Are Genetic Influences on Peptic Ulcer Dependent or Independent of Genetic Influences for Helicobacter pylori Infection?

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Background: Genetic factors play a role or roles in the etiology of peptic ulcer disease and the acquisition of Helicobacter pylori infection.

Objective: To evaluate the relative importance of genetic and environmental influences as well as the importance of H pylori on peptic ulcer disease.

Design: Cross-sectional study on monozygotic (MZ) and dizygotic (DZ) twins, reared apart or together.

Participants: Twins of the subregistry of the Swedish Twin Registry included in the Swedish Adoption/Twin Study of Aging.

Measurements: Peptic ulcer disease and H pylori status were assessed in MZ and DZ twin pairs reared apart or together. A total of 258 twin pairs had information regarding H pylori status and history of peptic ulcer. Helicobacter pylori status was assessed as the presence of anti-H pylori IgG.

Results: The intraclass correlations for peptic ulcer disease for MZ twins reared apart and together were 0.67, 0.65, 0.22, and 0.35, respectively, which indicates that genetic effects are important for liability to peptic ulcer. The correlation coefficient for MZ twins reared apart (0.67) provides the best single estimate of the relative importance of genetic effects (heritability) for variation in liability to peptic ulcer disease, and structural model fitting analyses confirmed this result (heritability, 62%). The cross-twin cross-trait correlations for MZ and DZ twins were examined to determine whether genetic effects for peptic ulcer were shared with or independent of genetic influences for H pylori. The cross-correlations for MZ and DZ twins were almost identical (0.25 and 0.29, respectively), suggesting that familial environmental rather than genetic influences mediate the association between peptic ulcer disease and H pylori infection.

Conclusions: Genetic influences are of moderate importance for liability to peptic ulcer disease. Genetic influences for peptic ulcer are independent of genetic influences important for acquiring H pylori infection.

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During the past 50 years, the ability of investigators to identify risk factors associated with peptic ulcer has been hampered by the heterogeneous nature of the disease. The prevalence and incidence of peptic ulcer varies worldwide in relation to geographic, racial, and social circumstances.1-4 There has also been some evidence that genetic factors play an important role in the etiology of peptic ulcer disease.5-7 However, the pattern of inheritance is not simple mendelian and the genetic basis is multifactorial. Risk factors for peptic ulcer include cigarette smoking and nonsteroidal anti-inflammatory drug use.1,8 Additional potential risk factors for peptic ulcer have been documented, including age, sex, alcohol and caffeine consumption, stress, and diet.1,8-12 However, the results concerning environmental risk factors for peptic ulcer are not conclusive.

During the past decade, an association between peptic ulcer disease and Helicobacter pylori infection was recognized.13-15 Because of the significant role of H pylori infection in peptic ulcer disease, there has been substantial interest in studying genetic and environmental influences (eg, socioeconomic status and crowding) on acquiring the infection. It has been reported previously16 that genetic factors are important for acquiring H pylori infection. These influences may be a source of genetic influences for developing peptic ulcer disease. Similarly, it is feasible that environmental risk factors that are of importance for acquiring H pylori infection are shared with or independent of genetic influences important for acquiring H pylori infection.
SUBJECTS AND METHODS

SAMPLE

The sample for this investigation was composed of twins from a subregistry of the Swedish Twin Registry, which includes entries for about 25,000 like-sexed twin pairs born in Sweden between 1886 and 1958. The subregistry, known as SATSA, consists of a number of twins who indicated that they had been separated before the age of 11 years and reared apart and a sample of twins reared together, matched on the basis of sex, age, and county of birth. When SATSA was initiated in 1984 with a mail-out questionnaire, both members of 758 pairs had completed the questionnaire, of whom 691 had serum available for evaluating H pylori status. Zygosity was first determined on the basis of physical similarities and confirmed on the basis of serological assay. One pair was excluded from the analyses because the certainty of zygosity (≥98%) could not be obtained. The distribution of age at separation is highly skewed: 52% of the twins reared apart were separated before their first birthday, 69% by their second birthday, 82% by the age of 3 years, and all by the age of 11 years.17 Reasons for separation varied; the majority were separated because of the death of 1 or both parents and/or economic hardship. Further details of the procedures, sample, and design of SATSA are described by Pedersen et al.17

EVALUATION OF H PYLORI STATUS

The presence of anti–H pylori IgG was assessed by means of a commercially available H pylori immunoassay test kit (HM-CAF; Enteric Products Inc, Stony Brook, NY). The test was scored positive when the optical density was greater than 2.0. The test has a sensitivity of more than 98% and a specificity of more than 95%.16 Helicobacter pylori infection is chronic and even lifelong. After successful antimicrobial therapy, the antibody titer becomes undetectable; however, the presence of serum antibody is a reliable indication of H pylori status.

