, all three CBA crosses showed an absence or great reduction of these histopathological features (table 2; fig 1), just as observed for the CBA/Ca mice. Thus, the CBA phenotype is dominant over at least three different backgrounds of responder mice, suggesting that the lack of gastritis observed in these mice is not due to any genetic deficiency. It is possible that the responsiveness to infection may be recessively inherited rather than non-responsiveness being dominantly inherited. This is unlikely, however, as virtually all mouse strains tested are helicobacter responsive.

The hypothesis that the lack of gastritis in CBA related strains is in fact due to immune suppression is supported by analyses of the serum antibody response. While high levels of *H felis* bacteria were present in the stomachs of the CBA and the CBA related F<sub>1</sub> crosses, these mice generated very low anti-*H felis* antibody levels. In contrast, the parental strains with the inflammatory phenotype (the C57BL/6, C3H/He, and SJL strains), produced a high or intermediate antibody profile. Comparisons of antibody levels of individual mice and the level of inflammation in those mice did not reveal any correlation (not shown). It is particularly interesting to compare the CBA and C3H/He cross; the C3H/He strain gave high antibody responses in all subclasses whereas the CBA and CBA×C3H/He strains gave little or no antibody response. This is of relevance because the CBA and C3H/He strains are MHC identical and so whatever mechanism is causing this large difference in phenotype, it is not related to differences in their MHC antigens.

A previous study in mice reported that both MHC and non-MHC genes were involved in the degree of gastritis induced by a helicobacter infection. Additionally, a recent study by Azuma *et al* analysed the frequency of certain MHC class II molecules in humans infected with *H pylori* and found that infected persons who lacked the HLA-DQA1*0102* allele had a higher frequency of atrophic gastritis and gastric adenocarcinoma. Thus, while in our murine model gastritis was not associated with products of the MHC, it seems that in other systems there can be a role for the genes of the MHC in the generation of an inflammatory response to helicobacter infection.

We found that crossing C3H/He mice with CBA/Ca created F<sub>1</sub> offspring which produced very low levels of both serum IgG2a and IgG1 anti-*H felis* antibodies. These antibodies are considered markers of Th1 and Th2 type immunity, respectively, and thus a reduction in both of these suggests that the lack of gastritis in the F<sub>1</sub> mice is not due to a switch in the Th profile, but is rather a generalised down regulation of the humoral immune response. Also of interest is the observation that the IgA serum antibody levels were reduced in all non-inflammatory strains; IgA is the antibody isotype normally secreted into the intestine and so is the antibody which is most likely to encounter the bacteria.

The gastrointestinal tract has evolved an immune system which is primed to induce a state of non-responsiveness—a phenomenon termed oral tolerance. Delivery of antigens orally can generate immune non-responsiveness which prevents reactions against food antigens and commensals living in the gut (reviewed in Strobel and Mowat). In contrast to the normal non-responsiveness to other gut inhabiting commensals, helicobacter infection induces an inflammatory response in most strains of mice. One possible mechanism for the lack of response in some mice to *H felis* and its antigens may involve LPS. We have shown that LPS non-responsive mice lack gastritis and LPS may be involved in the induction of oral tolerance, although its role is unclear. Why a break in tolerance should occur during *H felis* infection, but not for many other Gram negative bacteria which also produce LPS is unknown. Perhaps it is due either to the unique location of the helicobacter, or to the biochemical and biological differences between helicobacter LPS and the LPS of other Gram negative bacteria. While mechanisms of tolerance induction in helicobacter infection have not been investigated, the finding of reduced antibody levels and gastritis raises the possibility that such processes may occur in *H felis* infected CBA mice and their F<sub>1</sub> progeny.

It needs to be emphasised that the histopathological features observed in our mouse model do not completely mimic the human pathology. The characteristic antral chronic/active gastritis is missing. We have argued before that the lesions seen in mice represent a subset of the human pathology which may be particularly relevant to development of atrophy. We have suggested that atrophic changes may not necessarily be a direct consequence of long term active/chronic gastritis as has been hitherto assumed. In the human, subsets of atrophy and active/chronic inflammation cannot be distinguished, whereas in our mouse models they clearly are. Mucus metaplasia,
equivalent to that seen here, has been observed in some human specimens (Dixon, personal communication). We have also speculated that some type of immunological effects may be responsible for the changes in the proliferative zone of the body glands and the disappearance of the chief and parietal cells.9

In summary, we have shown that CBA mice do not develop body gastritis when infected with H felis, that this trait is dominantly inherited in three other strains of normally responsive mice, and that this nonresponsiveness is associated with a lack of an antibody response suggesting suppression of the inflammatory response normally mounted against chronic helicobacter infection. Further investigation of the mechanism of this apparent suppression of the development of functional atrophy will provide important insights into aspects of the human disease which may be relevant to the induction of gastric atrophy and ultimately gastric cancer.

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