ANALYSES

The primary aim of the analyses is to describe individual differences in liability to peptic ulcer by partitioning these differences (total variance) into genetic and environmental variance components. Quantitative genetic theory posits that total phenotypic variance is the sum of genetic variance, environmental variance, and twice the covariation of genetic and environmental effects. Genetic variance can be further partitioned into additive genetic variance, reflecting the effects of many segregating genes of equal effect, and nonadditive genetic variance caused by interactions within and among genetic loci. Environmental variance can be partitioned into environmental effects shared by family members (causing familial similarity) and nonshared environmental effects (causing differences among family members). An assumption of the present analyses, that there is no genotype-environment covariance, has been supported for most behavioral and biomedical phenotypes.19 Heritability is defined as the proportion of total variance attributable to genetic variance. In these models, all variance that is not genetic is considered environmental. Thus, the heritability statistic provides an estimate of the relative importance of genetic differences for individual differences in susceptibility to peptic ulcer in the population (relative to environmental effects). This statistic refers to the population and does not describe risk to an individual.

INTRACLASS CORRELATIONS

Intraclass correlations were calculated to measure the similarities within the twin pairs before the phenotypic variance was decomposed into genetic and environmental components. The intraclass correlations and their interpretation are as follows: (1) magnitude of MZA correlation: importance of genetic effects; (2) MZ correlations greater than DZ correlations: importance of genetic effects; (3) twins reared together more similar than twins reared apart: importance of shared rearing environments; (4) no or little difference of MZ and DZ correlations: importance of familial environmental effects; and (5) differences within MZ pairs (1 – MZ correlation): nonshared environmental influences. The intraclass correlation of MZA twins provides a direct and unbiased estimate of heritability. Because the phenotype, presence of peptic ulcer disease, is categorical (0 or 1), tetrachoric intraclass correlations were calculated by the PRELIS2 program (Scientific Software Inc, Chicago, Ill) for each of the 4 rearing-by-zygosity groups. Examination of intraclass correlations provides valuable insights regarding the relative importance of genetic and environmental factors. However, it is difficult to estimate the importance of several variables, eg, heritability, nonshared environment, shared rearing environment, and other forms of correlated environment, by separate comparisons of pairs of correlations. Hence, structural models based on quantitative genetic expectations of factors contributing to twin similarities and differences were fit to the data. The model used in the present study has been described in detail by Neale and Cardon.50

H pylori infection may also be of importance for developing peptic ulcer disease.

The present study examined a large cohort of twins to explore the relative importance of genetic influences for individual differences in liability to peptic ulcer disease and H pylori infection. We studied a sample of monozygotic (MZ) and dizygotic (DZ) twins, reared together (MZA, DZA) or reared apart (MZT, DZT), who were participants in the Swedish Adoption/Twin Study of Aging (SATSA).17 This sample allowed us to answer 2 major research questions: (1) What is the relative importance of genetic factors for liability to peptic ulcer disease?
The intraclass correlations for peptic ulcer disease for the 4 rearing-by-zygosity groups, MZA, MZT, DZA, and DZT, are presented in Table 1. Correlations for MZ and DZ twins are also pooled over rearing groups to maintain reasonable sample sizes. This pattern of correlations indicates that genetic effects are of modest importance for liability to peptic ulcer disease. Consistent with the intraclass correlations, the MZ probandwise concordance rate (39%), pooled over rearing status, was significantly greater than that for dizygotic pairs (15%) (P < .001) (Table 1). Furthermore, because twins reared together were not more similar than twins reared apart, there is no indication of shared rearing environments as a source of familial similarity for peptic ulcer. There were no significant sex differences in the intraclass correlations (Table 2), even though the prevalence rate was higher among men than women (7.5% and 5.3%, respectively).

The correlation coefficient for MZA twins (0.67) provides the best single estimate of the relative importance of genetic effects (heritability) for liability to peptic ulcer disease. By definition, the remaining variance (approximately 35%) is nongenetic and indicates the role of environmental factors for developing peptic ulcer disease. Structural model fitting analyses confirmed this finding. Heritability was estimated at 62%, and the remaining variance (38%) represented individual-specific, nonshared environmental variance ($\chi^2 = 0.63; P = .99$; Akaike Information Criterion, −9.37).

The association between H pylori and peptic ulcer was established in a case-control analysis and by tetrachoric correlation. A total of 299 unrelated individuals randomly selected from each twin pair had values for H pylori and peptic ulcer. The relative risk of those with H pylori and peptic ulcer was almost 2-fold that of those who did not have H pylori infection (relative risk, 1.9; 95% confidence interval, 0.80−4.39; $\chi^2 = 2.099; P = .14$). The tetrachoric correlation between H pylori and peptic ulcer was 0.27 ($P = .05$).

The second question addressed by the analyses was the extent to which there is genetic variance for peptic ulcer independent of genetic effects on H pylori infection. Possible genetic mediation of the association was evaluated by examining cross-twin cross-trait correlations, ie, ulcer in twin 1 with H pylori in twin 2. These cross-correlations can be interpreted in a fashion analogous to the intraclass correlations. If MZ cross-correlations are greater than DZ cross-correlations, the importance of genetic influences for the association between 2 traits is indicated. The correlations reported in Table 3 indicate that there is no genetic variation in common between the 2 measures (peptic ulcer and H pylori), because average MZ cross-twin correlations, 0.25, are not greater than average DZ cross-correlations, 0.29. This pattern of correlations suggests that the association between H pylori infection and peptic ulcer can be ascribed to familial environmental influences in common to both measures. Structural model fitting confirmed this finding (results not shown).

### Table 1. Probandwise Concordance Rates for Peptic Ulcer Disease in Monozygotic and Dizygotic Twins Reared Apart or Together

<table>
<thead>
<tr>
<th>Twin Type</th>
<th>No. of Pairs</th>
<th>No. of Discordant Pairs</th>
<th>No. of Concordant Pairs*</th>
<th>Probandwise Concordance Rate†</th>
<th>Intraclass Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monozygotic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reared apart</td>
<td>96</td>
<td>9</td>
<td>3</td>
<td>0.40</td>
<td>0.67</td>
</tr>
<tr>
<td>Reared together</td>
<td>159</td>
<td>13</td>
<td>4</td>
<td>0.38</td>
<td>0.65</td>
</tr>
<tr>
<td>Total</td>
<td>254</td>
<td>22</td>
<td>7</td>
<td>0.39</td>
<td>0.66</td>
</tr>
<tr>
<td>Dizygotic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reared apart</td>
<td>226</td>
<td>26</td>
<td>2</td>
<td>0.13</td>
<td>0.22</td>
</tr>
<tr>
<td>Reared together</td>
<td>211</td>
<td>20</td>
<td>2</td>
<td>0.17</td>
<td>0.35</td>
</tr>
<tr>
<td>Total</td>
<td>437</td>
<td>46</td>
<td>4</td>
<td>0.15</td>
<td>0.28</td>
</tr>
</tbody>
</table>

* Number of pairs concordant for being affected.
† Probandwise concordance rate = (number of affected twins in concordant pairs)/(total number of cases). Example: probandwise concordance rate for monozygotic total = (7+2)/(14+22) = 14/36 = 0.39.

### Table 2. Intraclass Correlations for Peptic Ulcer by Sex

<table>
<thead>
<tr>
<th>Twin Type</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monozygotic</td>
<td>0.30</td>
<td>0.37</td>
</tr>
<tr>
<td>Dizygotic</td>
<td>0.15</td>
<td>0.03</td>
</tr>
<tr>
<td>Total</td>
<td>0.21</td>
<td>0.17</td>
</tr>
</tbody>
</table>

### Table 3. Intraclass and Cross-Twin Correlations for Twin Pairs for Whom Information on Both Peptic Ulcer and Helicobacter pylori Infection Is Available

<table>
<thead>
<tr>
<th>Twin Type</th>
<th>No. of Pairs</th>
<th>Peptic Ulcer</th>
<th>H pylori</th>
<th>Cross-Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monozygotic</td>
<td></td>
<td></td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>Reared apart</td>
<td>32</td>
<td>0.65</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Reared together</td>
<td>61</td>
<td>0.65</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>0.68</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>Dizygotic</td>
<td></td>
<td></td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>Reared apart</td>
<td>85</td>
<td>0.21</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Reared together</td>
<td>80</td>
<td>0.33</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>165</td>
<td>0.25</td>
<td>0.28</td>
<td></td>
</tr>
</tbody>
</table>
The importance of genetic effects for *H pylori*-related diseases such as peptic ulcer, gastritis, and gastric cancer is currently of great interest. Although it is impossible to separate entirely environmental factors from genetic influences, early twin and family studies suggested a genetic component for these diseases.\(^5\)\(^-\)\(^7\) The present results showed that genetic effects are of moderate importance for liability to peptic ulcer in our population (heritability, 0.62), and the remaining variation can be explained by individual-specific environments. Despite the greater prevalence of peptic ulcer in men than women, there are no sex differences in twin similarity for peptic ulcer.

Previously, we established the importance of genetic factors for susceptibility to *H pylori* infection.\(^10\) The heritability of liability to *H pylori* infection was 0.63. Heritability is the proportion of total variance for liability to disease caused by genetic variance that describes the extent to which differences in liability to disease in the population are caused by genetic differences. To the best of our knowledge, no published study has evaluated whether genetic effects for developing peptic ulcer are independent of or shared with genetic effects important for acquiring *H pylori* infection. Comparisons of MZ and DZ cross-twin, cross-trait correlations and structural model fitting in the present study demonstrated that, despite the similarity in heritabilities for the 2 traits, the genetic influences for liability to peptic ulcer disease are independent of such genetic effects for acquiring *H pylori* infection. The relationship between *H pylori* and diseases such as peptic ulcer, chronic gastritis, and gastric cancer appears to be mediated by familial environmental factors, ie, environmental experiences or situations that are shared by family members. Examples of familial environmental factors that may mediate the association between *H pylori* and peptic ulcer disease are diet, smoking, and alcohol and coffee consumption.

Initially, the strongest evidence of a genetic influence on peptic ulcer came from studies showing an increased risk of duodenal ulcer in individuals with hyperpepsinogenemia.\(^21\)\(^-\)\(^22\) Those results have been questioned as it has become evident that elevated serum pepsinogen I level is also a feature of *H pylori* infection.\(^22\)\(^-\)\(^25\) The present results indicate that the association between peptic ulcer and *H pylori* reflects environmental rather than genetic mediation. Thus, environmental influences leading to *H pylori* infection and elevated serum levels of pepsinogen may result in peptic ulcer in susceptible individuals.

The occurrence of peptic ulcer disease has declined remarkably in the United States and Europe during the past 3 decades.\(^26\)\(^-\)\(^28\) Peptic ulcer was most prevalent among those born around the turn of the century and has decreased in all subsequent generations.\(^29\)\(^-\)\(^30\) The rapid change in the pattern of peptic ulcer in successive generations (ie, birth cohorts) more likely results from changes in environmental factors than changes in the genes of the affected patients. Multiple risk factors identified for peptic ulcer include family history, age, sex, race, social class, blood group, smoking, alcohol and coffee consumption, use of nonsteroidal anti-inflammatory drugs, stress, season of the year, and *H pylori* infection.\(^6\)\(^-\)\(^13\) None of these factors can be considered universal of essential characteristics of duodenal ulcer disease with the exception of *H pylori*-induced gastritis. Risk factors that are not shared by family members, such as use of nonsteroidal anti-inflammatory drugs, may represent examples of the individual-specific source of variance in liability to ulcer found in the present results.

In spite of the comprehensive design of our study, there may be some potential methodological problems. Although the results are interesting and informative, our data are based on self-reports, which could be subject to recall bias, resulting in overreporting or underreporting of the disease. However, the total prevalence rates of peptic ulcer disease among the Swedish population are 7.5% in men and 5.3% in women, which are comparable with those of other Scandinavian countries. On the basis of endoscopic findings, one Norwegian study reported an overall prevalence of 7.4% in men and 4.6% in women.\(^31\) Similar frequency estimates for lifetime prevalence of verified ulcers were found in an unselected Danish population initially identified with self-reported ulcer (7.7% among men and 3.6% among women).\(^32\) Another large cross-sectional questionnaire-based survey conducted in northern Norway reported a 5.3% prevalence of peptic ulcer in men and 2.1% in women.\(^31\) Thus, the prevalence of ulcer found in this study is comparable with that reported in the region. Furthermore, the pairwise concordance rates (0.24 and 0.08 for MZ and DZ pairs, respectively, not reported in Table 1) are comparable with those based on the Danish Twin Registry (0.26 and 0.14, respectively).\(^5\)

In summary, genetic influences are of moderate importance for peptic ulcer disease. Genetic factors of importance to peptic ulcer are independent of such factors for *H pylori* infection.

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